The NIH Response to COVID-19: An Update

Presentation to the 17th Meeting of the Clinical Center Research Hospital Board
National Institutes of Health

H. Clifford Lane, M.D.
Clinical Director and Deputy Director for Clinical Research and Special Projects

NIAID, NIH
April 23, 2021

Outline of the Presentation:

- Updates from the prior presentation on:
  - Organizational structure
  - Diagnostics
  - Therapeutics
  - Prevention
  - Treatment Guidelines

Daily Change in COVID-19 Cases, U.S.

January 22, 2020–April 14, 2021

TOTAL Cases Reported Since 1/22/20

31,231,869

NEW Cases Reported to CDC on 4/14/21

73,622

Change in 7-Day Case Average

+8.1%

Current 7-Day Case Average (4/8/21–4/14/21)

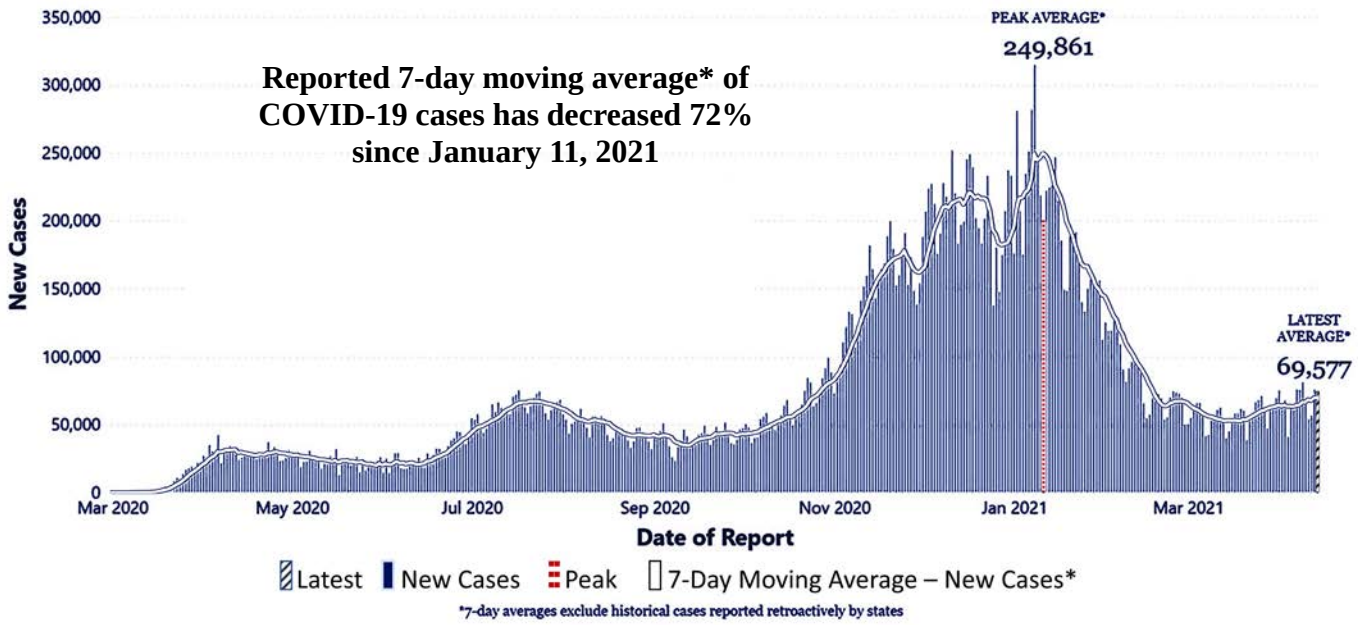
69,577

Prior 7-Day Case Average (4/1/21–4/7/21)

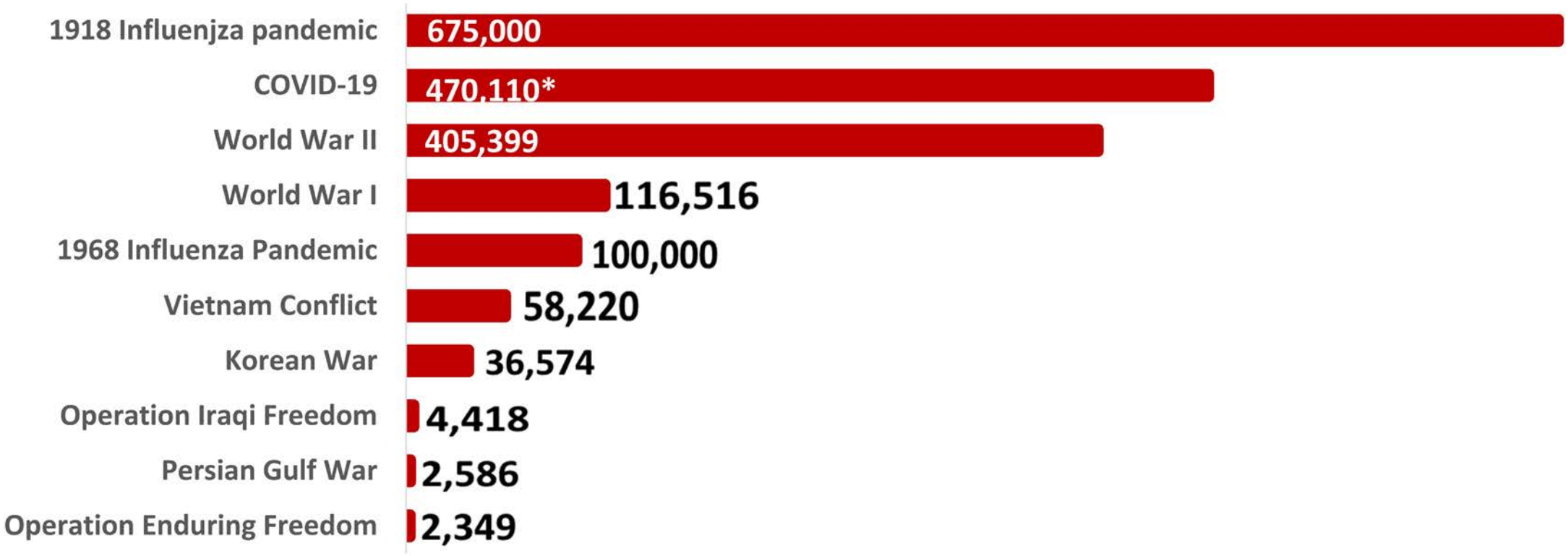
64,340

Peaks in New Cases and Highest 7-Day Moving Average

	Highest Daily Number of New Cases	Highest 7-Day Moving Average
Current	315,006 (1/8/21)	249,861 (1/11/21)
2nd Peak	75,534 (7/17/20)	67,390 (7/21/20)
1st Peak	42,533 (4/6/20)	31,944 (4/12/20)



U.S. Deaths from War and Major Pandemics



Adapted from L. Lambert, *Fortune*, 6/10/20.

***U.S. COVID-19 deaths as of February 11, 2021. Source: CDC.**

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
- Stephen Mnuchin
- Robert O'Brien
- Sonny Perdue
- Matthew Pottinger
- Robert Redfield
- Gene Scalia
- Joel Szabat

- Seema Verma
- Robert Wilkie

Jeff Zients is the White House Coronavirus Response Coordinator

Andy Slavitt is the House Senior Advisor on the COVID-19 response

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**

Biden Administration Announces Framework and Leadership for "The Operation"

- **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**
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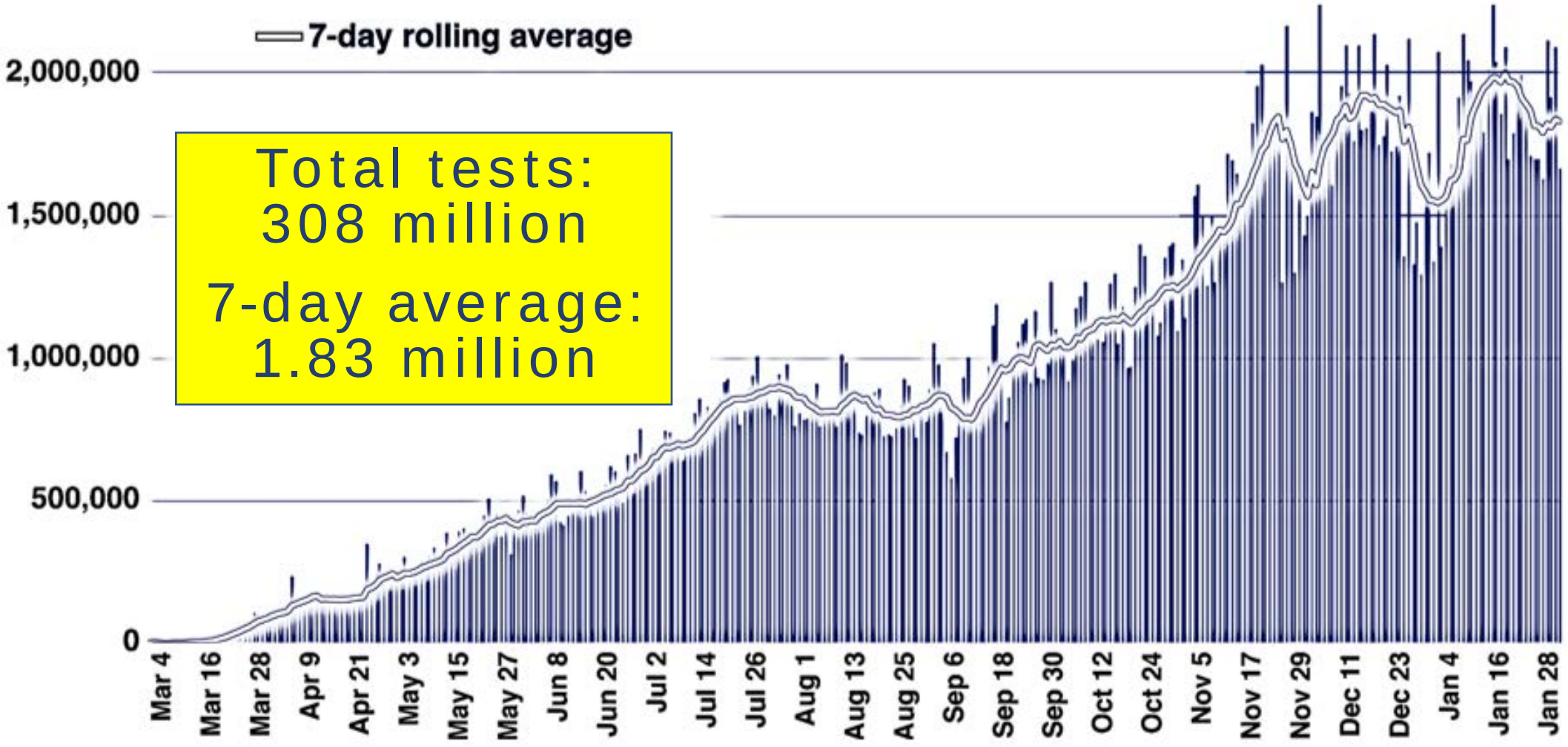
NIH Role in Diagnostic Research

- Director, NBIB 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 for 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 (e.g., AI, biosensors)
    - RADx^{SM} Advanced Technology Platforms: increase capacity

Daily COVID-19 Tests, United States

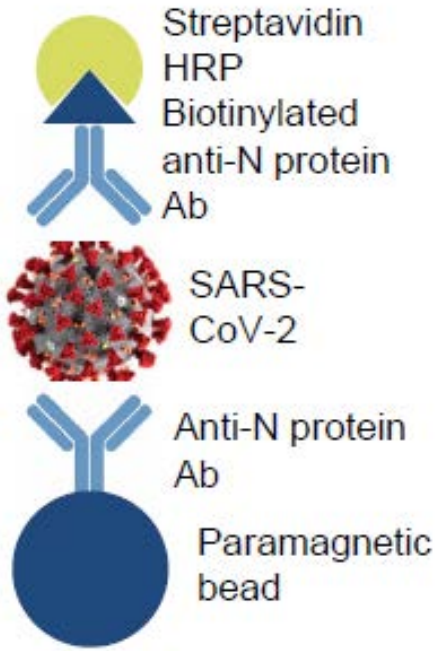


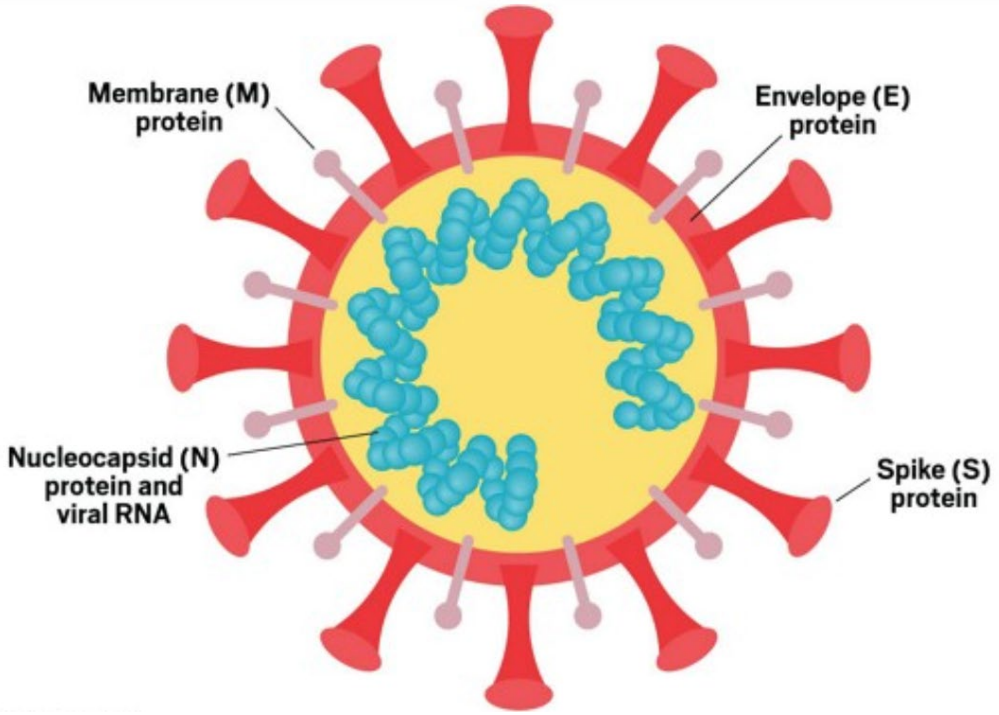
Total tests:
308 million

7-day average:
1.83 million

Source: COVID Tracking Project 2/1/2021

Quanterix Technology: Sensitive and Specific SARS-CoV-2 Nucleoprotein Antigen Detection



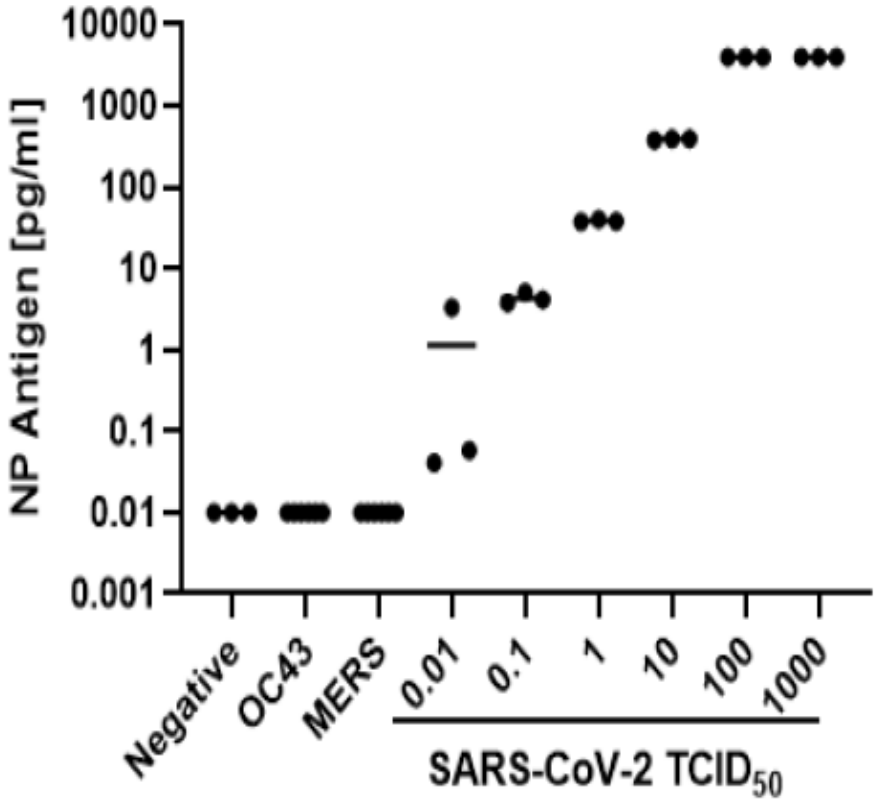


Sandwich immunoassay constructed on a paramagnetic bead. Immunocomplexes are separated in individual micro-wells in the Simoa disc, where signal is generated and digital readouts are measured.

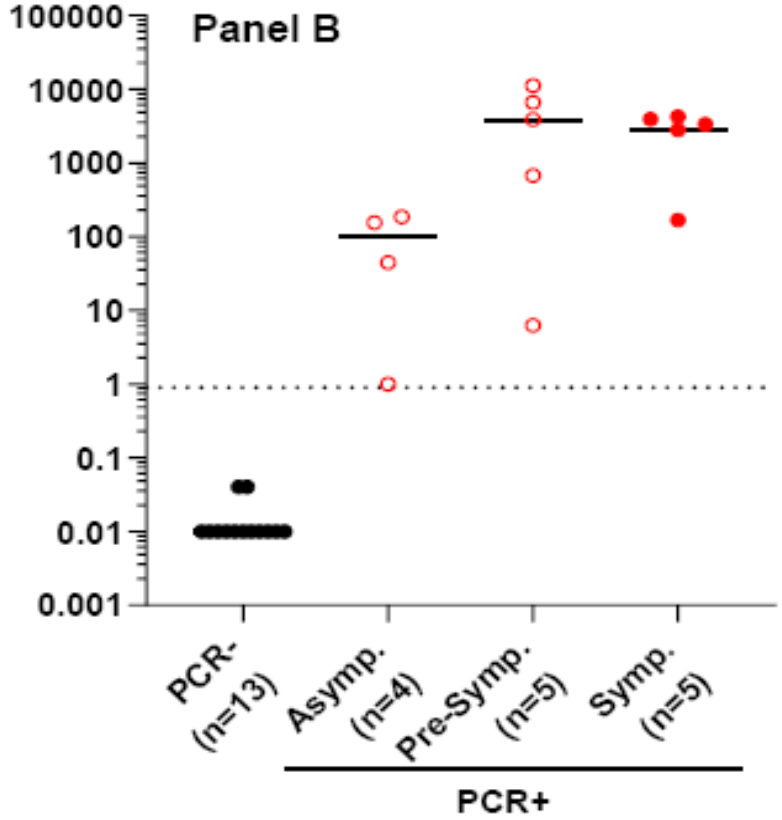
Shan et al., medRxiv 2020.08.14.20175356

Quanterix Technology (RADx) Allows for Highly Sensitive Analysis of Viral Antigen

Serum

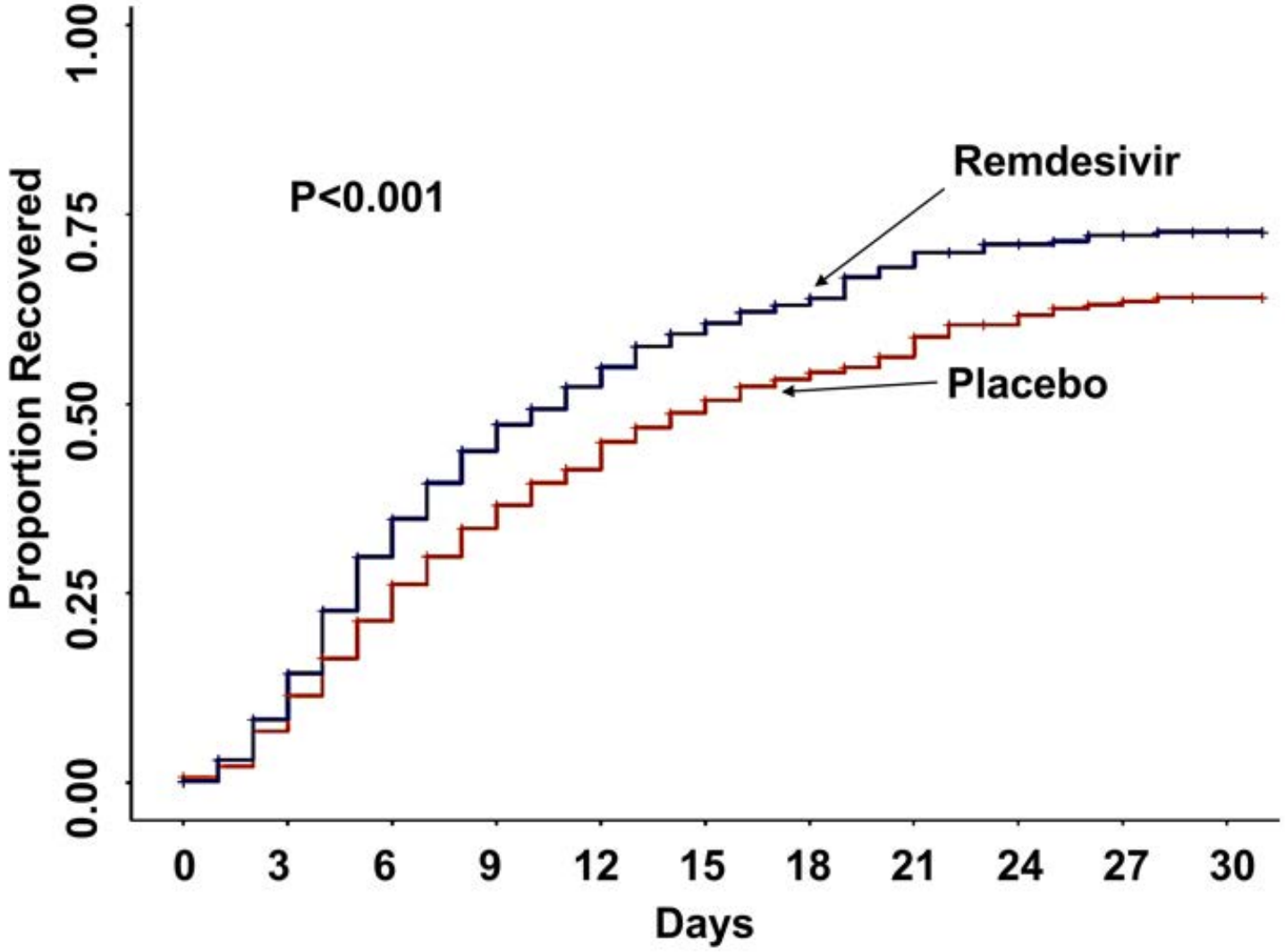


Dried blood spots



Shan et al., medRxiv 2020.08.14.20175356

Time to Recovery* in ACTT-1

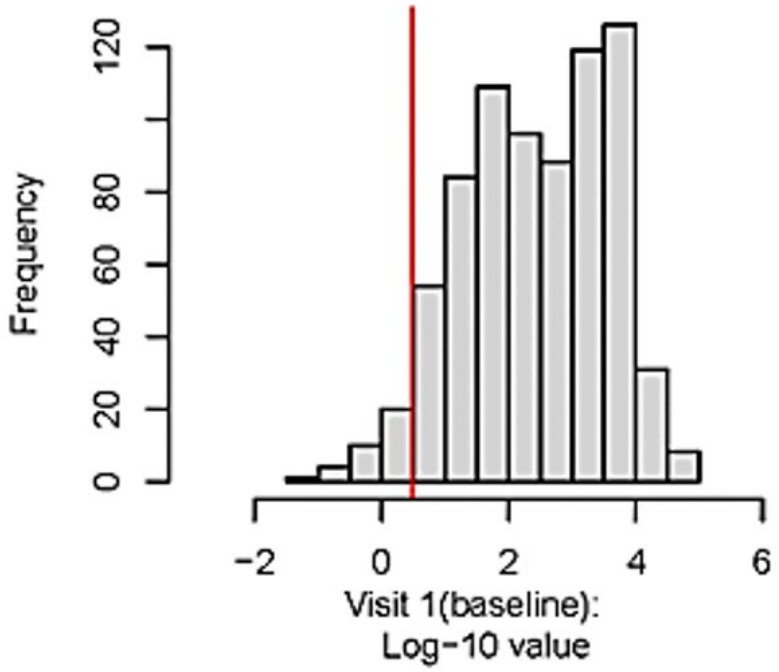


Ordinal Scale	Definition
1*	Not hospitalized, full activity
2*	Not hospitalized, limited activity
3*	Hospitalized, Non-medical
4	Hospitalized, not requiring O_2
5	Hospitalized, requiring O_2
6	High-flow O_2 or non-invasive vent.
7	Mechanical vent. or ECMO
8	Death

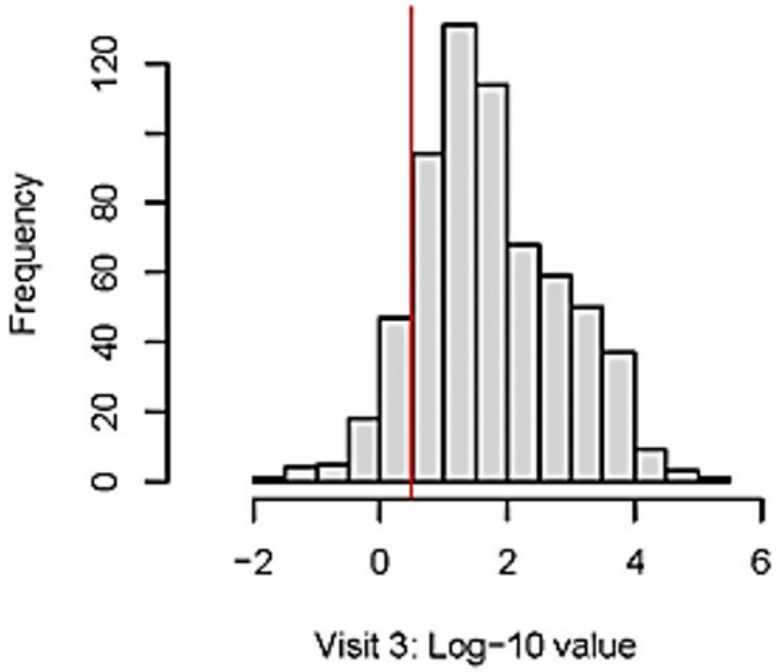
JH Beigel et al. N Engl J Med 2020
DOI: 10.1056/NEJMoa2007764

Distribution of NP Antigen Levels by Visits 1, 3, and 5

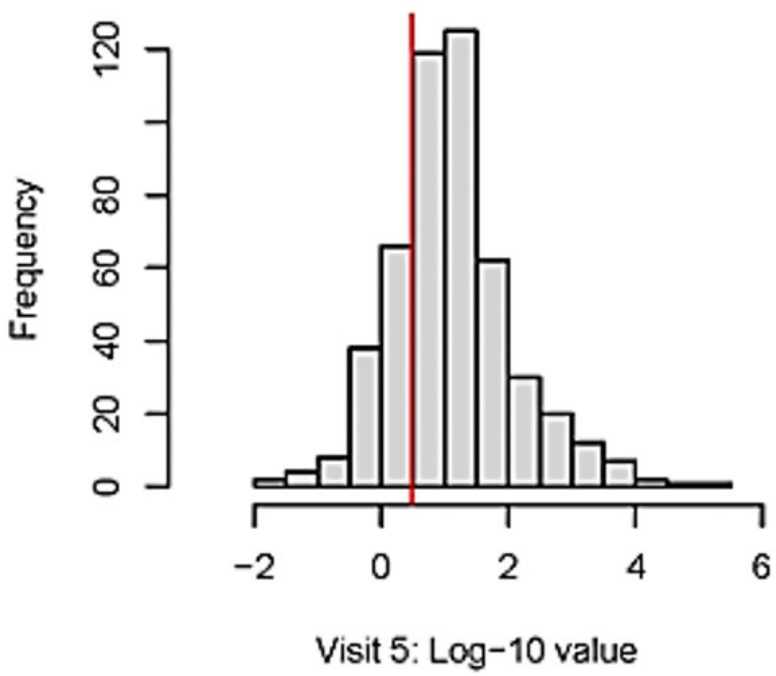
Prop below LOQ: 0.11



Prop below LOQ: 0.21



Prop below LOQ: 0.38



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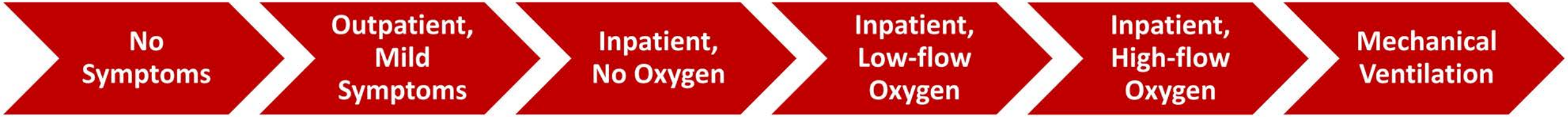
Different Stages of COVID-19 Illness

COVID-19+ Disease Progression →



Anti-viral Interventions

Immunomodulatory interventions

Different Therapies at Different Stages of COVID-19

COVID-19+ Disease Progression →

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

Anti-viral Strategies

Immunomodulatory Strategies

Anti-coagulation Strategies

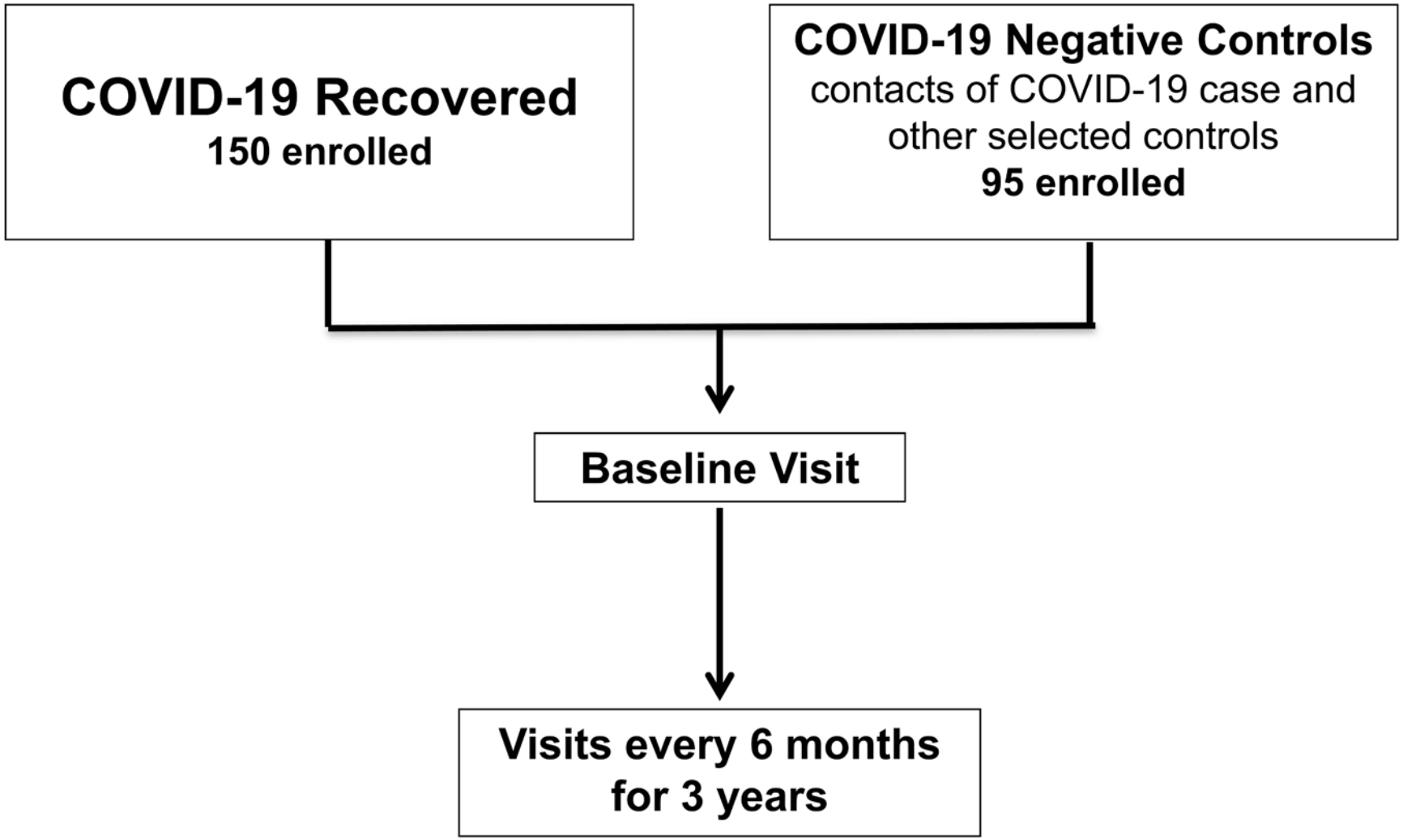
Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™
July 31, 2020
Morbidity and Mortality Weekly Report (*MMWR*)

Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network — United States, March–June 2020

MW Tenforde, LR Feldstein et al. for the IVY Network Investigators and CDC COVID-19 Response Team

- **Among symptomatic outpatients with positive test for SARS-CoV-2, 35% not returned to baseline health 2-3 weeks after testing**
  - **Older age and comorbidities associated with lack of return to baseline health**
  - **19% of young adults (19-34) with no comorbidities had not returned to baseline health**

Long-term Medical Sequelae of COVID-19
PI, Michael Sneller, M.D.



Study Procedures

- History and physical examination
- Routine laboratory testing (e.g., coagulation parameters, inflammatory markers, autoantibodies, BNP, troponins)
- Questionnaires to assess functional status
- SARS-CoV-2 serologies
- Leukapheresis to obtain mononuclear cells for research studies and storage
- Mental health evaluation (both groups)
  - Formal psychiatric interview
  - Mental health questionnaires
  - Cognitive function testing
- ECG and echocardiogram
- Cardiac MRI with adenosine stress test
- PFT and 6-minute walk test
- Other standard diagnostic test or consultation as clinically indicated

NIH Role in Therapeutic Research

- Extramural programs
  - The Adaptive COVID-19 Treatment Trial (ACCT 1-4)
  - The studies supported by ACTIV (ACTIV 1-6)
  - The ACTIV-associated studies
    - Convalescent plasma
    - Immune immunoglobulin
- Intramural programs
  - At least 7 protocols among 4 Institutes/Centers

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 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: First trial began Feb. 21, 2020; four trials have been completed

Results from the Adaptive COVID-19 Treatment Trial (ACTT-1 and -2)

- ACTT-1:
  - Remdesivir superior to standard care with respect to shorter time to recovery (10 days vs. 15 days) with a trend toward improved 28-day mortality (11.4% vs. 15.2%)
  - Formed the bases of licensure for remdesivir
- ACTT-2:
  - Remdesivir + baricitinib superior to remdesivir alone with respect to time to recovery (7 days vs. 8 days) with a trend toward improved 28-day mortality survival (5.1% vs. 7.8%)
  - Led to an EUA for baricitinib

Results from the Adaptive COVID-19 Treatment Trial (ACTT-3 and -4)

- **ACTT-3:**
  - **Remdesivir + interferon beta-1a was not superior to remdesivir alone**
- **ACTT-4:**
  - **Remdesivir + baricitinib was not superior to remdesivir + dexamethasone**

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

- **ACTIV-1 (NCATS): Immunomodulators in hospitalized patients**
- **ACTIV-2 (DAIDS/NIAID): Adaptive trial in outpatients**
- **ACTIV-3 (DCR/NIAID): Adaptive trial in hospitalized patients**
- **ACTIV-4 (NHLBI): Studies of anti-coagulation strategies**
- **ACTIV-5 (NIAID): Smaller sample sizes looking for a big effect**
- **ACTIV-6 (NCATS): Simple, adaptive trial in outpatients**

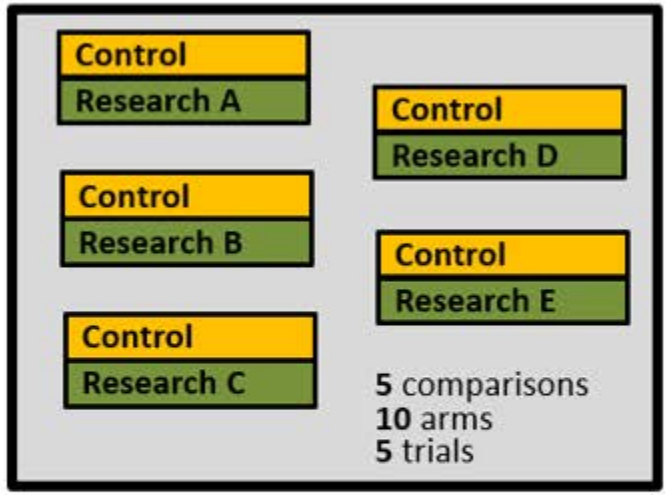
Current Status of the ACTIV-1 and -2 Trials

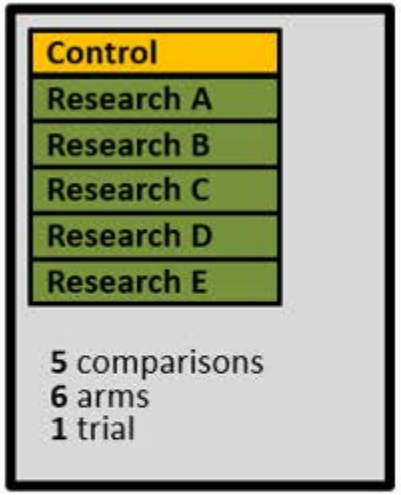
- **ACTIV-1 (NCATS): Immunomodulators in hospitalized patients**
  - **Ongoing study of placebo vs. abatacept, cenicriviroc, or infliximab**
- **ACTIV-2 (DAIDS/NIAID): Adaptive trial in outpatients**
  - **Study of placebo vs. bamlanivimab converted to open-label study, results pending**
  - **Ongoing study of placebo vs. inhaled beta interferon, AstraZeneca MoAb, or camostat mesilate**
  - **Planned amendment to convert control arm to combination MoAb**

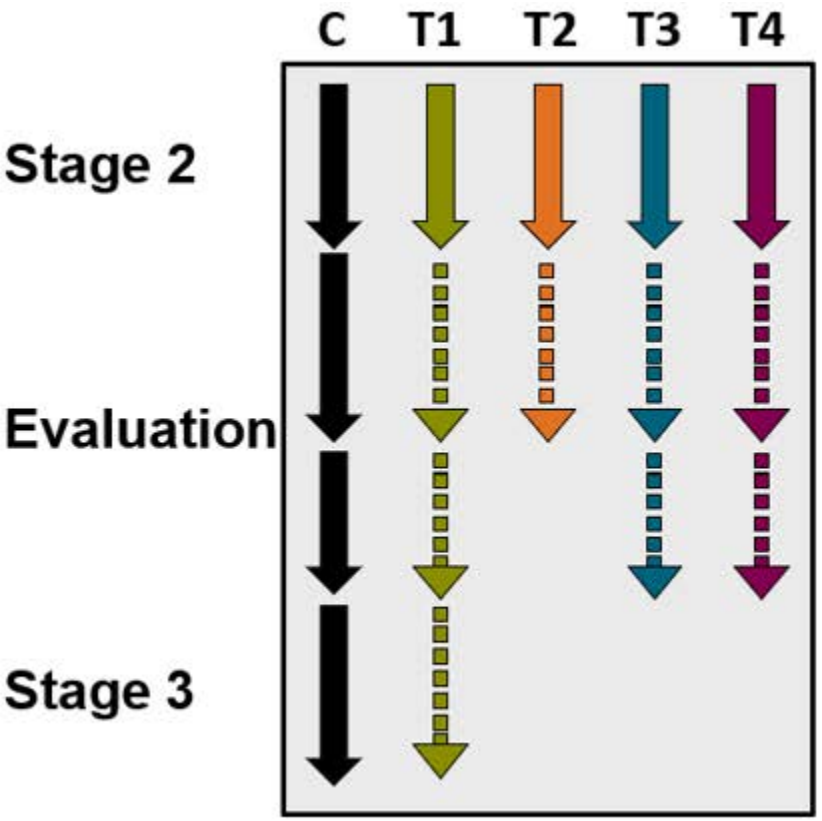
Current Status of the ACTIV-3 and -4 Trials

- ACTIV-3 (DCR/NIAID): Adaptive trial in hospitalized patients
  - Bamlanivimab + remdesivir not superior to remdesivir
  - Brii monoclonals + remdesivir not superior to remdesivir
  - Vir/GSK monoclonal + remdesivir not superior to remdesivir
  - Currently evaluating AZ MoAb and aviptadil
- ACTIV-4 (NHLBI): A series of 3 trials studying different anticoagulation strategies in outpatients, inpatients, and discharged patients
  - Full-dose anticoagulation not superior to prophylactic dose in ICU patients
  - Full-dose anticoagulation superior to prophylactic dose in moderately ill hospitalized patients

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

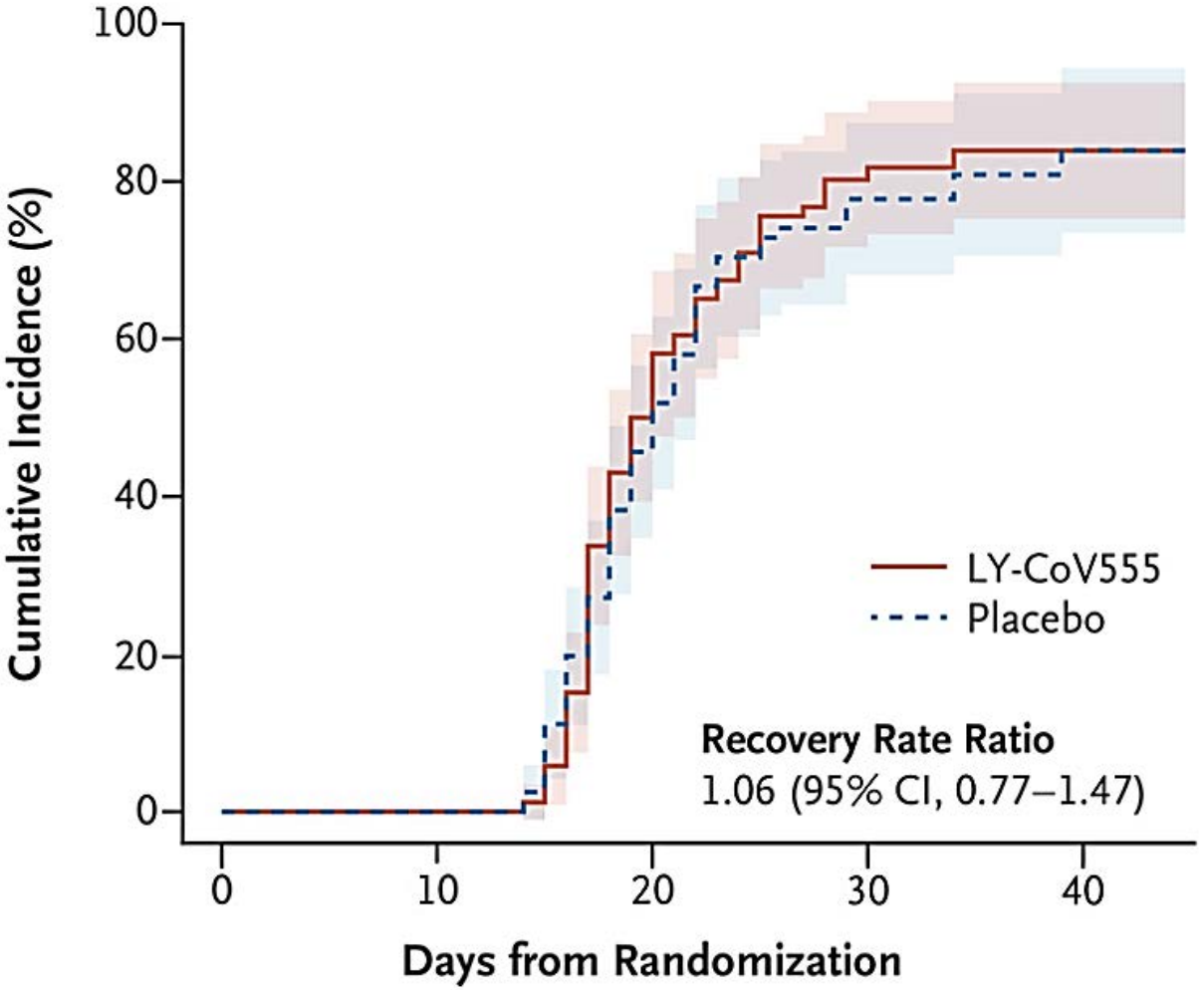






Mahesh Parmar, UK MRC, UCL

Time to Sustained Recovery: Bamlanivimab vs. Placebo

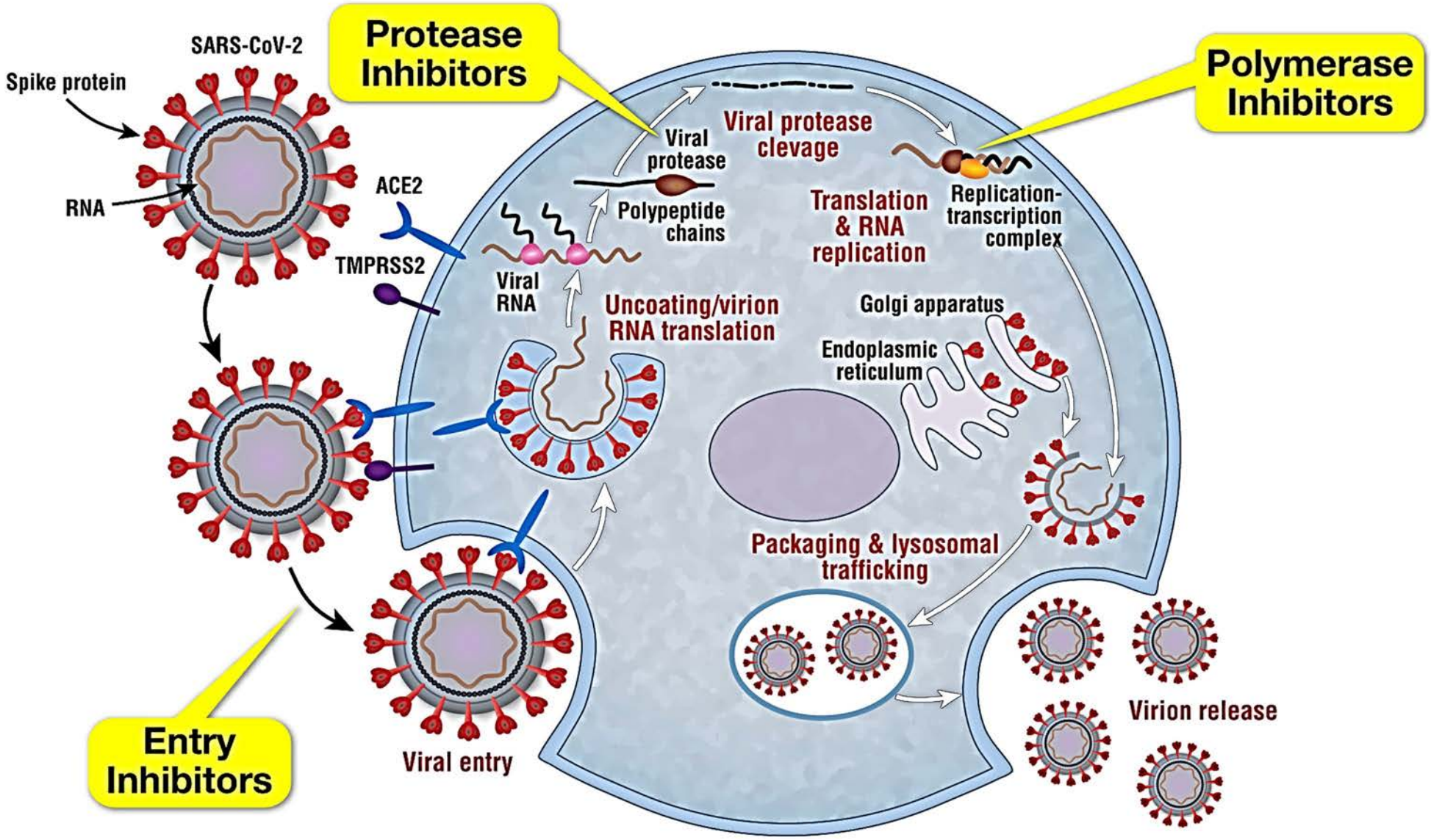


ACTIV-3/TICO LY-CoV555 Study Group, N Engl J Med 2021; 384:905-914.

Current Status of the ACTIV-5 and -6 and ACTIV-Associated Trials

- ACTIV-5 (DMID/NIAID): Several different interventions in hospitalized patients looking for a big effect to take into the ACTT or ACTIV platforms
  - Currently randomizing patients to lenzilumab (anti-GM-CSF)
- ACTIV-6 (NCATS): Several different interventions in an ambulatory patient population in a large, simple trial
  - Opening soon to randomize patients to ivermectin, others
- ACTIV-associated trials:
  - ITAC (NIAID) – immune IVIg + remdesivir not superior to remdesivir in hospitalized patients
  - C3PO (NHLBI) – convalescent plasma not superior to placebo in patients presenting to the ER with symptomatic COVID-19

SARS-CoV-2 Replication Cycle



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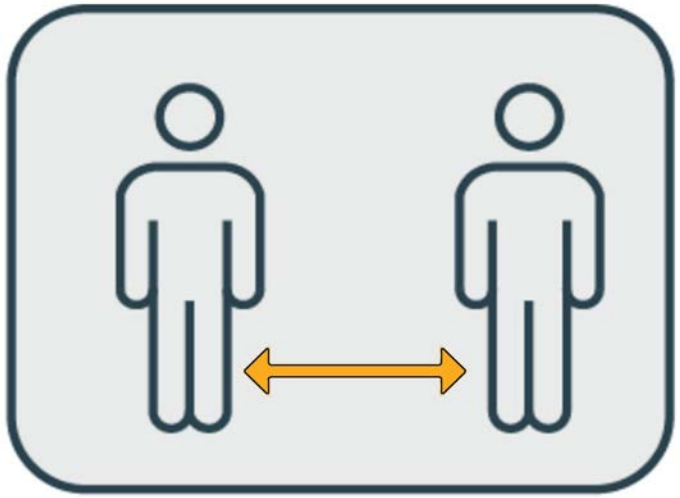
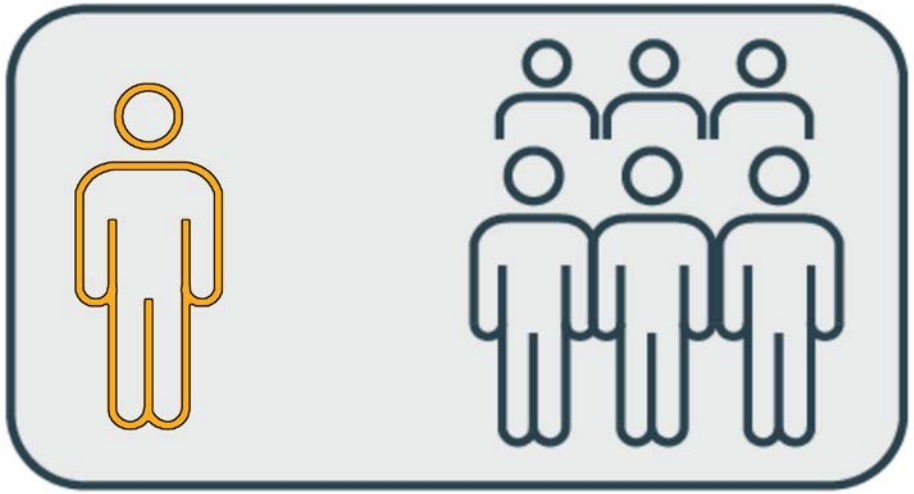
  - Therapeutics
  - Prevention
    - Public Health Measures
    - Prophylaxis with MoAb
    - Vaccines
  - Treatment Guidelines

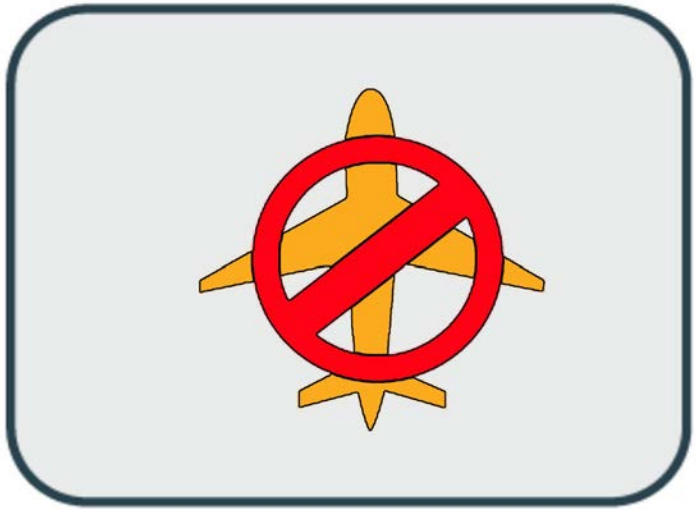
WEAR A MASK



STAY 6 FEET APART



AVOID CROWDS



AVOID TRAVEL

Monoclonal Antibodies Are Recommended for Treatment of High-Risk Ambulatory Patients and Are Available Under Emergency Use Authorization

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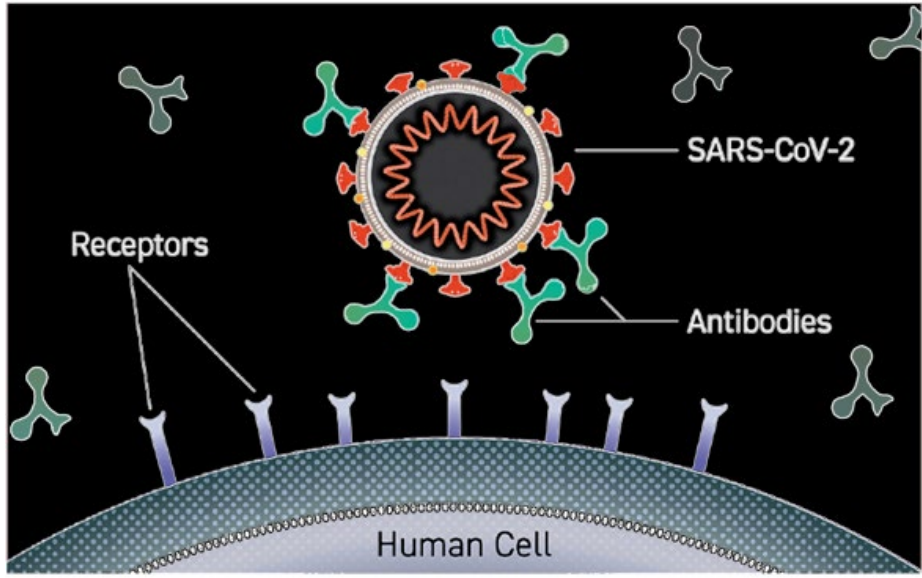
Monoclonal Antibodies May Also Play a Role in Post-Exposure Prophylaxis

Clinical Trials of Monoclonal Antibodies to Prevent COVID-19

- **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**



Anti-Spike MoAbs Prevent Disease and Infection

- **Bamlanivimab (Lilly)**
- Placebo controlled trial among 966 nursing home residents and employees
- Among 200 residents
  - 80% reduction COVID-19
  - 4 deaths in placebo
  - 0 deaths in treatment

M. Cohen, CROI 2021

- **Casirivimab + imdevimab (Regeneron)**
- Placebo controlled trial among 409 household contacts
  - COVID-19 incidence
    - 8/223 (8%) controls
    - 0/186 (0%) treatment
  - SARS-CoV-2 infection
    - 23/223 (10.3%) controls
    - 10/186 (5.4%) treatment

M. O'Brien, CROI 2021

News Release **March 24, 2021**

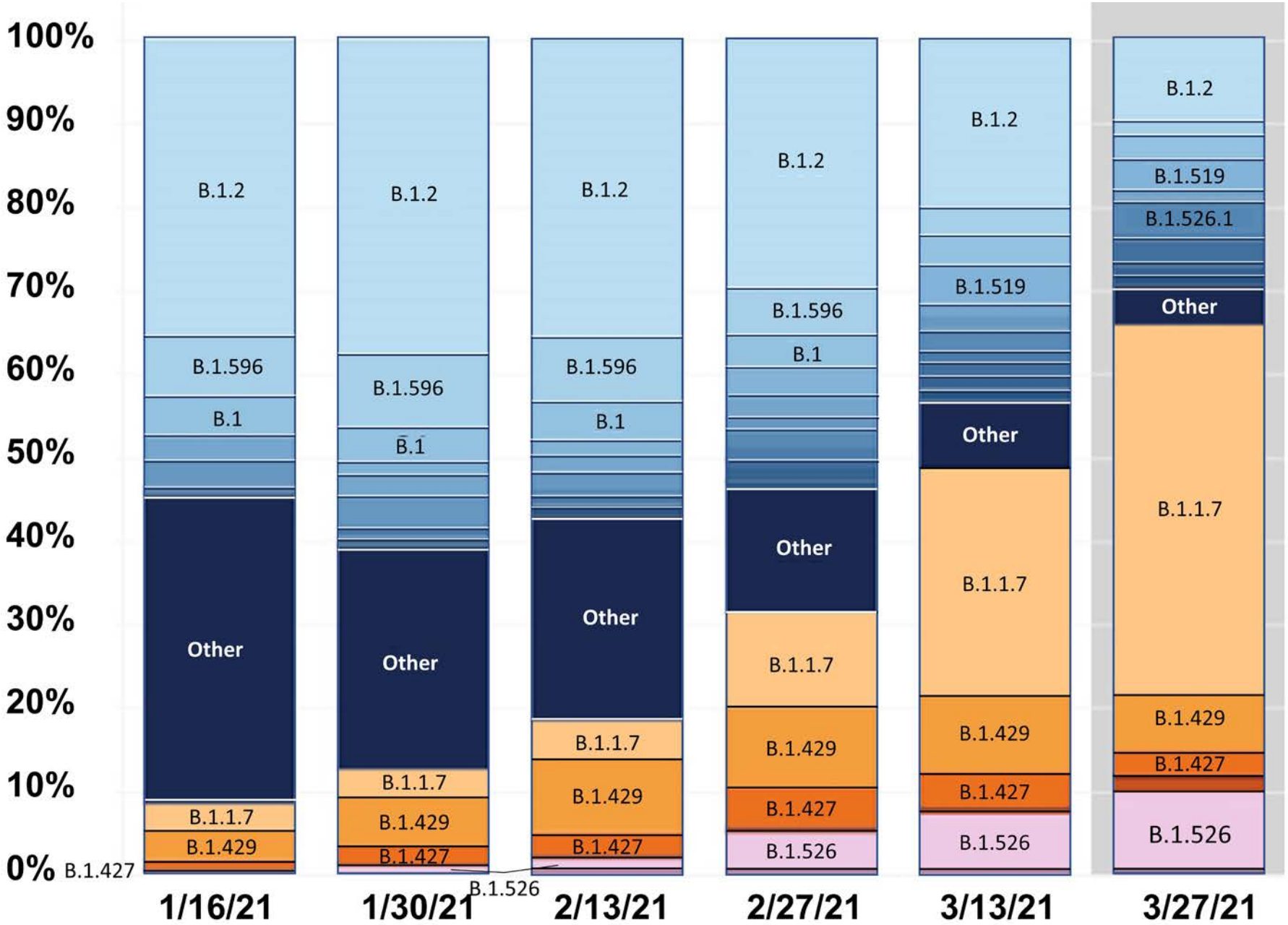
Update on COVID-19 Variants and Impact on Bamlanivimab Distribution

"The U.S. Government, in coordination with Eli Lilly and Company, will stop the distribution of bamlanivimab alone starting today, March 24, 2021."

Selected SARS-CoV-2 Variants

Lineage	Characteristics
B.1.1.7 (originally United Kingdom)	■ Increased transmissibility ■ Possibly increased disease severity ■ Covered well by currently authorized vaccines
B.1.351 (originally South Africa)	■ Possibly increased transmissibility ■ **Moderately to severely** reduced vaccine efficacy for some vaccines ■ *In vitro* studies suggest neutralization by certain monoclonal antibodies may be **severely** reduced
P.1 (originally Brazil)	■ Preliminary reports of increased transmissibility ■ Antibodies elicited by previous infection or vaccine may be less effective
B.1.427/B.1.429 (originally California)	■ Preliminary reports of increased transmissibility and disease severity
B.1.526 (originally New York)	■ Variable loss of neutralizing activity by some monoclonal and vaccine-induced antibodies

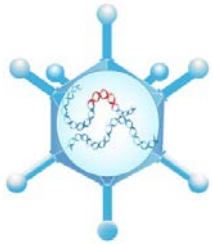
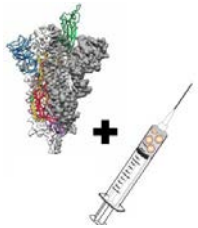
Dynamic Changes in the Populations of SARS-CoV-2



Selected COVID-19 Vaccine Candidates

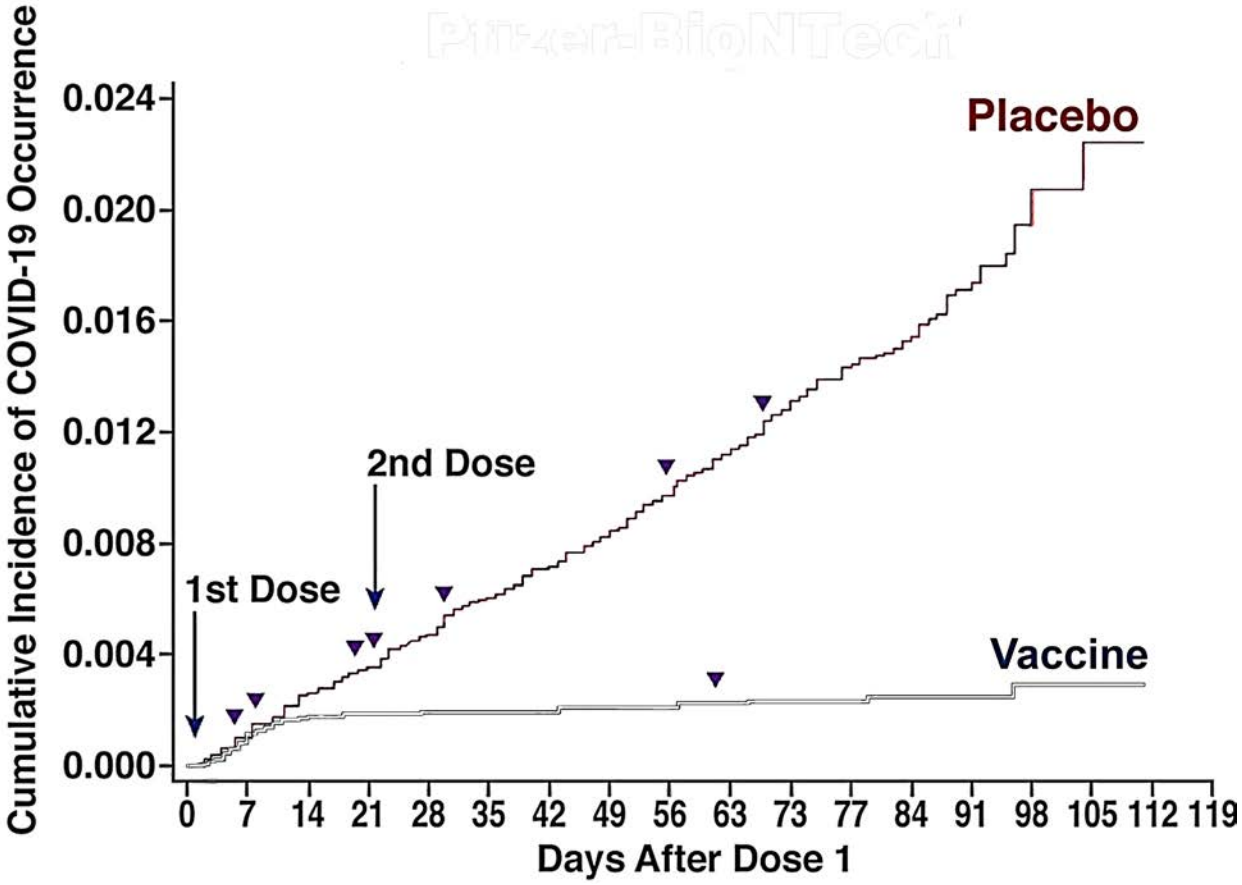
Platform	Developer	Phase 1/2	Phase 2/3
Nucleic acid	moderna	Enrolled	Ongoing
	BIONTECH Pfizer	Enrolled	Ongoing
Viral vector	UNIVERSITY OF OXFORD AstraZeneca	Enrolled	Ongoing
	janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson	Ongoing	Ongoing
	MERCK	Ongoing	—
Protein subunit	NOVAVAX Creating Tomorrow's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

Selected COVID-19 Vaccine Candidates

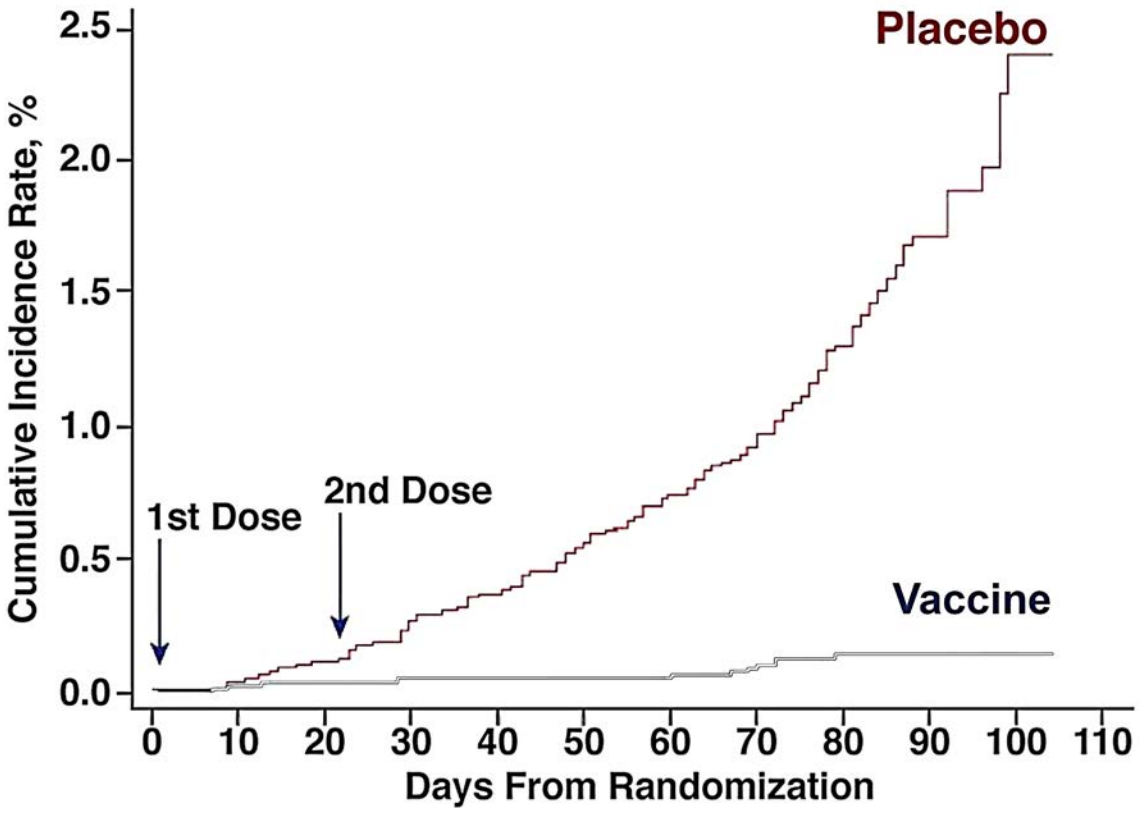
Platform	Developer	Status	
Nucleic acid (mRNA)	moderna	▪ **94% efficacy vs. symptomatic disease**	→ **EUA**
	BIONTECH Pfizer	▪ **95% efficacy vs. symptomatic disease**	→ **EUA**
Adenovirus Vector 	Janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson	▪ **72% efficacy in U.S. 85% efficacy overall vs. severe disease in U.S., South Africa, Latin America**	→ **EUA**
	AstraZeneca	▪ **63% efficacy vs. symptomatic disease (Phase 3 in U.K., Brazil, South Africa)**	→ **EUA**
Recombinant Protein and Adjuvant 	gsk SANOFI	▪ **Phase 2 starts**	→ **Feb. 2021**
	NOVAVAX Creating Tomorrow's Vaccines Today	▪ **85% efficacy vs. symptomatic disease (U.K. Phase 3)**	→ **EUA TBD**

Cumulative Incidence Curves for First COVID-19 Occurrence, Pfizer-BioNTech and Moderna Phase 3 Vaccine Trials

Pfizer-BioNTech



Moderna



Source: M Connors et al. *Ann Intern Med*, 1/19/2021.

Johnson & Johnson

Press Release

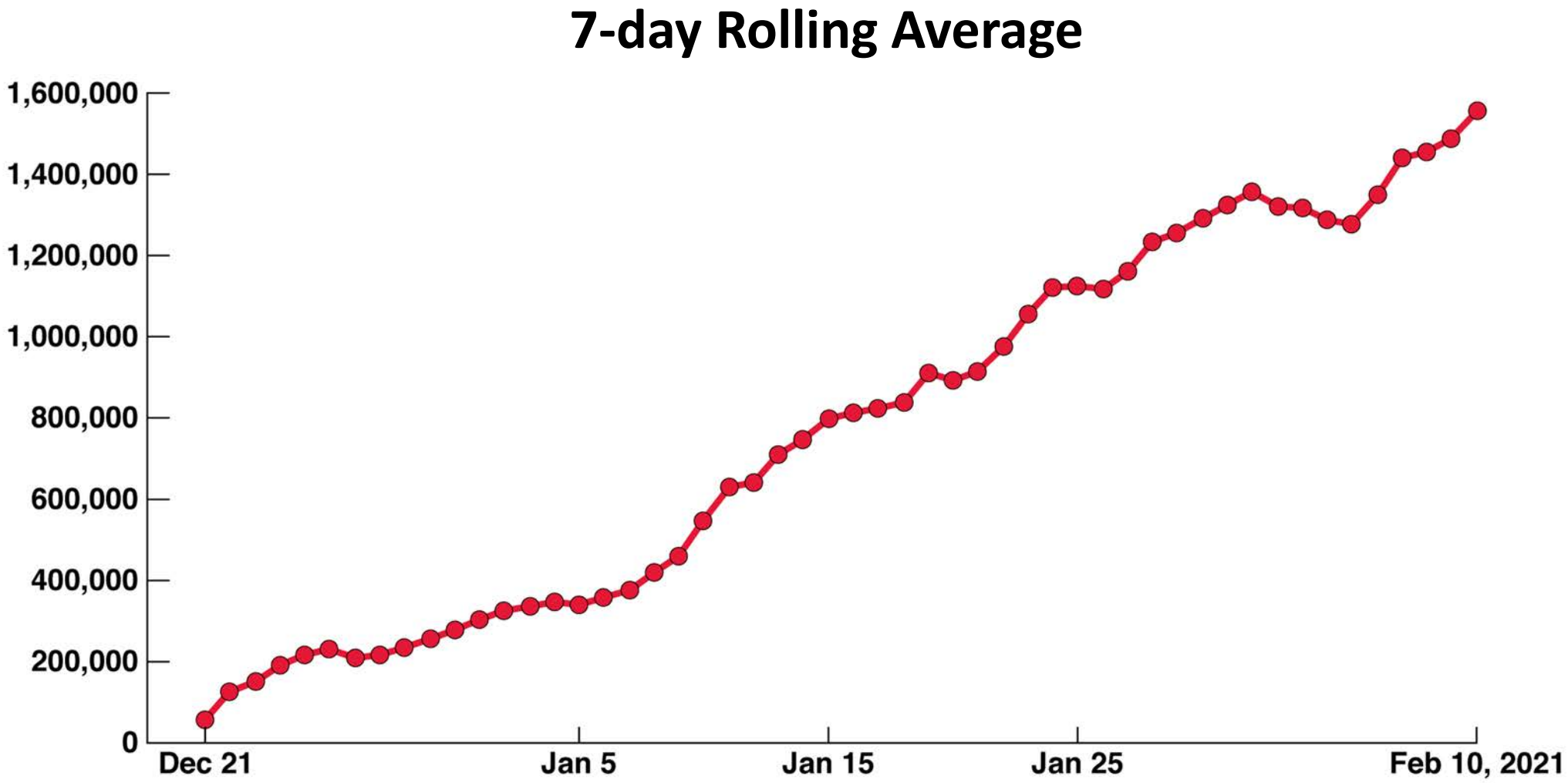
January 29, 2021

Johnson & Johnson Announces Single-Shot Janssen COVID-19 Vaccine Candidate Met Primary Endpoints in Interim Analysis of its Phase 3 Ensemble Trial

Efficacy:

- **66% overall vs. moderate-to-severe COVID-19**
  - **72% in U.S.**
  - **66% in Latin America**
  - **57% in South Africa**
- **85% vs severe disease across all age groups**
- **Protection generally consistent across all age groups**

Daily COVID-19 Vaccine Doses Administered, United States



Source: Our World in Data

Collins, Fauci, Azar Receive Moderna COVID-19 Vaccine at NIH, 12/22/2020

abc NEWS

January 11, 2021

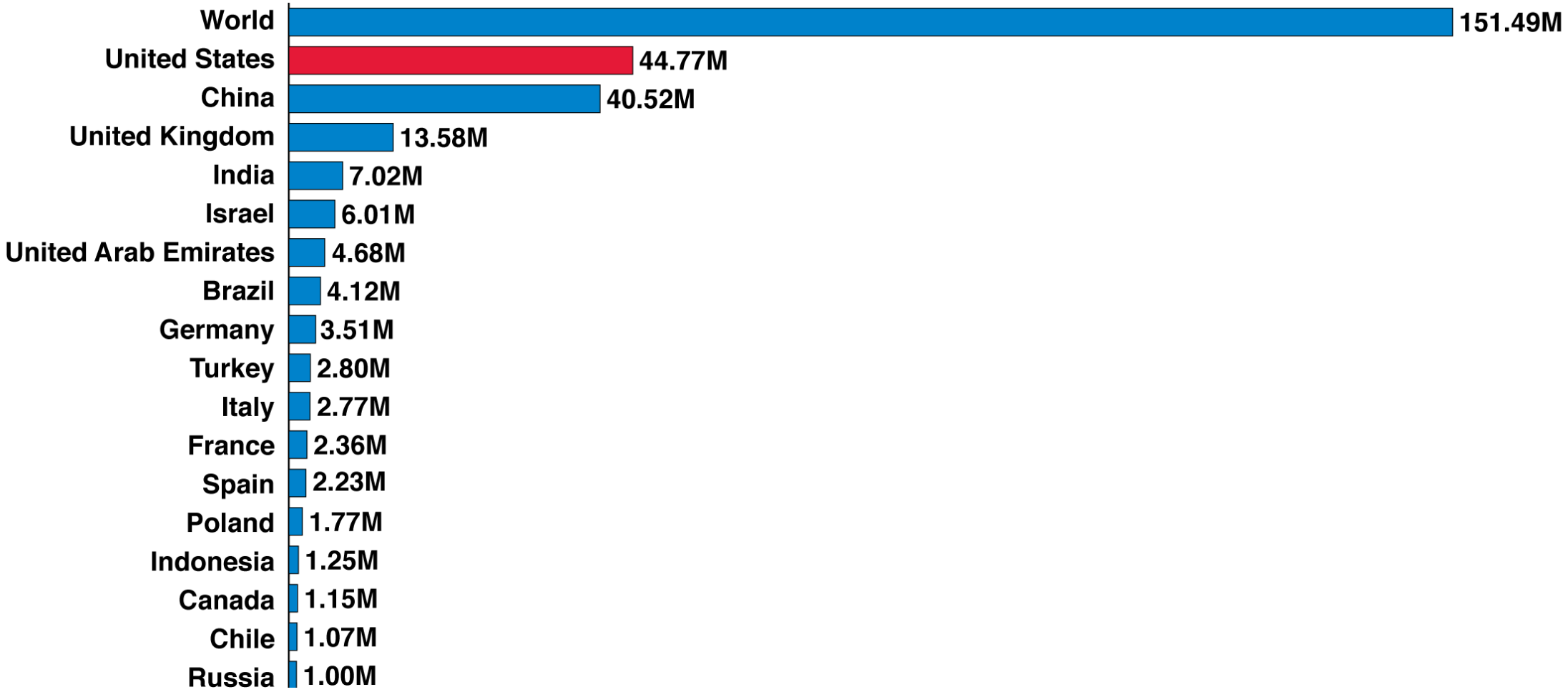
Joe Biden Receives Second Dose of COVID-19 Vaccine

NIH National Institutes of Health
Turning Discovery Into Health

January 26, 2021

Kamala Harris Receives Second Dose of COVID-19 Vaccine

Number of COVID-19 Vaccine Doses Administered, Worldwide as of 2-10-2021



Source: Our World in Data

Thrombocytopenic, thromboembolic, and hemorrhagic events have been observed after vaccination

VAERS data for All Vaccines 09 Apr 2021:

Adverse Event of Special Interest	Janssen	Pfizer-BioNTech	Moderna
Thromboembolism	55	627	550
Thrombocytopenia	10	117	115
Thromboembolism with thrombocytopenia	4	12	14
Immune thrombocytopenia	2	27	26
Cerebral venous sinus thrombosis	2	0	3
Hemorrhagic disorders	95	662	600
Hemorrhage with thrombocytopenia	7	60	59
Hemorrhage with immune thrombocytopenia	2	27	26
Disseminated intravascular coagulation	3	3	5
Thrombotic thrombocytopenic purpura	0	5	0

As of 09 Apr 2021 per CDC website:	Janssen	Pfizer	Moderna
Total doses administered:	4,917,225	90,256,586	79,551,820
Individuals vaccinated:	4,917,225	57,447,938	51,079,761

Outline of the Presentation:

- Updates from the prior presentation on:
  - Organizational structure
  - Diagnostics
  - Therapeutics
  - Prevention
  - Treatment Guidelines

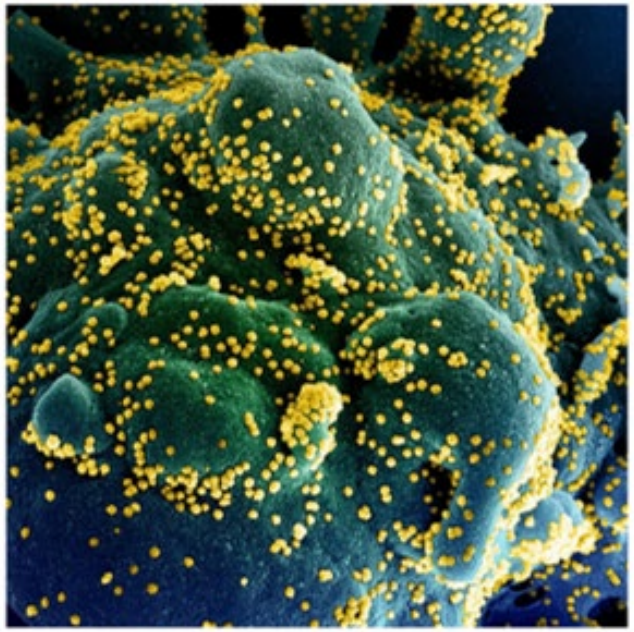
National Institutes of Health
Turning Discovery Into Health

Tuesday, April 21, 2020

News Release

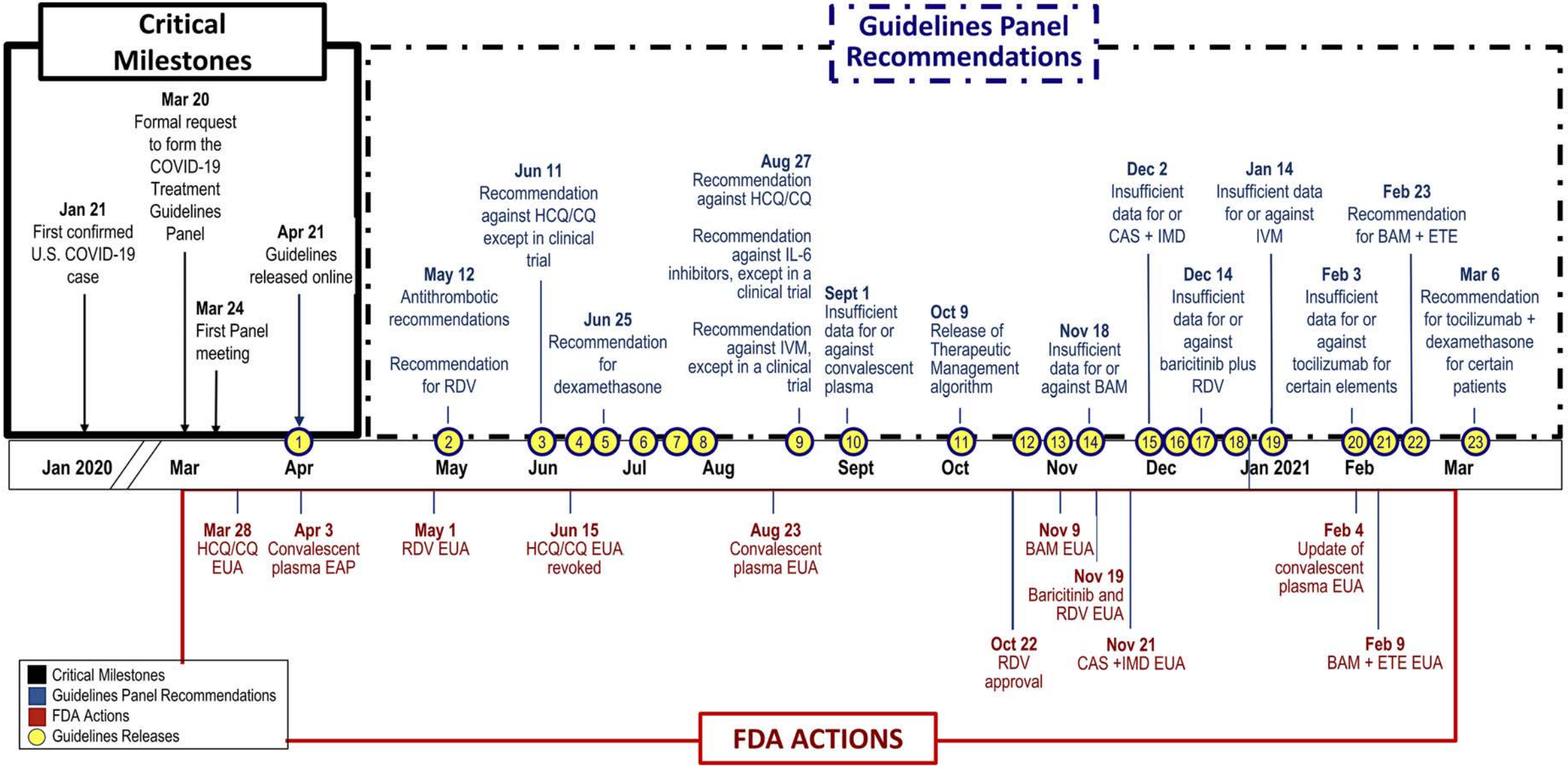
Expert U.S. Panel Develops NIH Treatment Guidelines for COVID-19

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



- **Covid19treatmentguidelines.nih.gov**

NIH COVID-19 Treatment Guidelines: The First Year – 14 Million Page Views



DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
Not Hospitalized, Mild to Moderate COVID-19	For patients who are not at high risk for disease progression, provide supportive care and symptomatic management **(AIII)** For patients who are at high risk for disease progression, (as defined by the FDA EUA criteria for treatment with anti-SARS-CoV-2 monoclonal antibodies), use one of the following combinations: • **Bamlanivimab plus etesevimab (AIIa)** • **Casirivimab plus imdevimab (AIIa)**
Hospitalized but Does Not Require Supplemental Oxygen	There are insufficient data to recommend either for or against the routine use of remdesivir. For patients at high risk of disease progression, the use of remdesivir may be appropriate.
Hospitalized and Requires Supplemental Oxygen	Use one of the following options: • **Remdesivir** (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone plus remdesivir** (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)** • **Dexamethasone** (e.g., when combination therapy with remdesivir cannot be used or is not available) **(BI)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	Use one of the following options: • **Dexamethasone (AI)** • **Dexamethasone plus Remdesivir (BIII)** For patients who were recently hospitalized with rapidly increasing oxygen needs and systemic inflammation: Add **tocilizumab** to one of the two options above **(BIIa)**
Hospitalized and Requires Invasive Mechanical Ventilation or ECMO	• **Dexamethasone (AI)** For patients who are within 24 hours of admission to the ICU: • **Dexamethasone plus tocilizumab (BIIa)**

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

Summary (October 2020)

- A large research effort has been launched across the U.S. 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.

Summary (April 2021)

- A large research effort continues 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.
- USG and NIH research has supported development of diagnostic platforms leading to EUAs, identified better therapeutics leading to 1 FDA licensure (remdesivir) and several EUAs (baricitinib, MoAbs), and led to EUAs for 3 vaccines with more anticipated.
- By continuing to work to in a coordinated fashion with clear priorities, it is hoped that the most effective countermeasures will get to the greatest number of people in the shortest period of time.