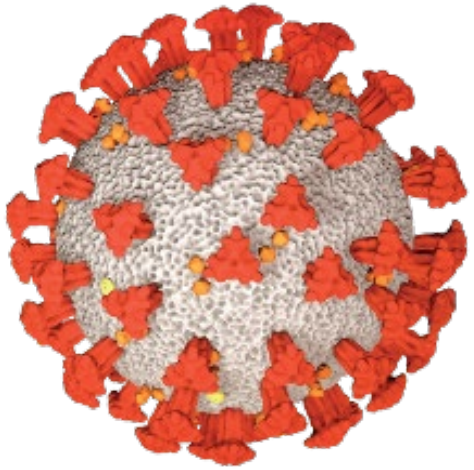
Preventing and Treating Covid-19
Where Do We Go From Here?



COVID-19
Prevention Network

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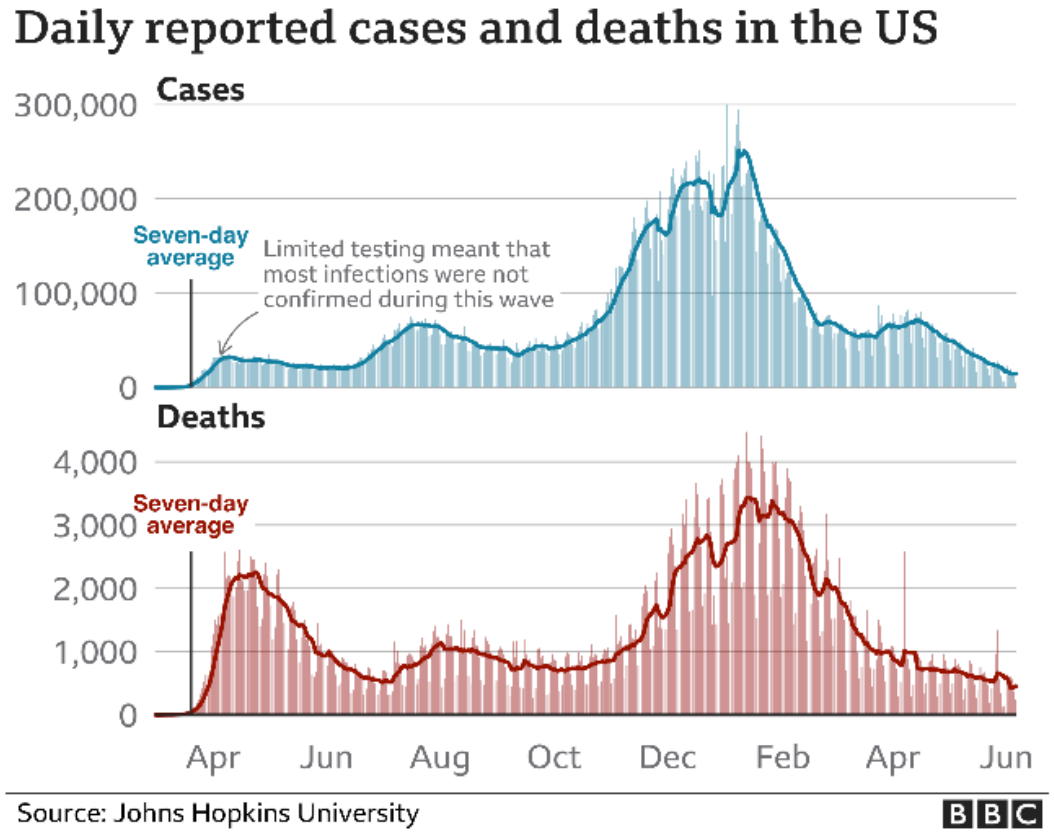
http://globalhealth.unc.edu | https://www.med.unc.edu/infdis

CURRENT SARS-CoV-2 EPIDEMIOLOGY, US

- Number total cases, US = ~33,000,000 (total deaths = ~594,000; 7 days case rate per 100,000 = 28 (NC=34)
- Number of people with one vaccine dose = ~171,000,000 (~52% US pop; ~61%, ≥12 years old; 64% ≥18; years old; ~86%, ≥65 years old)
- Number of people fully vaccinated = ~140,000,000 (US/NC - overall, ~42%/36%; ≥12 years old, 50%; ≥18 years old, 53%/46%; ~76%, ≥65 years)
- US/NC, 7-day test positivity = 2.1%/3.2%
- Driving factors for continued cases, hospitalizations, and deaths: 1) Elimination of mask requirements in some states; 2) Increase in SARS-CoV-2 variants; 3) Unvaccinated youth (hospitalization rate, ages 12-17 increased March-April compared with Jan/Feb)
- NC higher incidence of COVID-19 and lower vaccinations than US average

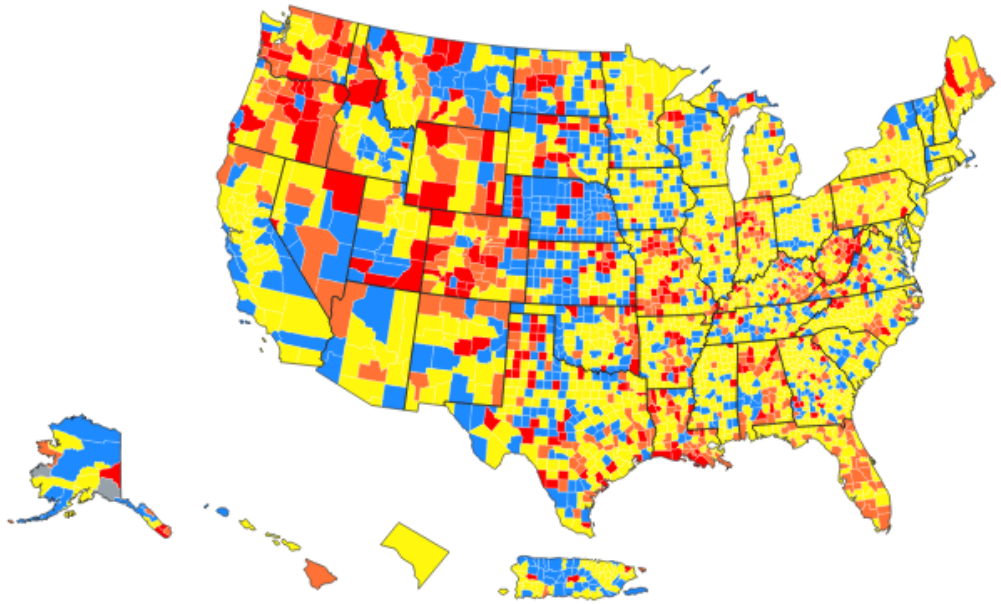
https://covid.cdc.gov/covid-data-tracker/#cases_casesper100klast7days

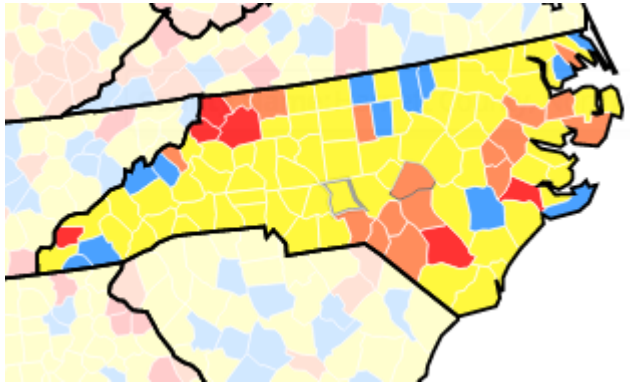


Cases per day, 7-day average = 14,349

Deaths per day, 7-day average = 414 (car accidents 2019=106)

COVID-19 CASES BY COUNTY, US, CDC





Level of Community Transmission	Number of U.S. Counties at this Level	Percent of U.S. Counties at this Level	Percentage Point Difference Since 7 Days Ago
High	280	8.7%	-3.6%
Substantial	445	13.82%	-8.26%
Moderate	1771	55%	3.85%
Low	723	22.45%	8.01%

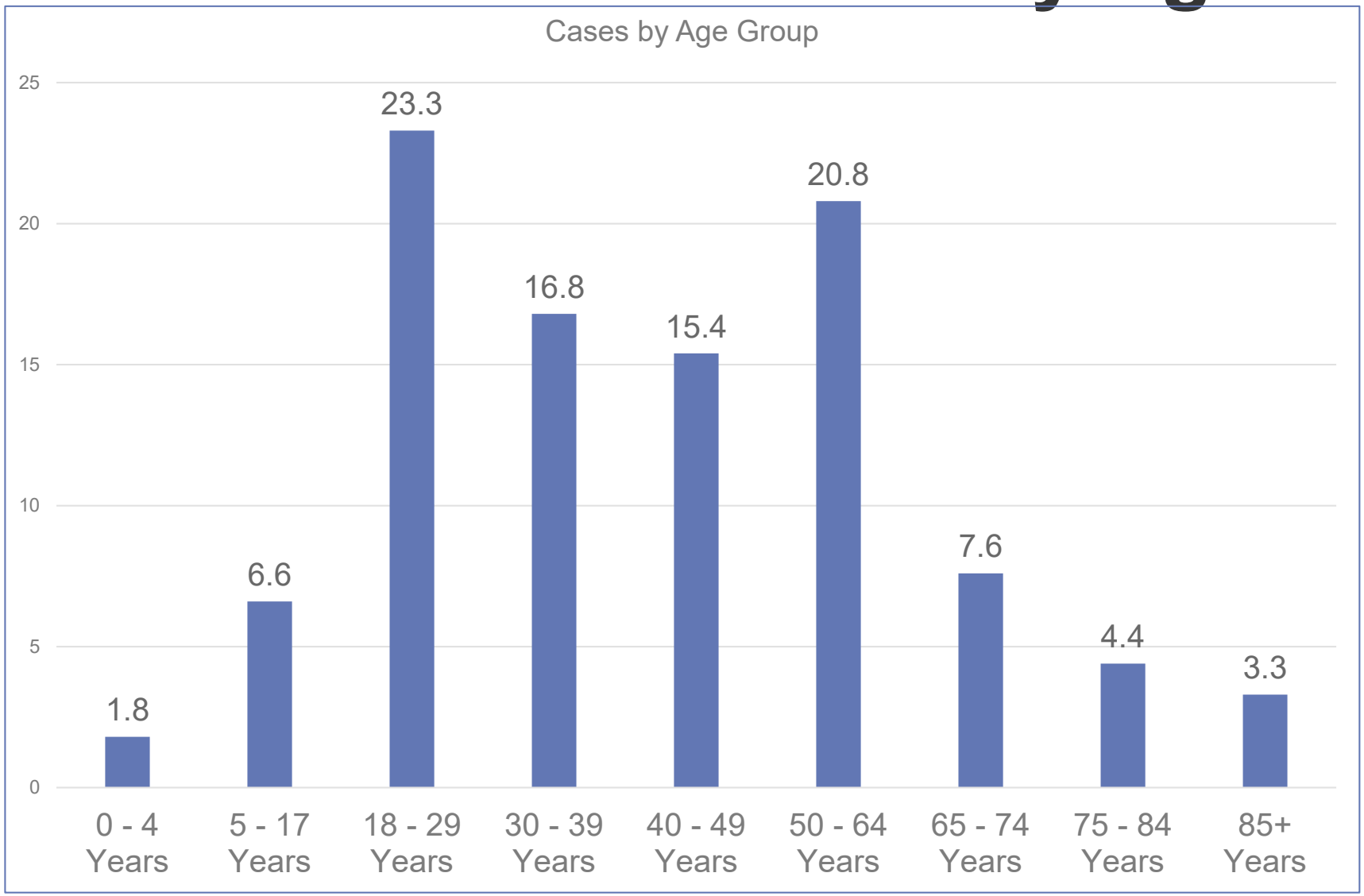
Indicator - If the two indicators suggest different transmission levels, the higher level is selected	Low Transmission Blue	Moderate Transmission Yellow	Substantial Transmission Orange	High Transmission Red
Total new cases per 100,000 persons in the past 7 days	0-9.99	10-49.99	50-99.99	≥100
Percentage of NAATs[1] that are positive during the past 7 days	0-4.99%	5-7.99%	8-9.99%	≥10.0%

CDC, Travel Page lists US as Level 3: COVID-19 high

"Make sure your are fully vaccinated before travel . Unvaccinated travelers should avoid nonessential travel"

https://covid.cdc.gov/covid-data-tracker/#county-view

Cases of COVID-19 by Age Group



Current cases among adults >65 years of age: 15.3%

Unclear from this data which proportion are symptomatic

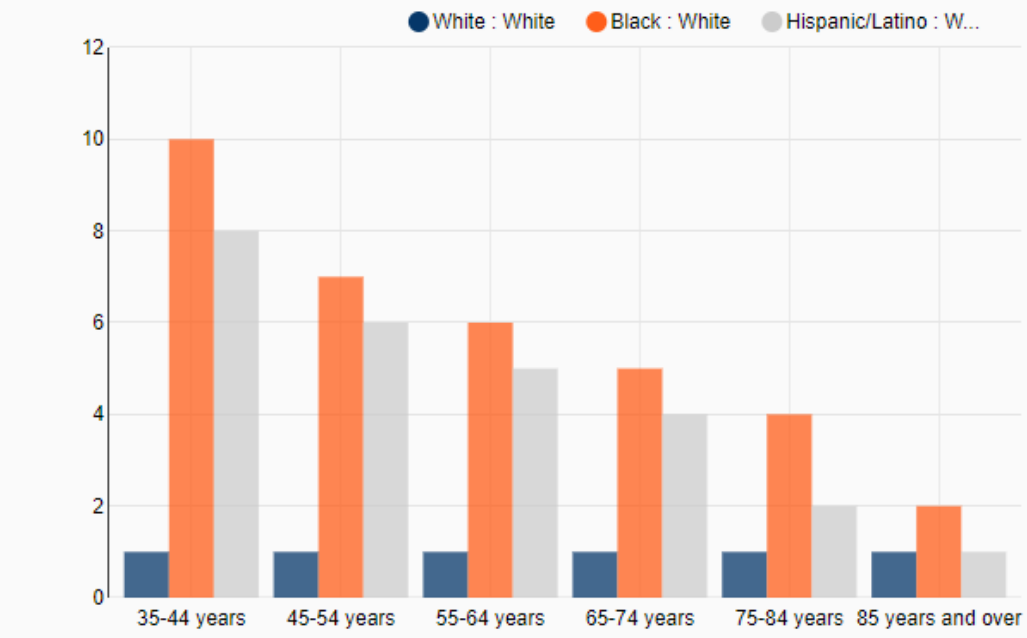
CDC Covid Data Tracker, downloaded 9/18/2020 https://covid.cdc.gov/covid-data-tracker/index.html#demographics

COVID-19 disease burden and outcome disparity are concentrated in sub-populations

COVID-19 Disease Burdens

- **Patients aged 60 and above** account for ~60% of hospital and ICU admissions and **~90% of deaths** while representing 20% of population
- **Patients with preexisting conditions** are 6-7 times more likely to be hospitalized and **more than 10 times more likely to die** than patients without preexisting conditions
- **Communities of color** are over-represented in cases and deaths by **~1.5-2x for Latinx and African American populations**, with huge disparities in outcomes for middle age

Figure 2. Huge race gaps in COVID-19 death rates, especially in middle age



Source: CDC data from 2/1/20-6/6/20 and 2018 Census Population Estimates for USA

BROOKINGS

Sources: CDC MMWR, 69 (24), p. 759; CDC Weekly Updates by Select Demographic and Geographic Characteristics, June 24, 2020; Brookings, Race gaps in COVID-19 deaths are even bigger than they appear, June 16, 2020

COVID-19 HOSPITALIZATION AND DEATH BY AGE

FACTORS THAT INCREASE COMMUNITY SPREAD AND INDIVIDUAL RISK


CROWDED SITUATIONS


CLOSE / PHYSICAL CONTACT

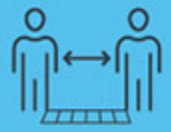

ENCLOSED SPACE


DURATION OF EXPOSURE

Rate ratios compared to 18-29 year olds	0-4 years	5-17 years	18-29 years	30-39 years	40-49 years	50-64 years	65-74 years	75-84 years	85+ years
HOSPITALIZATION[1]	4x lower	9x lower	Comparison Group	2x higher	3x higher	4x higher	5x higher	8x higher	13x higher
DEATH[2]	9x lower	16x lower	Comparison Group	4x higher	10x higher	30x higher	90x higher	220x higher	630x higher

ACTIONS TO REDUCE RISK OF COVID-19


WEARING A MASK


SOCIAL DISTANCING (6 FT GOAL)


HAND HYGIENE


CLEANING AND DISINFECTION

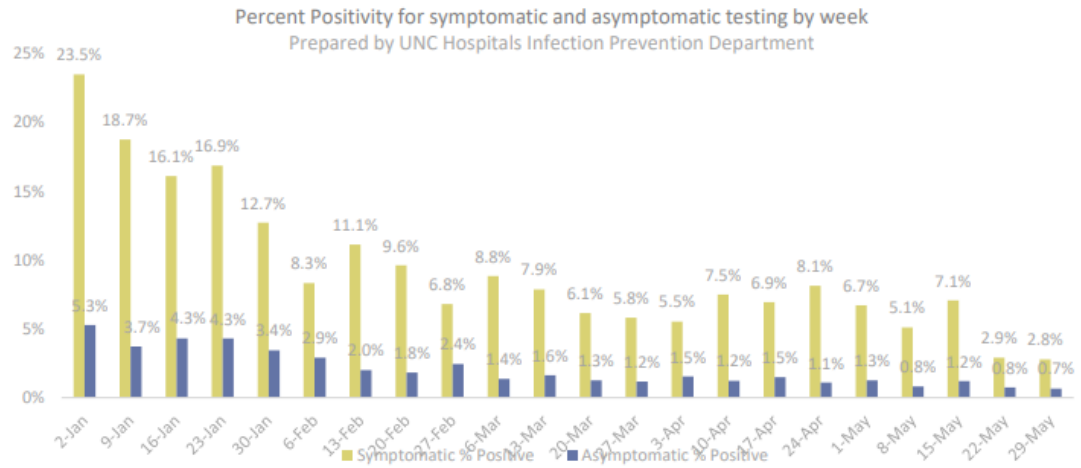
[1] Data source: COVID-NET (https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html, accessed 08/06/20). Numbers are unadjusted rate ratios.

[2] Data source: NCHS Provisional Death Counts (https://www.cdc.gov/nchs/nvss/vsrr/COVID19/index.htm, accessed 08/06/20). Numbers are unadjusted rate ratios.

cdc.gov/coronavirus

CS319360-A 08/10/2020

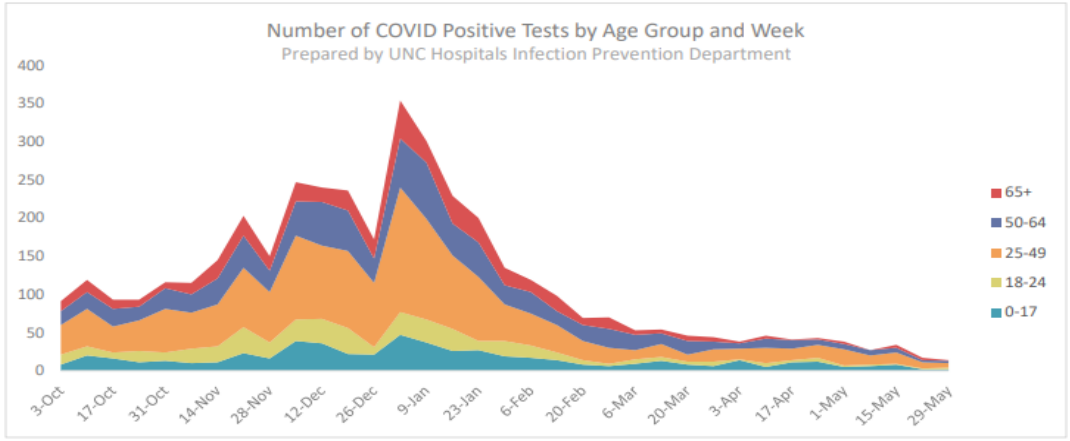
COVID-19, UNC-MC



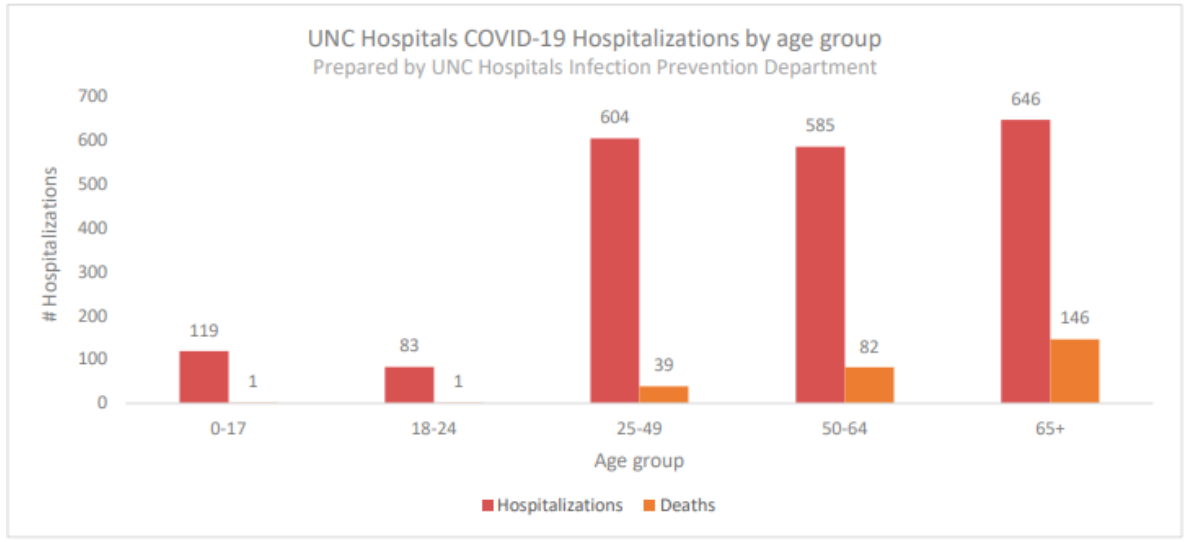
Percent positivity for COVID-19 tests performed by UNC McLendon labs for UNC Hospitals' facilities and includes re-tests. Symptomatic and asymptomatic testing categories determined by answer to question in COVID-19 test order.
FOR INTERNAL USE ONLY

UNCH Infection Prevention COVID-19 and Respiratory Virus Weekly Data Report

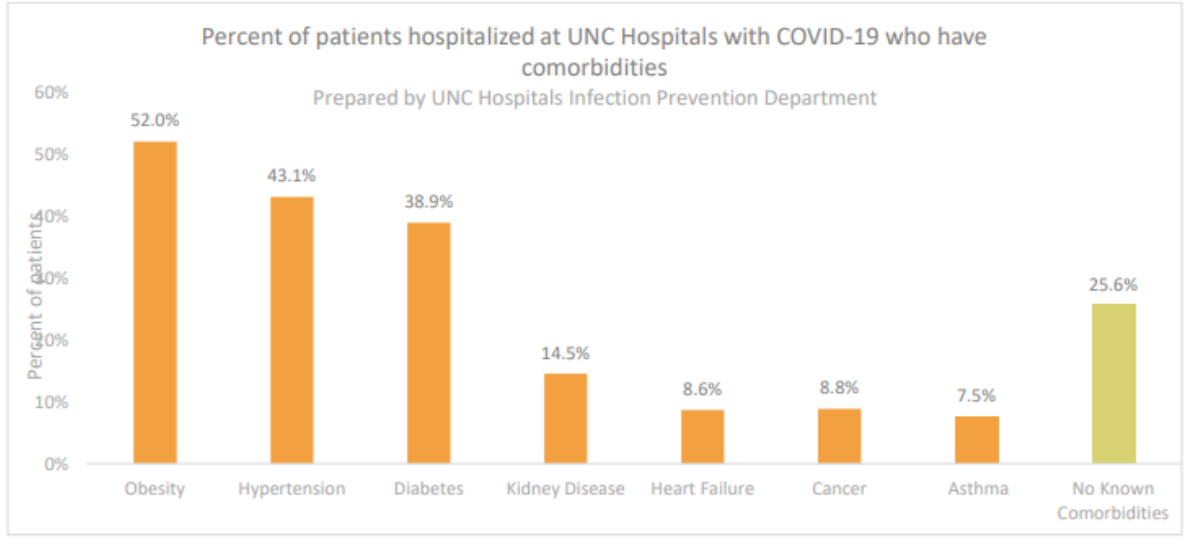
Reporting for week ending: 5/29/2021



Age category of people who test positive for COVID-19 by week of specimen collection. Includes COVID-19 PCR tests completed by UNC McLendon labs with a parent location of UNC Hospitals (includes outpatient and Chapel Hill RDC).



Cumulative COVID-19 Hospitalizations include patients who discharged and later readmitted. Cumulative deaths among hospitalized patients at UNC Hospitals for each age group shown in orange.



Cumulative percentage of underlying conditions for patients hospitalized with COVID-19. Patients who have multiple comorbidities are included in the percentage for each condition.

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

UNC SCHOOL OF MEDICINE

TRANSMISSION OF SARS CoV-2

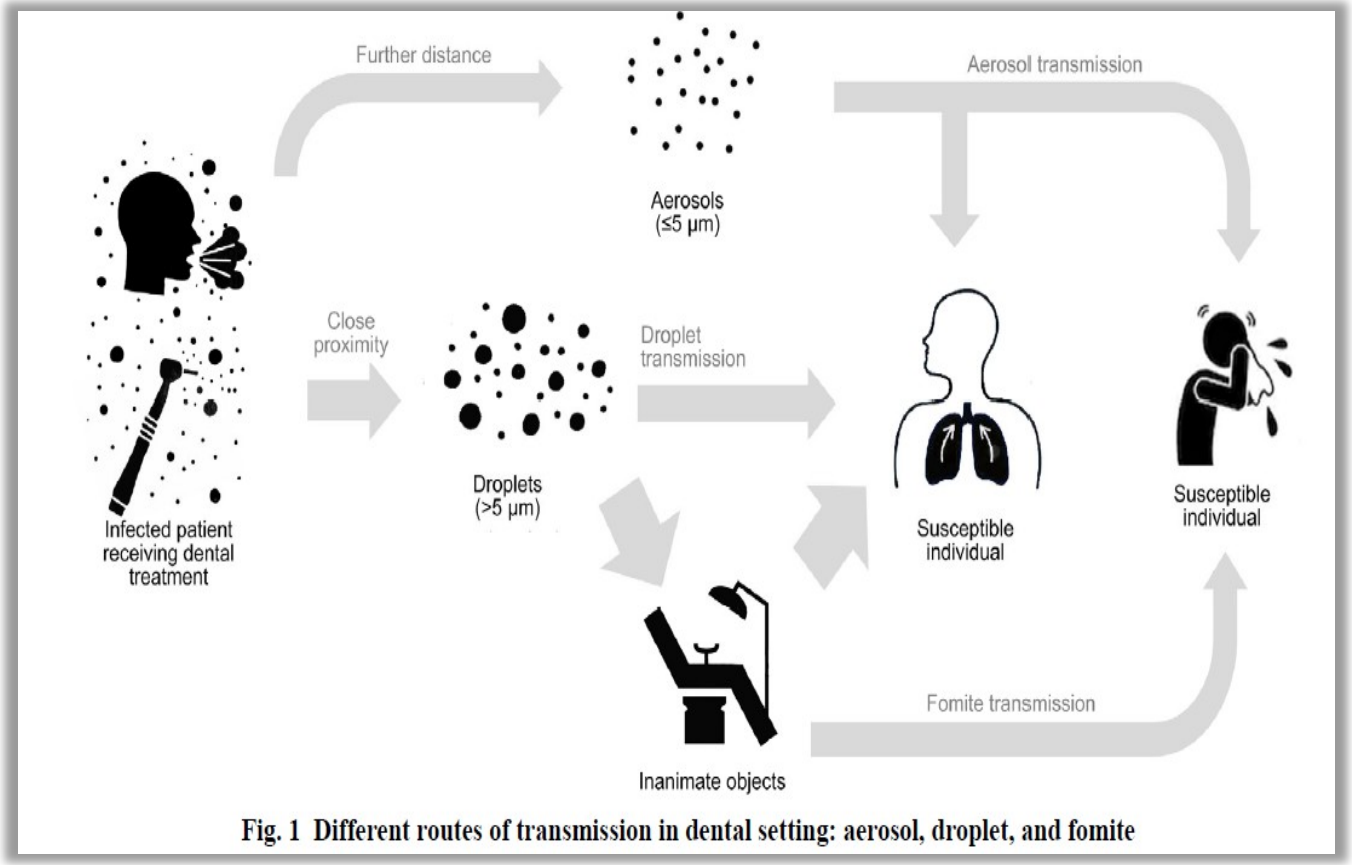


Fig. 1 Different routes of transmission in dental setting: aerosol, droplet, and fomite

- Droplet (≤6 feet) and direct contact predominant modes of transmission: Household transmission major mode of spread in China
- - Actual distance debatable
- Indirect (via the contaminated environment); Likely (unknown impact)
- Pre-symptomatic – transmission well documented
- Asymptomatic (infection demonstrated) – infectivity undefined
- Aerosolization of stool (viable virus occasionally demonstrated in stool) – no evidence for transmission
- Airborne (long distances) – minimal evidence for transmission
- Transplacental/vertical – possible rare cases
- Companion animals – may develop mild symptoms (cats, dogs, tigers, minks) – possible mink-to-human transmission
- Travel – Bus, Air – documented
- Blood, urine – no evidence for transmission

Ge Zi-yu, et al. Univ-Sci B (Biomed & Biotecyhnol) 2020;21(5):361-68

EDITORIAL

Myron S. Cohen & Lawrence Corey

Combination prevention for COVID-19

The coronavirus disease 2019 (COVID-19) pandemic has produced the fear and disorder inevitably provoked by emerging pathogens. As such, it should also inspire consideration of our experience with HIV over the past 40 years. As with HIV, the road to reducing infections with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, the cause of COVID-19), and attendant morbidity and mortality, requires medical and nonmedical strategies. The most important lesson learned from tackling HIV is to use a combination of prevention strategies.

The first step to stopping the spread of SARS-CoV-2 has already been taken—behavioral changes. This reflects a rapid but imperfect understanding of the transmission of this virus. At the beginning of the AIDS epidemic, changes in sexual behavior, condom promotion, and government interventions (closing "hotspots" of HIV transmission such as bathhouses) made a difference. For SARS-CoV-2, masks and gloves, hand hygiene, and "shelter in place" mandates have already demonstrated benefits. More efficient behavioral intervention requires better understanding of the rules governing SARS-CoV-2 transmission. What are the risks from exposure to respiratory droplets, airborne virus, and surface contamination? What concentration of SARS-CoV-2 is required for transmission? Evidence suggests that SARS-CoV-2 transmission is greatest very early in infection prior to development of symptoms—the same lesson learned from HIV. Given this rule [illegible] medical prevention strategies that will require large trials with 6000 to [illegible]000 participants [illegible] more in each [illegible] is moving

tiviral agents reduce the HIV viral load to a point where infected people no longer transmit. This approach, which uses combinations of powerful antiretroviral agents, is now the mainstay of HIV prevention worldwide.

For SARS-CoV-2, we have leapt into a cacophony of clinical trials of drug candidates with differing degrees of plausibility. Preliminary results from a large randomized controlled trial show that the antiviral drug remdesivir substantially reduced the duration of hospitalization for COVID-19. To date, COVID-19 testing results have been used primarily for patient isolation, contact tracing, and quarantine. But effective therapies will lend great urgency for the universal availability of rapid and reliable testing for SARS-CoV-2 infection, so that treatment can be provided when indicated.

Long-acting antiviral agents and monoclonal antibodies that neutralize SARS-CoV-2 may become important nonvaccine pharmacologic tools for prevention. Antiviral agents that prevent replication of SARS-CoV-2 could be used as pre-, peri-, or postexposure prophylaxis. Several different potent monoclonal antibody combinations designed to treat and prevent SARS-CoV-2 will enter clinical trials in June 2020.

Ultimately, a safe and effective vaccine is crucial for preventing COVID-19. Vaccine efforts started immediately after the discovery of SARS-CoV-2. Numerous vaccine candidates have been identified, and early-phase vaccine studies of several are underway. Proof of vaccine efficacy

"HIV has taught us that multiple concomitant prevention strategies are essential."

. Science. 2020 May 8;368(6491):551.

Emerg Infect Dis. 2006 Jan;12(1):15-22

PERSPECTIVE

1918 Influenza: the Mother of All Pandemics

Jeffery K. Taubenberger* and David M. Morens†

The "Spanish" influenza pandemic of 1918–1919, which caused ≈50 million deaths worldwide, remains an ominous warning to public health. Many questions about its origins, its unusual epidemiologic features, and the basis of its pathogenicity remain unans[illegible] The public health im[illegible] of the pand[illegible] doubt

proteins, making the 1918 virus indeed the "mother" of all pandemics.

In 1918, the cause of human influenza and its links to avian and swine influenza were unknown. Despite clinical and [illegible] similariti[illegible] influenza par[illegible]mics of

1918: A group of Americans in California with a message for their fellow countrymen

Stanford students were required to wear masks as the Spanish Flu of 1918 struck campus. (Stanford Special Collections University Archives)

637 million people traveled on National Day holiday (Oct. 1 - 8) in all parts of China

The Bund of Shanghai

The West Lake of Hangzhou

The Forbidden City of Beijing

The Beach of Qingdao

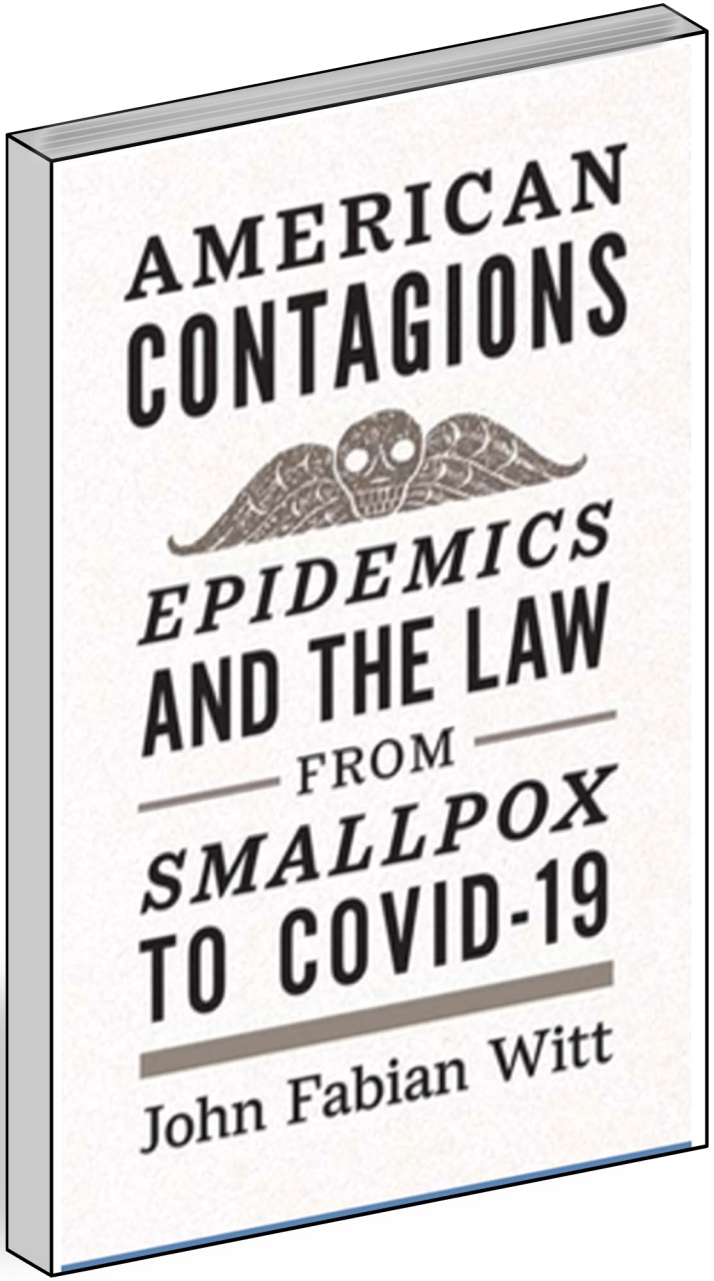
China's Long Term COVID-19 Control Strategy

A. China Long-term COVID-19 Control Strategy (Issued by the State Council) as the overall plan for government control efforts;

B. Civil Code of Conduct on COVID-19 Prevention and Control (Issued by the State Health Commission) as the censuses guideline for Chinese people;

C. Research on Vaccines and various drugs to provide better tools and measures;

D. National Health Security and Response Capacity building and strengthening



Fabian Witt, John. Yale University Press, 2020. https://doi.org/10.2307/j.ctv15wxn74. Accessed Dec. 20, 2020.

Biological Strategies to Prevent COVID-19

- **Active Immunity: Vaccination**

  -Individual benefit (?), Population level benefit (?) or Both
- **Passive Immunity**

  - Convalescent plasma (?), hyperimmuneglobulin (?), mAbs!!
- **Treatment as Prevention**

  -Most effective when transmission comes from symptomatic people

  (SARS-1, MERS-SARS…but perhaps NOT SARS-CoV-2)

Published online May 11, 2020

Science

A Strategic Approach to COVID-19 Vaccine R&D

L Corey, JR Mascola, AS Fauci & FS Collins

The full development pathway for an effective vaccine for SARS-CoV2 will require that industry, government, and academia collaborate in unprecedented ways, each adding their individual strengths. . . .We further discuss a collaborative platform for conducting harmonized, randomized controlled vaccine efficacy trials. This mechanism aims to generate essential safety and efficacy data for several candidate vaccines in parallel, so as to accelerate the licensure and distribution of multiple vaccine platforms and vaccines to protect against COVID-19

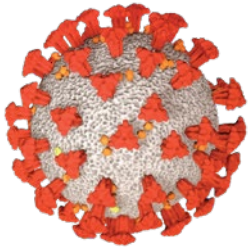
Three Entities with Distinct Roles in COVID-19 Response

Operation Warp Speed

USG body responsible for strategic approach, coordination and resource allocation

Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)

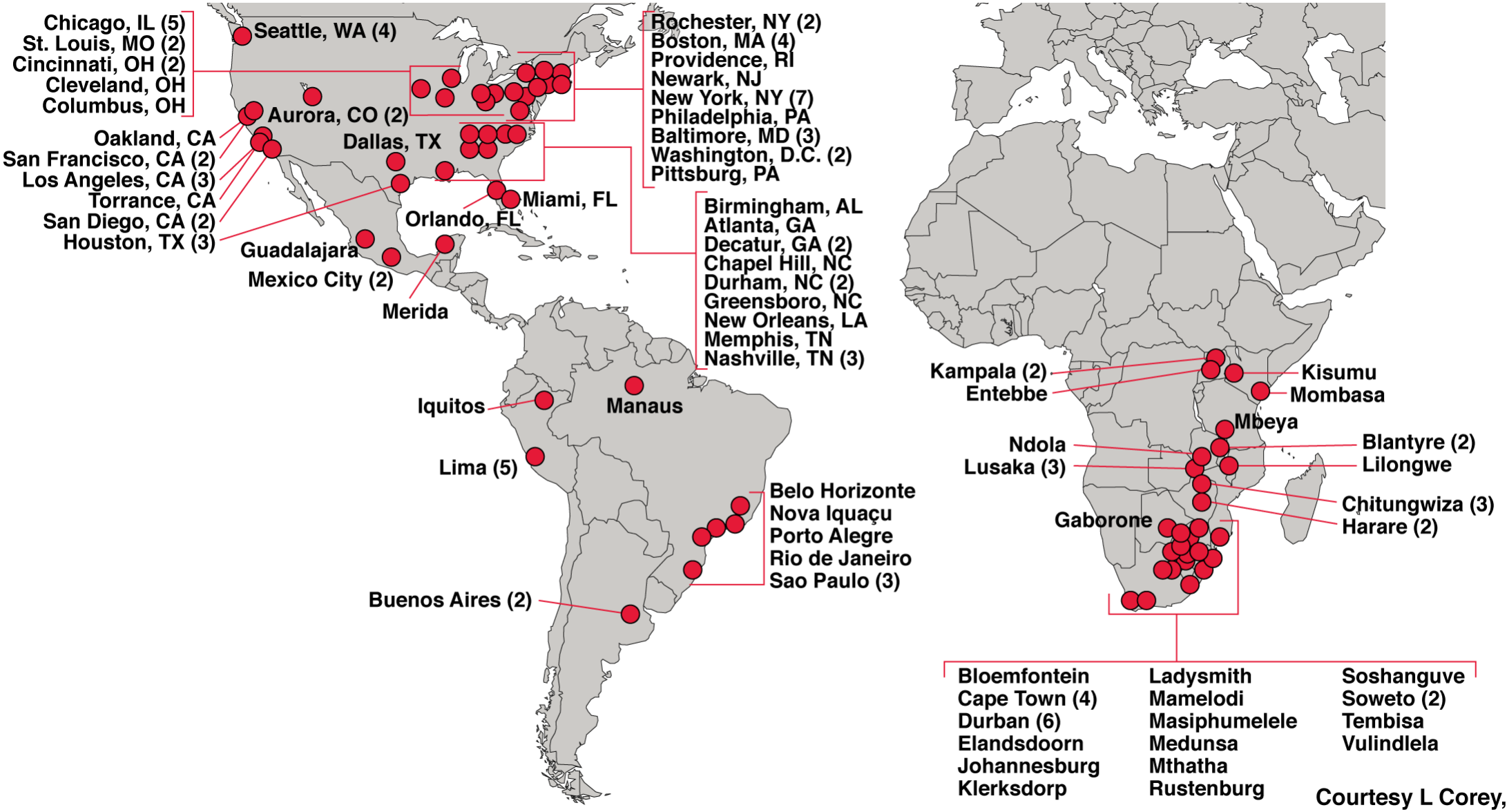
NIH established Public-private partnership for coordinating COVID-19 response



COVID-19 Prevention Network

NIH Funded networks - Phase 3 trial execution

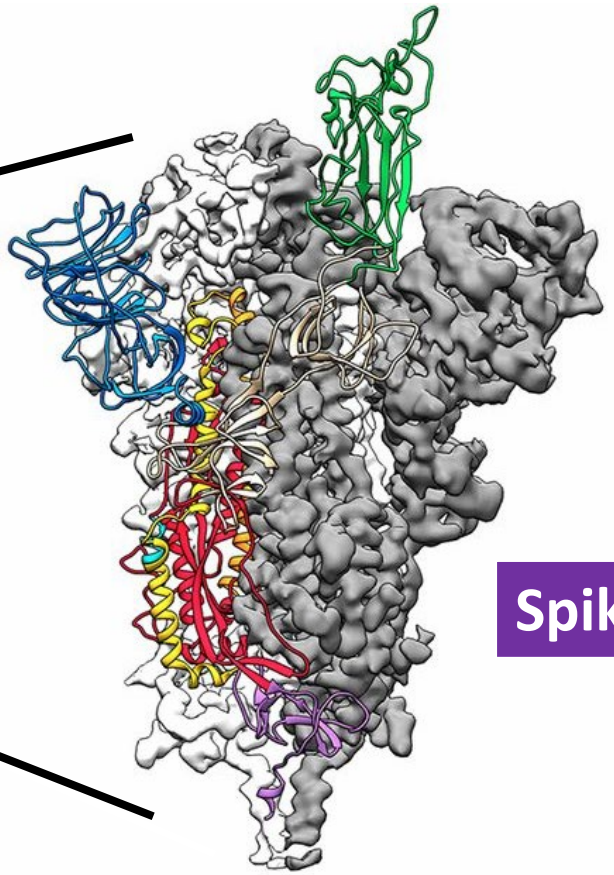
CoVPN Clinical Sites



Courtesy L Corey, HVTN

Coronavirus Biology and Nomenclature

corona = crown or circle of light

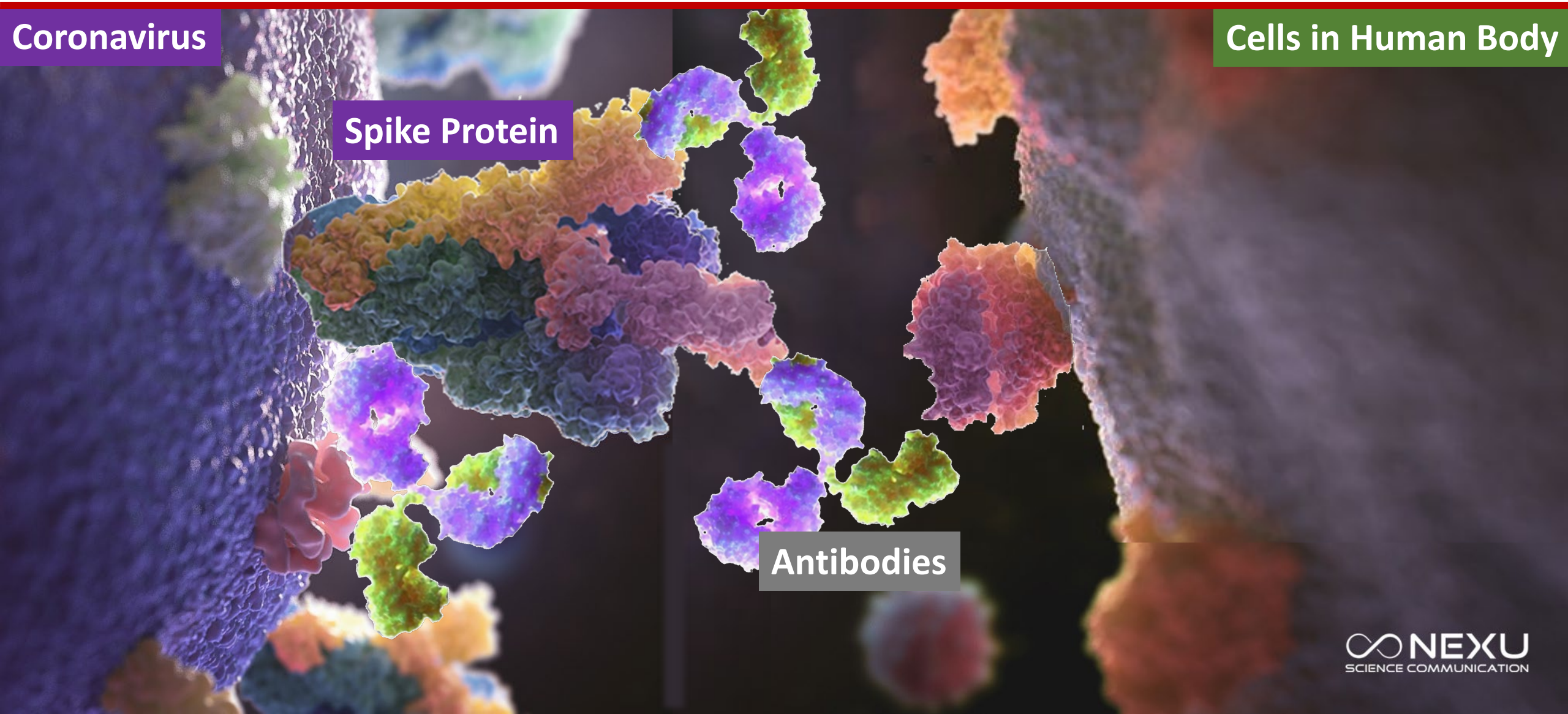


Spike Protein

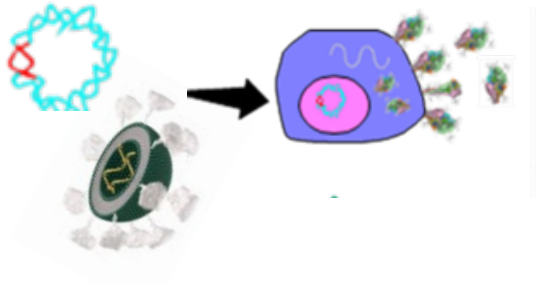
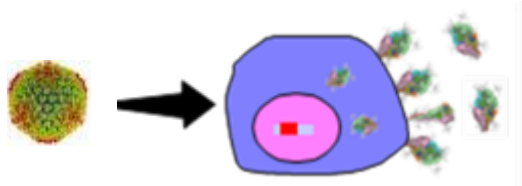
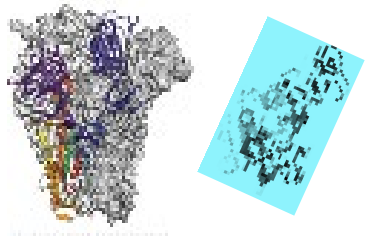
Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, Graham BS, McLellan JS. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020 Feb 19:eabb2507. doi: 10.1126/science.abb2507.

Antibodies can Prevent SARS-CoV-2

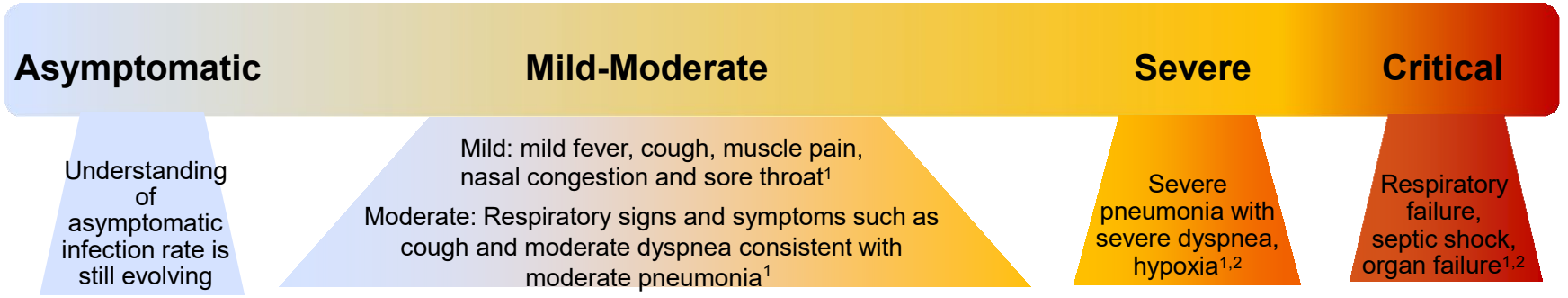
- **Antibodies** are produced after a person gets vaccinated, or can be passively administered
- **Antibodies** bind **coronavirus spike protein** to block infection and protect against COVID-19 disease. .



Vaccine Platforms and Immune Response

	Antibody	CD4	CD8	Pros	Additional Considerations
Nucleic acid (mRNA or DNA) 	++	++	+	Rapid translation RNA can be modified No prior immunity	RNA-Requires formulation LNP DNA requires electroporation
Adenoviral Vectors 	++	++	+++	In clinical trials (Ebola, Malaria, HIV, Cancer) Most potent inducer CD8 T cells	Influenced by prior immunity from natural adenovirus exposure
Protein + adjuvant 	+++	++	-	Gold standard for high antibody titers	Adjuvant is critical Limited/no CD8

COVID-19 Disease Spectrum: Vaccine Endpoints



- Individuals of all ages are at risk for infection and severe disease. However, the probability of fatal disease is highest in people aged ≥ 65 years and those living in a nursing home or long-term care facility. Other high risks population are those with underlying conditions including:[3]
  - Hypertension
  - Cardiovascular disease
  - Diabetes
  - Chronic respiratory disease
  - Cancer
  - Renal disease
  - Obesity
- Pediatric multisystem inflammatory syndrome: Syndrome characterized by persistent fever and features of Kawasaki disease and/or toxic shock syndrome in patients <21 years old with confirmed or suspected SARS-CoV-2 infection[4,5,6]

1. Cascella et al, Features, Evaluation and Treatment Coronavirus (COVID-19). StatPearls Publishing, Treasure Island, FL; 2020.
2. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19
3. NIH COVID-19 Treatment Guidelines https://www.covid19treatmentguidelines.nih.gov/overview/
4. Jones et al, Hosp Pediatr 2020
5. https://www.nytimes.com/2020/05/05/nyregion/children-Kawasaki-syndrome-coronavirus.htm
6. https://www1.nyc.gov/assets/doh/downloads/pdf/han/alert/2020/covid-19-pediatric-multi-system-inflammatory-syndrome.pdf

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, $5x10^{10}$ viral particles
Doses	Two injections, 21 days apart	Two injections, 28 days apart	Single dose
Vial Availability	Concentrated solution for injection; MDV (0.45mL before dilution)	Solution for injection; MDV (5 mL, 7.5 mL)	Solution for injection; MDV (2.5 mL)
Preparation	Dilute with 1.8 mL 0.9% sodium chloride	NA	NA
Doses/Vial	6 doses (0.3 mL/dose)	10-15 doses (0.5 mL/dose) [dependent on vial size]	5 doses (0.5 mL/dose)
Eligibility	Age ≥12 years	Age ≥18 years	Age ≥18 years
Administration Route	Intramuscular (IM)	Intramuscular (IM)	Intramuscular (IM)
Clinical Data	~95% against COVID-19, 7 days after 2nd dose (100% efficacious, ages 12-17)	~95% against COVID-19, 14 days post-2nd dose (100% efficacious, ages 12-17)	~77% efficacious at preventing **severe/critical** cases at 14 days; 85% effective at 28 days; 100% efficacious against hospitalizations and deaths
Stability – Unpunctured Vial			
Ultra-Low (-80˚ to -60˚C)	Until labeled expiration date	NA	NA
Frozen (-50˚ to -15˚C)	14 days*	Until labeled expiration date	NA**
Refrigerated (2˚ to 8˚C)	30 days¥	30 days¥	Until labeled expiration date¥
Room Temp. (9˚ to 25˚C)	2 hours	24 hours	12 hours
Stability – After First Puncture/Prepped in Syringe			
Refrigerated (2˚-8˚C)	6 hours	12 hours	6 hours
Room Temp. (9˚-25˚C)	6 hours	12 hours	2 hours

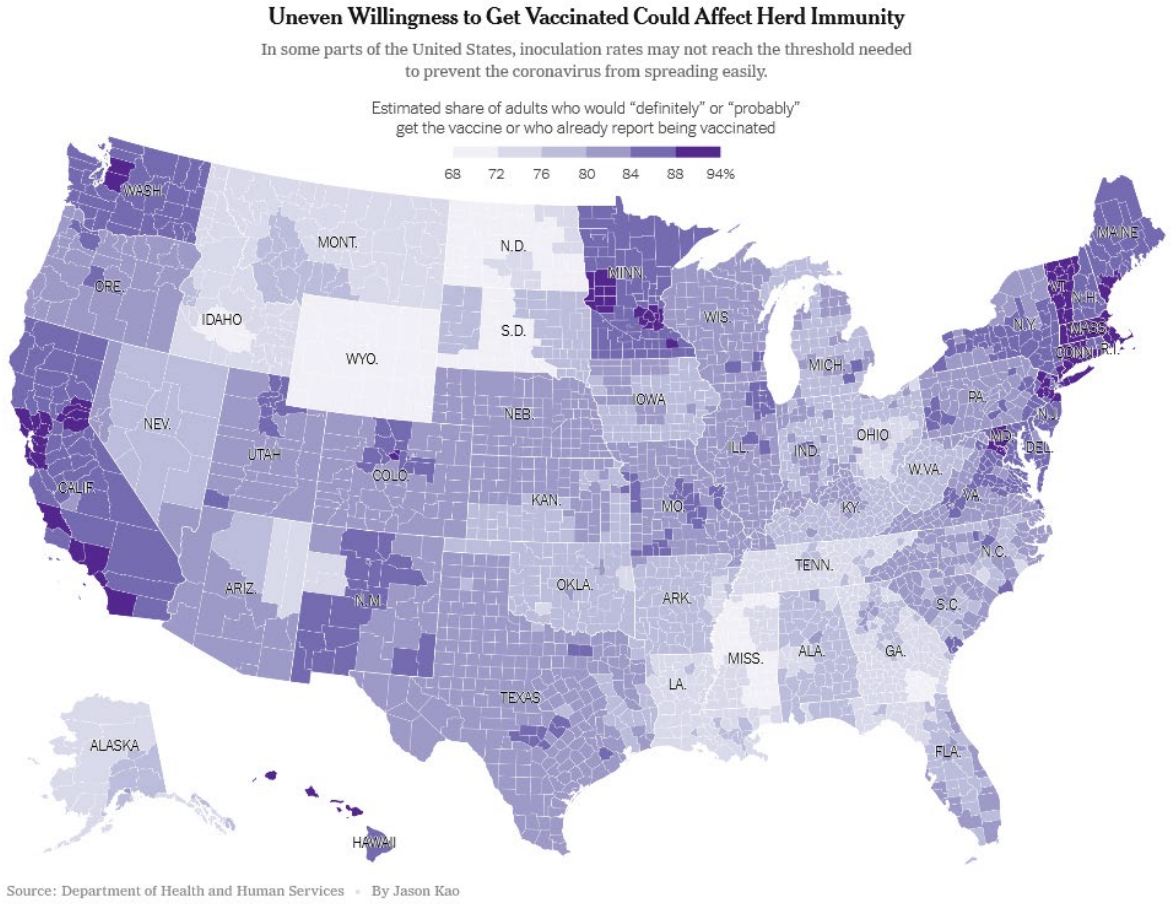
* Vials stored frozen may return to ultra-low conditions one time; total time at frozen temp should not exceed 2 weeks
** May be shipped frozen from manufacturer; do not store in freezer once received.
¥Do not refreeze vials once thawed.

Pfizer EUA Fact Sheet: http://labeling.pfizer.com/ShowLabeling.aspx?id=14471&format=pdf&#page=12
Moderna EUA Fact Sheet: https://www.modernatx.com/covid19vaccine-eua/eua-fact-sheet-providers.pdf
Janssen EUA Fact Sheet: https://www.janssenlabels.com/emergency-use-authorization/Janssen+COVID-19+Vaccine-HCP-fact-sheet.pdf

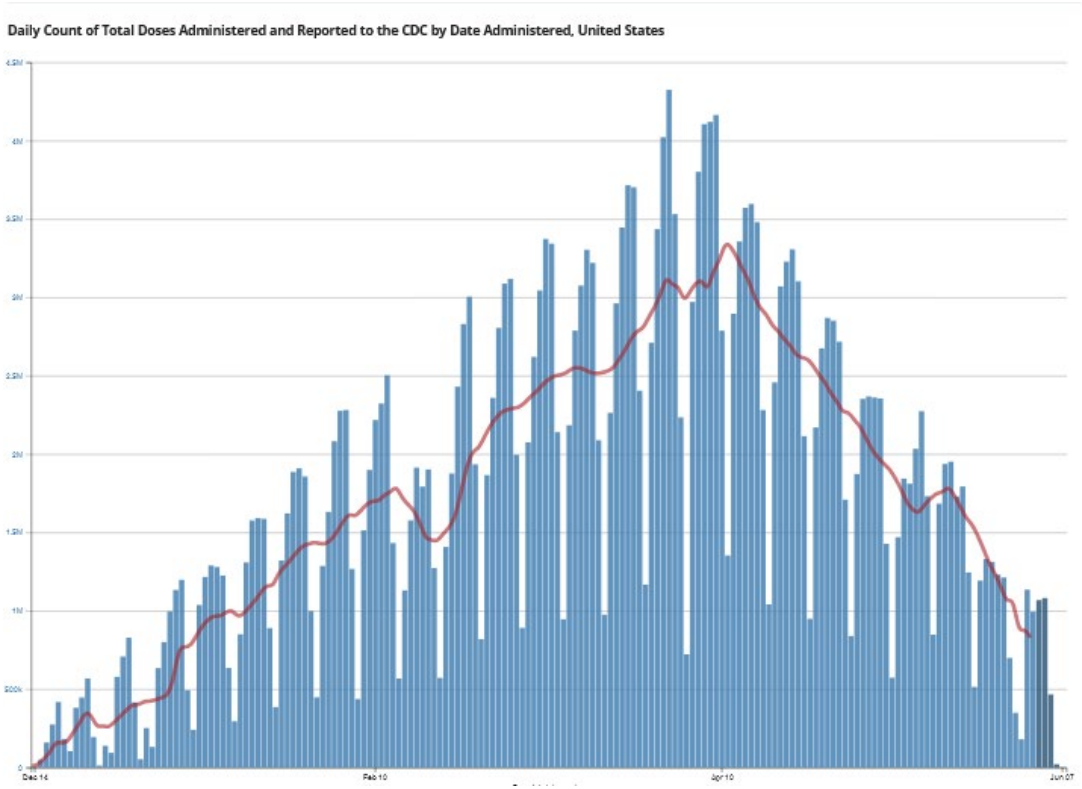
Last Updated: 05.20.21

UNC Health

COVID-19 VACCINE HESITANCY, US



Vaccinations per day over time, CDC



https://www.nytimes.com/2021/05/03/health/covid-herd-immunity-vaccine.html?action=click&module=Spotlight&pgtype=Homepage
https://covid.cdc.gov/covid-data-tracker/#vaccination-trends

UNC Health
SCHOOL OF MEDICINE

COVID-19 VACCINE BREAKTHROUGH INFECTIONS

COVID-19 breakthrough infections, CDC, 1/1/21-4/30/21'

- A total of 10,262 SARS-CoV-2 vaccine breakthrough infections had been reported from 46 U.S. states and territories as of April 30, 2021.
- Based on preliminary data, 2,725 (27%) vaccine breakthrough infections were asymptomatic, 995 (10%) patients were known to be hospitalized, and 160 (2%) patients died. The median age of patients who died was 82 years (interquartile range = 71–89 years).
- Sequence data were available from 555 (5%) reported cases, 356 (64%) of which were identified as SARS-CoV-2 variants of concern, including B.1.1.7 (199; 56%), B.1.429 (88; 25%), B.1.427 (28; 8%), P.1 (28; 8%), and B.1.351 (13; 4%). Similar to US surveillance.
- Limitation=reinfection vs prolonged test positivity

MMWR 2021;70(21):792-793.

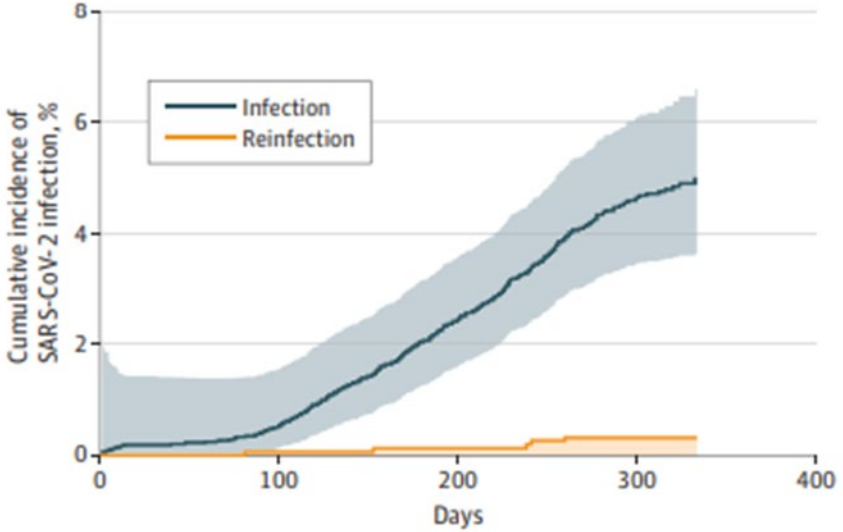
COVID-19 breakthrough infections, Chicago nursing homes

- Twenty-two possible breakthrough SARS-CoV-2 infections occurred among fully vaccinated persons ≥14 days after their second dose of COVID-19 vaccine. Two thirds of persons were asymptomatic. A minority of persons with breakthrough infection experienced mild to moderate COVID-19–like symptoms; two COVID-19–related hospitalizations and one death occurred. No facility-associated secondary transmission was identified.
- Among the 15 facilities with breakthrough cases, attack rates for unvaccinated and vaccinated residents were 15% (89 of 604) and 0.8% (15 of 1,781), respectively. Among staff members, attack rates for unvaccinated and vaccinated persons were 6% (62 of 992) and 1% (12 of 1,135), respectively.

MMWR 2021;70(17):632-638.

COVID-19 REINFECTIONS

"Natural Immunity?"



No. days at risk

RT-PCR positive	10988	137085	325798	496586
RT-PCR negative	31742	491579	2040576	3499503

Vitale J, et al. JAMA Intern Med, 28 May 2021

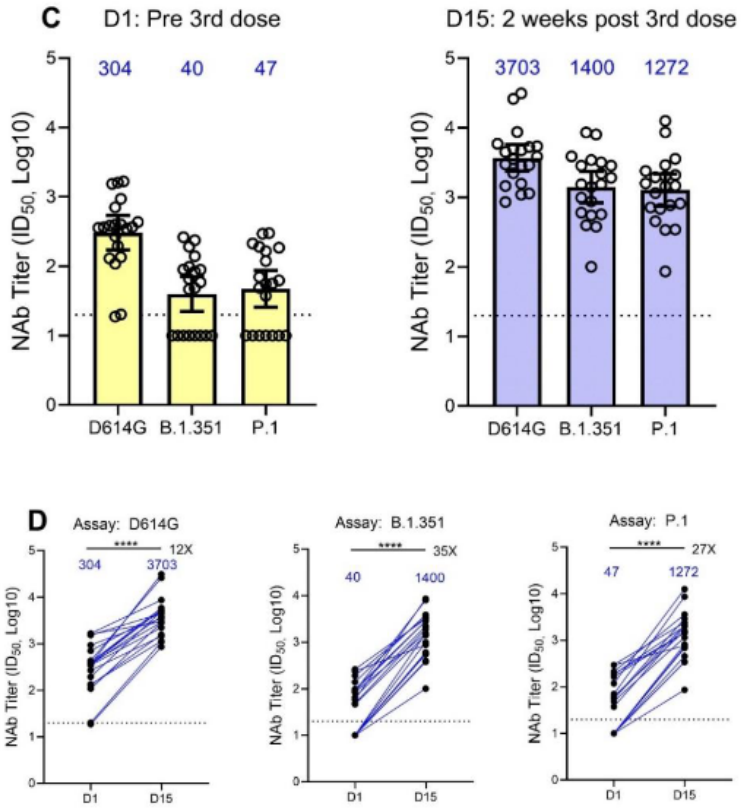
- Goal: Assess SARS-CoV-2 reinfection 1 year after primary infection, Italy
- Reinfection: 2nd RT-PCR+ >90 days after complete resolution of primary infection plus 2 consecutive negative PCR tests between episodes
- Results: Of 13 496 persons who initially were not infected withSARS-CoV-2, 528 (3.9%; 95% CI, 3.5%-4.2%) subsequently developed a primary infection. The incidence density per 100 000 person days was 1.0 (95% CI, 0.5-1.5) for reinfections compared with 15.1 (95% CI, 14.5-15.7) for new infections, while the incidence rate ratio adjusted for age, sex, ethnicity, and the sanitarian area was 0.07 (95% CI, 0.06-0.08). After analyzing the cumulative incidence during follow-up, we confirmed that the 2 cohorts were significantly different (hazard ratio, 0.06;95% CI, 0.05-0.08; log-rank test P<0.001) (Figure)
- Of the 5 reinfections, 1 patient was hospitalized; mean (SD) between primary and 2nd episode, 230 (90) days
- Conclusion: Reinfections are rare events and patients who have recovered from COVID-19 have a lower risk of reinfection. Natural immunity to SARS-CoV-2appears to confer a protective effect for at least a year

Preliminary Analysis of Safety and Immunogenicity of a SARS-CoV-2 Variant Vaccine Booster (Moderna)

Abstract (selected)

Booster provided ~6 months after primary series. The modified vaccines include a monovalent mRNA-1273.351 encoding for the S protein found in the B.1.351 variant and multivalent mRNA-1273.211 comprising a 1:1 mix of mRNA-1273 and mRNA-1273.351. As single 50 µg booster vaccinations, both mRNA-1273 and mRNA-1273.351 had acceptable safety profiles and were immunogenic. Antibody neutralization titers against B.1.351 and P.1 variants measured by SARS-CoV-2 pseudovirus neutralization (PsVN) assays before the booster vaccinations, ~6-8 months after the primary series, were low or below the assay limit of quantification, although geometric mean titers versus the wild-type strain remained above 3levels likely to be protective. Two weeks after the booster vaccinations, titers against the wild-type original strain, B.1.351, and P.1 variants increased to levels similar to or higher than peak titers after the primary series vaccinations. Although both mRNA-1273 and mRNA-1273.351 boosted neutralization of the wild-type original strain, and B.1.351 and P.1 variants, mRNA-1273.351 appeared to be more effective at increasing neutralization of the B.1.351 virus versus a boost with mRNA-1273.

Figure 3C and D: Immunogenicity After Boosting with 50 µg of mRNA-1273.351



Ku W, et al.
https://www.medrxiv.org/content/10.1101/2021.05.05.21256716v1.full.pdf

COVID-19 and Biological Prevention Strategies?

- Active Immunity

  -Vaccines
- **Passive Immunity**

  -Convalescent Plasma

  -Monoclonal Antibodies

JCI The Journal of Clinical Investigation

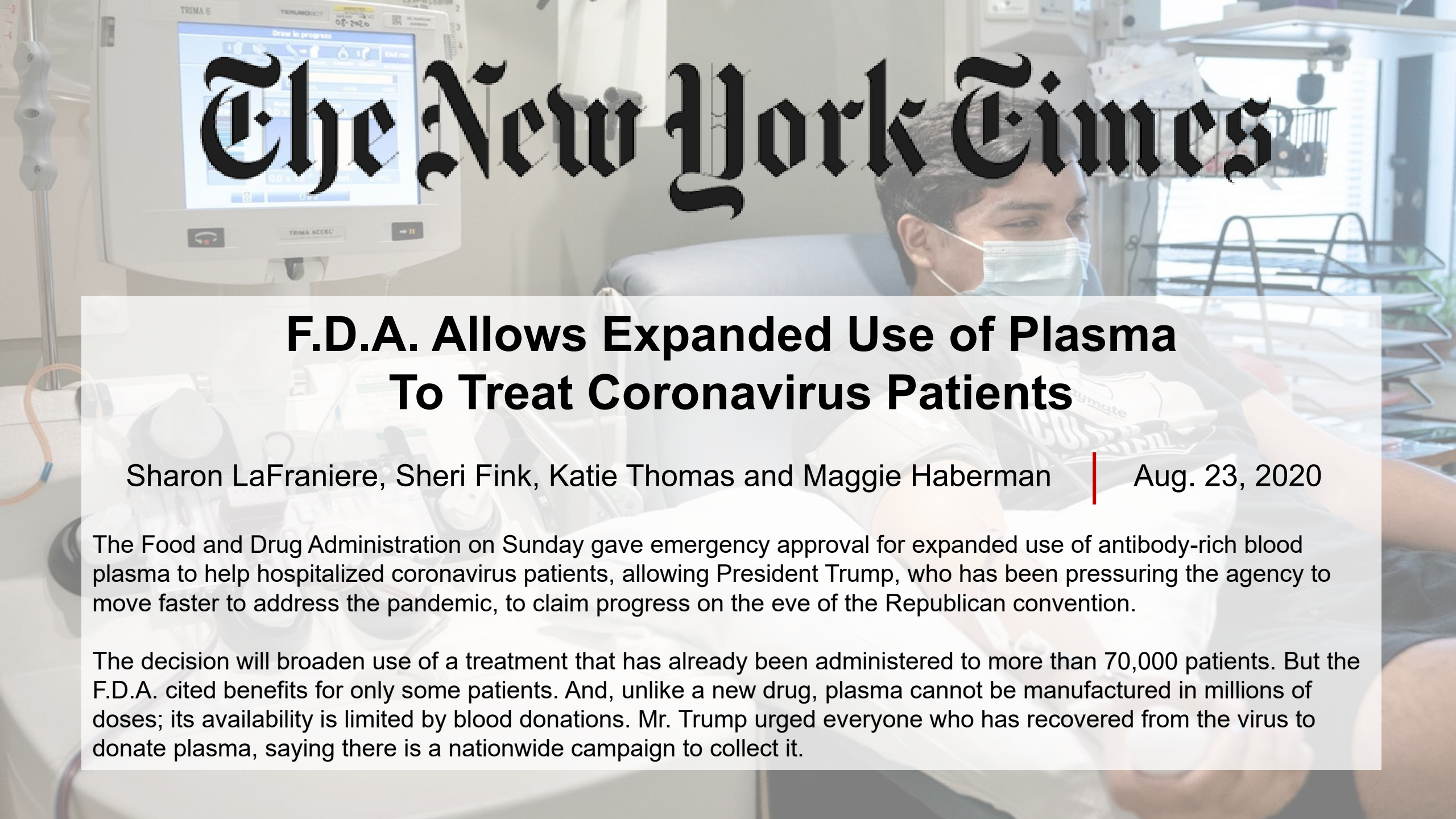
SARS-CoV-2 viral load and antibody responses: the case for convalescent plasma therapy

Arturo Casadevall, … , Michael J. Joyner, Liise-anne Pirofski

J Clin Invest. 2020. https://doi.org/10.1172/JCI139760.

Commentary In-Press Preview

Most patients with COVID-19 lack antibody to SARS-CoV-2 in the first 10 days of illness while the virus drives disease pathogenesis. SARS-CoV-2 antibody deficiency in the setting of a tissue viral burden suggests that using an antibody as a therapeutic agent would augment the antiviral immune response. In this issue of the *JCI*, Wang and collaborators describe the kinetics of viral load and antibody responses of 23 individuals with COVID-19 with mild and severe disease. The researchers found: 1) individuals with mild and severe disease produced neutralizing IgG to SARS-CoV-2 10 days after disease onset; 2) SARS-CoV-2 persisted longer in those with severe disease; and 3) there was cross-reactivity between antibodies to SARS-CoV-1 and SARS-CoV-2, but only antibodies from patients with COVID-19 neutralized SARS-CoV-2. These observations provide important information on the serological response to SARS-CoV-2 of hospitalized patients with COVID-19 that can inform the use of convalescent plasma therapy.



The New York Times

F.D.A. Allows Expanded Use of Plasma To Treat Coronavirus Patients

Sharon LaFraniere, Sheri Fink, Katie Thomas and Maggie Haberman | Aug. 23, 2020

The Food and Drug Administration on Sunday gave emergency approval for expanded use of antibody-rich blood plasma to help hospitalized coronavirus patients, allowing President Trump, who has been pressuring the agency to move faster to address the pandemic, to claim progress on the eve of the Republican convention.

The decision will broaden use of a treatment that has already been administered to more than 70,000 patients. But the F.D.A. cited benefits for only some patients. And, unlike a new drug, plasma cannot be manufactured in millions of doses; its availability is limited by blood donations. Mr. Trump urged everyone who has recovered from the virus to donate plasma, saying there is a nationwide campaign to collect it.

Science

Isolation of potent SARS-CoV-2 neutralizing antibodies and protection from disease in a small animal model

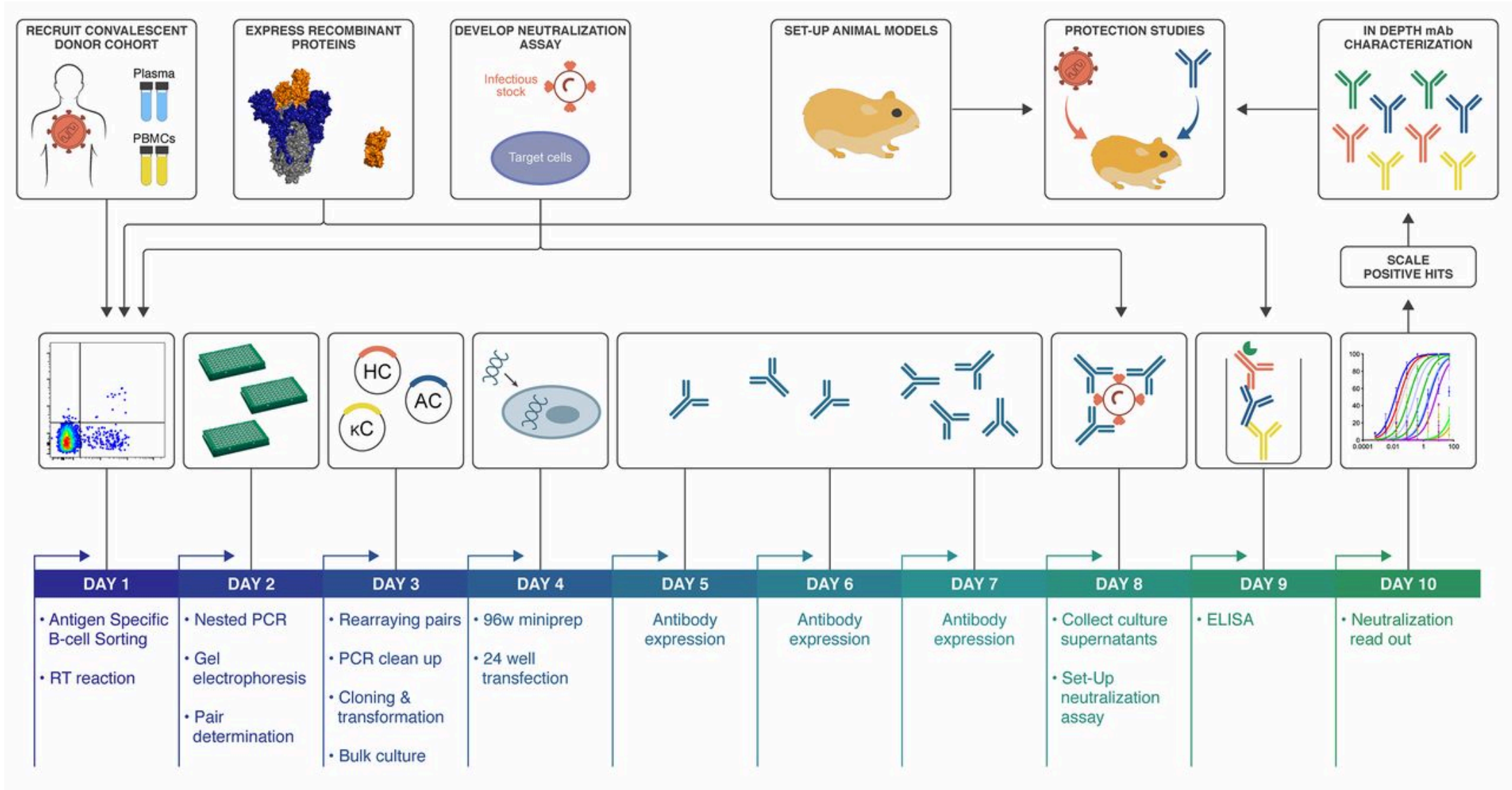


Fig. 1 SARS-CoV-2 neutralizing antibody isolation strategy.

Science. 2020 Jun 15;eabc7520. doi: 10.1126/science.abc7520

SARS-CoV-2 Spike Protein mAbs

Lilly First in Human May 2020	LY-CoV-555, high affinity neutralizing antibody against RBD, isolated from a recovered SARS-CoV-2 patient Lilly in collaboration with AbCellera. First in human in hospitalized patients, May 2020. LY-JS-016 (CB6) with prophylactic efficacy demonstrated in NHP (Shi et al., Nature 2020), Lilly in collaboration with JunShi First in human in healthy volunteers, June 2020.
REGENERON science to medicine® First in Human June 2020	Two SARS-CoV-2 spike directed mAbs from their humanized Ab mouse platform and isolated from human convalescent serum First in human hospitalized patients, June 2020.
VIR First in Human July 2020	Vir mAb, S309, isolated from a SARS-CoV patient that is cross-reactive with SARS-CoV-2,
AstraZeneca First in Human July 2020	AZ has selected a 2 mAb combination against the SARS-CoV-2 spike protein (AZD7442) Plan Phase I single dose escalation study in normal volunteers, August 2020 (DARPA)
The Rockefeller University 1901 SCIENCE FOR THE BENEFIT OF HUMANITY	Michel Nussenzweig developed cocktail of two mAbs isolated from convalescent plasma, target two non-overlapping epitopes of the receptor binding domain Bristol Myers Squibb will manufacture antibodies

Table 1. Summary of Current Efforts towards Developing Neutralizing Antibodies against SARS-CoV-2 (as of 28 July 2020)[a]

Lead	Target	Platform/technology/ source	Format	Investigator(s) for COVID-19	Status (clinical trial number)	Refs
LY-CoV555	Spike protein	DARPA pandemic prevention platform	Human IgG1	Abcellera Biologics/Eli Lilly/VRC-NIAID	Phase I/II (NCT04411628 and NCT04427501)	iv
JS016	RBD	Convalescent patients	Human antibody	Institute of Microbiology CAS/ Junshi Biosciences/Eli Lilly	Phase I (NCT04441918)	iv
REGN-COV2	Spike protein	VelociMab/ convalescent patients	Dual human antibodies	Regeneron	Phase I/II/III (NCT04425629, NCT04426695, and NCT04452318)	[88,89]
TY027	Spike protein	Convergent analytics	NA	Tychan	Phase I (NCT04429529)	iv
SCTA01	SARS-CoV-2	NA	NA	Sinocelltech	Phase I (NCT04483375)	iv
BRII-196/198	SARS-CoV-2	Convalescent patients	Human antibody	Tsinghua University/Brii Biosciences	Phase I (NCT04479631 and NCT04479644)	iv
CT-P59	SARS-CoV-2	NA	Antibody/cocktail	Celltrion	Phase I (NA)	iv
COVI-GUARD	SARS-CoV-2	Convalescent patients/ human libraries	Human antibody	Mount Sinai Health System/Sorrento	Phase I expected	iv
AZD7442	SARS-CoV-2	Patients/humanized mice/display	Dual human antibodies	AstraZeneca/Vanderbilt U	Phase I expected	iv
COVI-SHIELD	SARS-CoV-2	Convalescent patients/ human libraries	Three human antibodies	Mount Sinai Health System/Sorrento	Phase I expected	iv
NA	SARS-CoV-2	Individual B cell isolation	Human antibody	AbCellera/Eli Lilly	Phase I expected	iv
VIR-7831 and VIR-7832	SARS-CoV-2	Convalescent patients	Human antibody	GSK/Vir Biotechnology	Phase I expected	iv
NA	SARS-CoV-2	RTMTM technology platform	Human antibody	Neurimmune/Ethris	Phase I expected	iv
NA	SARS-CoV-2	Fully human antibody library/patients	Human antibody	YUMAB and its CORAT partners	Phase I expected	iv
NA	SARS-CoV-2	Vanderbilt custom antibody libraries	NA	Vanderbilt U/Ology Bioservices	Phase I expected	iv
47D11	SARS-CoV-2	Harbour's H2L2 Harbour mice	Human antibody	AbbVie/Harbour Biomed/Utrecht U/Erasmus Med Center	Phase I expected	[41]
SAB-185	SARS-CoV-2	Convalescent patients	Polyclonal	Sab Biotherapeutics/ DOD/BARDA	Phase I expected	iv
4A8	NTD	Convalescent patients	Human antibody	Academy of Military Medical Sciences	Preclinical	[73]
NA	ACE2/spike	AI/high-speed mutagenesis	Single-domain	Bioduro LLC	Preclinical	iv
NA	NA	Adaptive's Immune Medicine	NA	Amgen Inc./Adaptive Biotechnologies Inc.	Preclinical	iv
CR3022	RBD	Convalescent patients/phage display	Human IgG1	Scripps Research Institute	Preclinical	[68]
S309	RBD	Convalescent patients	Human IgG1	Vir Biotechnology	Preclinical	[70]
BD-386-2	RBD	Individual B cell isolation	Human antibody	Peking U/Sino Biological/WuXi Biologics	Preclinical	[50]
CA1 and CB6-LALA	RBD	Convalescent patients	Human antibody	CAS/NCRCIF/SMS-UCAS	Preclinical	[71]
P2C-1F11/P2B-2F6/ P2A-1A3	RBD	Convalescent patients	Human antibody	Shenzhen TPH/SUST/Tsinghua U	Preclinical	[72]
H11-D4/H11-H4	RBD	Phage display	Single-domain	U of Oxford	Preclinical	[115]
311mab-31B5311/32D4	RBD	Convalescent patients	Human antibody	Peking Union Medical College	Preclinical	[64]
COVA 2-15	RBD	Convalescent patients	Human antibody	U of Amsterdam/Cornell U	Preclinical	[53]
414-1	RBD	Convalescent patients	Human antibody	Fudan U/Active Motif China	Preclinical	[52]
H014	RBD	Hybridoma	Humanized antibody	U of CAS/CAS/Academy of Military Medical Sciences	Preclinical	[37]
NA	RBD	Hybridoma	Single-domain	VIB/Ghent U	Preclinical	iv
NA	SARS-CoV-2	Convalescent patients	Human antibody	Tekara/Pennsylvania-based CSL Behring	Preclinical	iv
B38 and H4	SARS-CoV-2	Convalescent patients	Human antibody	Institute of Microbiology CAS/Junshi Biosciences/Lilly	Preclinical	[45]
rCIG	SARS-CoV-2	Convalescent patients	Polyclonal	Gigagen Inc.	Preclinical	iv
XAV-19	SARS-CoV-2	Humanized animal	Antibody cocktail	LFB SA/Xenothera SAS	Preclinical	iv
NA	SARS-CoV-2	Omniab(transgenic animal)/AI	PolyTope mAb	Immunoprecise Antibodies	Preclinical	iv
NA	SARS-CoV-2	Convalescent patients	Human antibody	Fairjourney Biologics SA/Iontas	Preclinical	iv
NA	SARS-CoV-2	Convalescent patients	Human antibody	Just-Evotec Biologics/Ology Bioservices	Preclinical	iv
NA	SARS-CoV-2	NA	IgM/IgA	Atreca/Beigene/IGM Biosciences	Preclinical	iv
VHH-72	Spike protein	Llama immunization	Nanobody-Fc	Ghent U/U of Texas at Austin	Preclinical	[39]
n3088/3130	Spike protein	Phage display	Humanized nanobody	Fudan U	Preclinical	[111]
80R	Spike protein	Phage display	Human IgG1	Dana-Farber Cancer Institute	Preclinical	[41]
ADI-55689/56046	Spike protein	Convalescent patients	Human antibody	Adimab LLC	Preclinical	[113]
NA	Spike protein	VNAR phage display	Single-domain	Ossianix	Preclinical	iv
NA	Spike protein	Beacon platform	Human antibody	Ablexis/AlivaMab Discovery Services/Berkeley Lights	Preclinical	iv

Trends Pharmacol Sci. 2020 Jul 31;S0165-6147(20)30166-8.

COVID-19 mAb Applications: PX and TX

Monoclonal Abs (mAbs):

- Offer immediate protection for those exposed or unvaccinated in high risk settings
- Can be provided to people unlikely to respond to a vaccine, or allergic
- **They could stop viral replication and block progression of disease**
- *Can help predict requirements for a vaccine by identifying required titers of neutralizing antibodies*

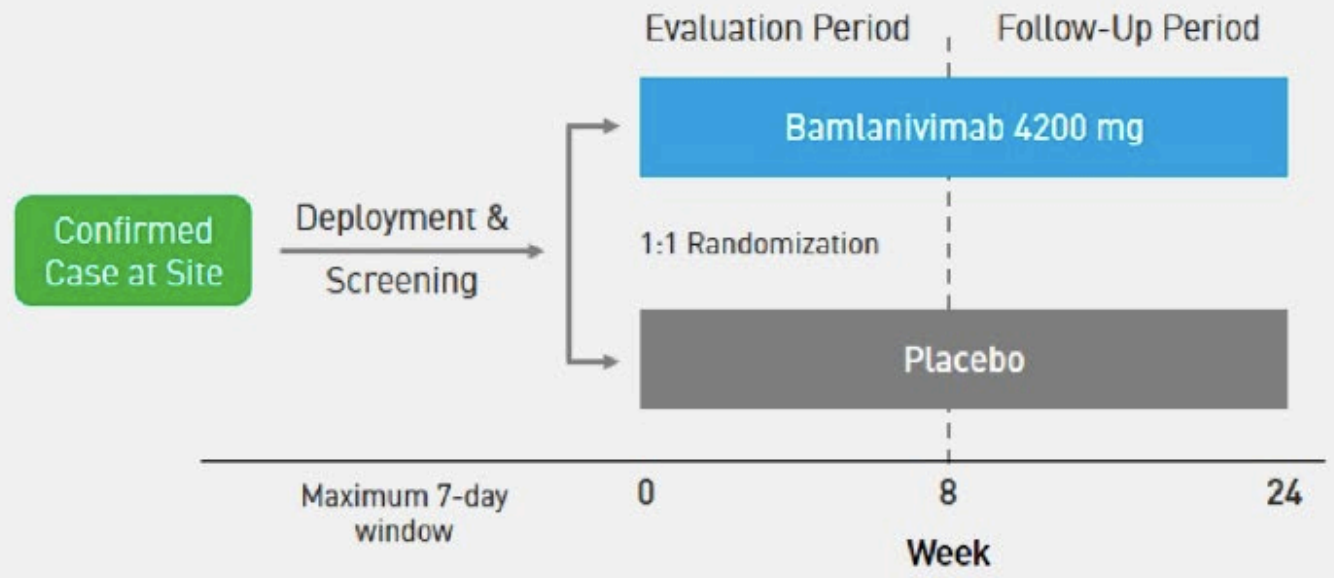
Target Populations for mAbs:

- Nursing homes, both residents and attendants
- High incidence workplaces (e.g. meat packing plants)
- Index case contacts (e.g. household contacts)

BLAZE-2: POST-EXPOSURE PROPHYLAXIS

N=966 (666 staff; 300 residents)

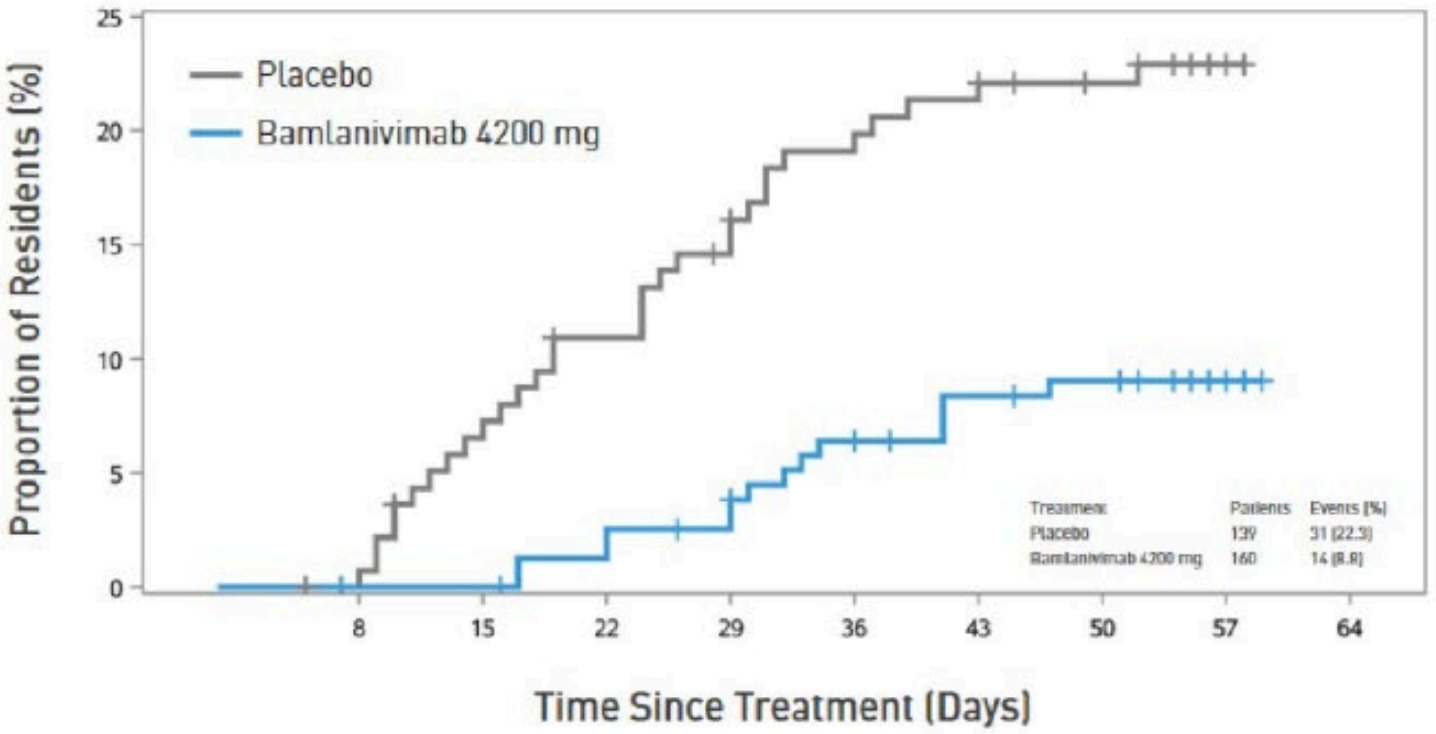
STUDY DESIGN



To facilitate rapid prophylaxis and treatment of residents and facility staff, participants were enrolled prior to assessment of baseline SARS-CoV-2 status. This allowed for separate **prevention** and **treatment** analysis populations.

MOBILE RESEARCH UNITS

RESIDENTS WITH SYMPTOMATIC COVID-19 (Prevention Population)



COVID-19 PREVENTION

Odds ratio: 0.20
p-value: 0.00026

Up to 80% reduction in risk

DEATH DUE TO COVID-19

Placebo: 4 of 139 residents
Bamlanivimab: 0 of 160 residents

No deaths due to COVID-19 on bamlanivimab

Notes:

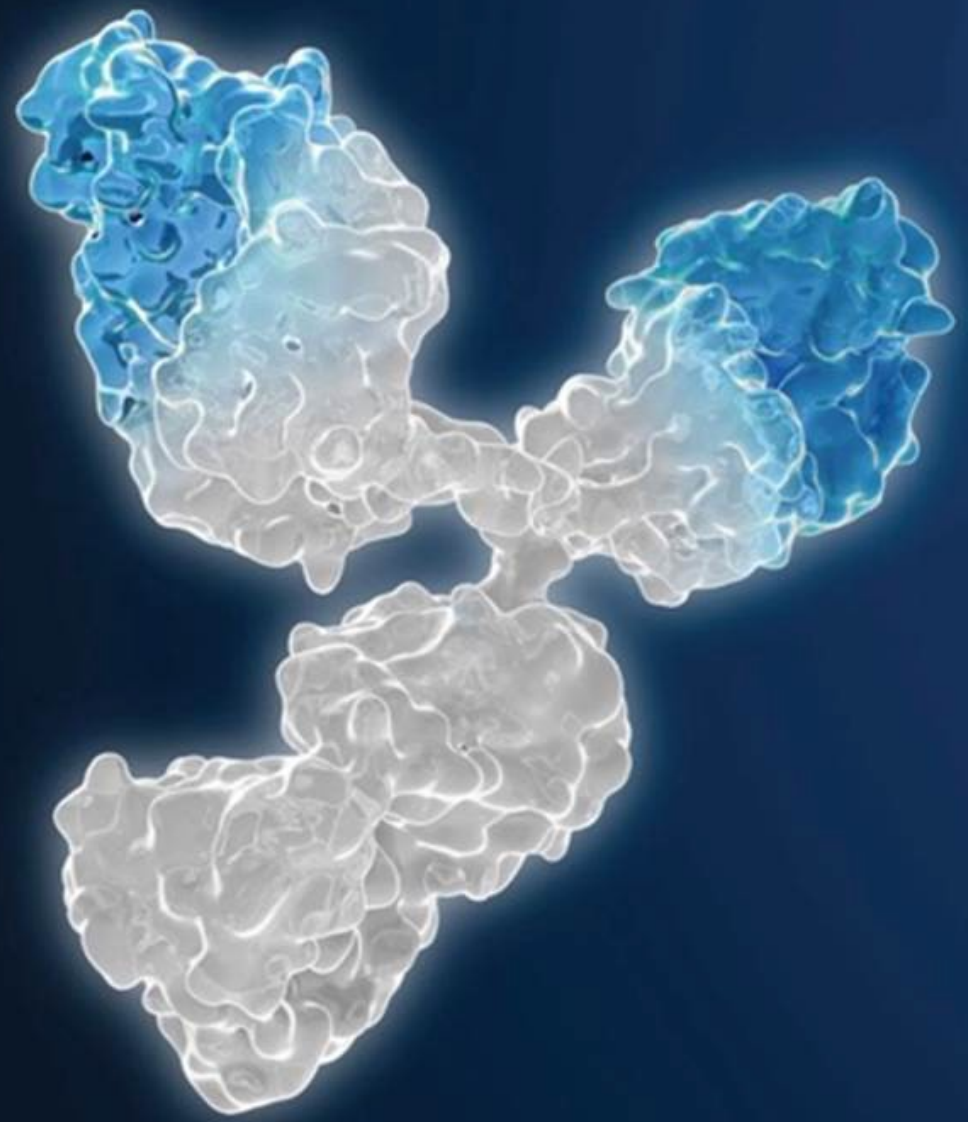
No significant effect in rate of COVID-19 diagnosis, which was relatively low, in staff.

Lower viral loads at time of detection among those getting the mAb

https://investor.lilly.com/news-releases/news-release-details/lillys-neutralizing-antibody-bamlanivimab-ly-cov555-prevented

DEATH DUE TO ANY CAUSE (RESIDENTS)

	N	Deaths	Rate
Placebo	24	4	17%
Bamlanivimab 4200 mg	17	0	0%



R10933-10987-COV-2069

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Assessing the Efficacy and Safety of Anti-Spike SARS-CoV-2 Monoclonal Antibodies in Preventing SARS-Cov-2 Infection in Household Contacts of Individuals Infected with SARS-CoV-2

REGENERON

SCIENCE TO MEDICINE®

01 July 2020

Phase 3 Clinical Trial of Casirivimab And Imdevimab as Passive "Vaccine" to Prevent COVID-19 in Household Contacts

- Household contacts of COVID-19 case (N=400 prelim analysis) randomized to CASI+IMDE 1,200 mg subQ vs Placebo
- Passive vaccination with CASI+IMDE resulted in 100% prevention of symptomatic infection (8/223 placebo vs. 0/186 CASI+IMDE), and approximately 50% lower overall rates of infection (symptomatic and asymptomatic) (23/223 placebo vs. 10/186 CASI+IMDE)
- Infections occurring with CASI+IMDE therapy were all asymptomatic
  - Infections occurring in the placebo group had, on average, more than 100-fold higher peak viral load.
  - Infections in the CASI+IMDE group lasted no more than 1 week, while approximately 40% of infections in the placebo group lasted 3-4 weeks.
  - No infected individuals in the CASI+IMDE group had high viral loads (>10^4 copies/mL) compared to 62% of the infected placebo group (13/21 placebo vs. 0/9 CASI+IMDE).

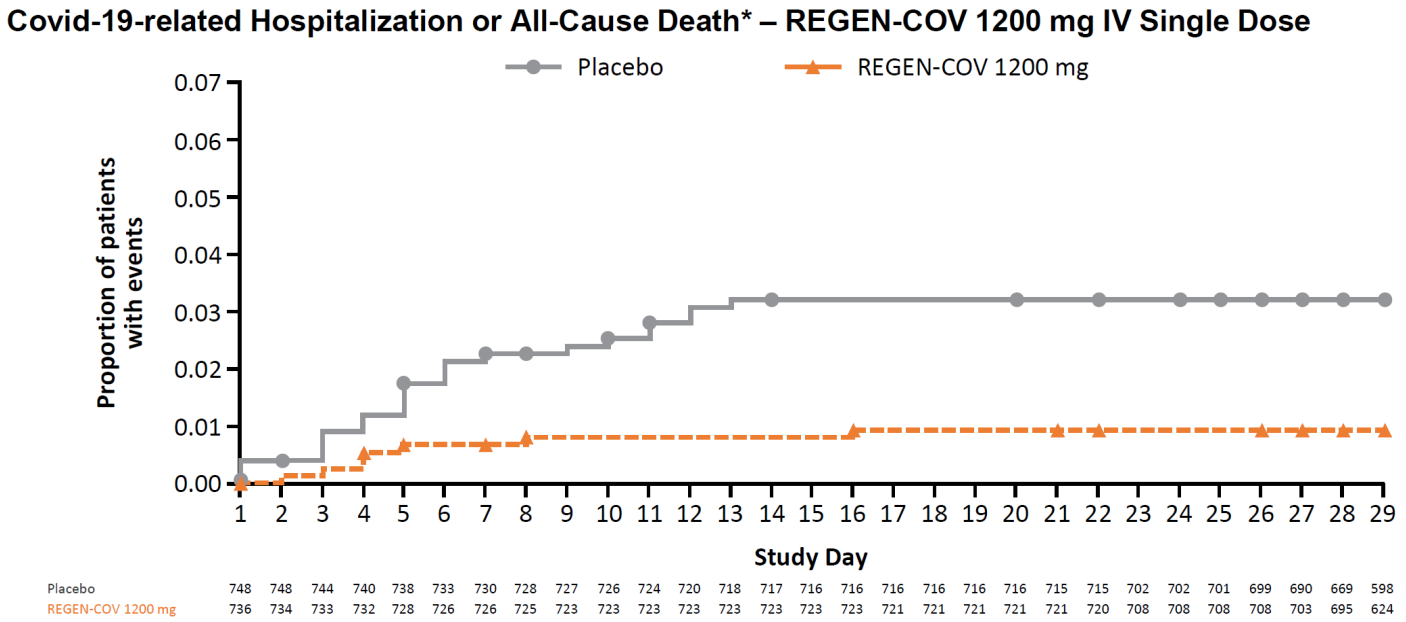
https://newsroom.regeneron.com/news-releases/news-release-details/regeneron-reports-positive-interim-data-regen-covtm-antibody.

Casirivimab and Imdevimab EUA (IV and SQ) Mild/Moderate COVID-19

- mAb cocktail of casirivimab 600 or 1200 mg and imdevimab 600 or 1200 mg (REGEN-COV™, Regeneron)
- Recommended by NIH Treatment Guidelines
- Given within 5 days of symptoms;
- Antiviral activity with 1200 mg SQ (four 2.5 mL injections) but also with 600 mg and 300 mg SQ

Clinical Efficacy of REGEN-COV

	2400mg vs Placebo	1200mg vs Placebo
COVID-19 related hospital or all-cause death through day 29	18/1355 (1.3%) vs 62/1341 (4.6%); p<0.0001	7/736 (1.0%) vs 24/748 (3.2%); p=0.0024
Time to COVID-19 symptoms resolution	Median 10 vs 14 days; p<0.0001	Median 10 vs 14 days; p<0.0001



https://www.medrxiv.org/content/10.1101/2021.05.19.21257469v1.full.pdf
https://www.regeneron.com/downloads/treatment-covid19-eua-fda-letter.pdf
https://www.covid19treatmentguidelines.nih.gov/anti-sars-cov-2-antibody-products/anti-sars-cov-2-monoclonal-antibodies/

SAR-2 Monoclonal Antibodies in Development

- FDA EUA
  - Bamlanivimab – withdrawn
  - Bamlanivimab plus etesevimab – withdrawn from somestates because of resistance (VOC)
  - Casirivimab and imdevimab – IV and SQ (when IV not feasible)
  - All above have short ½ life (weeks)
  - Sotrovimab (long half life, months)
- In development (all with long ½ life)
  - BRII – two MAbs IV– likely at least one antibody active to VOC
    - FC receptor modification decreases effector function
  - Rockefeller BMS two MAbs SQ likely at least one active against VOC
  - AstraZeneca two MAbs IM likely at least one active against VOC

Current EUA Criteria for Outpatient Treatment
Very Broad

- The FDA defines **high-risk for progression to severe COVID-19**, for adults and children 12 years or older and weighing at least 40 kg:
    - Older age (for example, age ≥ 65 years)
    - Obesity or being overweight (for example, BMI > 25 kg/m^2, or if age 12-17, BMI > 85%ile for age and gender)
    - Pregnancy
    - Chronic kidney disease
    - Diabetes
    - Immunosuppressive disease or immunosuppressive treatment
    - Cardiovascular disease (including congenital heart disease) or hypertension
    - Chronic lung disease (for example, COPD, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension
    - Sickle cell disease
    - Neurodevelopmental disorders or other conditions that confer medical complexity (for example genetic or metabolic syndromes and severe congenital anomalies)
    - Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19))

HPTN
HIV Prevention Trials Network

Variants: They're Here

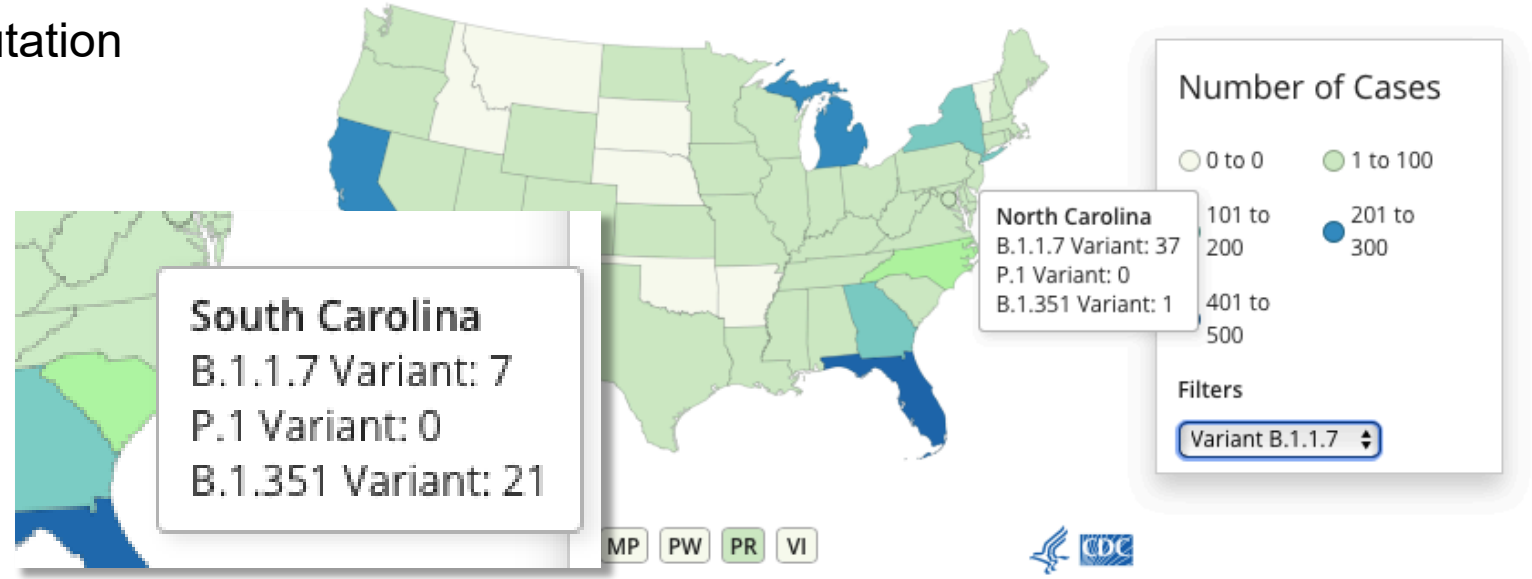
- Major variants
  - **B.1.1.7** – UK -> More infectious, Maybe more severe disease
  - **B.1.351** – South Africa -> Reduced protection by some vaccines (not Moderna or Pfizer), reduced effect of some COVID-19 antibody treatments
  - **P.1** – Brazil -> shares E484K mutation with B.1.351

US COVID-19 Cases Caused by Variants

Updated Feb. 23, 2021 Languages Print

Variant	Reported Cases in US	Number of States Reporting
B.1.1.7	1881	45
B.1.351	46	14
P.1	5	4

Emerging Variant Cases in the United States*†



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

MEDPAGE TODAY®

First COVID Treatment Ads Hit the Airwaves

— Regeneron hoping patients ask their doctors about monoclonal antibodies

by Kristina Fiore, Director of Enterprise & Investigative Reporting, MedPage Today

May 10, 2021

CVS pharmacy®

HSA/FSA Eligible

At-home COVID-19 test kits

PCR tests

Detect active COVID-19 infections and provide results in 1-2 days after sample is received by the lab.

Rapid antigen tests

Detect active COVID-19 infections and provide results in minutes.

Table 2: Pseudovirus Neutralization Data for SARS-CoV-2 Variant Substitutions with Casirivimab and Imdevimab Together

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]

[a] Pseudovirus expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: del69-70, del145, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H.

[b] Pseudovirus expressing the entire variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: D80Y, D215Y, del241-243, K417N, E484K, N501Y, D614G, A701V.

[c] No change: <2-fold reduction in susceptibility.

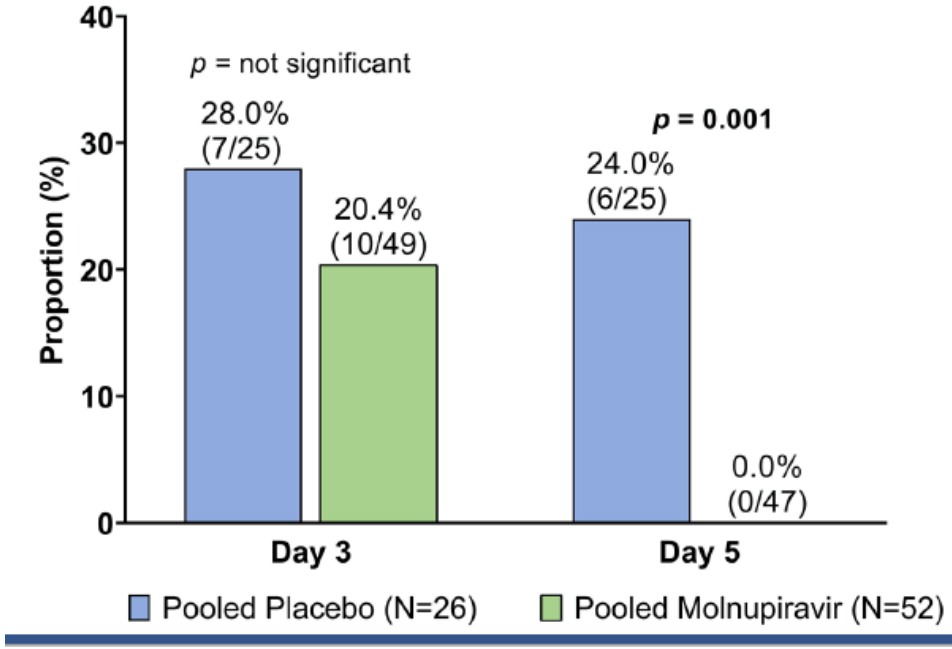
[d] Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).

Molnupiravir

- Oral inhibitor of replication of SARS CoV-2: viral error catastrophe
- Big Blue assay: not mutagenic or genotoxic in mammals
- Phase 2a randomized trial in outpatients with symptomatic SARS CoV-2 infection
- Molnupiravir or placebo twice daily for 5 days

- N=202 treated participants; 182 with evaluable swabs; 43% positive baseline Cx

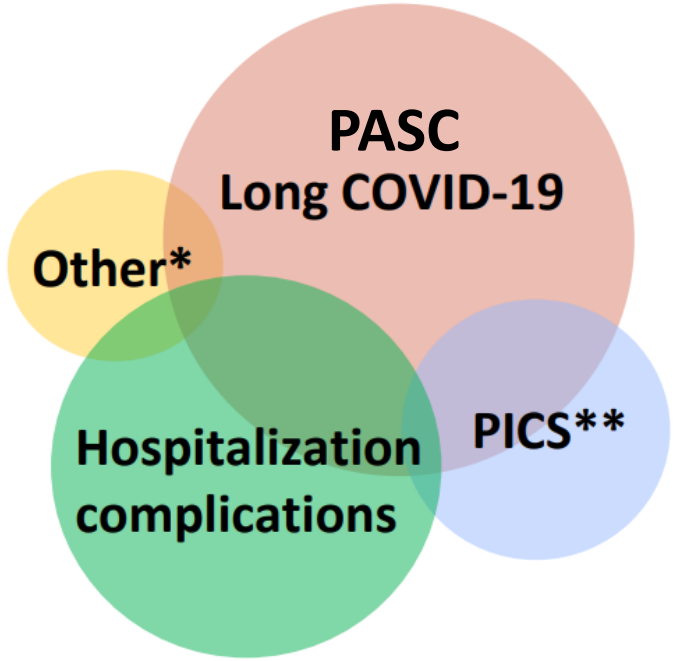
Figure 1. Proportion of overall participants with positive viral culture by RT-PCR (for participants positive at baseline)



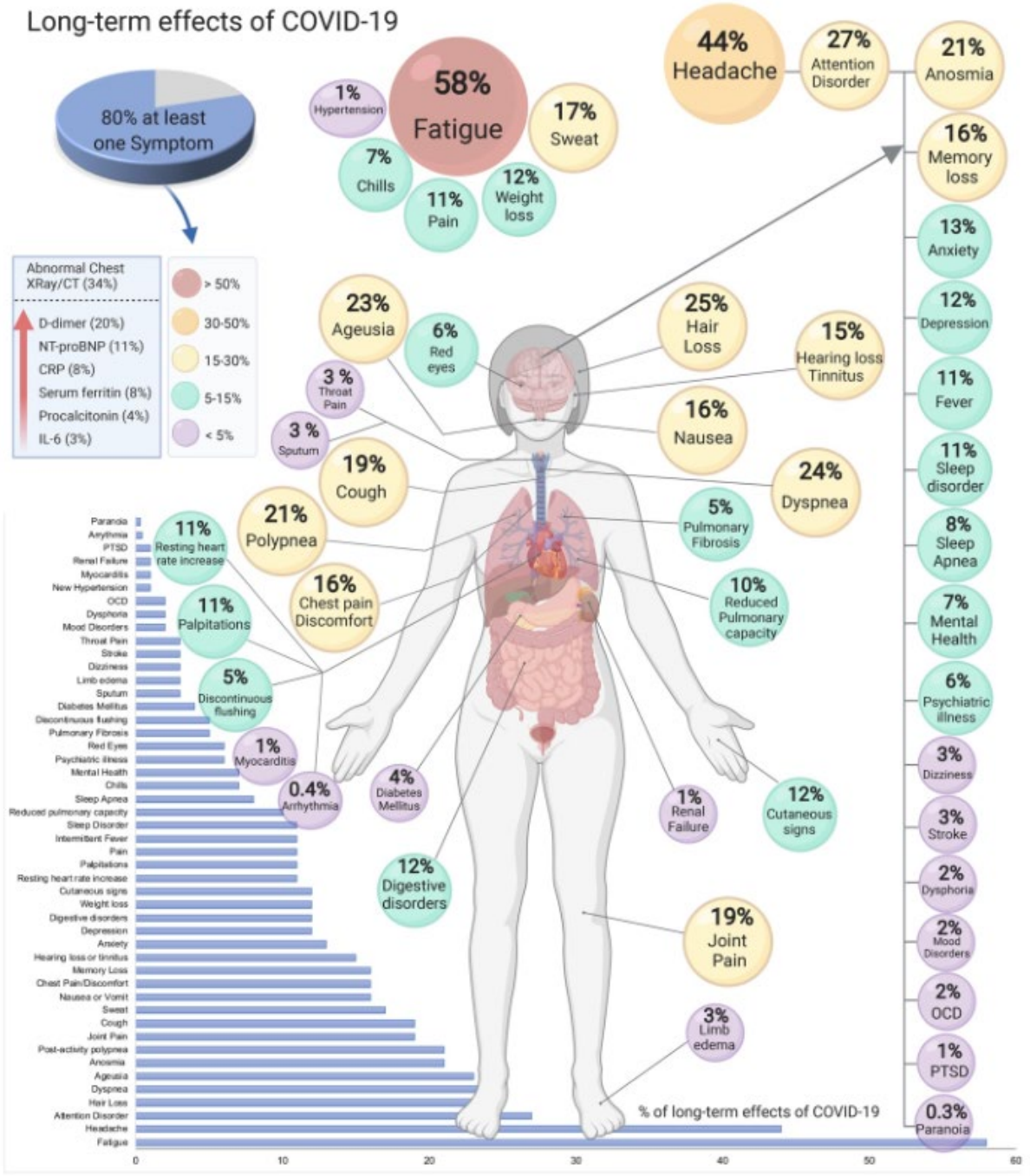
Painter W, Fischer W et al, CROI 2021, #777

Post-Acute Sequelae of COVID-19 (PASC)

PASC may **overlap with other complications** of COVID-19 infection making it **difficult to define**.



*Multisystem inflammatory disorder, Guillain-Barre, among others
**Post-Intensive Care Syndrome
https://emergency.cdc.gov/coca/ppt/2021/012821_slide.pdf



Systematic review and meta-analysis

- All paper published prior to 1 Jan. 2021 with >100 patients studied
- 18,251 publications screened; 15 included
- 55 long-term effects estimated
- Follow-up time, 14 to 110 days post-COVID-19
- It was estimated that 80% (95% CI, 65-92) of COVID-19 patients developed one or more long-term symptoms
- Five most common symptoms = fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%), and dyspnea (24%)

Lopez-Leon S, et al.
https://www.medrxiv.org/content/10.1101/2021.01.27.21250617v2

COVID-19 RECOVERY CLINIC: UNC MEDICAL CENTER

UNC Center for Rehabilitation Care
1807 N. Fordham Blvd. (near Lowe's)

~250 patients seen since clinic opened in February
75% of patients are females
Ages: 15-17, 2%; 18-49, 47%; 50-64, 33%; 65+, 17%

UNC HEALTH

COVID Recovery Clinic

Designed to provide comprehensive, multi-disciplinary care for adult survivors of COVID-19 infection who have ongoing medical complications, residual symptoms, and/or loss of functional independence.

Common Post-COVID Symptoms

Respiratory
- Cough
- Dyspnea

Cardiovascular
- Chest tightness and pain
- Palpitations

Musculoskeletal
- Joint pain
- Muscle pain
- Muscle weakness

Neurological
- Cognitive impairment
- Dizziness
- Headache
- Peripheral neuropathy
- Sleep disturbance

Gastrointestinal
- Abdominal Pain
- Diarrhea
- Nausea

Constitutional
- Altered smell and taste
- Decreased endurance
- Fatigue
- Fever
- Sleep disturbance

Mental Health
- Anxiety
- Depression

Dermatological
- Skin rashes

Hybrid Virtual + In-Person Clinic: Offering Care Throughout North Carolina

Core Clinical Team: Physical Medicine and Rehabilitation (PM&R), Internal Medicine, Psychiatry, Neuropsychology, Physical Therapy, Occupational Therapy and Speech Therapy

Collaborative Clinical Team: Cardiology, Pulmonology, Nephrology, Infectious Diseases, Hematology, Neurology, Clinical Nutrition, Behavioral Counseling

Eligibility
- **Age 18 +**
- **Documented History of COVID+ test**
- **At least 4 weeks after symptom onset / COVID diagnosis**

Referrals

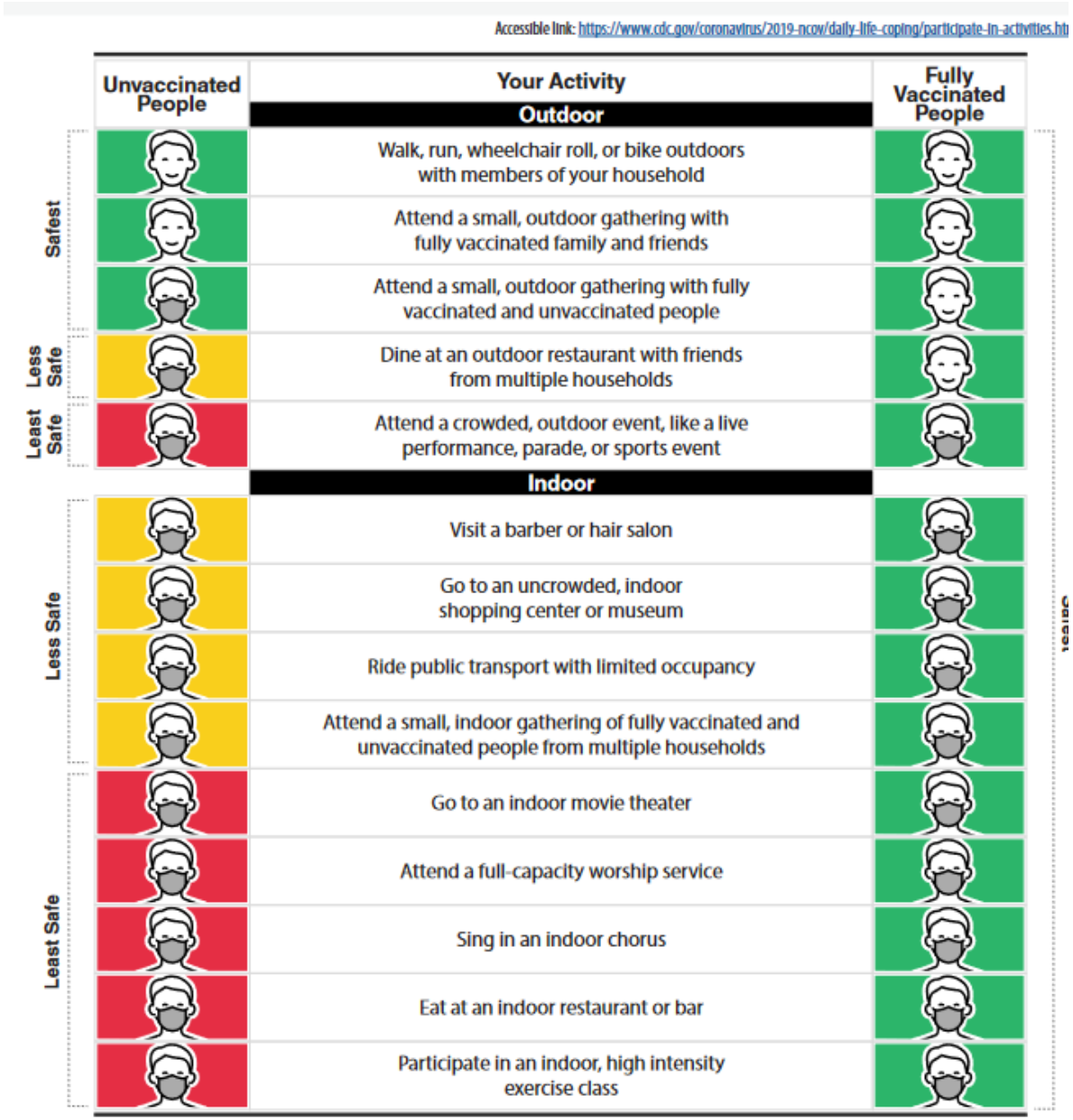
To refer a patient, please submit an "Ambulatory Referral to Physical Medicine & Rehabilitation" with comment **"COVID Recovery Clinic."**

UNC Center for Rehabilitation Care
984-974-9747
1807 N. Fordham Blvd., Chapel Hill, NC, 27514

CDC MASK GUIDANCE, VACCINATED PERSONS

For now, fully vaccinated people should continue to:

- Take precautions in indoor public settings like wearing a well-fitted mask
- Wear well-fitted masks when visiting indoors with unvaccinated people who are at increased risk for severe COVID-19 disease or who have an unvaccinated household member who is at increased risk for severe COVID-19 disease
- Wear well-fitted masks when visiting indoors with unvaccinated people from multiple households
- Avoid indoor large-sized in-person gatherings
- Get tested if experiencing COVID-19 symptoms
- Follow guidance issued by individual employers
- Follow CDC and health department travel requirements and recommendations



https://www.cdc.gov/coronavirus/2019-ncov/vaccines/fully-vaccinated-guidance.html

Big Conclusions: 2021

- Behavior changes required to stop the spread of SARS-CoV-2 in the US failed
- Entirely novel mRNA vaccines prevent symptomatic COVID-19 infections
  -Modena and Pfizer "rolled out" these novel vaccines in December
- Vaccines most likely work through generation of antibodies that "neutralize" Sars-Cov-2
- Monoclonal antibodies that neutralize Sars-Cov-2 can be easily generated
  EUA has been granted for Lilly and Regeneron combinations for early treatment
- Two NIH supported prophylaxis studies show MAbs prevent SARS-CoV-2
  -Lilly study of nursing home clients and attendants (soon to be analyzed)
  -Regeneron study of households (very large amount of data)
- Ongoing studies are examining the effects of empiric treatment
  of asymptomatic SARS-CoV-2 infection

Ultimately, integration of behavior changes and biological tools will be essential to stop the epidemic spread of SAR-CoV-2; sadly, we are far behind other countries.

We know "endemic" and sporadic cases of COVID-19 will now become "a new disease"