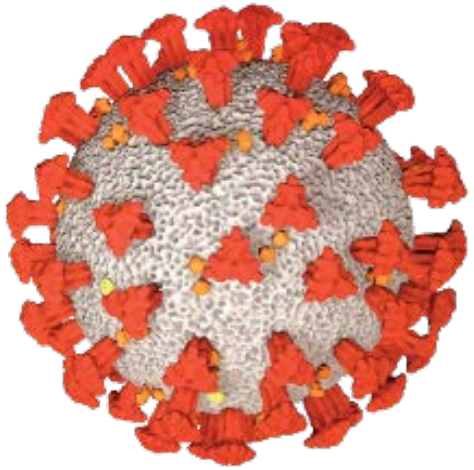
Prevention of Covid-19
HOW DO WE END THE PANDEMIC??



COVID-19
Prevention Network

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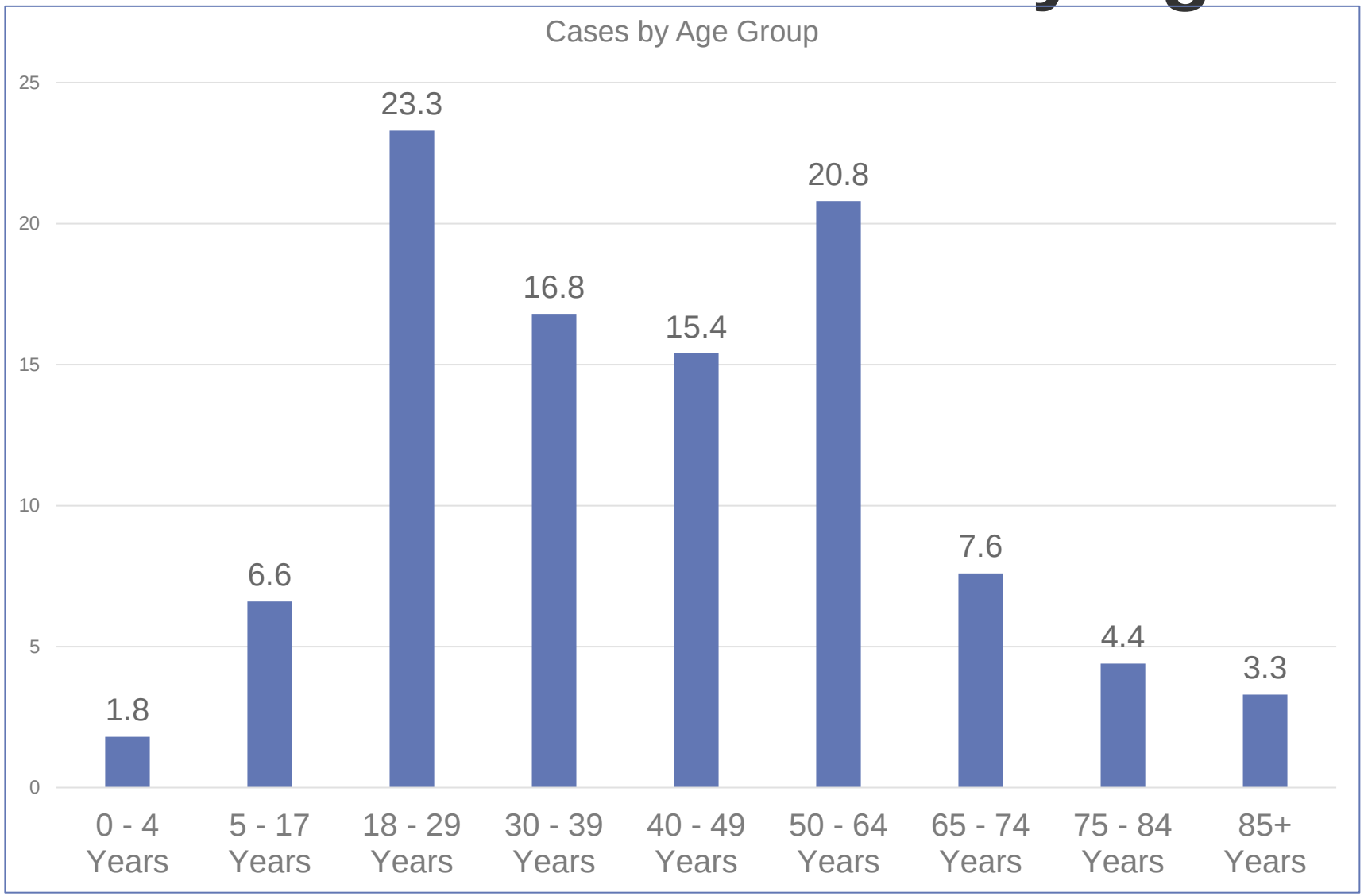
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

130 Mason Farm Road, Suite 2115, CB 7030 | Chapel Hill, NC
http://globalhealth.unc.edu | https://www.med.unc.edu/infdis

Cases of COVID-19 by Age Group

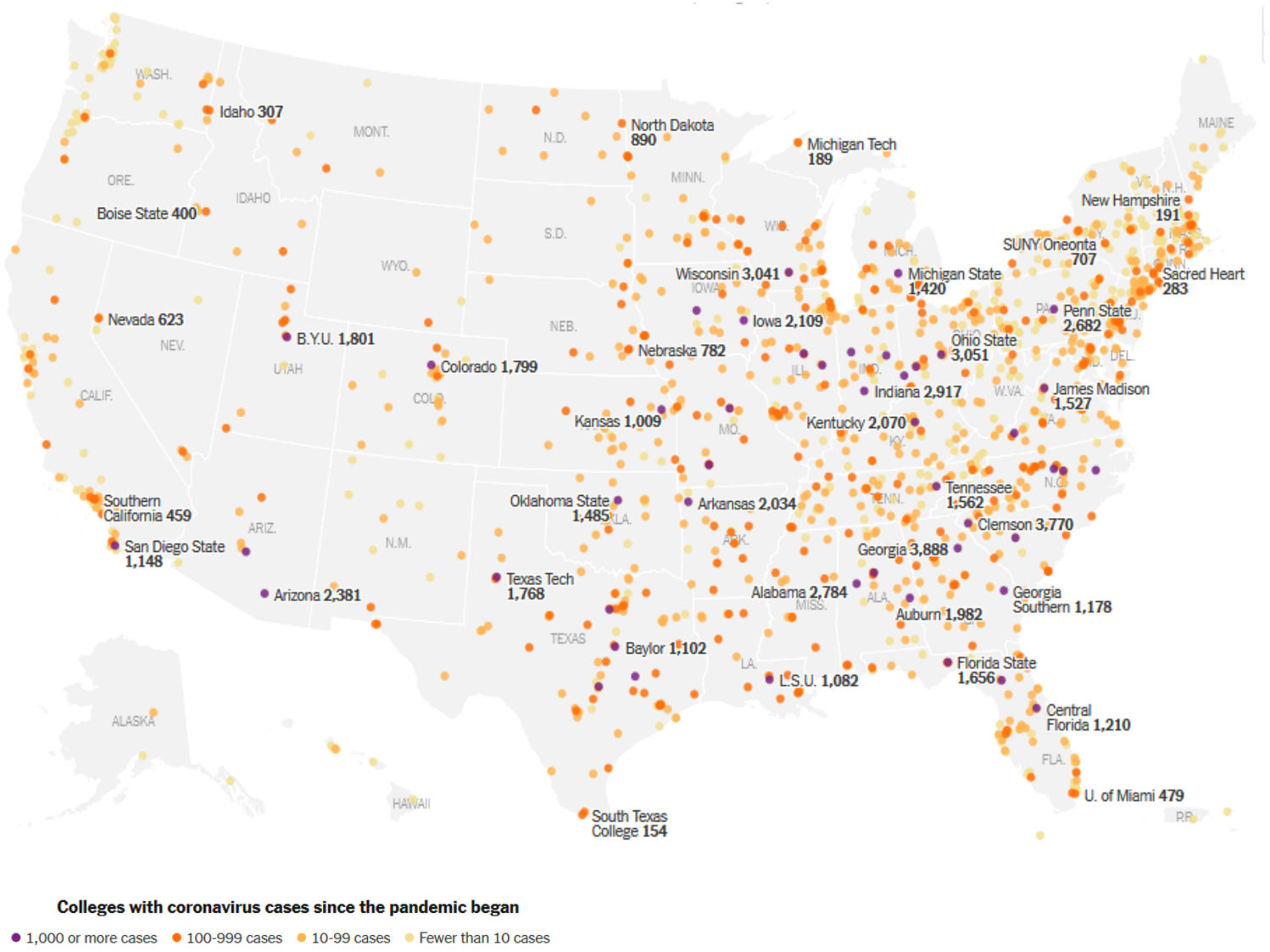


Current cases among adults >65 years of age: 15.3%

Unclear from this data which proportion are symptomatic

COVID-19 Prevention Network

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



Tracking Covid at U.S. Colleges and Universities

By The New York Times Updated Oct. 8, 2020

178,000+ Cases | **1,400+** Colleges

Thousands of new coronavirus cases continue to emerge on college campuses. A New York Times survey of more than 1,700 American colleges and universities — including every four-year public institution and every private college that competes in N.C.A.A. sports — has revealed more than 178,000 cases and at least 70 deaths since the pandemic began.

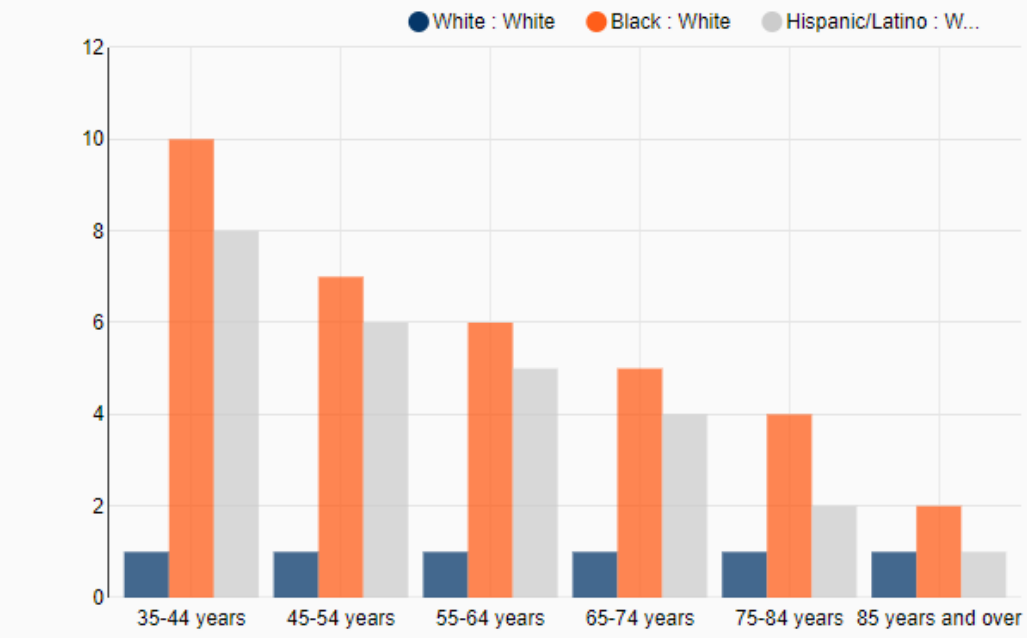
https://www.chronicle.com/newsletter/academe-today/2020-10-12

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

FNIH

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

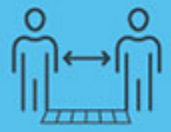

ENCLOSED SPACE


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

Why is this Happening? The Epidemic Spread of an Infection

Ro = bDC

When Ro >1 epidemic is sustained

b = Efficiency of transmission

D = Duration of infectiousness

C = Number of people (partners) exposed

Anderson and May, 1966

TRANSMISSION OF SARS CoV-2

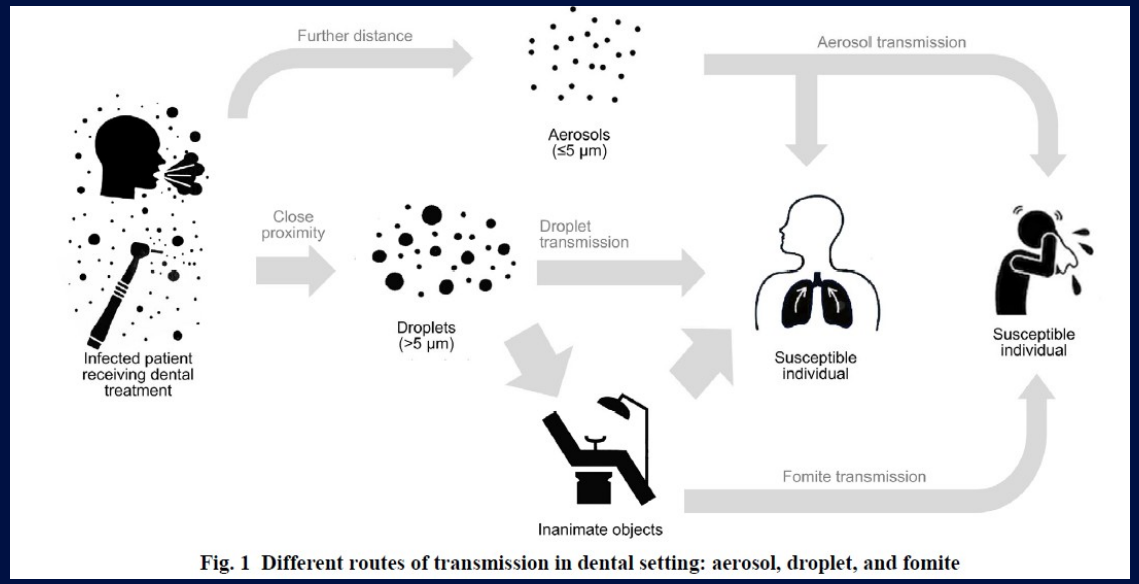


Fig. 1 Different routes of transmission in dental setting: aerosol, droplet, and fomite

COVID-19 infection in closed setting (e.g., cruise ships, nursing homes) leads to high attack rates

- 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 lessons learned from HIV. Given this rule

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

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 will require large trials with 6000 to [illegible]000 participants [illegible] more in eac[illegible] is moving

. 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 travelled in 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

Biological Strategies to Prevent COVID-19

- **Treatment as Prevention**

  -Most effective when transmission comes from symptomatic people

  (SARS-1, MERS-SARS…but perhaps NOT SARS-CoV-2)
- **Active Immunity: Vaccination**

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

  - Convalescent plasma (?), hyperimmuneglobulin (?), mAbs!!

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

Conceptual Framework for COVID-19 Vaccine Development

We need to develop multiple vaccine platforms.

No single vaccine platform can be manufactured at enough scale to immunize the 4.4 billion adult population on the planet and 3 billion children

- 220 million adults in US alone.

Use known platforms to cover the field scientifically. Manufacturing scalability is a key factor.

Coordinated USG effort to involve global vaccine manufacturing companies.

There must be an unprecedented coordinated approach to test, manufacture the vaccine at scale, and deliver the vaccine into peoples' arms throughout the world.

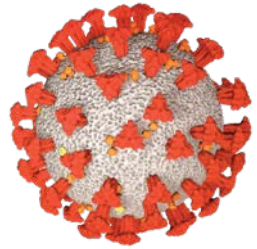
Three Entities with Distinct Roles in COVID-19 Response

Operation Warp Speed

USG body responsible for strategic approach, coordination and resource allocation

Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)

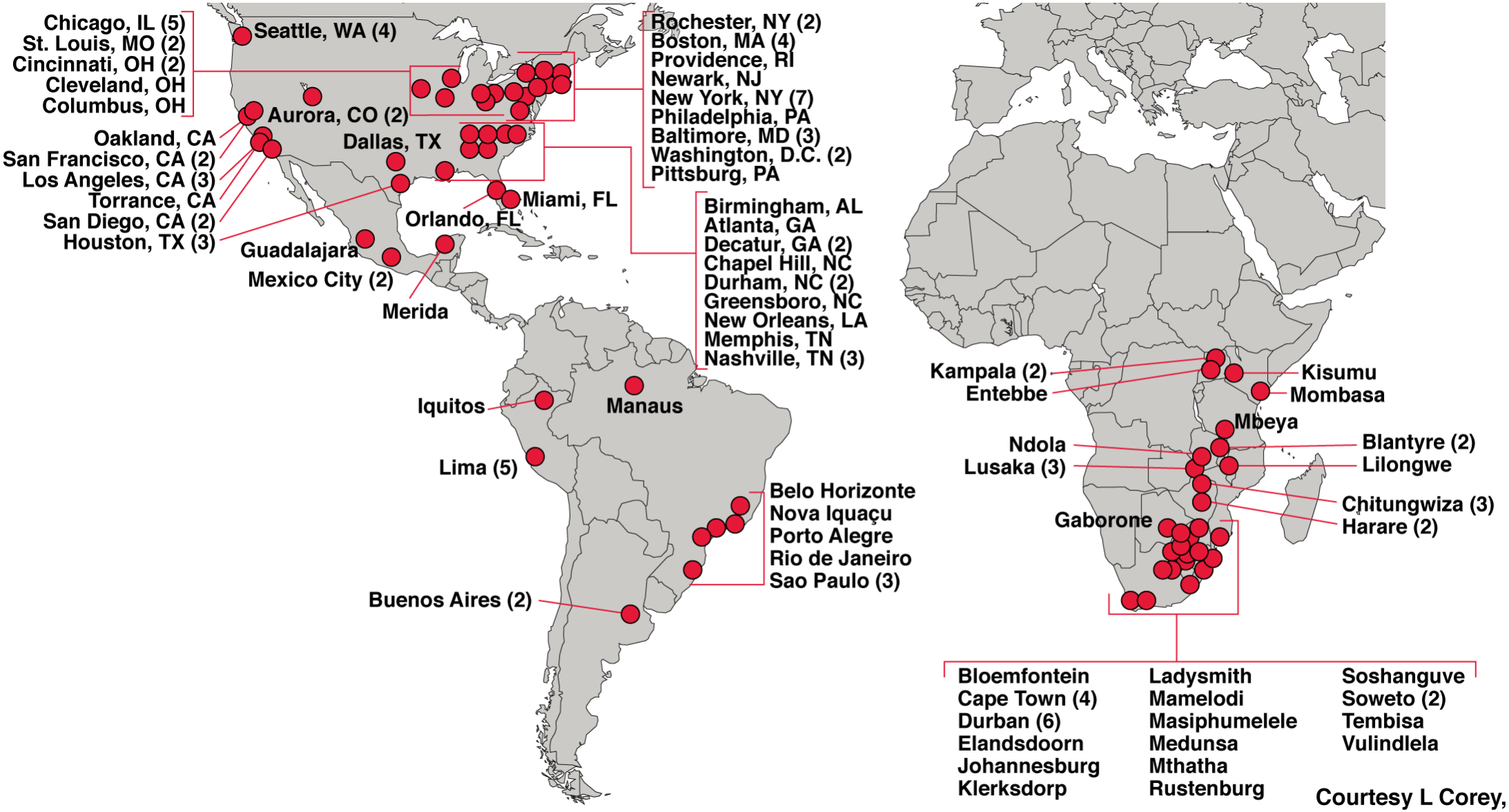
NIH established Public-private partnership for coordinating COVID-19 response



COVID-19 Prevention Network

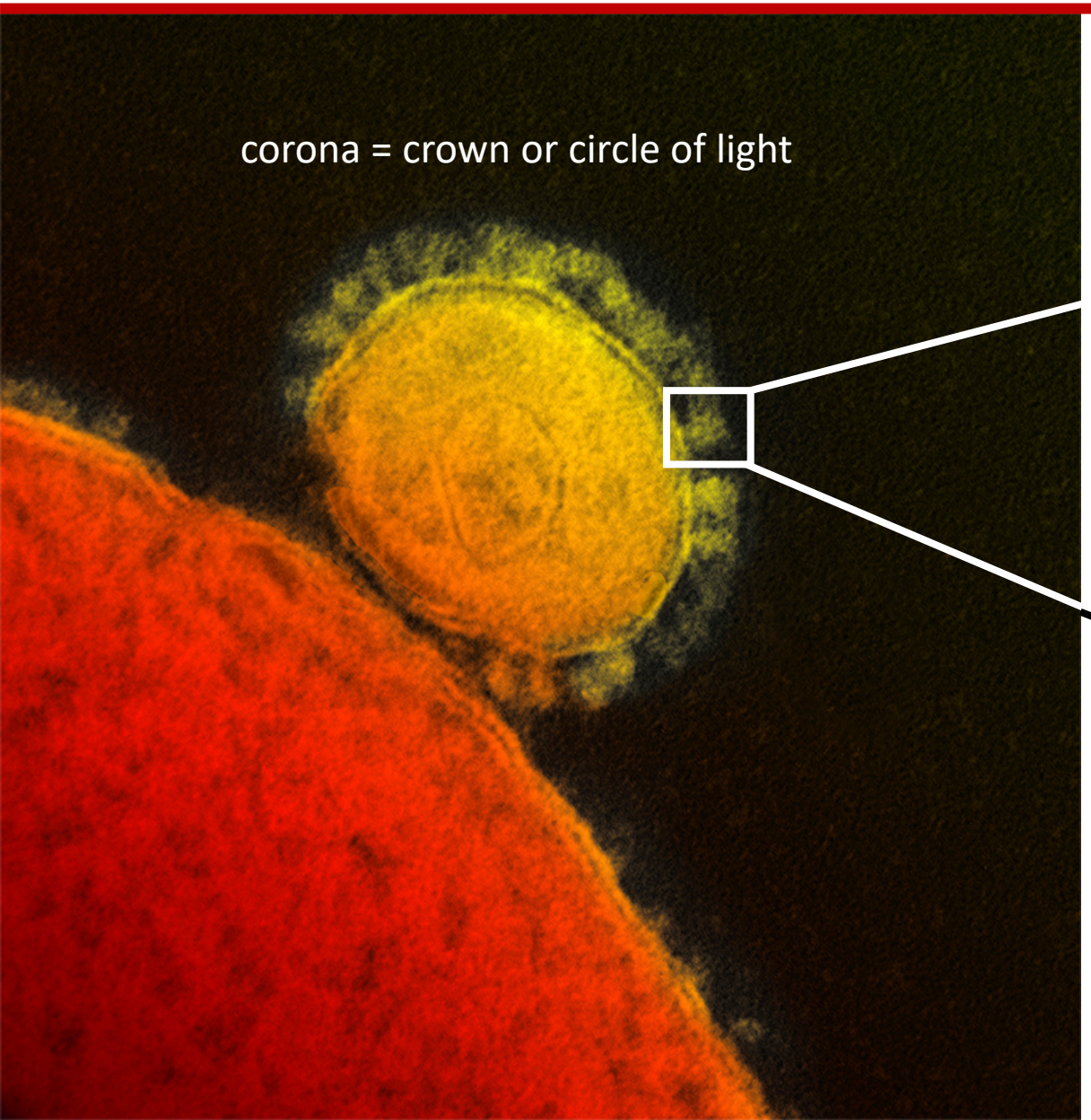
NIH Funded networks - Phase 3 trial execution

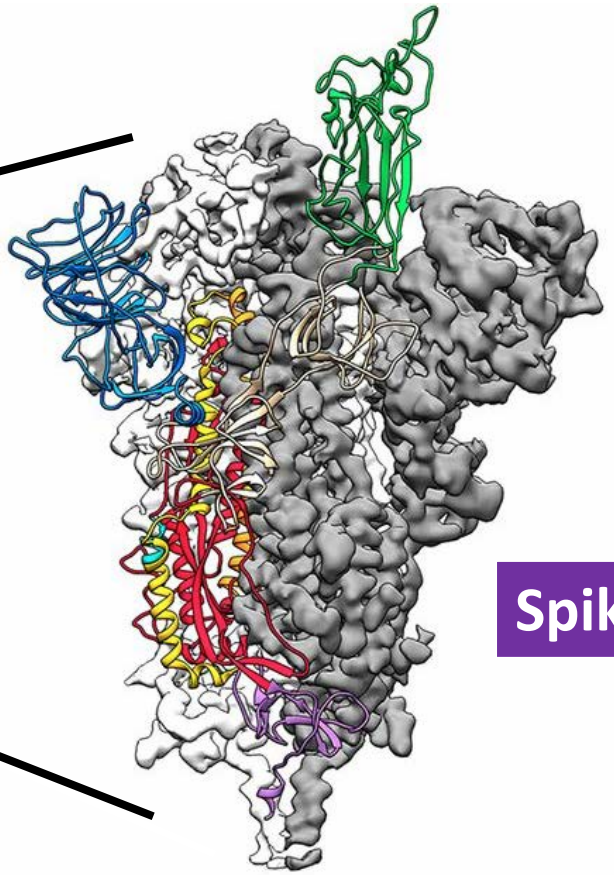
CoVPN Clinical Sites



Courtesy L Corey, HVTN

Nomenclature

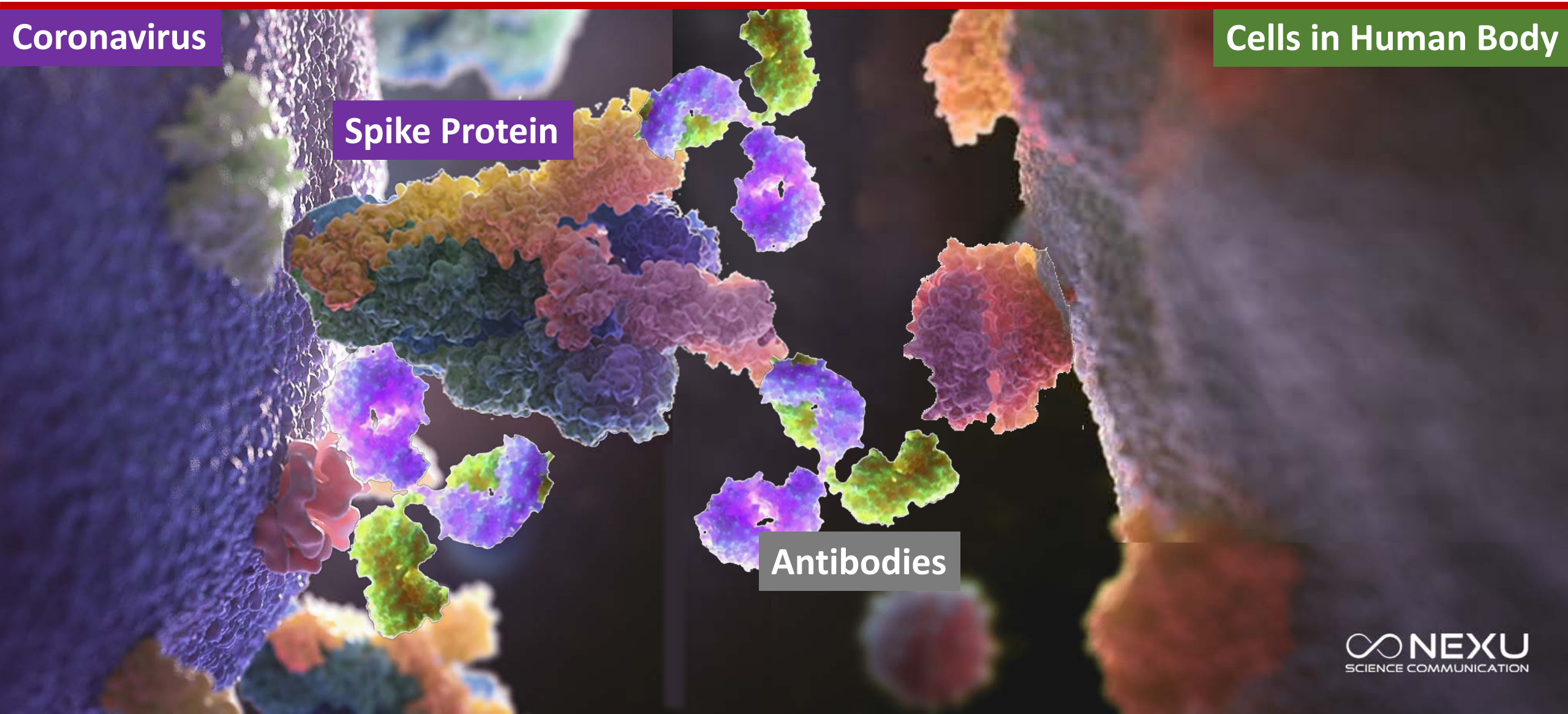




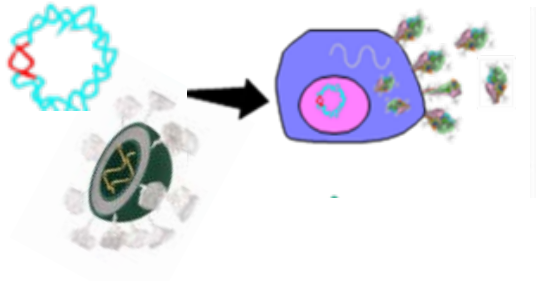
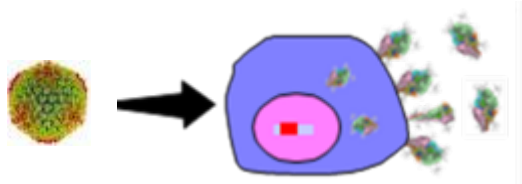
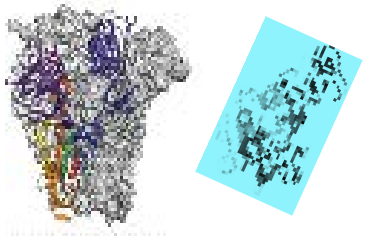
Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, Graham BS, McLellan JS. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020 Feb 19:eabb2507. doi: 10.1126/science.abb2507.

Antibodies can Prevent SARS-CoV-2

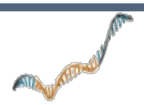
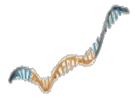
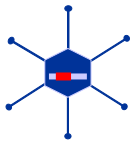
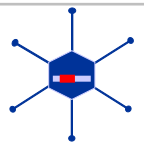
- **Antibodies** are produced after a person gets vaccinated, or can be passively administered
- **Antibodies** bind **coronavirus spike protein** to block infection and protect against COVID-19 disease. .



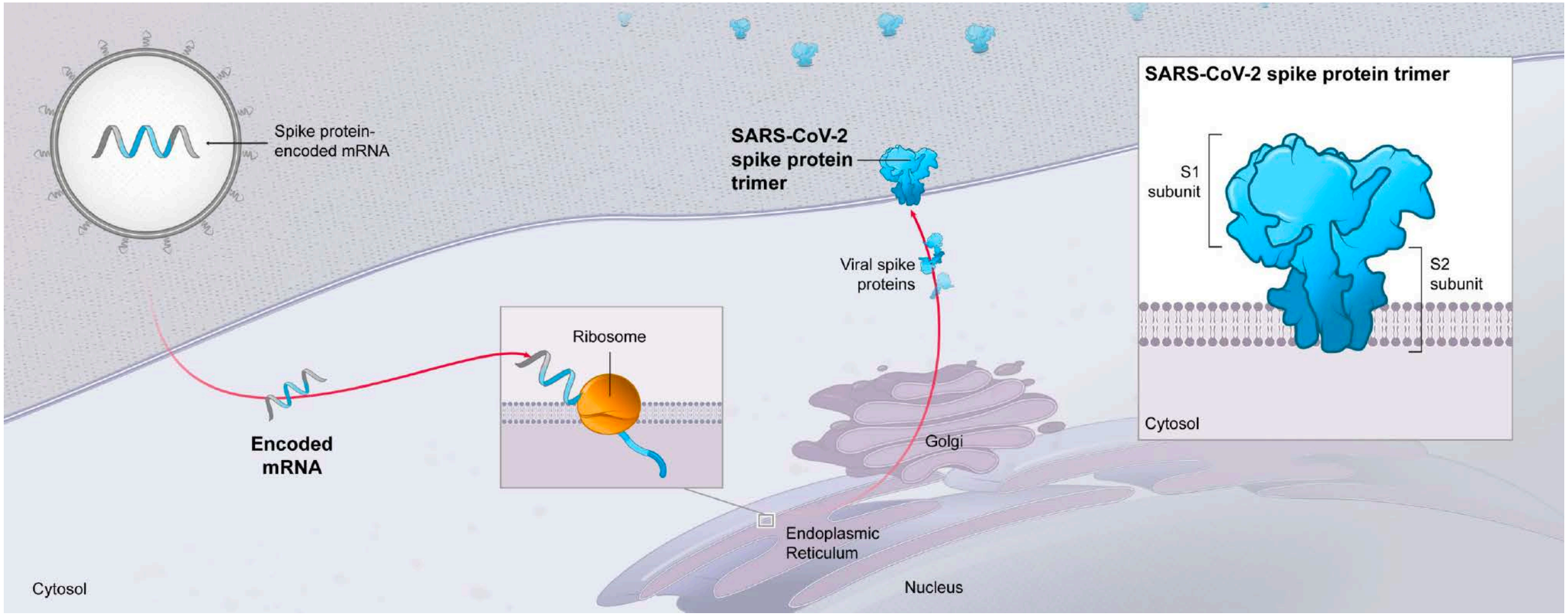
Vaccine Platforms and Immune Response

	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

Overview of OWS* CoVID-19 Vaccine Candidates

Company	Platform	Product	Vaccination dose/schedule	Phase 3 Approx. Start
moderna	 mRNA	mRNA: encodes 2P-stabilized Spike, TM, FI	2 doses at 100 µg (0, 28 days)	Ongoing
BIONTECH Pfizer	 mRNA	mRNA: encodes stabilized SARS-CoV-2 Spike	2 doses at 30µg (0, 21 days)	Ongoing
UNIVERSITY OF OXFORD AstraZeneca	 Ad Vector	Replication incompetent ChAdOx1 wild type Spike; △F; TM	2 doses at 5 × 10^{10} vp, (0, 28 days)	Ongoing
janssen PHARMACEUTICAL COMPANIES of Johnson & Johnson	 Ad Vector	Replication Incompetent Ad26; stabilized Spike; △F; TM	1 dose at 5 × 10^{10} vp	Ongoing
NOVAVAX Creating Tomorrow's Vaccines Today	 Recombinant protein Adjuvanted	Baculovirus Expressed trimeric Stabilized Spike, △F; TM; trimerization domain; Matrix M	2 doses at 5 µg with Matrix M (0, 21 days)	Fall 2020
gsk SANOFI	 Recombinant protein Adjuvanted	Baculovirus Expressed trimeric Stabilized Spike, △F; TM; trimerization domain; AS03	5/15 µg +AS03 (0, 21 days)	Fall 2020

mRNA 1273 Immunization Strategy

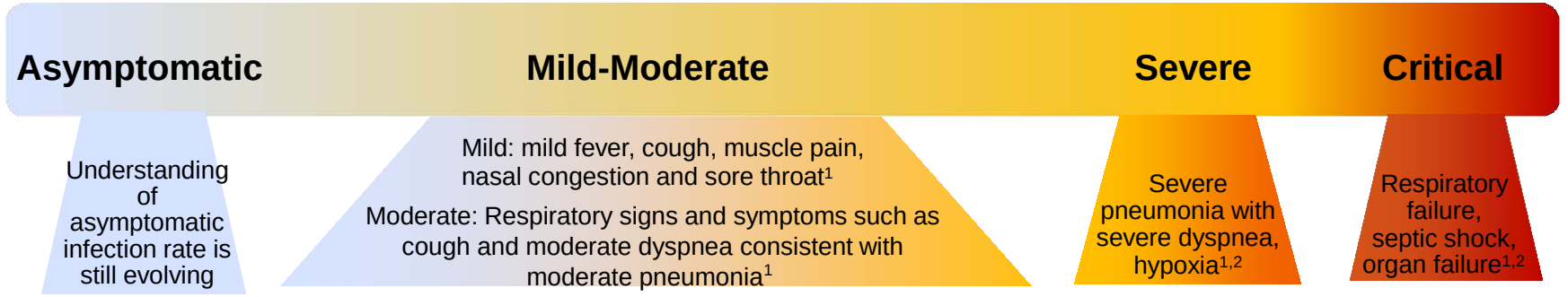


COVID-19
Prevention Network

Stabilized S-2P Spike Protein Expressed Transmembrane *in vivo*

Image courtesy of Moderna Therapeutics

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

Pfizer and BioNTech Announce Vaccine Candidate Against COVID-19 Achieved Success in First Interim Analysis from Phase 3 Study

Monday, November 09, 2020 - 06:45am

- *Vaccine candidate was found to be more than 90% effective in preventing COVID-19 in participants without evidence of prior SARS-CoV-2 infection in the first interim efficacy analysis*
- *Analysis evaluated 94 confirmed cases of COVID-19 in trial participants*
- *Study enrolled 43,538 participants, with 42% having diverse backgrounds, and no serious safety concerns have been observed; Safety and additional efficacy data continue to be collected*
- *Submission for Emergency Use Authorization (EUA) to the U.S. Food and Drug Administration (FDA) planned for soon after the required safety milestone is achieved, which is currently expected to occur in the third week of November*
- *Clinical trial to continue through to final analysis at 164 confirmed cases in order to collect further data and characterize the vaccine candidate's performance against other study endpoints*

NEW YORK & MAINZ, GERMANY--(BUSINESS WIRE)-- Pfizer Inc. (NYSE: PFE) and BioNTech SE (Nasdaq: BNTX) today announced their mRNA-based vaccine candidate, BNT162b2, against SARS-CoV-2 has demonstrated evidence of efficacy against COVID-19 in participants without prior evidence of SARS-CoV-2 infection, based on the first interim efficacy analysis conducted on November 8, 2020 by an external, independent Data Monitoring Committee (DMC) from the Phase 3 clinical study.

Pfizer Media:
Amy Rose
212-733-7410
Amy.Rose@pfizer.com

https://www.businesswire.com/news/home/20201109005539/en/

moderna

Moderna's COVID-19 Vaccine Candidate Meets its Primary Efficacy Endpoint in the First Interim Analysis of the Phase 3 COVE Study

November 16, 2020

First interim analysis included 95 participants with confirmed cases of COVID-19

Phase 3 study met statistical criteria with a vaccine efficacy of 94.5% (p <0.0001)

Moderna intends to submit for an Emergency Use Authorization (EUA) with U.S. FDA in the coming weeks and expects the EUA to be based on the final analysis of 151 cases and a median follow-up of more than 2 months

CAMBRIDGE, Mass.--(BUSINESS WIRE)--Nov. 16, 2020-- Moderna, Inc. (Nasdaq: MRNA), a biotechnology company pioneering messenger RNA (mRNA) therapeutics and vaccines to create a new generation of transformative medicines for patients, today announced that the independent, NIH-appointed Data Safety Monitoring Board (DSMB) for the Phase 3 study of mRNA-1273, its vaccine candidate against COVID-19, has informed Moderna that the trial has met the statistical criteria pre-specified in the study protocol for efficacy, with a vaccine efficacy of 94.5%. This study, known as the COVE study, enrolled more than 30,000 participants in the U.S. and is being conducted in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH), and the Biomedical Advanced Research and Development Authority (BARDA), part of the Office of the Assistant Secretary for Preparedness and Response at the U.S. Department of Health and Human Services.

The primary endpoint of the Phase 3 COVE study is based on the analysis of COVID-19 cases confirmed and adjudicated starting two weeks following the second dose of vaccine. This first interim analysis was based on 95 cases, of which 90 cases of COVID-19 were observed in the placebo group versus 5 cases observed in the mRNA-1273 group, resulting in a point estimate of vaccine efficacy of 94.5% (p <0.0001).

Moderna Media:
Colleen Hussey
Corporate Communications
617-335-1374
Colleen.Hussey@modernatx.com

https://www.businesswire.com/news/home/20201116005608/en/

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

By Noah Weiland, Sharon LaFraniere and Sheri Fink | Aug. 19, 2020

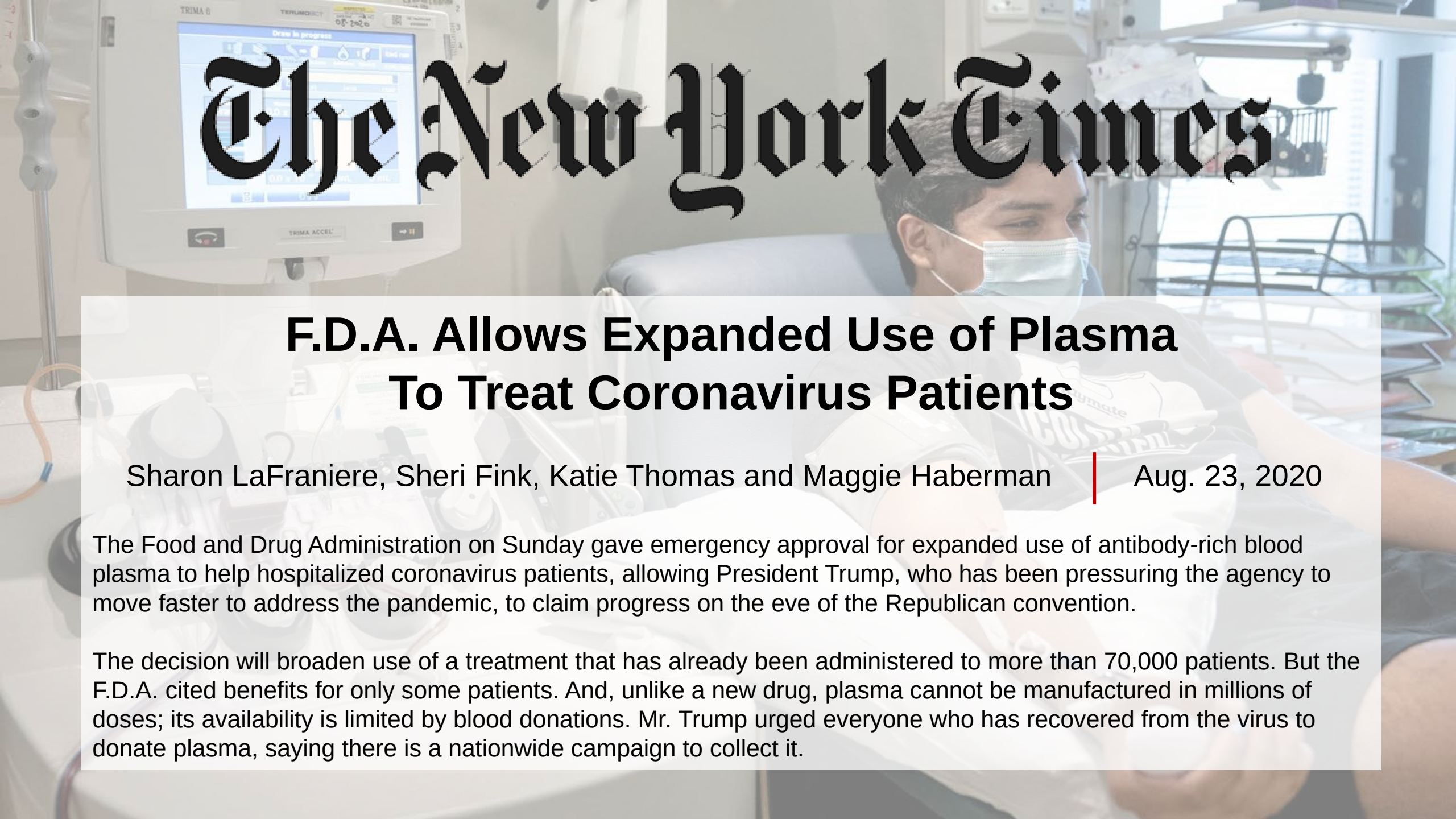
F.D.A.'s Emergency Approval of Blood Plasma Is Now on Hold

WASHINGTON — Last week, just as the Food and Drug Administration was preparing to issue an emergency authorization for blood plasma as a Covid-19 treatment, a group of top federal health officials including Dr. Francis S. Collins and Dr. Anthony S. Fauci intervened, arguing that emerging data on the treatment was too weak, according to two senior administration officials.

The authorization is on hold for now as more data is reviewed, according to H. Clifford Lane, the clinical director at the National Institute of Allergy and Infectious Diseases. An emergency approval could still be issued in the near future, he said.

Several top health officials — led by Dr. Collins, the director of the National Institutes of Health; Dr. Fauci, the government's top infectious disease expert; and Dr. Lane — urged their colleagues last week to hold off, citing recent data from the country's largest plasma study, run by the Mayo Clinic. They thought the study's data to date was not strong enough to warrant an emergency

https://www.nytimes.com/2020/08/19/us/politics/blood-plasma-covid-19



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.

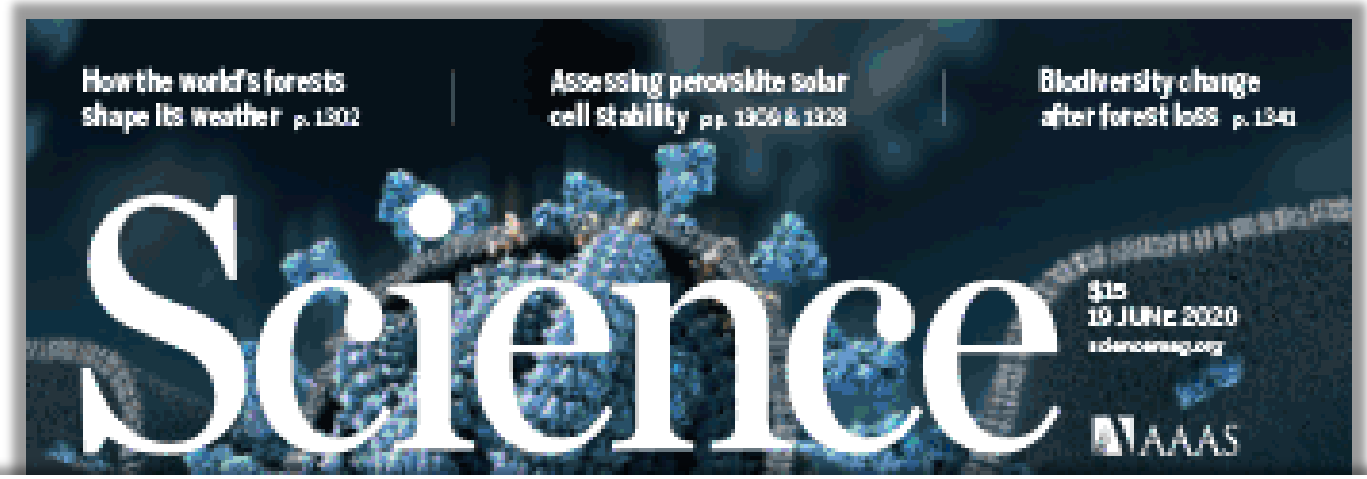
The decision will broaden use of a treatment that has already been administered to more than 70,000 patients. But the F.D.A. cited benefits for only some patients. And, unlike a new drug, plasma cannot be manufactured in millions of doses; its availability is limited by blood donations. Mr. Trump urged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

Limitations of Convalescent Plasma?

- Convalescent plasma may become difficult to obtain
- It is difficult to know all the components in the plasma provided

  Convergent Antibody Responses to SARS-CoV-2 Infection in Convalescent Individuals, Nussensweig et al. https://doi.org/10.1101/2020.05.13.092619doi
- We don't know "preventive" neutralizing antibody titers: 1/640?
- Convalescent plasma as an alternative may "challenge" RCTs

  … "why choose randomization if an intervention is available"



Science

RESEARCH ARTICLES

Cite as: T. F. Rogers *et al.*, *Science* 10.1126/science.abc7520 (2020).

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

Thomas F. Rogers[1,2*], Fangzhu Zhao[1,3,4*], Deli Huang[1*], Nathan Beutler[1*], Alison Burns[1,3,4], Wan-ting He[1,3,4], Oliver Limbo[3,5], Chloe Smith[1,3], Ge Song[1,3,4], Jordan Woehl[3,5], Linlin Yang[1], Robert K. Abbott[4,6], Sean Callaghan[1,3,4], Elijah Garcia[1], Jonathan Hurtado[1,4,7], Mara Parren[1], Linghang Peng[1], Sydney Ramirez[6], James Ricketts[1], Michael J. Ricciardi[8], Stephen A. Rawlings[2], Nicholas C. Wu[9], Meng Yuan[9], Davey M. Smith[2], David Nemazee[1], John R. Teijaro[1], James E. Voss[1], Ian A. Wilson[3,4,9], Raiees Andrabi[1,3,4], Bryan Briney[1,4,7], Elise Landais[1,3,4,5], Devin Sok[1,3,4,5†], Joseph G. Jardine[3,5†], Dennis R. Burton[1,3,4,10†]

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Science

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

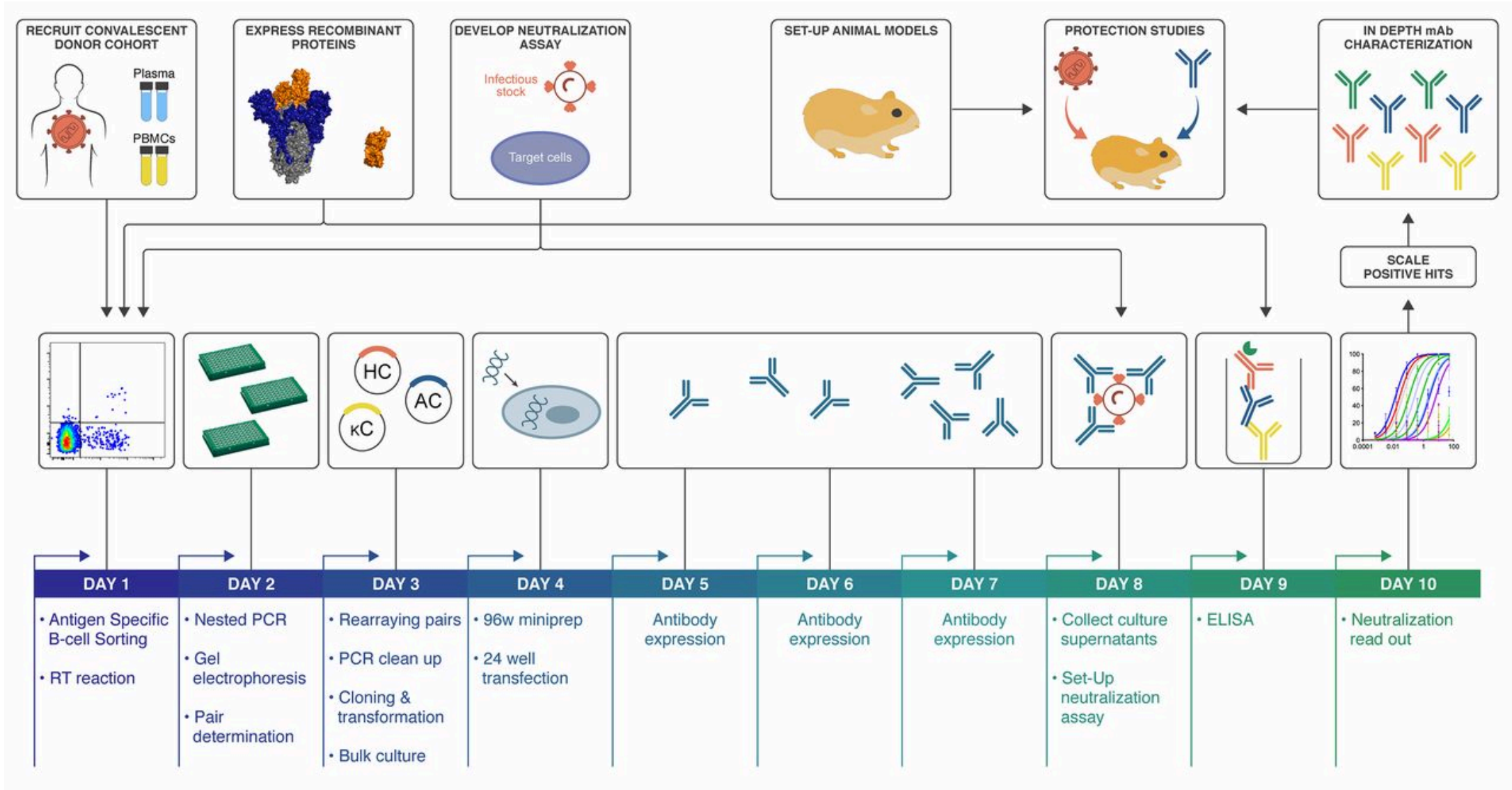

Fig. 1 SARS-CoV-2 neutralizing antibody isolation strategy.

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

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.

SARS-CoV-2 Spike Protein mAbs

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.**
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.**
First in Human July 2020	**Vir mAb, S309, isolated from a SARS-CoV patient that is cross-reactive with SARS-CoV-2,**
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)**
	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**

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)

Eli Lilly and Company

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www.lilly.com

For Release: September 16, 2020 6:45 a.m. ET

Refer to: Molly McCully; mccully_molly@lilly.com; 317-478-5423 (Media)
Kevin Hern; hern_kevin_r@lilly.com; 317-277-1838 (Investors)

Lilly announces proof of concept data for neutralizing antibody LY-CoV555 in the COVID-19 outpatient setting

- *Primary endpoint of viral load change from baseline at day 11 was met for one of three doses; consistent effects of viral reduction seen at earlier time points*
- *Rate of hospitalizations and ER visits was 1.7 percent (5/302) for LY-CoV555 versus 6 percent (9/150) for placebo—a 72 percent risk reduction in this limited population*
- *LY-CoV555 was well-tolerated across all doses with no drug-related serious adverse events reported*

INDIANAPOLIS, September 16, 2020 – Eli Lilly and Company (NYSE: LLY) today announced proof of concept data from an interim analysis of the BLAZE-1 clinical trial, showing a reduced rate of hospitalization for patients treated with LY-CoV555. The randomized, double-blind, placebo-controlled Phase 2 study evaluated LY-CoV555, a SARS-CoV-2 neutralizing antibody, for the treatment of symptomatic COVID-19 in the outpatient setting. The trial enrolled mild-to-moderate recently diagnosed COVID-19 patients across four groups (placebo, 700 mg, 2800 mg, and 7000 mg).

FDA NEWS RELEASE

EUA was issued to Eli Lilly and Company.

For Immediate Release: November 09, 2020

Coronavirus (COVID-19) Update: FDA Authorizes Monoclonal Antibody for Treatment of COVID-19

Today, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for the investigational monoclonal antibody therapy bamlanivimab for the treatment of mild-to-moderate COVID-19 in adult and pediatric patients. Bamlanivimab is authorized for patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kilograms (about 88 pounds), and who are at high risk for progressing to severe COVID-19 and/or hospitalization. This includes those who are 65 years of age or older, or who have certain chronic medical conditions.

While the safety and effectiveness of this investigational therapy continues to be evaluated, bamlanivimab was shown in clinical trials to reduce COVID-19-related hospitalization or emergency room visits in patients at high risk for disease progression within 28 days after treatment when compared to placebo.

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

"As illustrated by today's action, the FDA remains committed to expediting the development and availability of potential COVID-19 treatments and providing sick patients timely access to new therapies where appropriate, while at the same time supporting research to further evaluate whether they are safe and effective," said FDA Commissioner Stephen M. Hahn, M.D. "Through our Coronavirus Treatment Acceleration Program, the FDA continues to work around the clock and use every tool at our disposal toward these efforts."

Inquiries

Media:

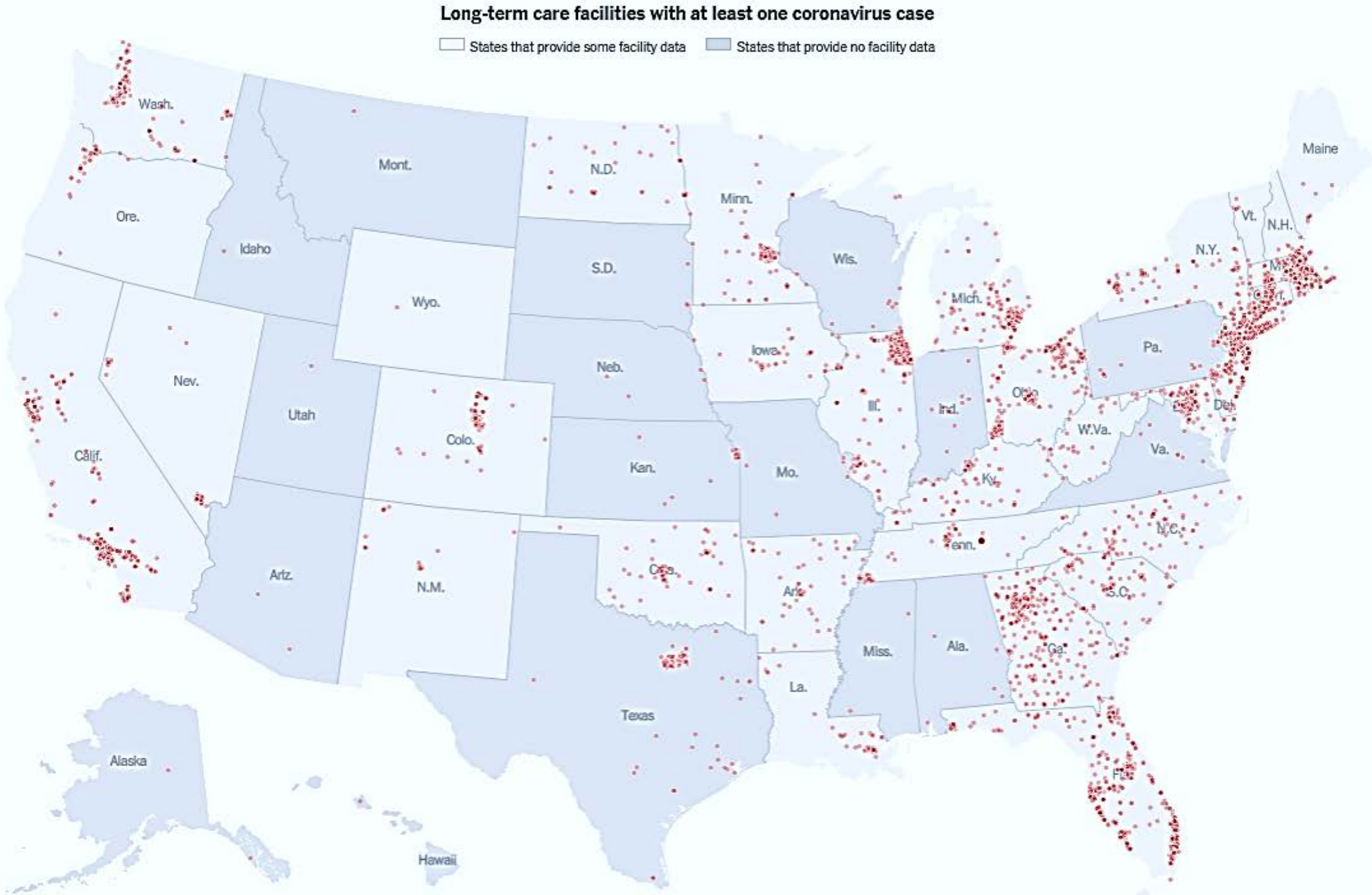
Chanapa Tantibanchachai

202-384-2219

Consumer:

888-INFO-FDA

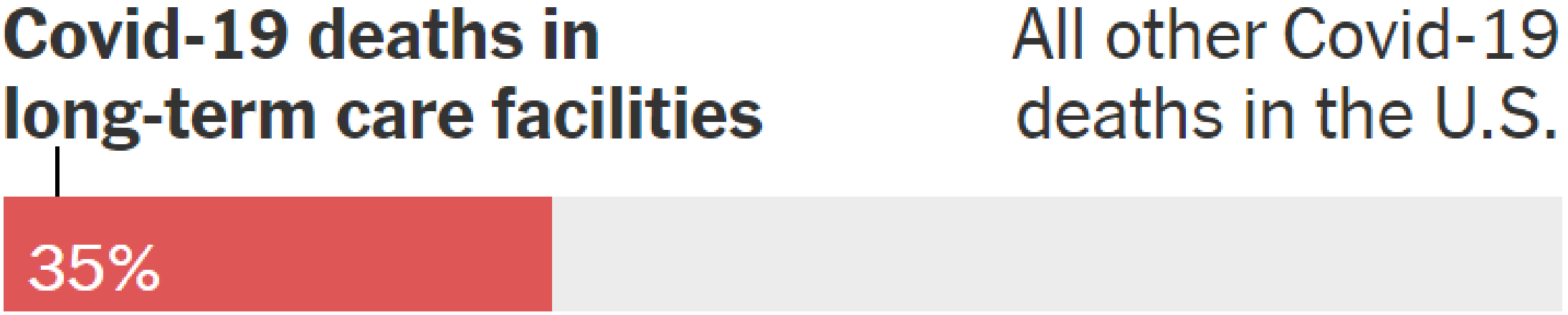
https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibody-treatment-covid-19



The New York Times. **Yourish, K.K.** May 11, 2020

The New York Times

One-Third of All U.S. Coronavirus Deaths Are Nursing Home Residents or Workers



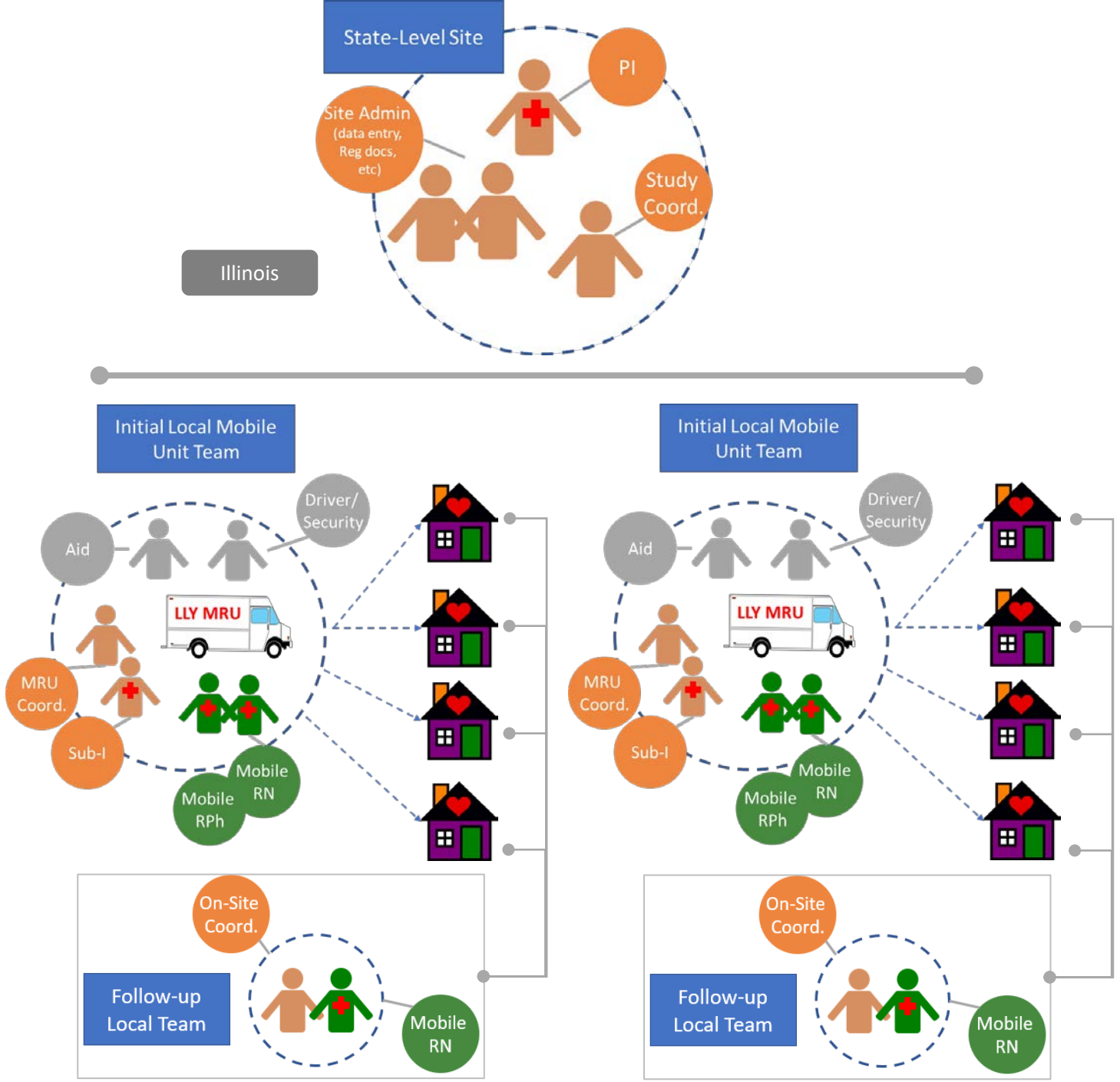
The New York Times. Karen Yourish, K.K. Rebecca Lai, Danielle Ivory and Mitch Smith Updated May 11, 2020

a NIAID and Lilly Collaborative Study

BLAZE-2 (J2X-MC-PYAD; CoVPN 3501)

PROTOCOL OVERVIEW

A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of LY3819253 in Preventing SARS-CoV-2 infection and COVID-19 in Skilled Nursing and Assisted Living Facility Residents and Staff


State-Level Site
PI
Site Admin
(data entry,
Reg docs,
etc)
Study
Coord.
Illinois
Initial Local Mobile
Unit Team
Driver/
Security
Aid
LLY MRU
MRU
Coord.
Sub-I
Mobile
RN
Mobile
RPh
On-Site
Coord.
Follow-up
Local Team
Mobile
RN
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Unit Team
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Coord.
Follow-up
Local Team
Mobile
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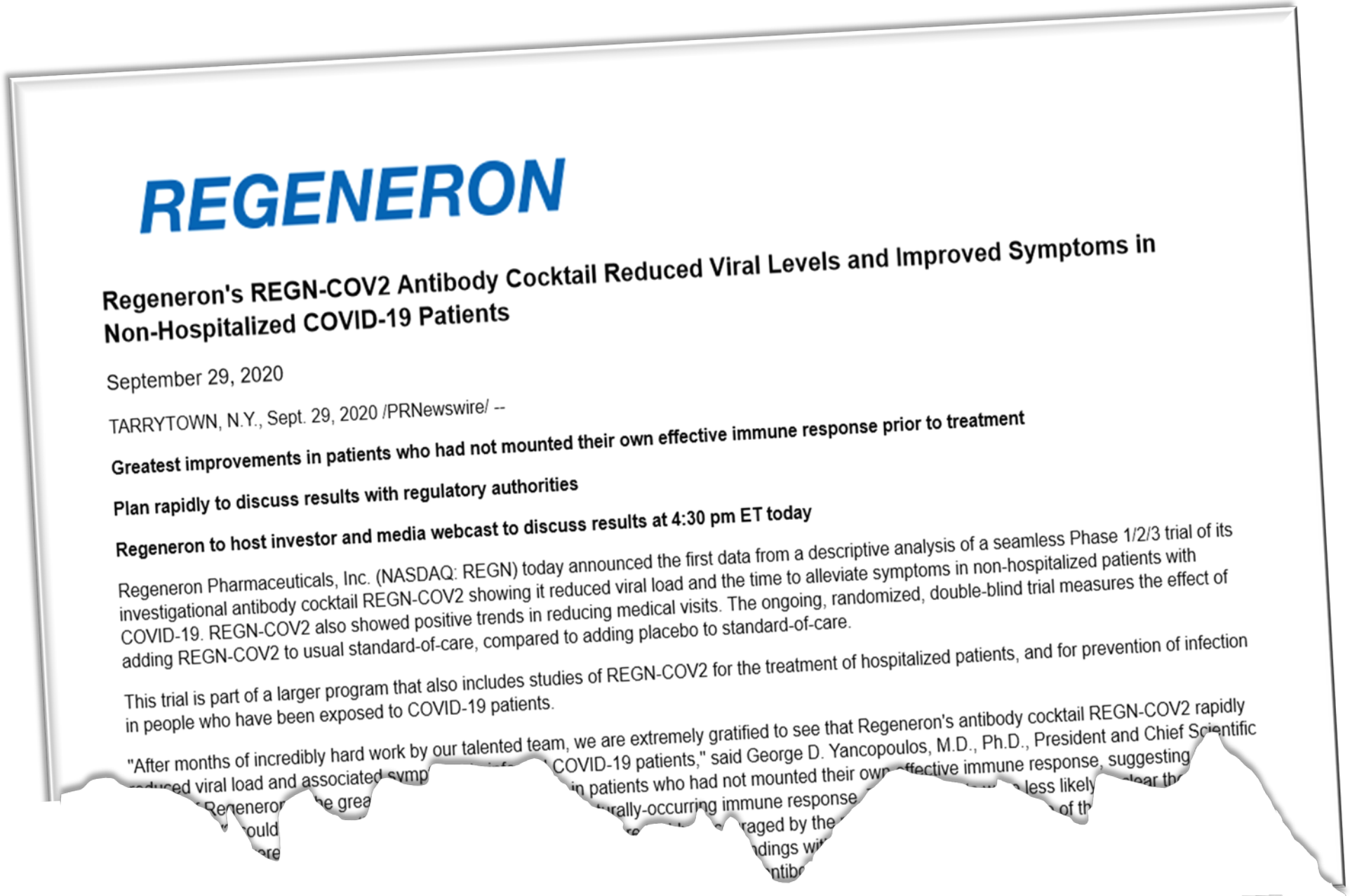


REGENERON

Regeneron's REGN-COV2 Antibody Cocktail Reduced Viral Levels and Improved Symptoms in Non-Hospitalized COVID-19 Patients

September 29, 2020

TARRYTOWN, N.Y., Sept. 29, 2020 /PRNewswire/ --

Greatest improvements in patients who had not mounted their own effective immune response prior to treatment

Plan rapidly to discuss results with regulatory authorities

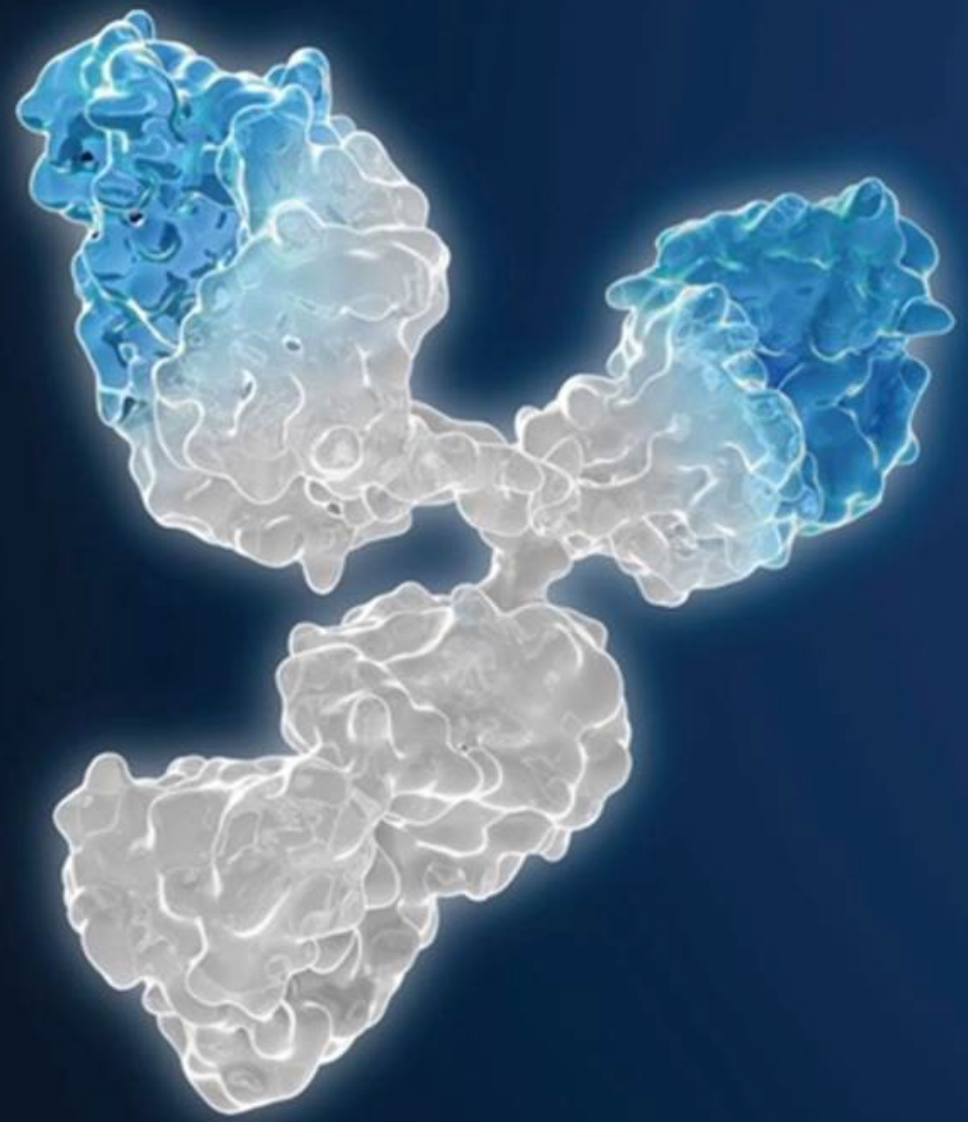
Regeneron to host investor and media webcast to discuss results at 4:30 pm ET today

Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) today announced the first data from a descriptive analysis of a seamless Phase 1/2/3 trial of its investigational antibody cocktail REGN-COV2 showing it reduced viral load and the time to alleviate symptoms in non-hospitalized patients with COVID-19. REGN-COV2 also showed positive trends in reducing medical visits. The ongoing, randomized, double-blind trial measures the effect of adding REGN-COV2 to usual standard-of-care, compared to adding placebo to standard-of-care.

This trial is part of a larger program that also includes studies of REGN-COV2 for the treatment of hospitalized patients, and for prevention of infection in people who have been exposed to COVID-19 patients.

"After months of incredibly hard work by our talented team, we are extremely gratified to see that Regeneron's antibody cocktail REGN-COV2 rapidly

PRNewswire. Tarrytown NY, September 29, 2020



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

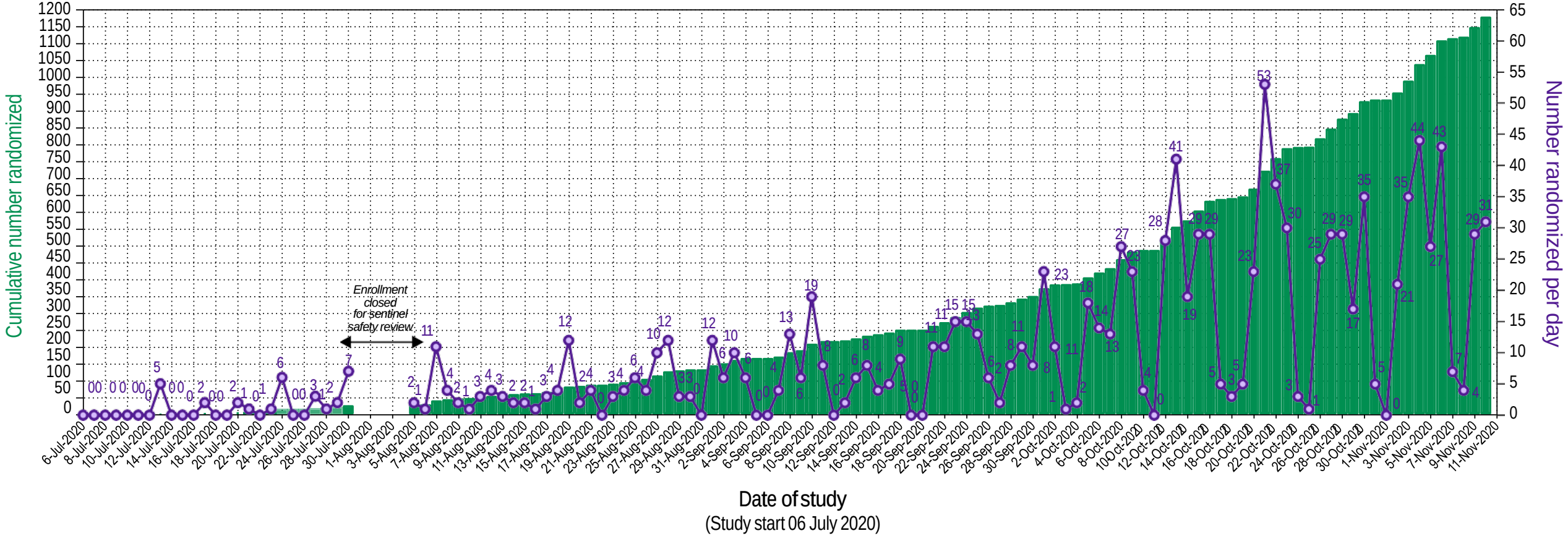
REGENERON

SCIENCE TO MEDICINE®

01 July 2020

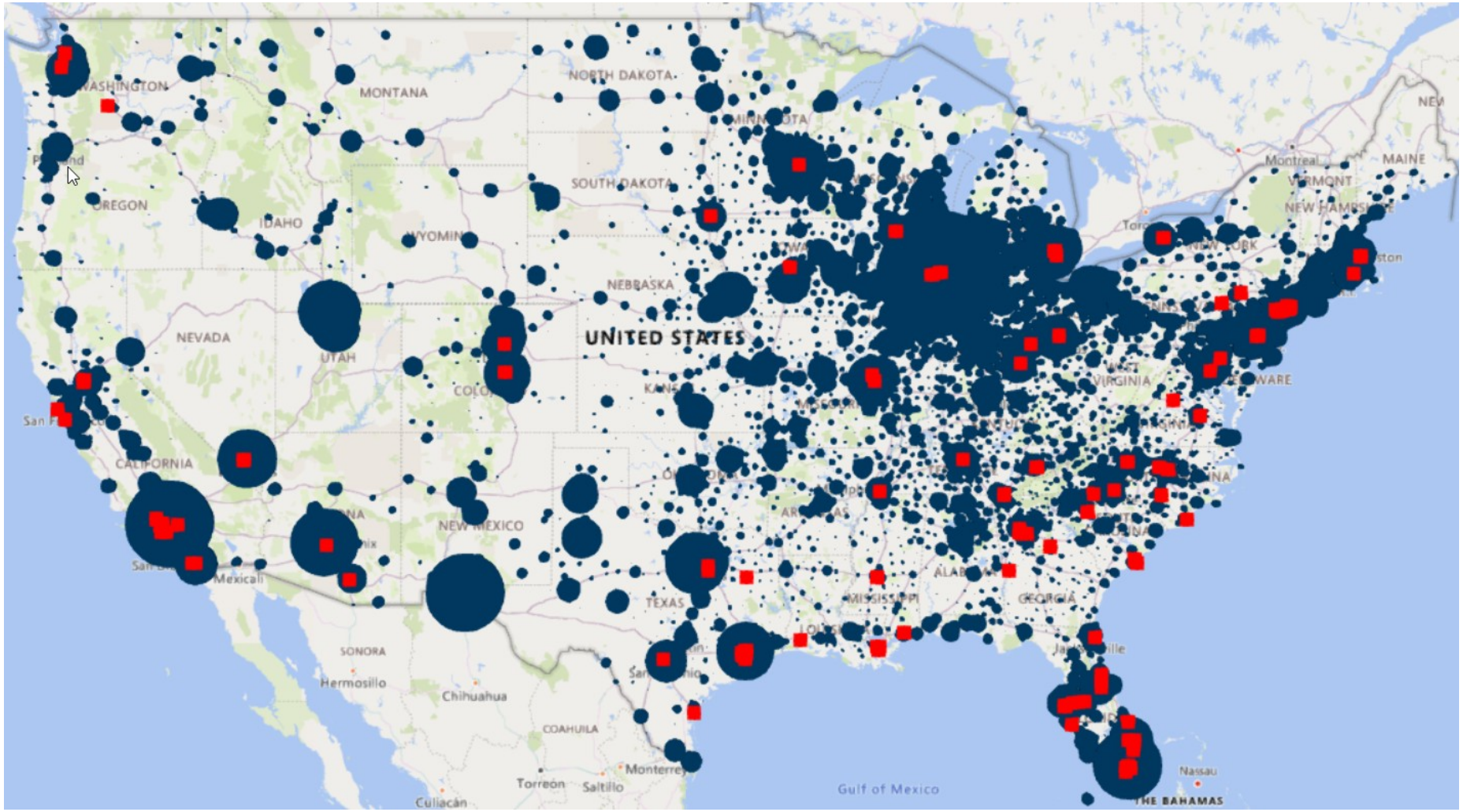
Enrollment up to 10 November 2020

(1182 enrolled; 127 total sites open for enrollment, including 19 CoVPN sites; 30 subjects enrolled at 5 CoVPN sites; 99 subjects enrolled at two sites in Romania and Moldova)



Note: 496 subjects have completed EAP (Visit 8, Day 29) as of 10 November 2020

Study active sites and cases throughout the United States



Red = Active sites
Blue = Columbia case count

Big Conclusions: November 19, 2021

- Behavior changes required to stop the spread of SARS-CoV-2 in the US have failed
- Entirely novel mRNA vaccines appear to prevent symptomatic COVID-19 infections

  -Modena and Pfizer will try to “roll 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 Bamlanivimab (LillY) , and is likely for a RGN combination
- Two NIH supported prophylaxis studies are enrolling subjects to 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 also 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. And we will face “endemic” and sporadic cases of COVID-19 as a new disease

Volunteers Needed For Vaccine and MaB Studies

https://www.coronavirusprevention network.org/