NIH Responses to COVID-19
Presentation to the 16th Meeting of the Clinical Center Research Hospital Board National Institutes of Health

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Clinical Director
Deputy Director for Clinical Research and Special Projects
NIAID, NIH
October 16, 2020

Outline of the Presentation

- Early Efforts
- Organizational structure
- Diagnostics
- Therapeutics and Treatment Guidelines
- Prevention


Doctors Dodd (Biostatistician) and Davey (Principal Investigator)
2019 David Sackett Award
Trial of the Year
Society for Clinical Trials

The New England Journal of Medicine

Established in 1812 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY

Published online July 17, 2020

Research in the Context of a Pandemic

HC Lane and AS Fauci

Scientifically robust and ethically sound clinical research remains the quickest and most efficient pathway to effective treatment and prevention strategies for patients with COVID-19.

The Washington Post

January 9, 2020

China Identifies New Strain of Coronavirus as Source of Pneumonia Outbreak

Early NIH Efforts in COVID-19

- Used the published SARS-CoV-2 sequences and obtained samples from the first US survivors to begin work on countermeasures (NIAID/VRC)
  - RNA vaccine (Moderna)
  - Monoclonal antibody (Lilly)
- Initiated an RCT of the most promising antiviral at the time (Remdesivir/Vekury™); ACTT-1 randomized controlled trial (NIAID/DMID)
- Participation in the WHO Mission to China

The US Journey Began January 20, 2020

- Jan. 20 – First US case diagnosed in recent traveler to Wuhan, China
- Jan. 20 – Diamond Princess departed Yokohama for a 14-day cruise with stops in China, Vietnam, and Taiwan
  - Jan. 25 – patient who disembarked in Hong Kong diagnosed
  - Feb. 3 – ship quarantined in Yokohama
  - Among 3711 passengers and crew
    - 712 (19%) became infected
      - 331 (47%) no initial Sx
      - 128 (18%) never had Sx
      - 14 (2%) died

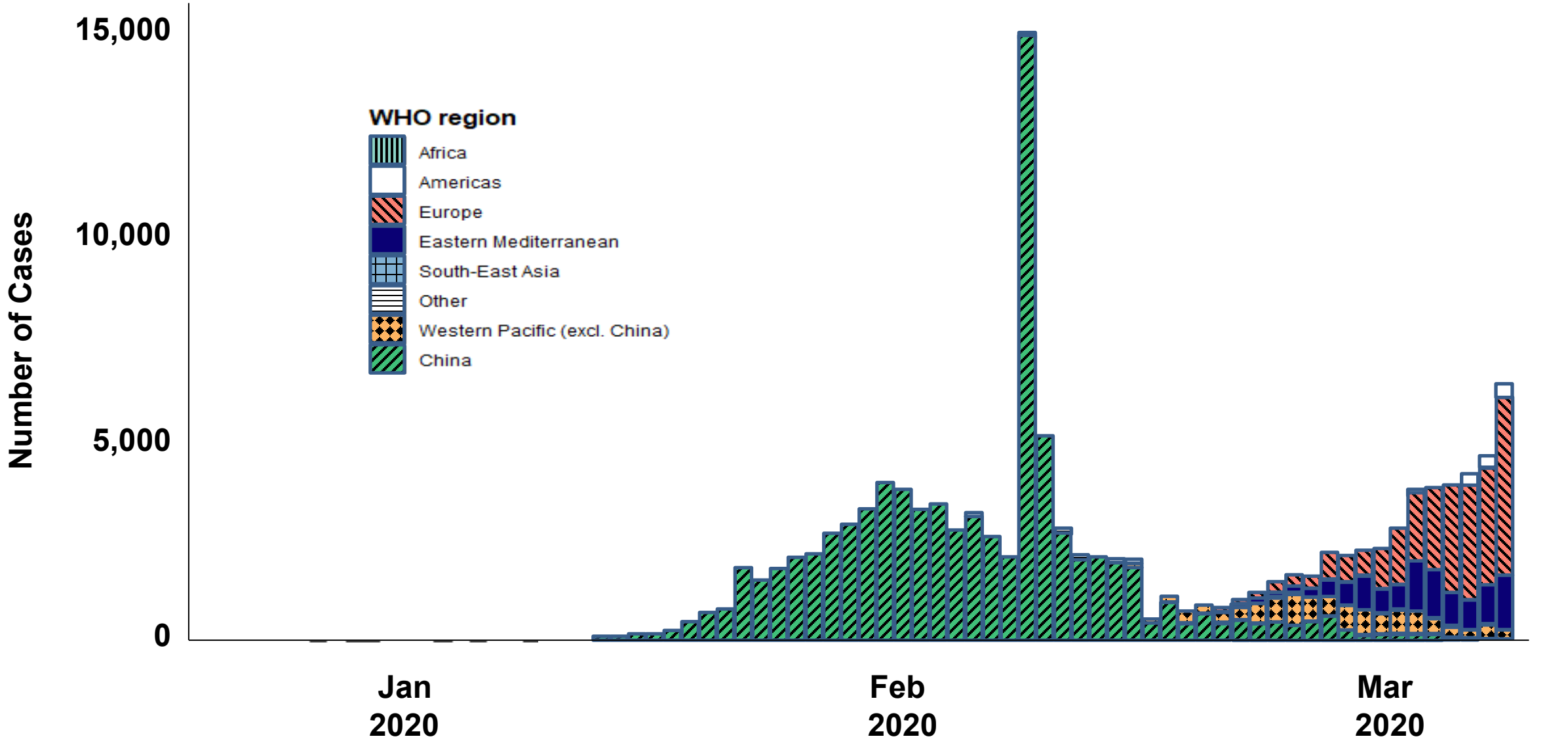
February 16-24: NIAID's Cliff Lane Serves as Member of WHO-China Joint Mission on COVID-19

- 25 experts from China, Germany, Japan, Korea, Nigeria, Russia, Singapore, United States, and WHO
- Mission headed by Bruce Aylward of WHO and Wannian Liang of the People's Republic of China
- Report published online Feb. 28, 2020, notes challenges with coordination of treatment research

Timeline of the COVID-19 Outbreak in China

- First diagnosed cases date from early December 2019
  - Some but not all linked to seafood market in Wuhan
- Betacoronavirus directly sequenced and cultured from a bronchoalveolar lavage on December 30
- Diagnostic tests developed within 2 weeks
- As of Feb. 20, there had been 75,465 confirmed cases
- At its peak, one fever clinic in Wuhan was seeing 500 patients/day in late January; 50/day by mid-February

Number of Confirmed Cases of COVID-19 Notified Under IHR or From Official Government Sources as of 12 Mar 6AM



Organization Structure of the USG Research Response From an NIH Perspective

- White House Task Force
- Operation Warp Speed
- Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership
- NIH plays a key and/or leadership role in all of these

January 29: White House Coronavirus Task Force Announced

Chair: VP Mike Pence
Response Coordinator: Deborah Birx

- Jerome Adams
- Alex Azar
- Stephen Biegun
- Robert Blair
- Ben Carson
- Francis Collins
- Ken Cuccinelli
- Kelvin Droegemeier
- Thomas Engels
- Anthony Fauci
- Joe Grogan
- Stephen Hahn
- Derek Kan
- Larry Kudlow
- Chris Liddell
- Steven Mnuchin
- Robert O'Brien
- Sonny Perdue
- Matthew Pottinger
- Robert Redfield
- Gene Scalia
- Joel Szabat

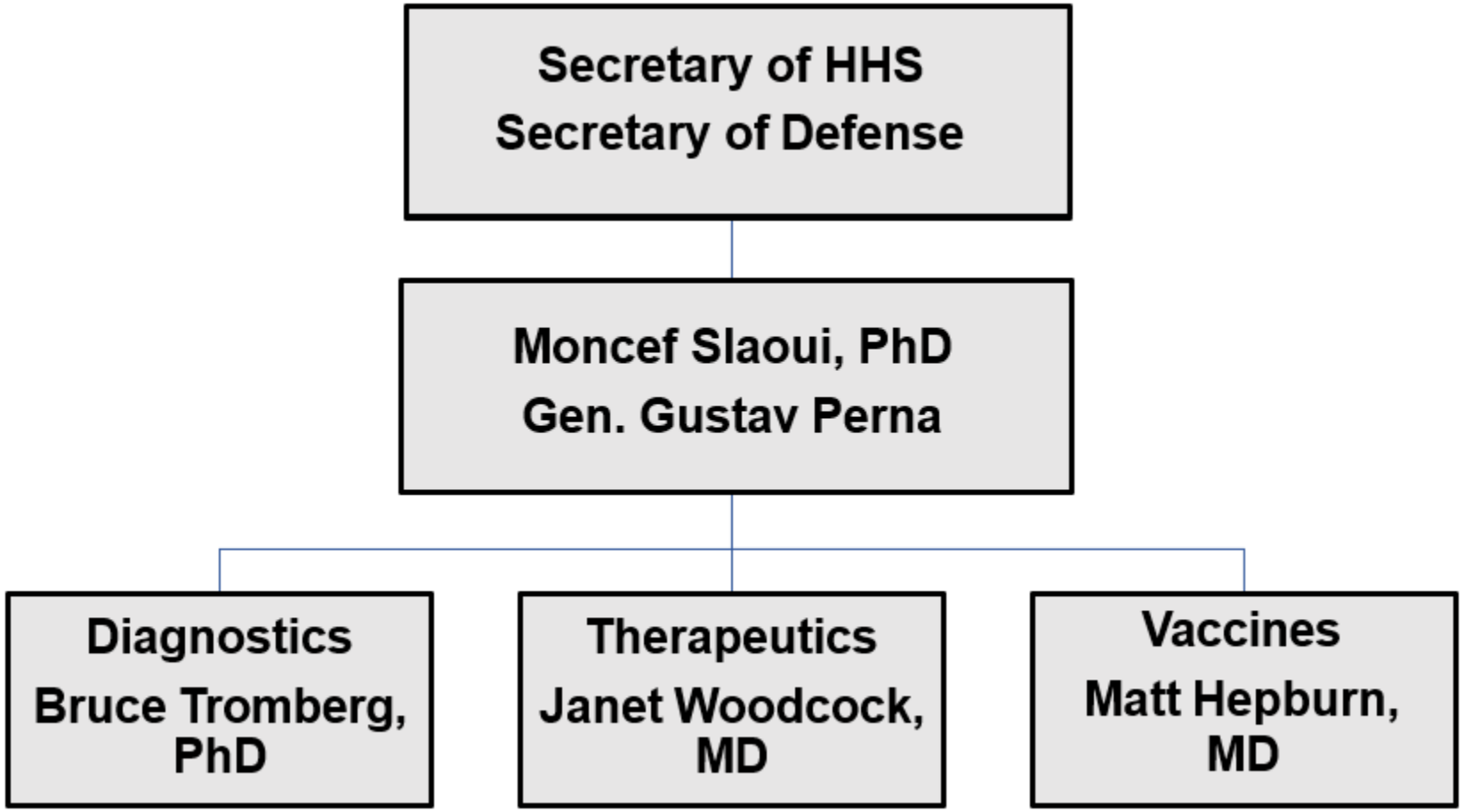
- Seema Verma
- Robert Wilkie

Health and Human Services
Press Release
May 15, 2020

Trump Administration Announces Framework and Leadership for 'Operation Warp Speed'

- National program to accelerate development, manufacturing, and distribution of COVID-19 vaccines, therapeutics, and diagnostics
- Public-private partnership between HHS (CDC, FDA, NIH, BARDA), DoD, other federal agencies, and private firms
- Chief Scientific Advisor: Moncef Slaoui, PhD
- Chief Operating Officer: General Gustave F. Perna

Leadership of Operation Warp Speed



National Institutes of Health
Turning Discovery Into Health

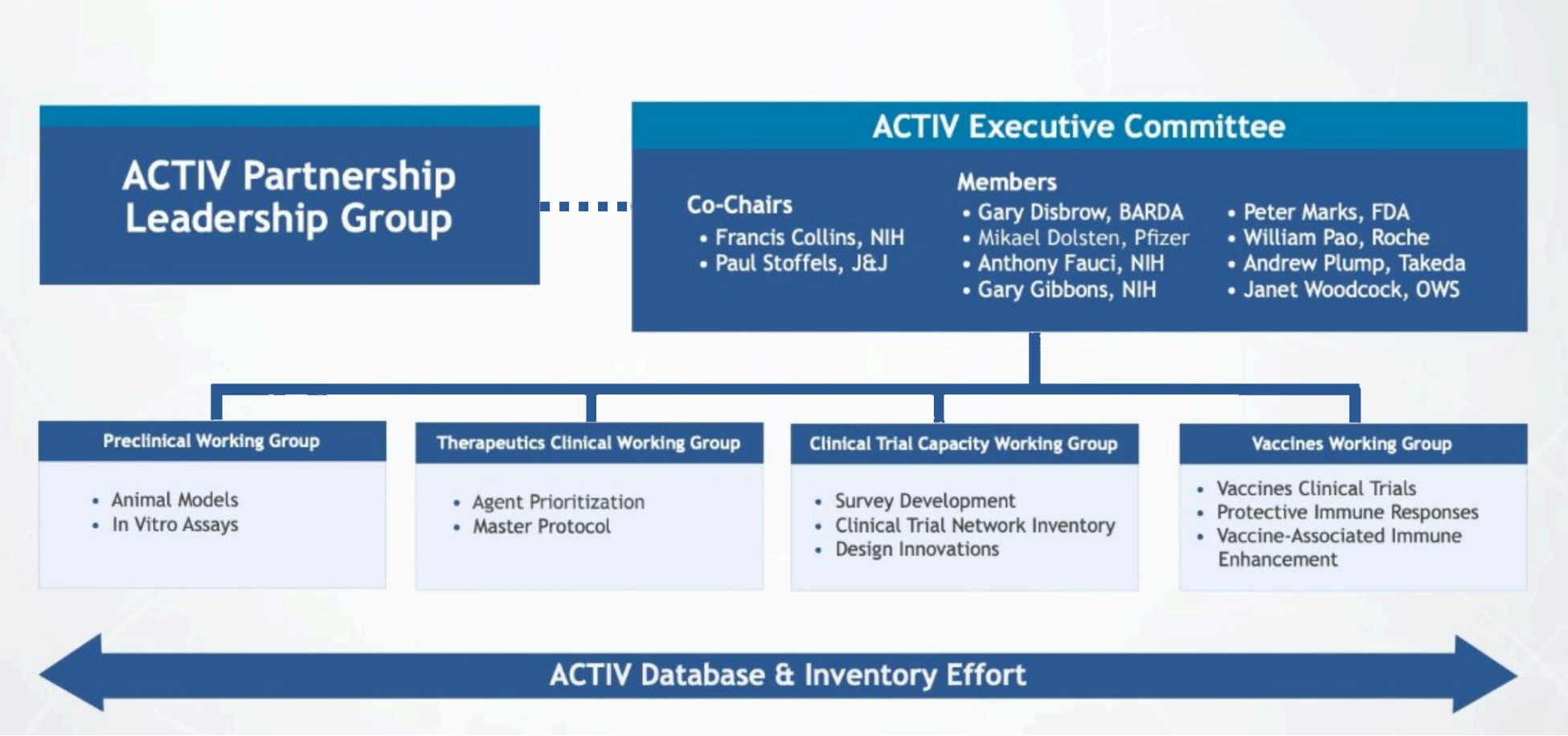
Friday, April 17, 2020

News Release

NIH to Launch Public-Private Partnership to Speed COVID-19 Vaccine and Treatment Options

- The Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) partnership will:
  - Standardize and share pre-clinical evaluation methods in an open forum
  - Prioritize and accelerate clinical evaluation of therapeutic candidates with near-term potential
  - Maximize clinical trial capacity and effectiveness
  - Advance vaccine development

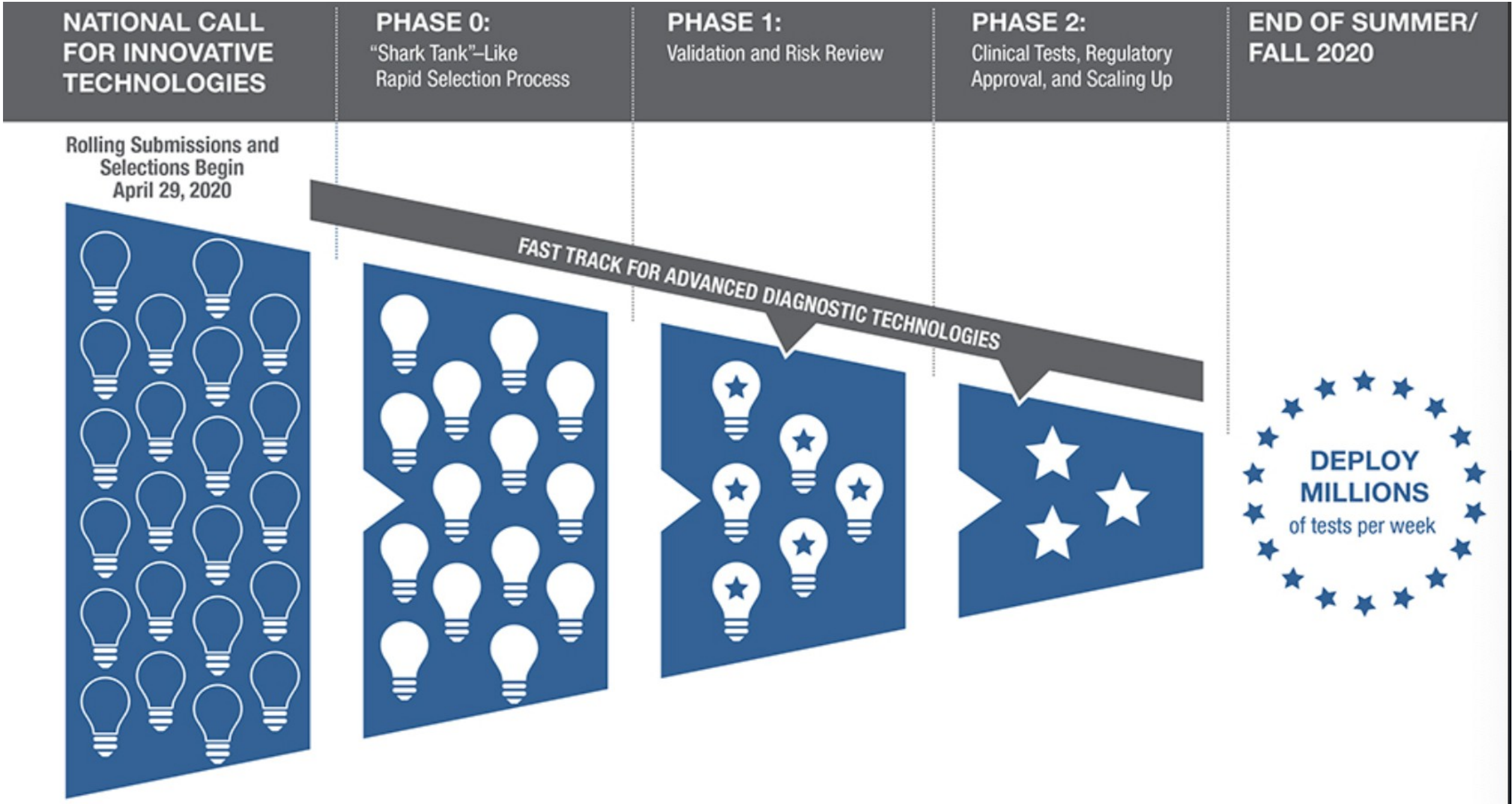
Structure of the Accelerating COVID-19 Therapeutic Interventions and Vaccines



NIH Role in Diagnostic Research

- Director, NIBIB, has lead for this aspect of Operation Warp Speed
- Rapid Acceleration of Diagnostics (RADx^{SM})
  - A way to fund innovative ideas for new COVID-19 testing
  - Looking or ways to obtain accurate, quick results
  - Testing must be inexpensive, user friendly, and widely accessible
  - Consists of 4 programs
    - RADx^{SM} x-Tech: development of new strategies, shark tank
    - RADx^{SM} -UP: develop testing strategies in real-world settings
    - RADx^{SM} Radical: nontraditional approaches (AI, biosensors, etc.)
    - RADx^{SM} Advanced Technology Platforms: increase capacity

NIH Rapid Acceleration of Diagnostics (RADx) Initiative for COVID-19



NIH Role in Therapeutic Research

- Extramural Programs
  - The Adaptive COVID-19 Treatment Trial (ACCT 1-3)
  - The Studies Supported by OWS/ACTIV
    - ACTIV 1-5
  - The Studies Associated with ACTIV
    - Convalescent Plasma
    - Immune immunoglobulin
- Intramural Programs
  - At least 7 protocols among 4 Institutes/Centers

The Adaptive COVID-19 Treatment Trial (ACTT; DMID/NIAID; John Beigel, PI)

- A randomized, controlled trial with an adaptive platform
- Eligibility: Adult patients hospitalized with COVID-19 and evidence of pulmonary disease
- Primary Endpoint: Time to recovery (ordinal scale 1, 2 or 3)
- Timeline: Study opened Feb. 21, 2020
- Has completed first two versions; enrolling into the third
  - ACTT-1: Standard of care vs. remdesivir
  - ACTT-2: Remdesivir vs. remdesivir + baricitinib
  - ACTT-3: Remdesivir vs. remdesivir + interferon-β

The New England Journal of Medicine

Established in 1812, THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY

published online October 8, 2020

Remdesivir for the Treatment of Covid-19 – Final Report

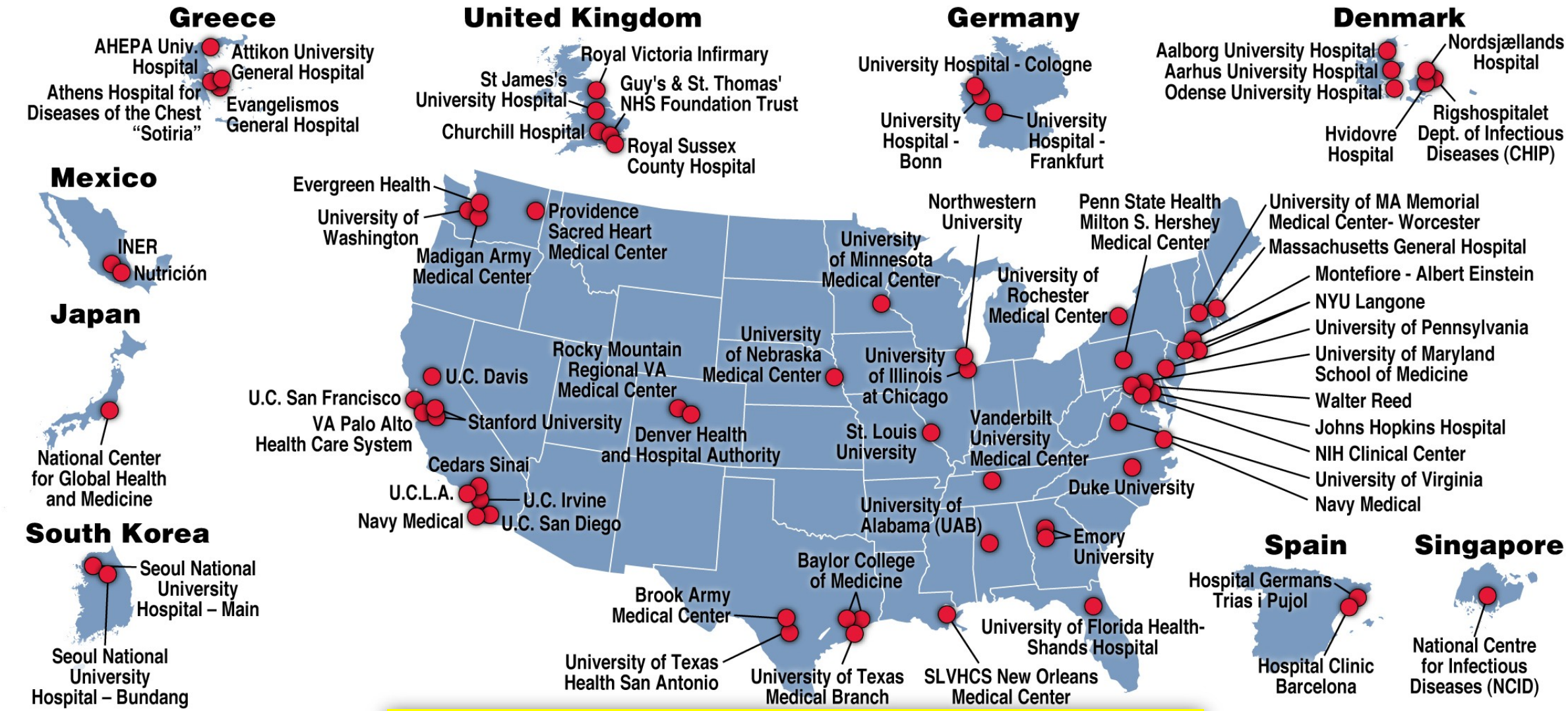
JH Beigel, HC Lane et al. for the ACTT-1 Study Group Members

Hospitalized patients on remdesivir recovered more quickly than those on placebo (median 10 days vs 15 days, $p<0.001$)

A trend toward decreased mortality: hazard ratio = 0.73 (95% CI: 0.52-1.03)

1,062 patients from 10 countries (U.S., Europe, and Asia)

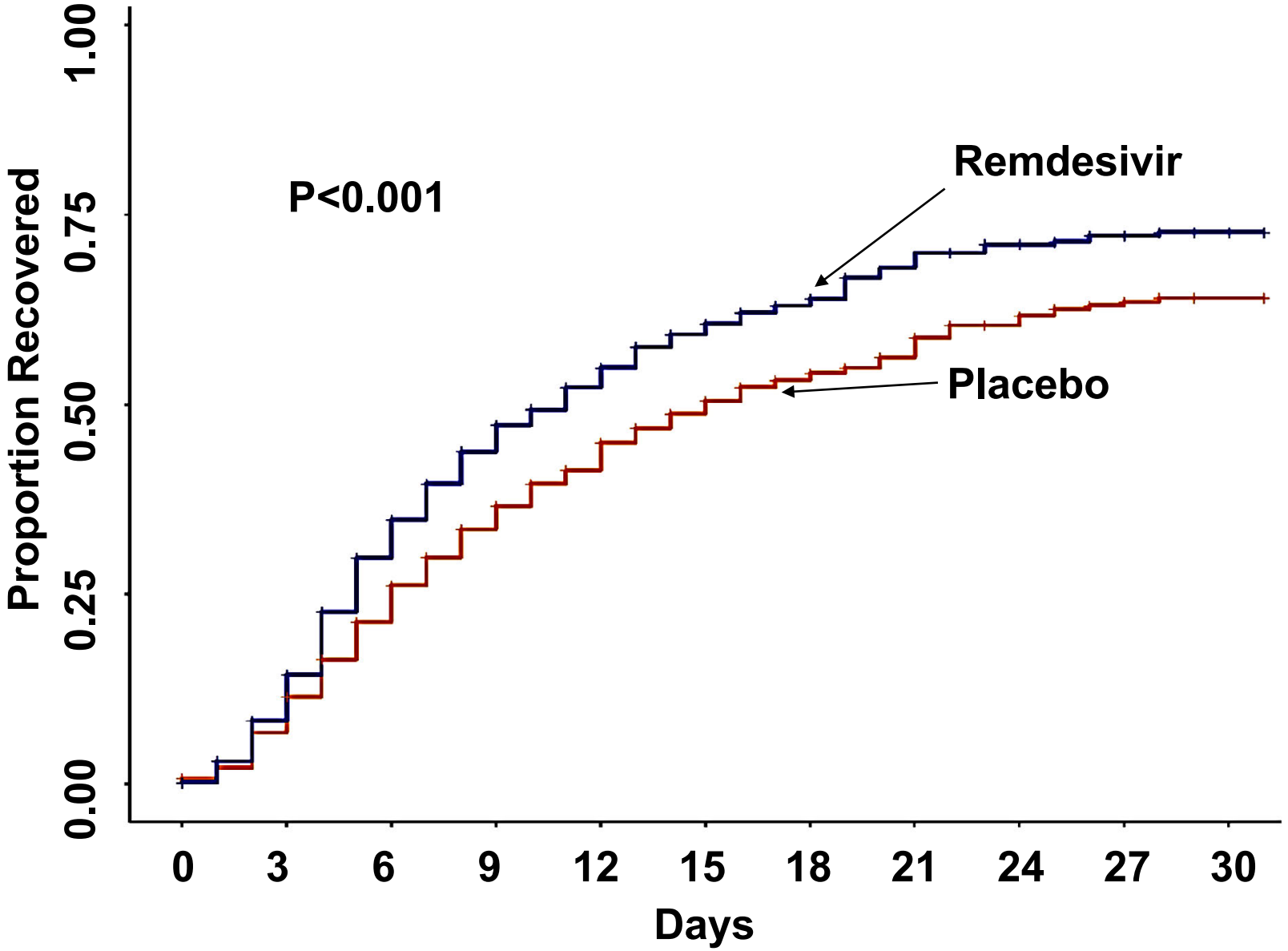
NIAID Adaptive Randomized, Controlled Treatment Trial for COVID-19



1,062 enrollees at trial close, 4/19/2020

AS Fauci/NIAID

Time to Recovery* for Remdesivir and Placebo Arms



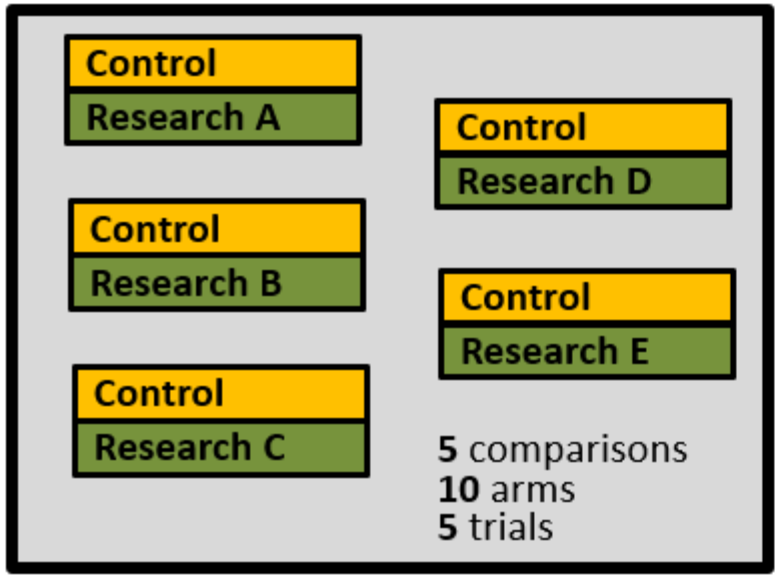
Ordinal Scale	Definition
1*	Not hospitalized, full activity
2*	Not hospitalized, limited activity
3*	Hospitalized, non-medical
4	Hospitalized, not requiring O_2
5	Hospitalized, requiring O_2
6	High-flow O_2 or non-invasive vent.
7	Mechanical vent. or ECMO
8	Death

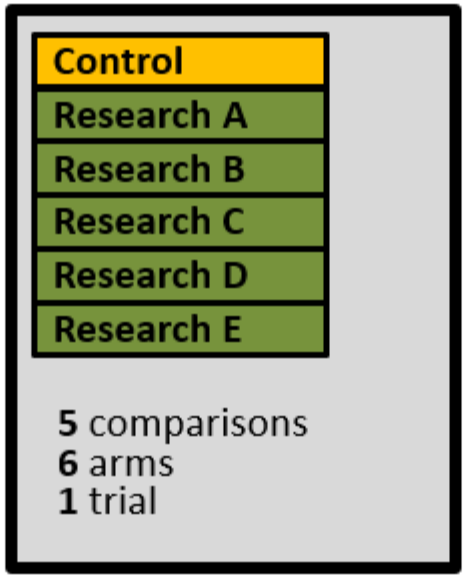
JH Beigel et al. N Engl J Med 2020
DOI: 10.1056/NEJMoa2007764

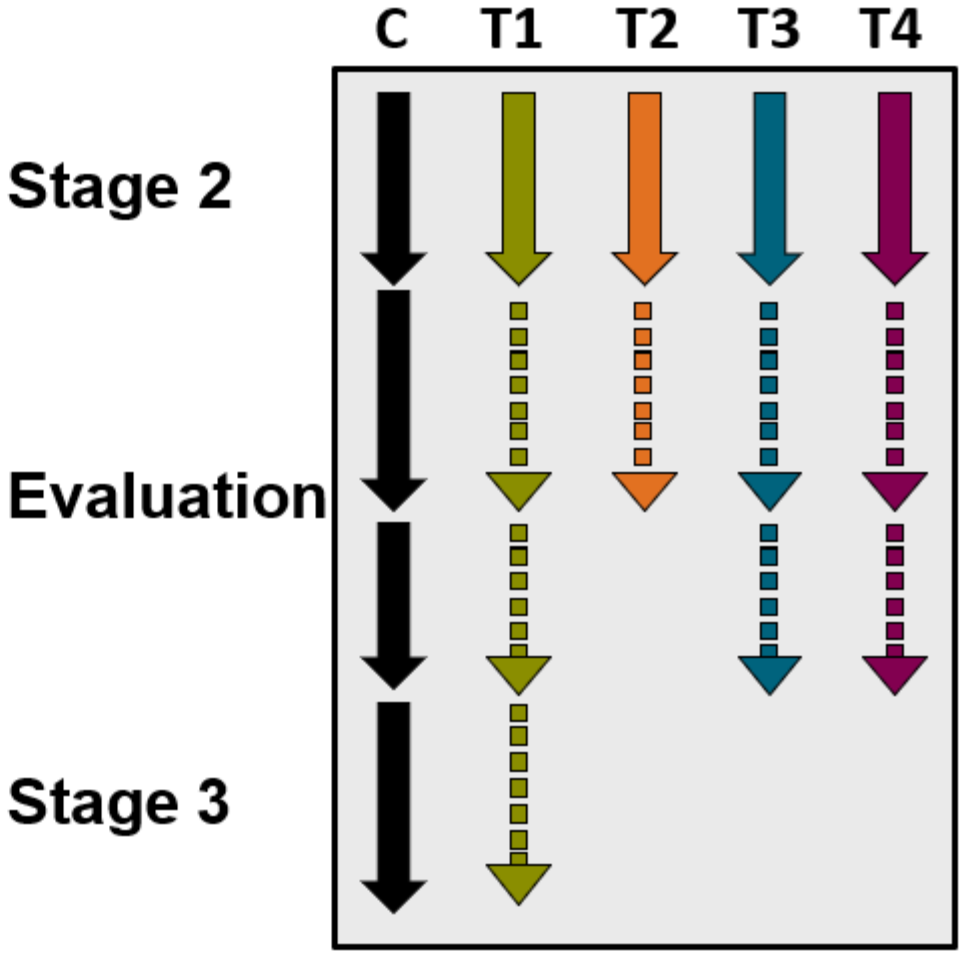
Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Trials

- ACTIV-1 (NCATS): Immunomodulators in hospitalized patients
  - Currently placebo vs. abatacept, cenicriviroc or infliximab
- ACTIV-2 (DAIDS/NIAID): Adaptive trial in outpatients
  - Currently placebo vs. Lilly MoAb CoV555
- ACTIV-3 (DCR/NIAID): Adaptive trial in hospitalized patients
  - Currently placebo vs. Lilly MoAb CoV555
- ACTIV-4 (NHLBI): A series of 3 trials studying different anti-coagulation strategies in outpatients, inpatients and discharged patients
- ACTIV-5 (NIAID): Several different interventions looking for a big effect to then take into one of the other ACTT or ACTIV platforms

Therapeutics for Inpatients with COVID-19 (TICO; INSIGHT 014; ACTIV-3) A Multi-Arm, Multi-Stage Trial

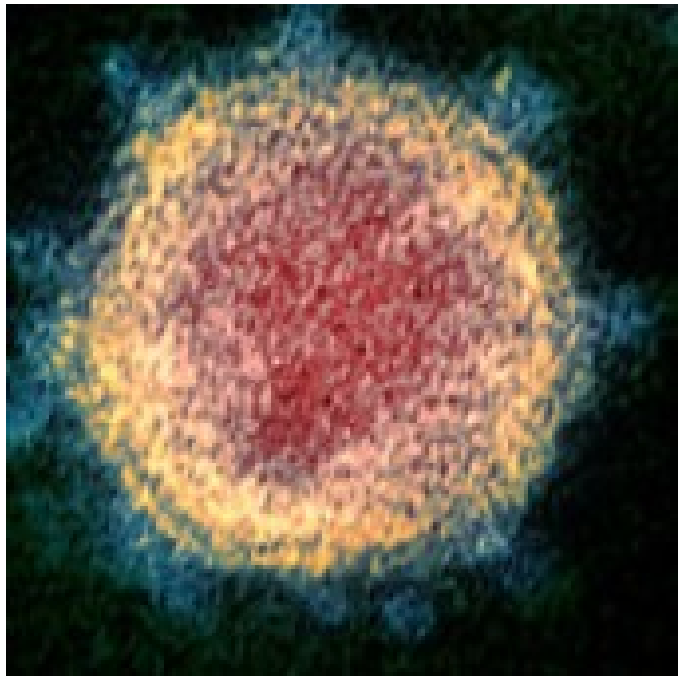


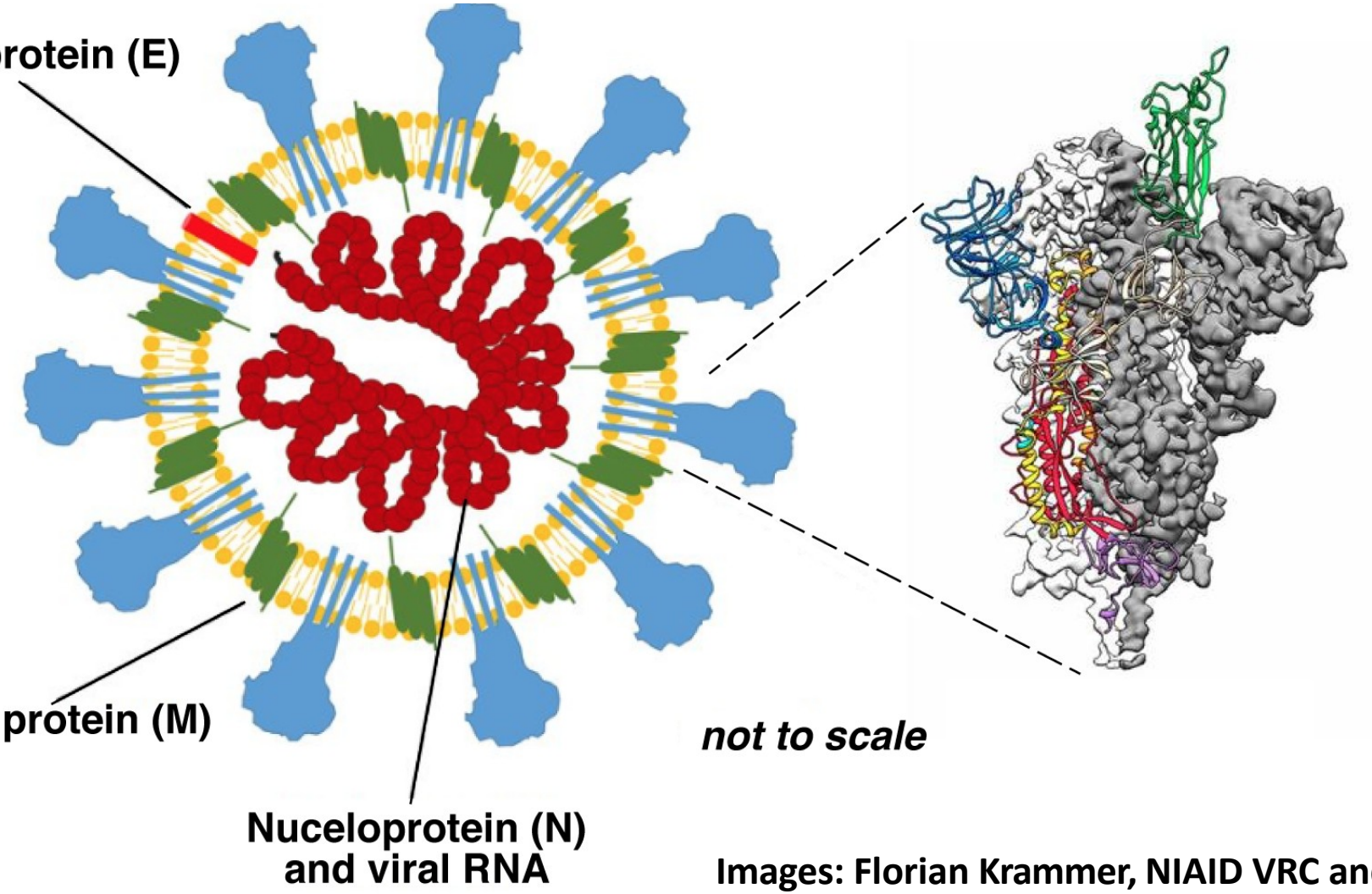




Mahesh Parmar, UK MRC, UCL

SARS-CoV-2 and the Surface Spike Protein





Images: Florian Krammer, NIAID VRC and RML

SARS-CoV-2 Spike Protein mAbs

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 in hospitalized patients June 2020; NIAID/Regeneron trial in July 2020
AbCellera Lilly First in Human *May* 2020	One or two SARS-CoV-2-specific mAbs, convalescent plasma First in human hospitalized patients, May 2020; NIAID/Lilly clinical trial late June 2020
VIR First in Human July 2020	Vir mAb, S309, isolated from a SARS1 patient, cross-reacts with SARS-CoV-2 Collaboration under active discussion for nursing home trial
AstraZeneca First in Human *July* 2020	AZ has selected a 2 mAb combination against the SARS-CoV-2 spike protein Plan Phase I single dose escalation study in normal volunteers, August 2020 (DARPA) Collaboration under active discussion (BARDA funding sought for Phase 3 trial)
The Rockefeller University 1901 SCIENCE FOR THE BENEFIT OF HUMANITY First in Human Fall 2020	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

Slide Courtesy of Mary Marovich, NIAI

Lilly Anti-SARS-CoV-2 Antibodies LY-CoV555 and LY-CoV016 (1)

- Bind complementary regions of the SARS-CoV-2 spike protein
- Monotherapy with LY-CoV555 (NIAID/VRC) - Sept 16 Lilly release
  - Outpatients with mild to moderate COVID randomized to 1 of 3 doses of antibody (700, 2800, or 7000 mg) or to placebo
  - Statistically significant reduction in NP swab viral load compared to placebo at day 11 in 1 of the 3 dose groups
  - COVID-19-related hospitalizations or ER visits in 5/302 (1.7%) in pooled antibody groups vs. 9/150 (6%) in placebo
  - Rate of resistant variants higher in treated patients (8 vs. 6%)

Lilly Anti-SARS-CoV-2 Antibodies LY-CoV555 and LY-CoV016 (2)

- Combination therapy added LY-CoV016 (Chin. Acad. Sci.)
- Preliminary results from October 7 Lilly press release
  - Outpatients with mild to moderate COVID-19 randomized to combination therapy (n=112) or placebo (n=156)
  - Reduction in NP swab viral load at day 11 (p=0.01)
  - Time-weighted change in symptom score at day 11 (p=0.009)
  - Lower rates of COVID-related hospitalizations and ER visits in antibody treated group (p=0.049)

ACTIV-Associated Trials

- Three randomized, controlled trials of convalescent plasma
  - Passive Immunity Trial Of the Nation for COVID-19 (PassItOn; n=500 inpatients; Dolly Parton/NCATS; PI = Todd Rice, Vanderbilt)
  - Convalescent Plasma to Limit COVID-19 Complications in Hospitalized Patients (n=300 inpatients; NCATS; PI = Mila Ortigoza, NYU Langone Health)
  - Convalescent Plasma in Outpatients With COVID-19 (C3PO; n=600; NHLBI; SIREN [Emergency Room] Network)
- Two randomized, controlled trials of immune immunoglobulin
  - INSIGHT 013 (n=500 inpatients; NIAID; PI = Mark Polizotto)
  - INSIGHT 012 (n=1000 outpatients; NIAID; PI pending)

Intramural Therapeutic Studies in COVID-19

- Clinical Center
  - Plasma collection
- NCI
  - Study of tocilizumab
  - Study of acalabrutinib
- NHLBI
  - Study of fostamatinib
  - EAP for convalescent plasma infusion
- NIAID
  - Participation in the ACTT series of studies
  - Study of zotatifin
  - Study of long-acting IL-7

Additional Intramural Clinical Studies in COVID-19 (Overall 28 Protocols; 12 ICs)

- Clinical Center
  - Saliva vs. NP swab
  - Pathogenesis
- NCI
  - Pathogenesis
- NEI
  - Biobank
  - Pathogenesis
- NHGRI
  - Genomics
  - Pathogenesis
- NIAID
  - 2 Serosurveys
  - Specimen collection / biobank
  - Phase 1 vaccine
  - Long-term follow-up
  - Pathogenesis
- NIDCR
  - Pathogenesis
- NIDDK
  - Pathogenesis
- NIEHS
  - Serosurvey
  - Observational cohort
- NIMH
  - Mental Health Response
- NINDS
  - Observational Cohort
- NIAAA
  - Observational Cohort
- NHLBI
  - Markers of thrombosis

National Institutes of Health
Turning Discovery Into Health

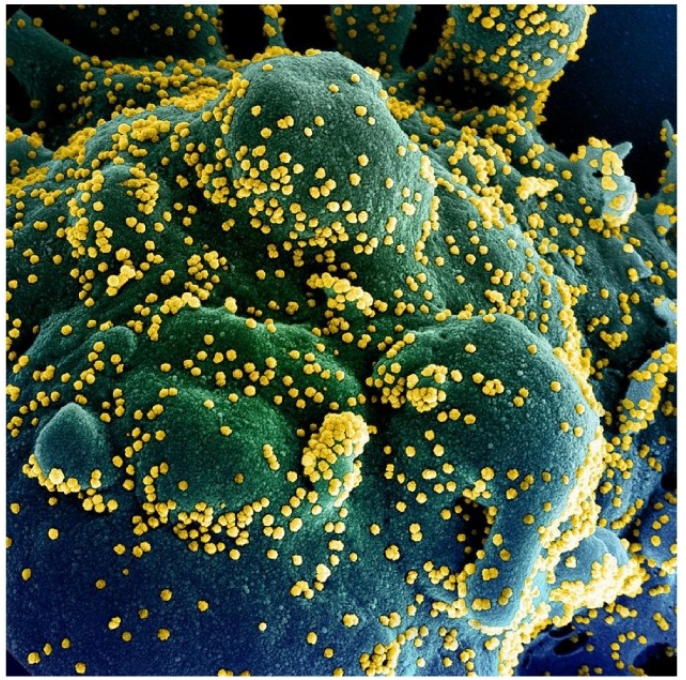
Tuesday, April 21, 2020

News Release

Expert U.S. Panel Develops NIH Treatment Guidelines for COVID-19

"Living document" expected to be updated often as new clinical data accrue

Covid19treatmentguidelines.nih.gov



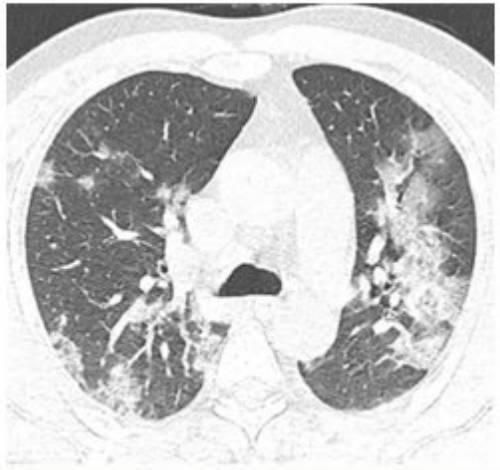
NIH COVID-19 Treatment Guidelines

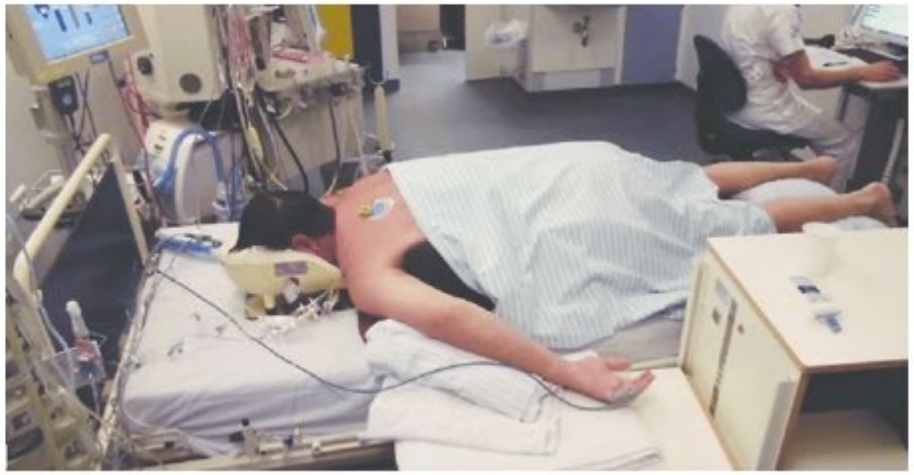
- March 20 – charge from HHS to establish a COVID-19 Management Guidelines Panel
- March 21 – first meeting of Panel Leadership
- March 23 – formal letters of invitation from Dr. Fauci
- March 24 – first meeting of Panel
- April 5/6 – final review and approval of first version
- April 21 – first version released with 1 million views the first week; 5 updates, 4.8 million page views since

Different Stages of COVID-19 Illness

COVID-19+ Disease Progression →

No Symptoms → Outpatient, Mild Symptoms → Inpatient, No Oxygen → Inpatient, Low-flow Oxygen → Inpatient, High-flow Oxygen → Mechanical Ventilation





Anti-viral Interventions

Immunomodulatory interventions

Some Key Recommendations from the Guidelines Panel

- The Panel recommends against the use of chloroquine or hydroxychloroquine for the treatment of COVID-19 in hospitalized patients (AI)
- The Panel recommends remdesivir for 5 days or until hospital discharge, for patients who require supplemental oxygen but not those who require high-flow oxygen or mechanical ventilation (AI)
- The Panel recommends dexamethasone 6 mg per day for up to 10 days or until hospital discharge, for the treatment of COVID-19 in hospitalized patients who are mechanically ventilated (AI)
- There are insufficient data to recommend either for or against the use of convalescent plasma for the treatment of COVID-19

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS *Recommendations are listed in order of preference in each category below; However, all options are considered acceptable.*
Not Hospitalized **Or** **Hospitalized but Does Not Require Supplemental Oxygen**	No specific antiviral or immunomodulatory therapy recommended The Panel **recommends against** the use of **dexamethasone (AI)** See the Remdesivir section for a discussion of the data on using this drug in hospitalized patients with moderate COVID-19.
Hospitalized and Requires Supplemental Oxygen (but Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)	**Remdesivir** 200mg IV for one day, followed by remdesivir 100mg IV once daily for 4 days or until hospital discharge, whichever comes first **(AI)** —or— **Remdesivir** (dose and duration as above) plus **dexamethasone** 6mg IV or PO for up to 10 days or until hospital discharge, whichever comes first **(BIII)** If **remdesivir** cannot be used, **dexamethasone** may be used instead **(BIII)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	**Dexamethasone** plus **remdesivir** at the doses and durations discussed above **(AIII)** —or— **Dexamethasone** at the dose and duration discussed above **(AI)**
Hospitalized and Requires Invasive Mechanical Ventilation or ECMO	**Dexamethasone** all the dose and duration discussed above (AI) —or— **Dexamethasone** plus **remdesivir** for patients who have recently been intubated at the doses and durations discussed above **(CIII)**

Research to Prevent COVID-19

- Monoclonal antibodies for prophylaxis (Myron Cohen, PI)
  - Nursing homes
  - Meat-packing industry
- Vaccines (Larry Corey, PI)
  - Multiple candidates being evaluated
  - Separate trials, “harmonized” designs
  - INDs held by the companies
  - Sites from the COVID-19 prevention network and CROs
  - Single phase 3 DSMB for all US trials except Pfizer
  - Four products have entered phase 3

National Institute of Allergy and Infectious Diseases

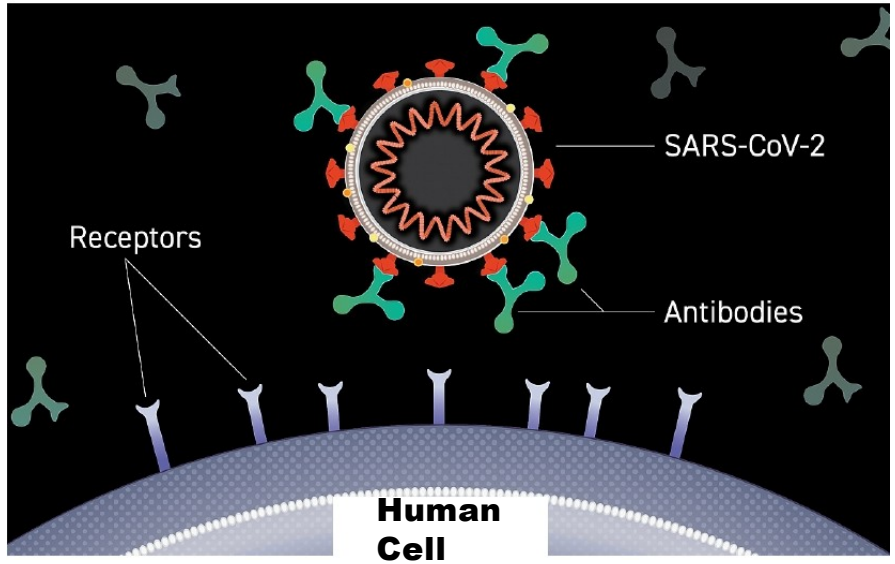
August 10, 2020

News Release

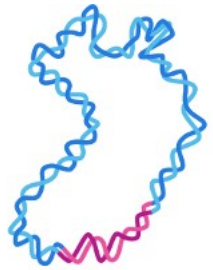
Clinical Trials of Monoclonal Antibodies to Prevent COVID-19 Now Enrolling

Two **Phase** 3, randomized, placebo-controlled clinical trials

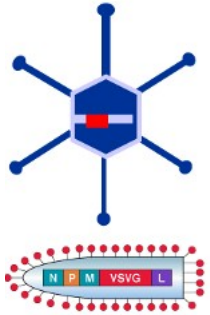
- Regeneron double-mAb **combination REGN-COV-2;** n=2,000
- Eli **Lilly/AbCellera mAb LY-CoV555; n=2,400**



Three Types of Approaches Being Pursued for a COVID-19 Vaccine

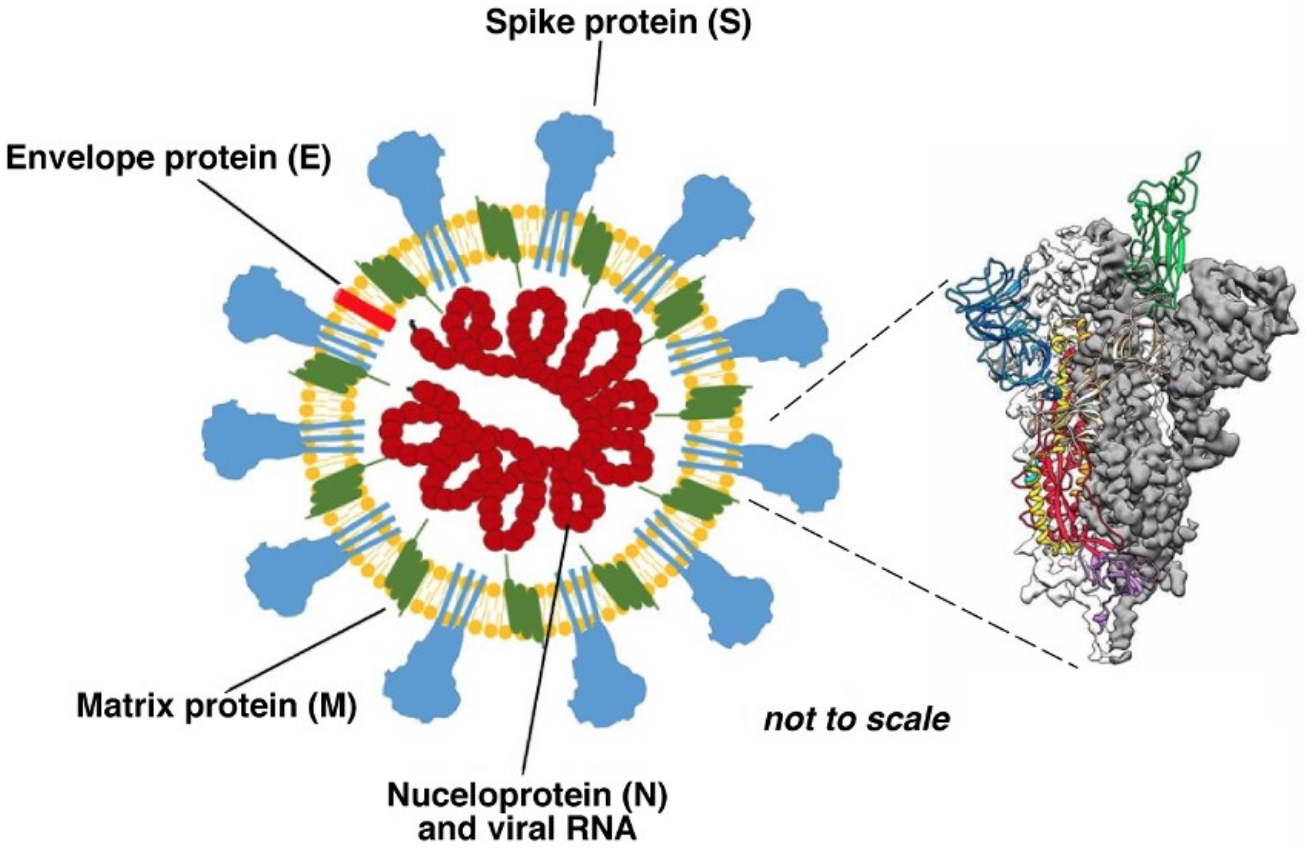


Genetic immunization (DNA and RNA vaccines)



Viral vector

Recombinant protein

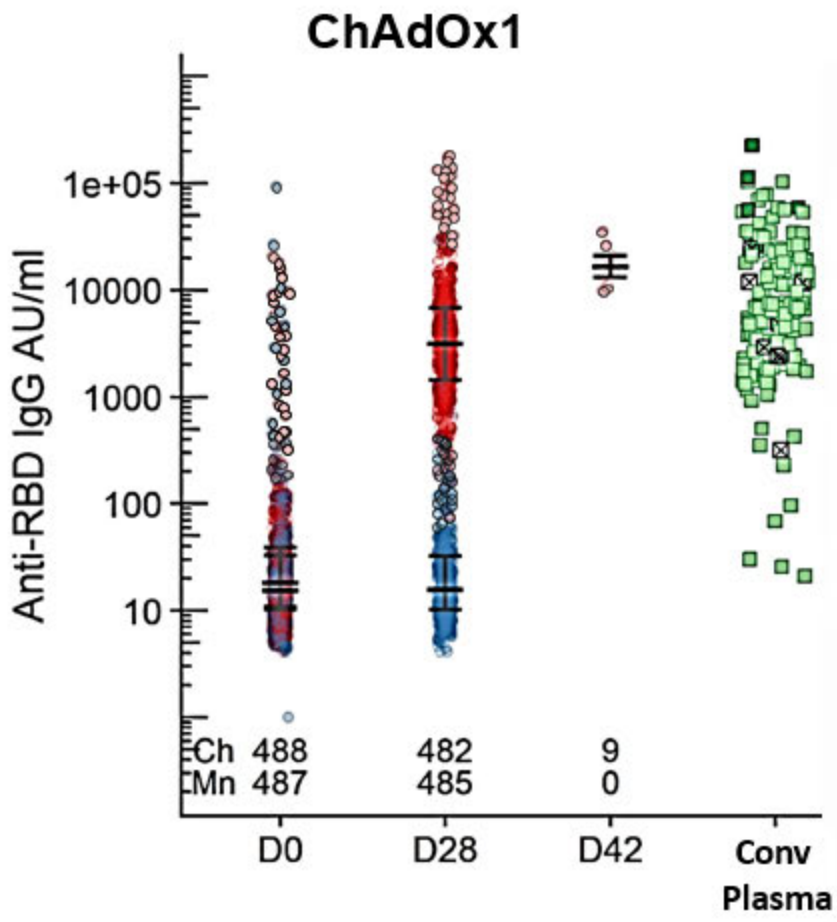


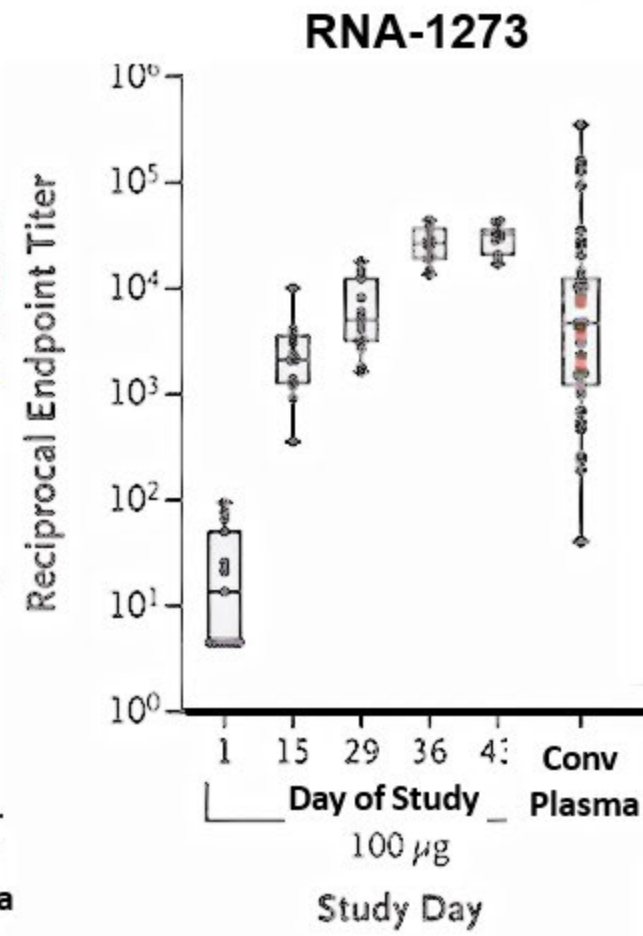
Images: Florian Krammer; NIAID VRC

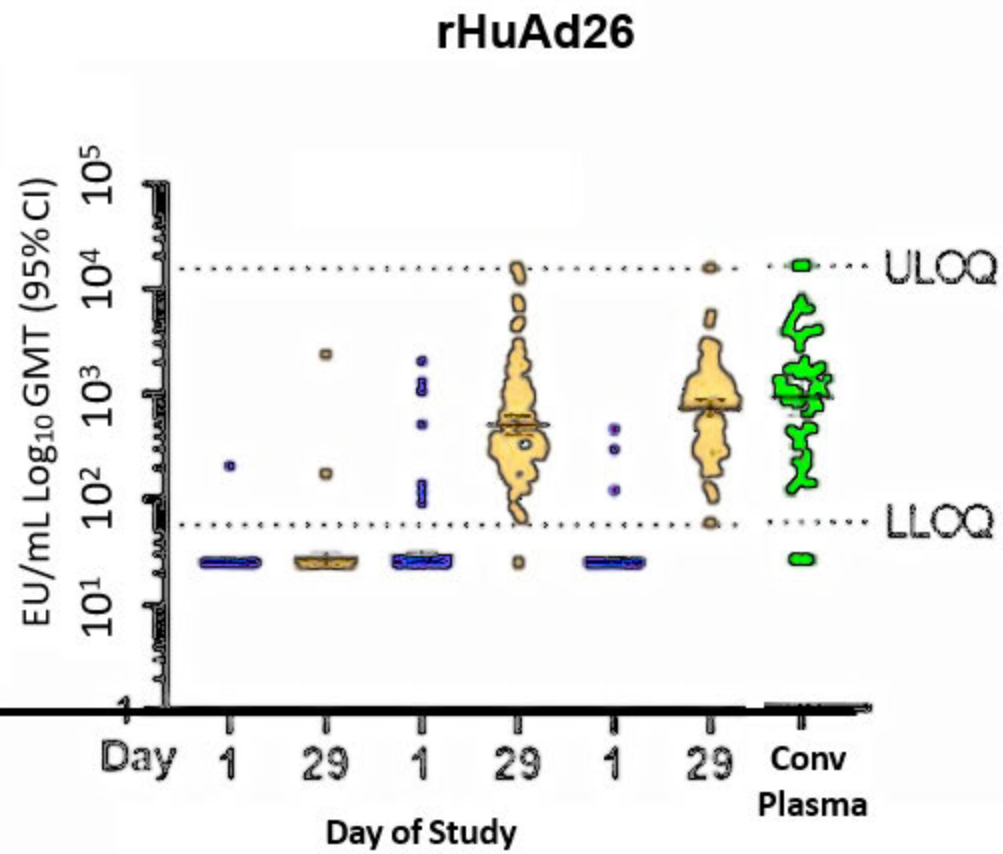
Selected COVID-19 Vaccine Candidates

Platform	Developer	Phase 1/2	Phase 2/3
Nucleic acid	moderna	Enrolled	Ongoing
	BIONTECH	Enrolled	Ongoing
Viral vector	UNIVERSITY OF OXFORD AstraZeneca	Enrolled	Ongoing
	janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson	Ongoing	Ongoing
	MERCK	Ongoing	—
Protein subunit	NOVAVAX Creating Tomorrow's Vaccines Today	Ongoing	Ongoing
	gsk SANOFI	Ongoing	—

Antibody Titers from Phase I trials of AstraZeneca ChAdOx1, Moderna RNA-1273 and JnJ rHuAd26







FDA Guidance for Emergency Use Authorization for a COVID-19 Vaccine

- Based on the totality of scientific evidence available, including data from adequate and well-controlled trials, if available, it is reasonable to believe that the product may be effective to prevent, diagnose, or treat such serious or life-threatening disease or condition that can be caused by SARS-CoV-2 (section 564 of the FD&C Act (21 U.S.C. 360bbb-3)). Phase 3 findings to support an EUA would need to include:
  - A point estimate of efficacy of at least 50%
  - A lower bound confidence interval of >30%
  - A median follow-up duration of at least 2 months
  - A total of 5 more cases of severe disease in the placebo group
  - Safety data in patients with prior SARS-CoV-2 infection

Comparison of "Harmonized" Phase III Vaccine Protocols

	Pfizer (RNA)	Moderna (RNA)	AstraZeneca (rChAdOx1)	Janssen (rHuAd26)
Primary Endpoint	Symptomatic COVID-19	Symptomatic COVID-19	Symptomatic COVID-19	Moderate-severe COVID-19
Sample Size	44,000	30,000	30,000	60,000
Efficacy Target (95% CI)	60% (30%)	60% (30%)	50% (30%)	60% (30%)
Number of Events for 90% Power	164	151	150	154
Number of Interim Analyses	4	2	1	Weekly after 1st
Statistical Method for Interim Analyses	Pocock	O'Brien-Fleming	O'Brien-Fleming	Modified O'Brien-Fleming
Number of Events at 1st Interim Analysis	32	53	75	50% at > 2 mos F/U; ≥ 20 cases (5 severe)

Summary

- A large research effort has been launched across the US government to study the pathogenesis, diagnosis, treatment and prevention of SARS-CoV-2 infection and COVID-19.
- NIH is playing a major role in this effort from both policy and operational perspectives.
- Early successes include demonstration of the clinical efficacy of remdesivir, launch of coordinated therapeutic and diagnostic research portfolios and involvement in the launch of 3 of the 4 ongoing phase 3 vaccine trials.
- By working to keep these efforts coordinated and setting clear priorities, it is hoped that the most effective countermeasures will get to the greatest number of people in the shortest period of time.