COVID Management Update
March 2022

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UAB MEDICINE







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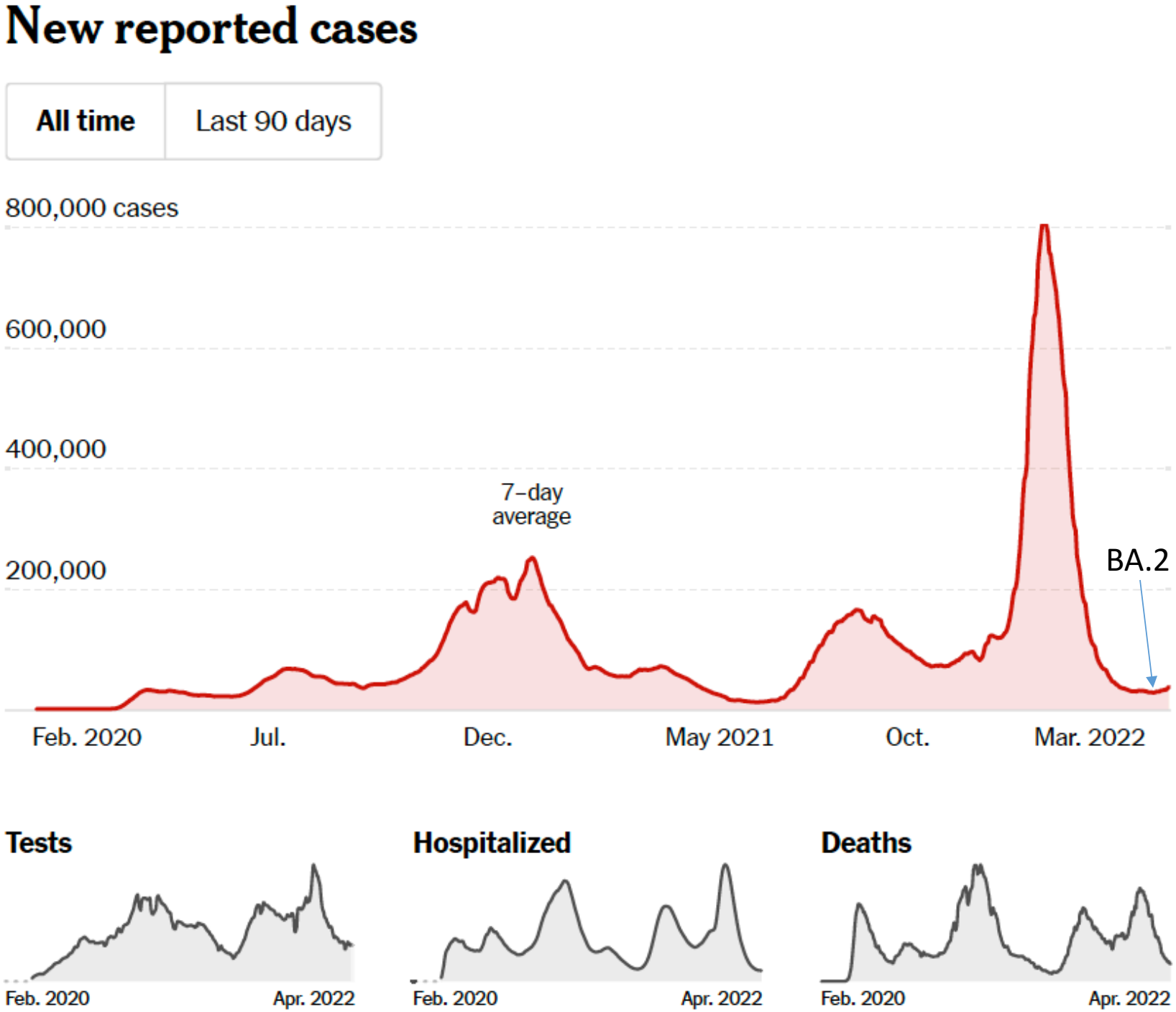
United States April 2022:



Rapidly Developing Pandemic

Coronavirus death toll hits 812, surpassing SARS fatalities

Tthere are 37,251 cases in China, according

By **Ivan Pereira**

February 9, 2020, 4:25 PM • 4 min read

The death toll from the coronavirus surpassed the numl
were killed by the 2002-2003 SARS outbreak, Chinese h

As of Sunday, 812 people died in China after contractin
according to the World Health Organization, and there
confirmed cases in the country.

+ MORE: Death toll from coronavirus set to surpass SARS

There were 89 coronavirus deaths and 2,657 new confir
in the country in the 24 hours leading up to Sunday's u
the WHO.

During the SARS outbreak, there were 774 reported fata
cases.

Iran confirms 13 more coronavirus cases, two deaths - Health Ministry

WORLD NEWS FEBRUARY 21, 2020 / 1:18 AM / 6 MONTHS AGO

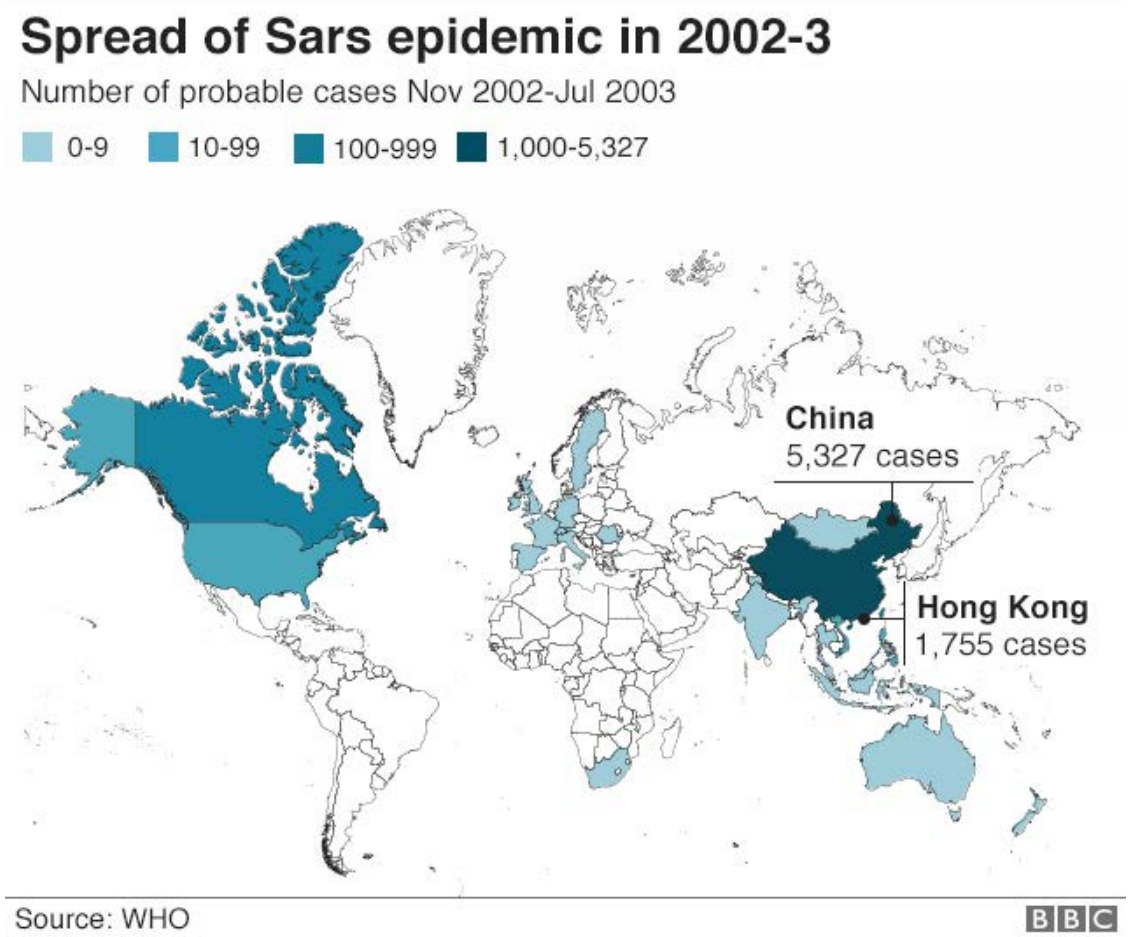
First Italian dies of coronavirus as outbreak flares in north

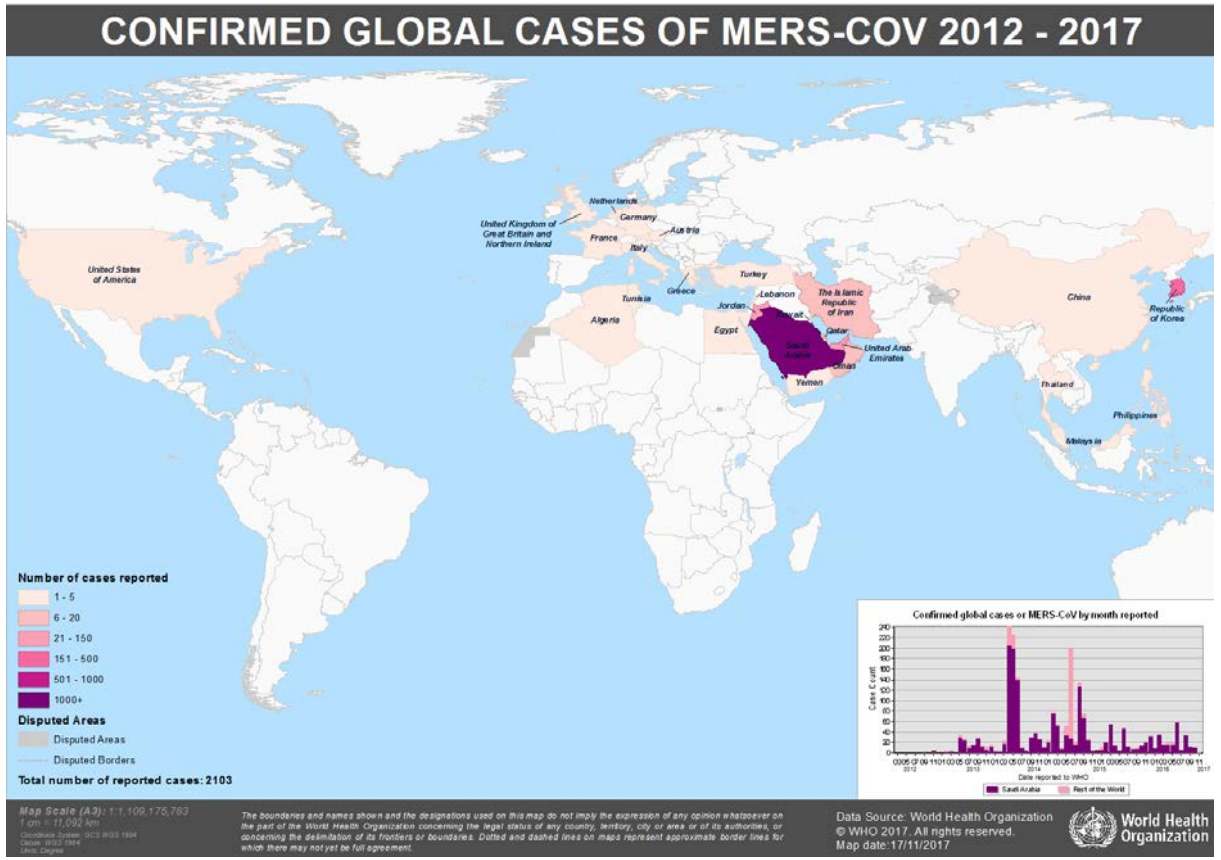
Elisa Anzolin, Angelo Amante

4 MIN READ

MILAN (Reuters) - An elderly man in the northern city of Padua has died after being infected with the coronavirus, becoming the first Italian victim of the disease, Health Minister Roberto Speranza said on Friday.

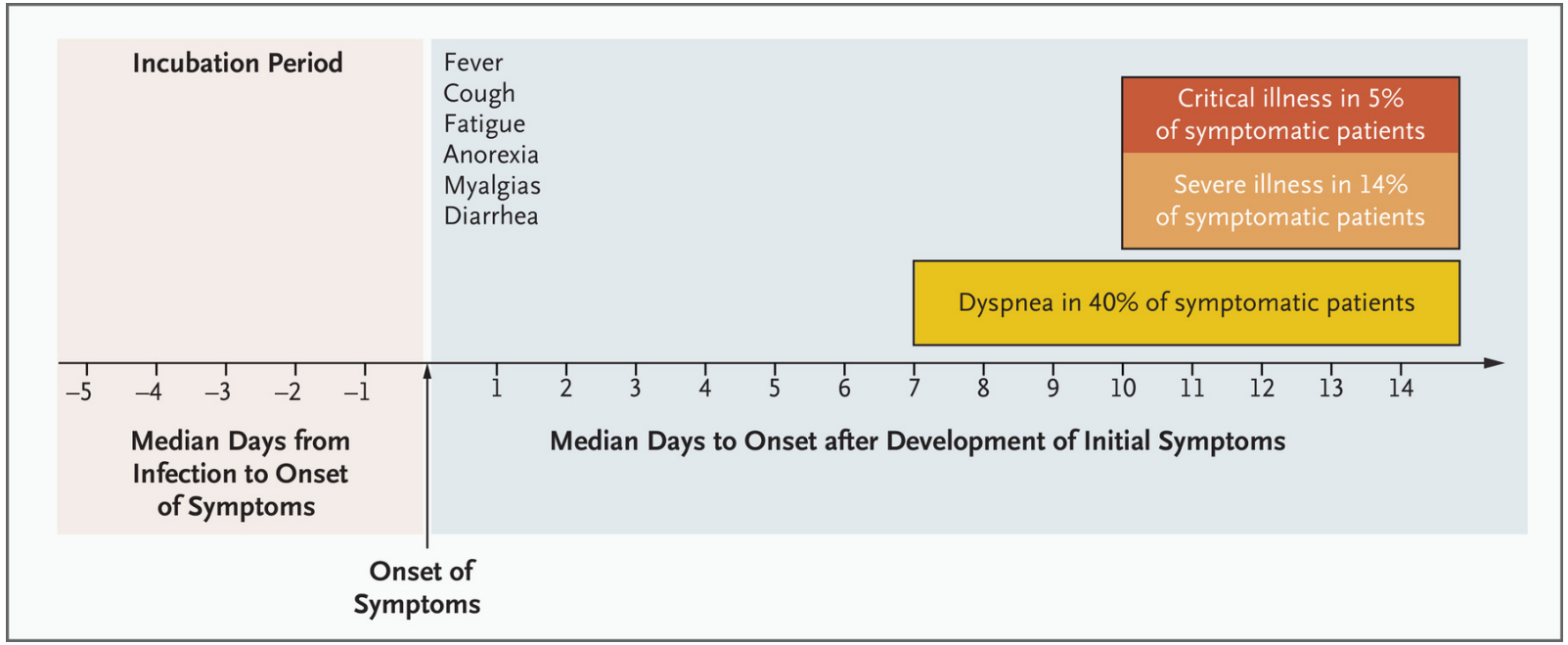
Coronaviruses - Déjà vu all over again



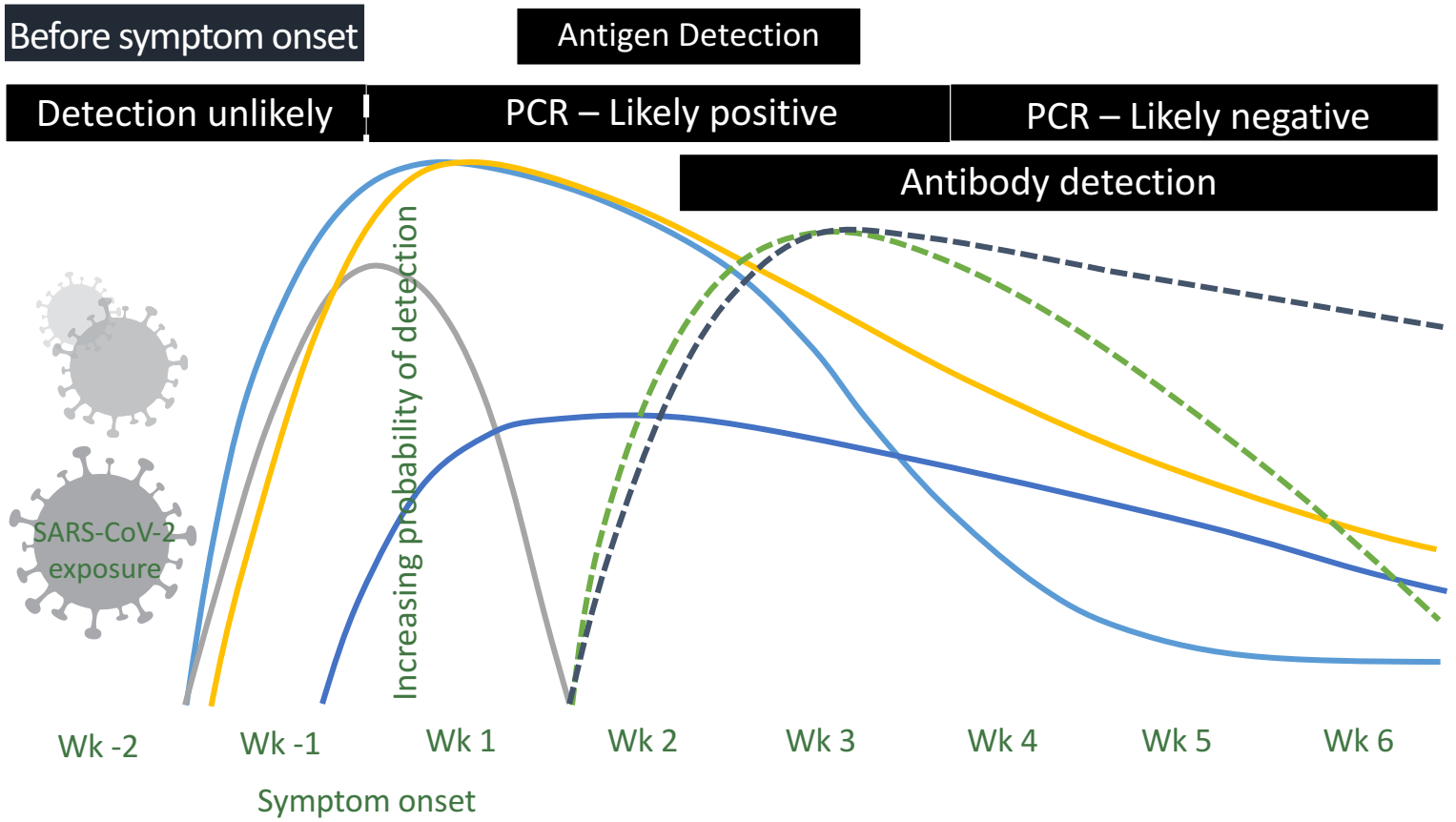


COVID Syndrome

- Illness begins with an asymptomatic phase of viral replication followed by onset of flu-like symptoms
- A subset of individuals develop respiratory symptoms, some of which can be severe



Temporal Considerations for Diagnosis of COVID-19



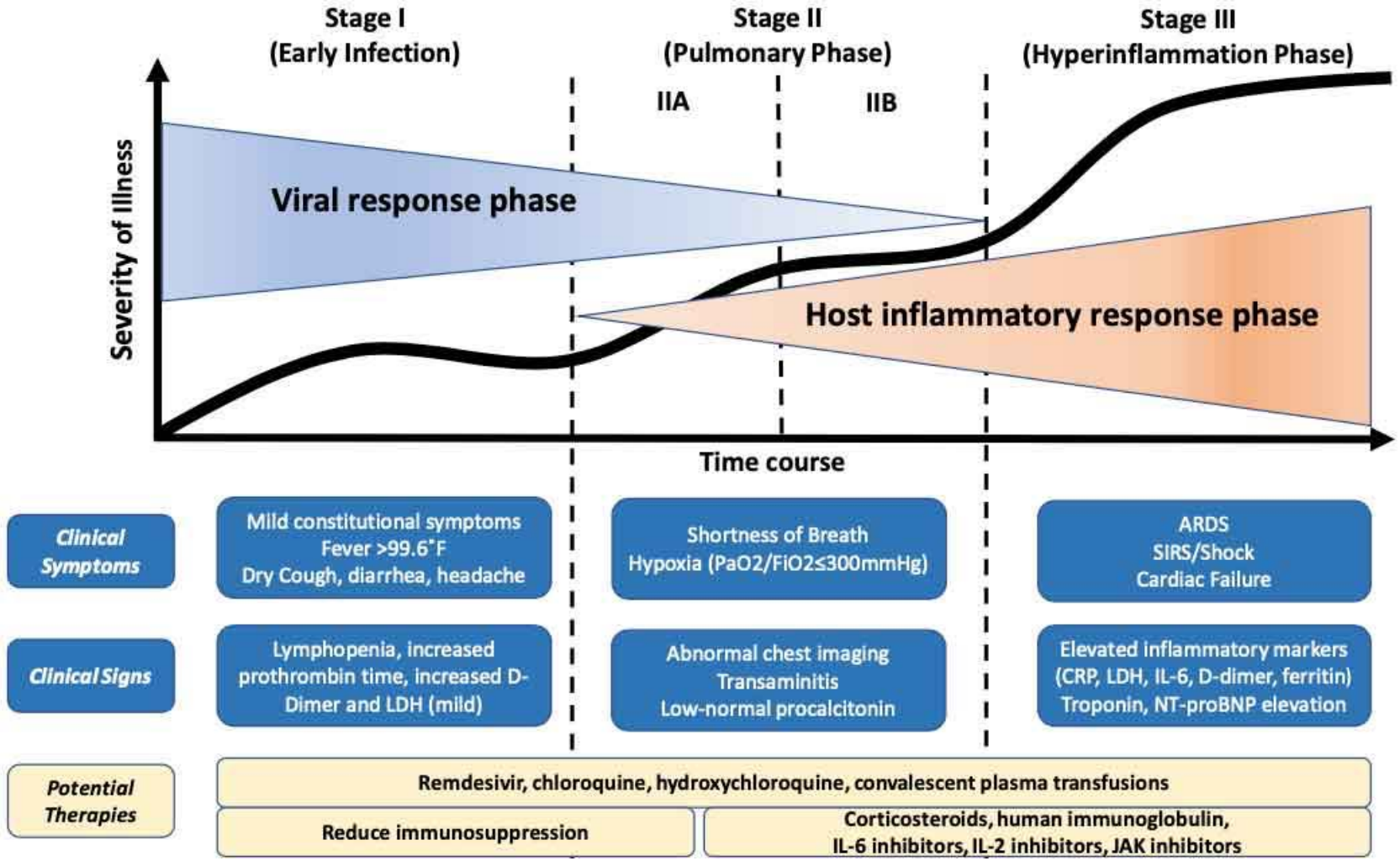
- Nasopharyngeal swab PCR
- Virus isolation from respiratory tract
- Bronchoalveolar lavage/sputum PCR
- Stool PCR
- IgM antibody
- IgG antibody

Viral RN detectable in respiratory tract 2-3 days before symptoms appear

Slide credit: clinicaloptions.com

COVID Syndrome

- The delayed onset of critical illness in patients with Covid-19 suggests a maladaptive immune response to infection
- Timing of this process is not uniform, particularly in immunosuppressed populations

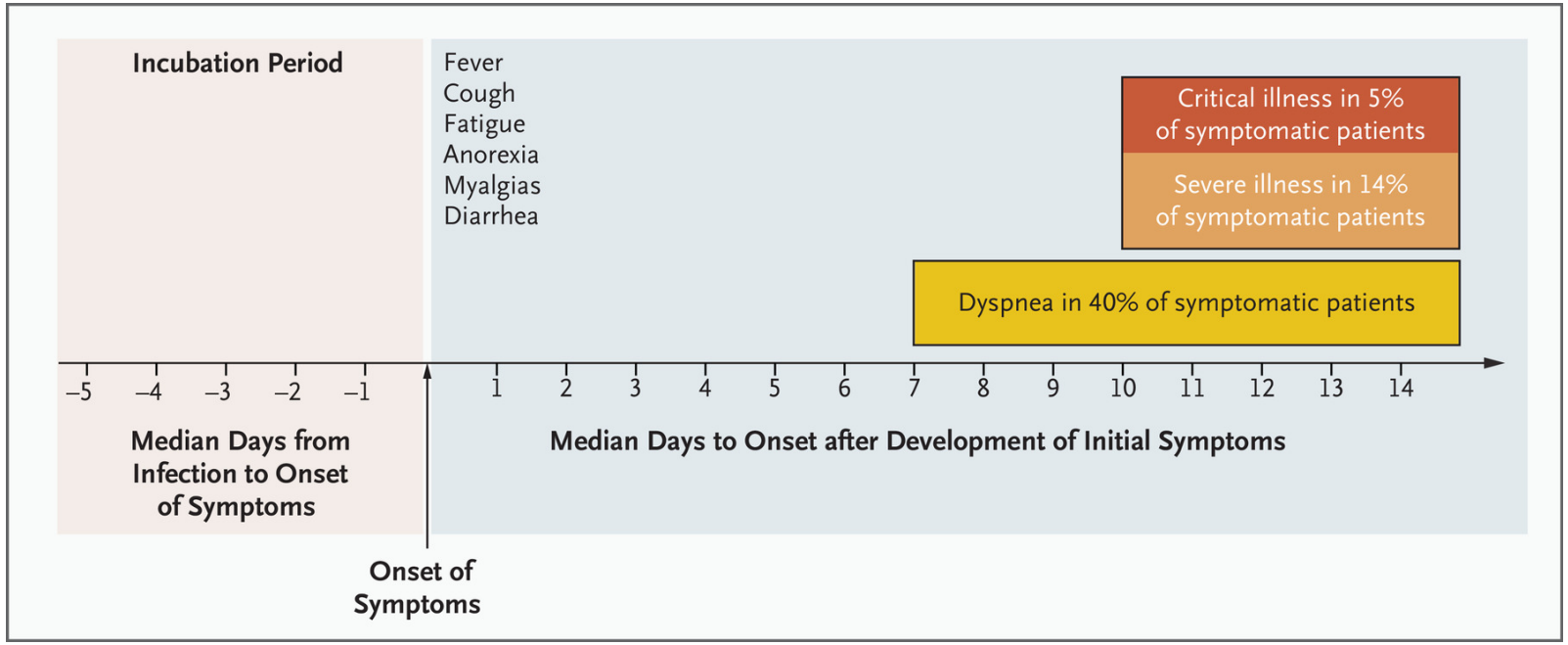


Siddiqi et al, *Heart and Lung Transplantation* 2020

What about Immunosuppressed/ Transplant patients?

- Timeline is far more variable
  - Mild disease is still often observed
  - Can have prolonged ‘viremic’ symptoms
  - Late presentation with respiratory distress can occur

Typical disease timeline

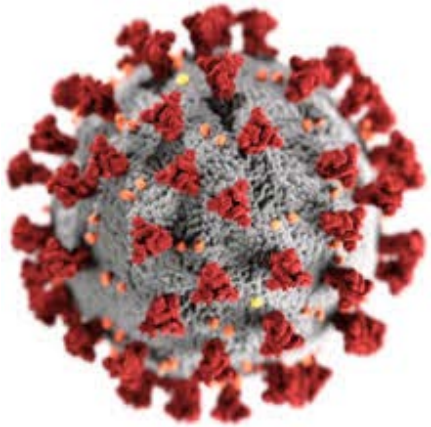


Principles of COVID Treatments

- Direct targeting of virus
  - Disrupting viral replication via antivirals
  - Clearance of virus via antibody
- Immune modulation
  - Suppression of pathologic inflammation to limit tissue damage

Strategies for a Successful Antiviral Therapeutic

- Pathogen specific therapy, "***the cure for the common cold***"
  - hundreds of different viral pathogens
- Timely therapy
  - Necessary to initiate antiviral early for meaningful benefit
- Well-tolerated
  - In order to treat early enough for benefit, will likely treat a higher number
- Viral resistance?



Remdesivir

- Developed by Gilead Sciences as antiviral
- Prodrug that metabolizes into an ATP analogue
- Inhibits RNA synthesis by interaction with RNA polymerase
- First tested in humans as a therapeutic for Ebola

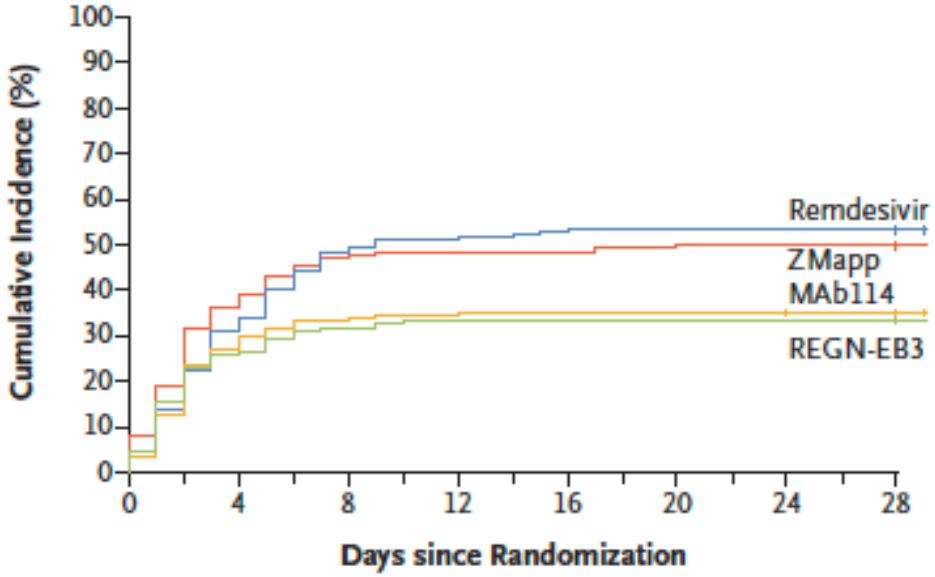
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 12, 2019 VOL. 381 NO. 24

A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics

Sabue Mulangu, M.D., Lori E. Dodd, Ph.D., Richard T. Davey, Jr., M.D., Olivier Tshiani Mbaya, M.D., Michael Proschan, Ph.D., Daniel Mukadi, M.D., Mariano Lusakibanza Manzo, Ph.D., Didier Nzolo, M.D., Antoine Tshomba Oloma, M.D., Augustin Ibanda, B.S., Rosine Ali, M.S., Sinaré Coulibaly, M.D., Adam C. Levine, M.D., Rebecca Grais, Ph.D., Janet Diaz, M.D., H. Clifford Lane, M.D., Jean-Jacques Muyembe-Tamfum, M.D., and the PALM Writing Group, for the PALM Consortium Study Team*

A Incidence of Death, Overall



No. at Risk

ZMapp	169	137	108	96	89	87	87	87	87	86	86	85	85	85	85
Remdesivir	175	151	121	105	91	86	86	85	83	82	82	82	82	82	82
MAb114	174	152	127	119	116	114	114	113	113	113	113	113	113	112	112
REGN-EB3	155	131	115	110	106	104	103	103	103	103	103	103	103	103	103

Cell Research

LETTER TO THE EDITOR OPEN

Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro

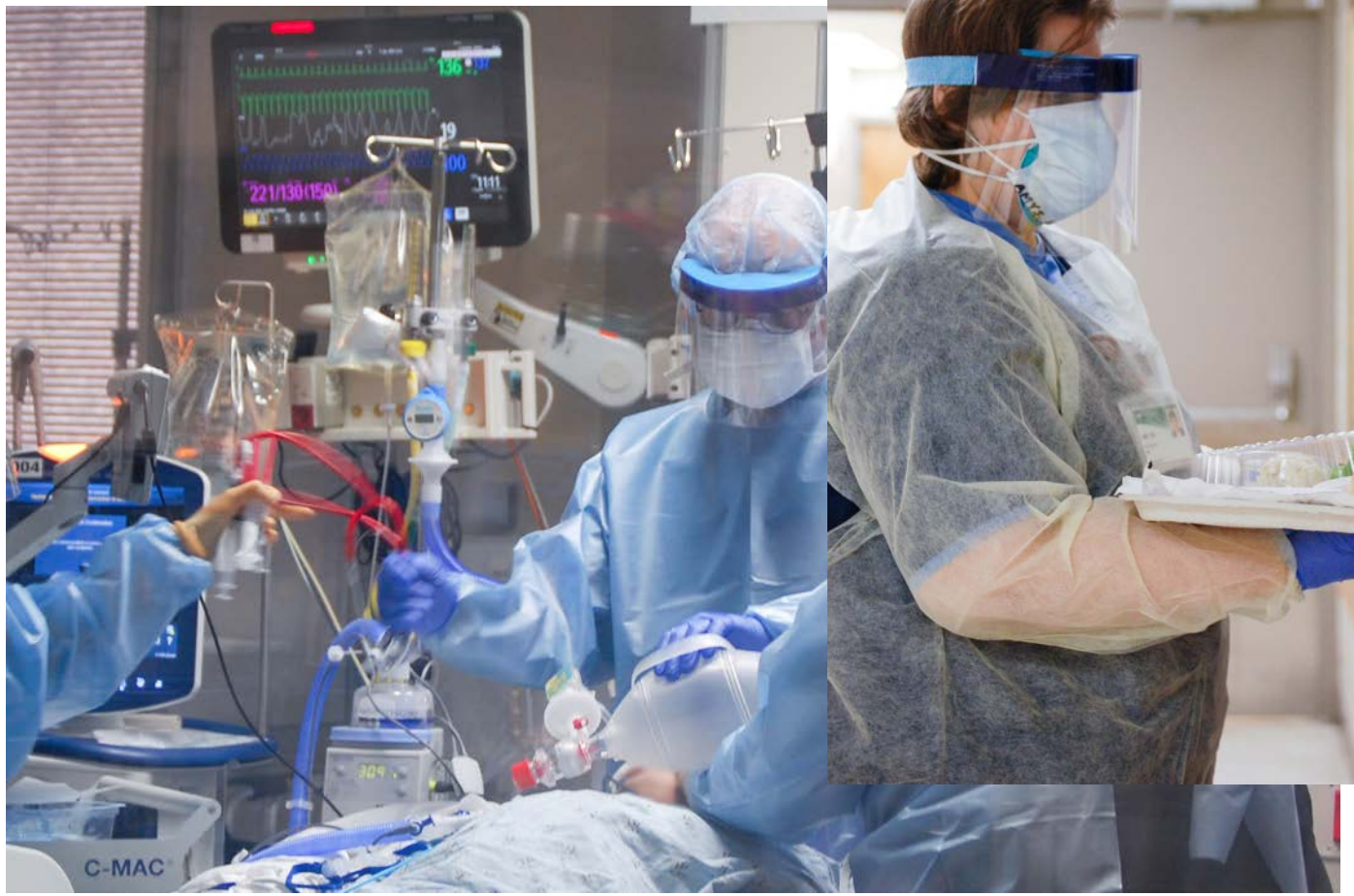
Cell Research (2020) 30:269–271; https://doi.org/10.1038/s41422-020-0282-0

- As an emerging pathogen, SARS-CoV-2 did not have any clinically proven therapeutics
  - Significant amount of preclinical research had been reported in the search for therapeutic treatments for the related coronaviruses: SARS and MERS

Clinical Trials in COVID Pandemic

- **Everything is harder!**

- Mitigating exposure
- PPE consumption
- Participant interactions
- Collecting/Processing specimens



NIAID Adaptive Randomized, Controlled Treatment Trial for COVID-19

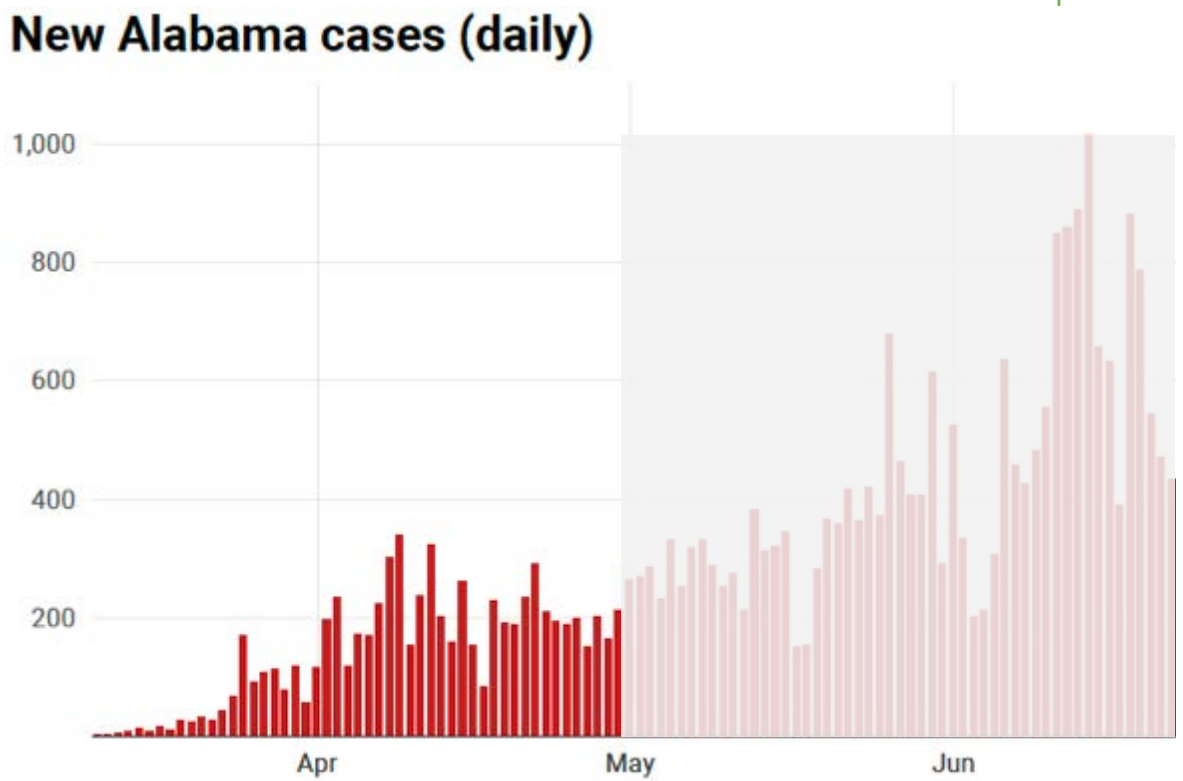
ACTT – Phase I

- Adaptive, randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of novel therapeutic agents in hospitalized adults diagnosed with COVID-19
- Phase I primary outcome is time to recovery by Day 29, key secondary outcome is improvements in the 8-point ordinal scale at Day 15
- Subjects assessed daily while hospitalized. If discharged, study visit at Days 15, 22, and 29 as an outpatient
- Study opened on February 21st, UAB opened March 26th

ACTT Implementation

Key Tasks

- Who has COVID?
  - Requires accurate, rapid testing
- Screening
  - Have to be able to quickly find COVID patients
- Consent
  - Sounds easy enough….
    - Paper consent? Electronic platform? Verbal consent? What about getting access to witness?
- Collecting Study Samples
  - Processing: Who, where, when; Storage; Documentation
- Providing study product
  - Inpatient wards, ICU, PPE, entering/exiting room
- Medical supervision of study
- Data capture, Data entry, Source Docs, Source Doc uploading, Data, Data…..
- There's Outpatient follow-up!

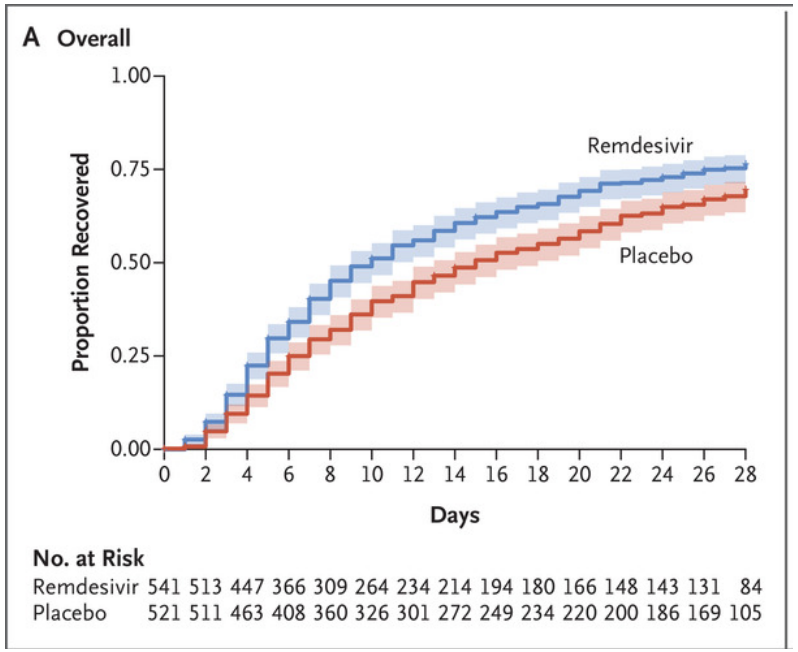


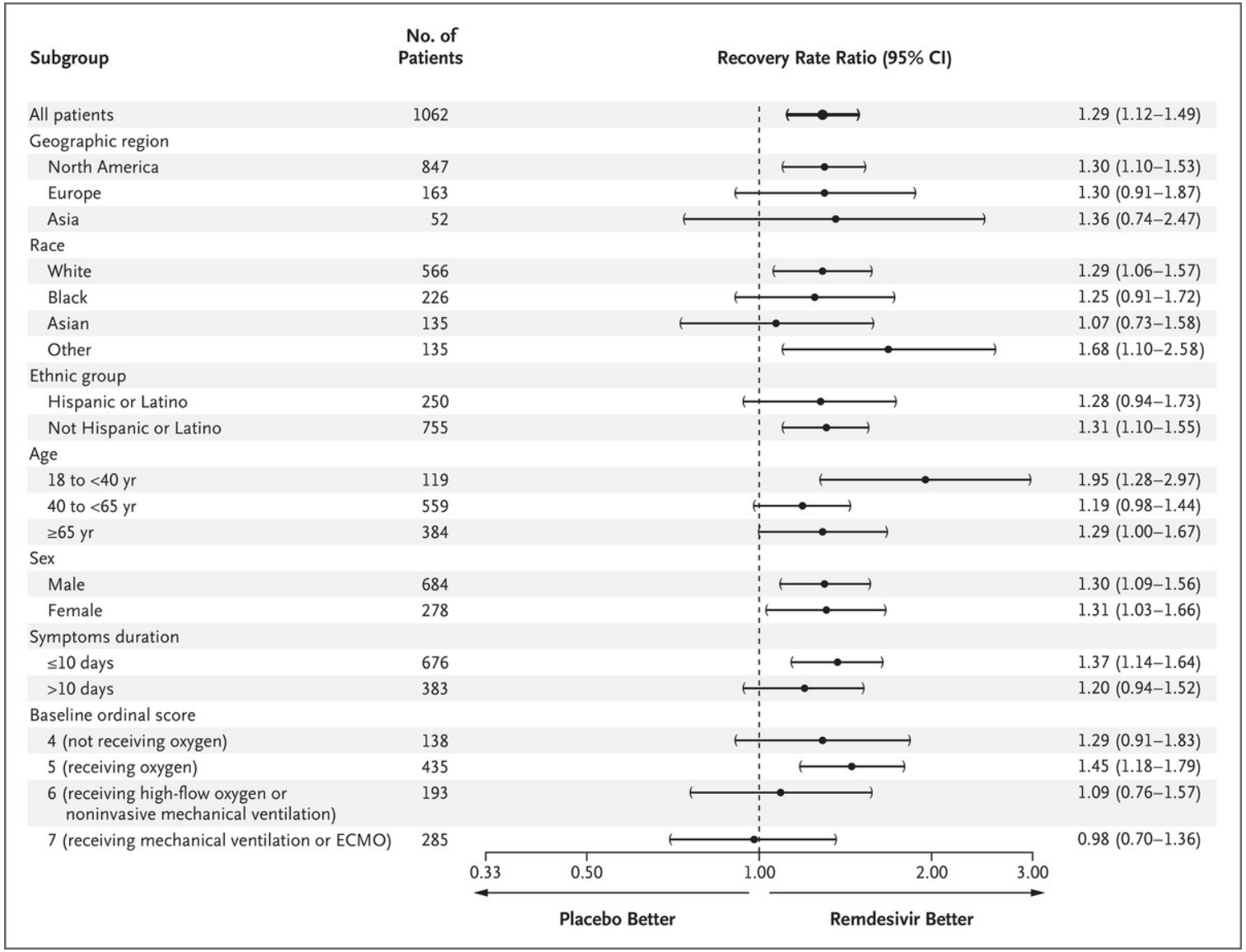
- Rapid increase in community cases and hospitalizations
- Dramatic changes to hospital workflow to accommodate increasing patients with highly infectious disease
- Limited therapeutic options with minimal data

ORIGINAL ARTICLE

Remdesivir for the Treatment of Covid-19 — Final Report

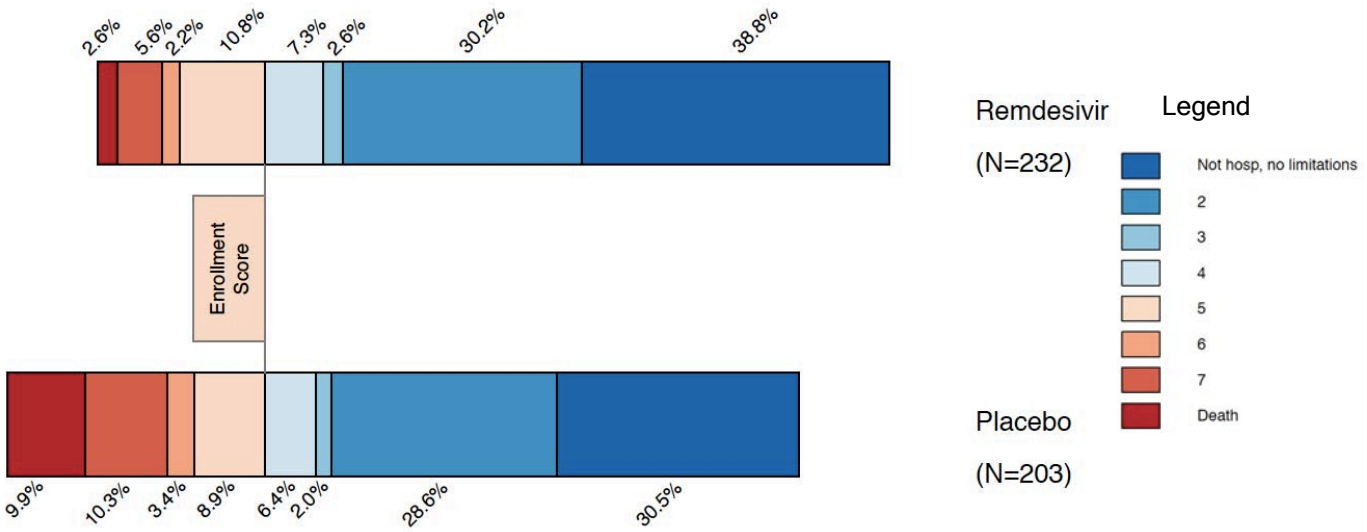
J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*





ACTT-1 Findings

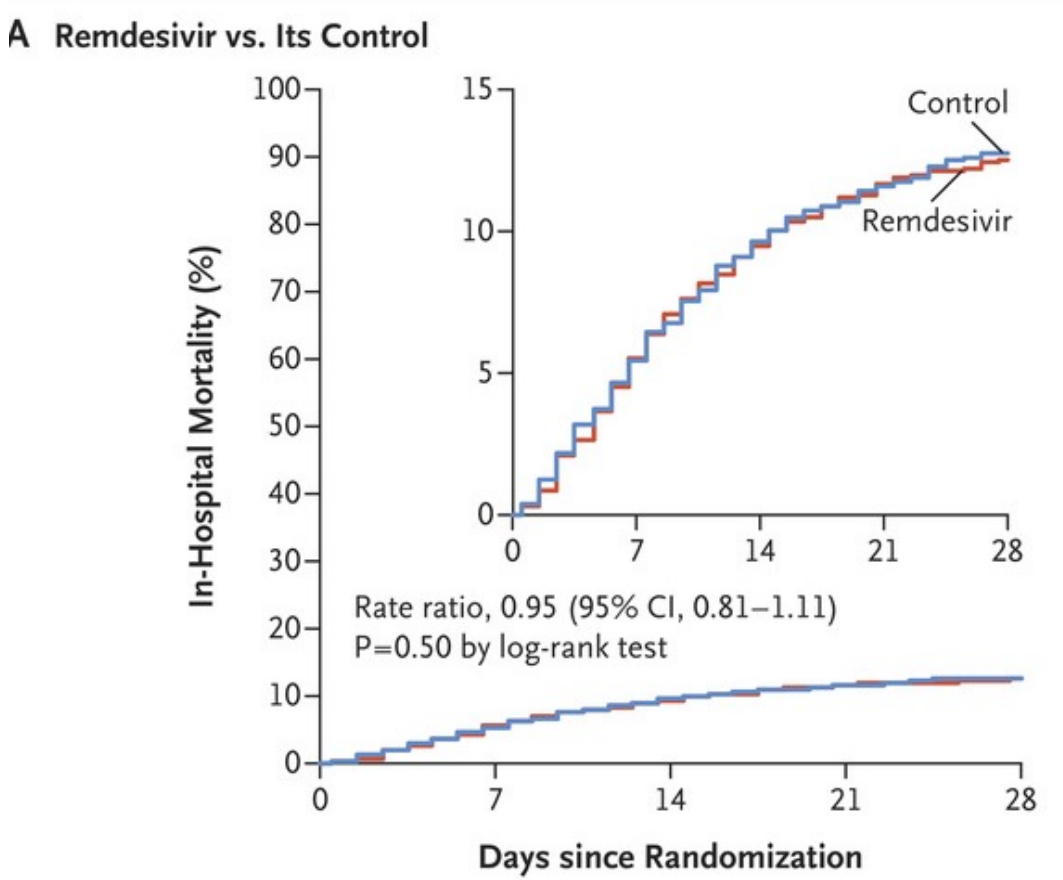
Ordinal Score 5 (low flow oxygen)



	Remdesivir (N=541)	Placebo (N=521)
Recovery		
No. of recoveries	399	352
Median time to recovery (95% CI) — days	10 (9–11)	15 (13–18)
Rate ratio (95% CI)†	1.29 (1.12–1.49 [P<0.001])	
Mortality through day 14‡		
Hazard ratio for data through day 15 (95% CI)	0.55 (0.36–0.83)	
No. of deaths by day 15	35	61
Kaplan–Meier estimate of mortality by day 15 — % (95% CI)	6.7 (4.8–9.2)	11.9 (9.4–15.0)
Mortality over entire study period‡		
Hazard ratio (95% CI)	0.73 (0.52–1.03)	
No. of deaths by day 29	59	77
Kaplan–Meier estimate of mortality by day 29 — % (95% CI)	11.4 (9.0–14.5)	15.2 (12.3–18.6)
Ordinal score at day 15 (±2 days) — no. (%)§		

WHO Solidarity Trial

- COVID-19 inpatients were randomized to Remdesivir, Hydroxychloroquine, Lopinavir and Interferon-β1a (based upon what was locally available) and open control designed to assess effects on in-hospital mortality
- No study drug reduced mortality (in any subgroup), initiation of ventilation or hospitalization duration
- Remdesivir RR=0.95 (0.81-1.11, p=0.50);



Remdesivir

- ACTT study approach with placebo controlled, randomized and blinded study met primary end point of time to recovery
- This observation was in line with numerous other findings on the study
- Solidarity study demonstrates what mortality benefit there may be is limited
- Antiviral approach is valid, if not optimal in patients with moderate to severe disease

FDA NEWS RELEASE

FDA Approves First Treatment for COVID-19

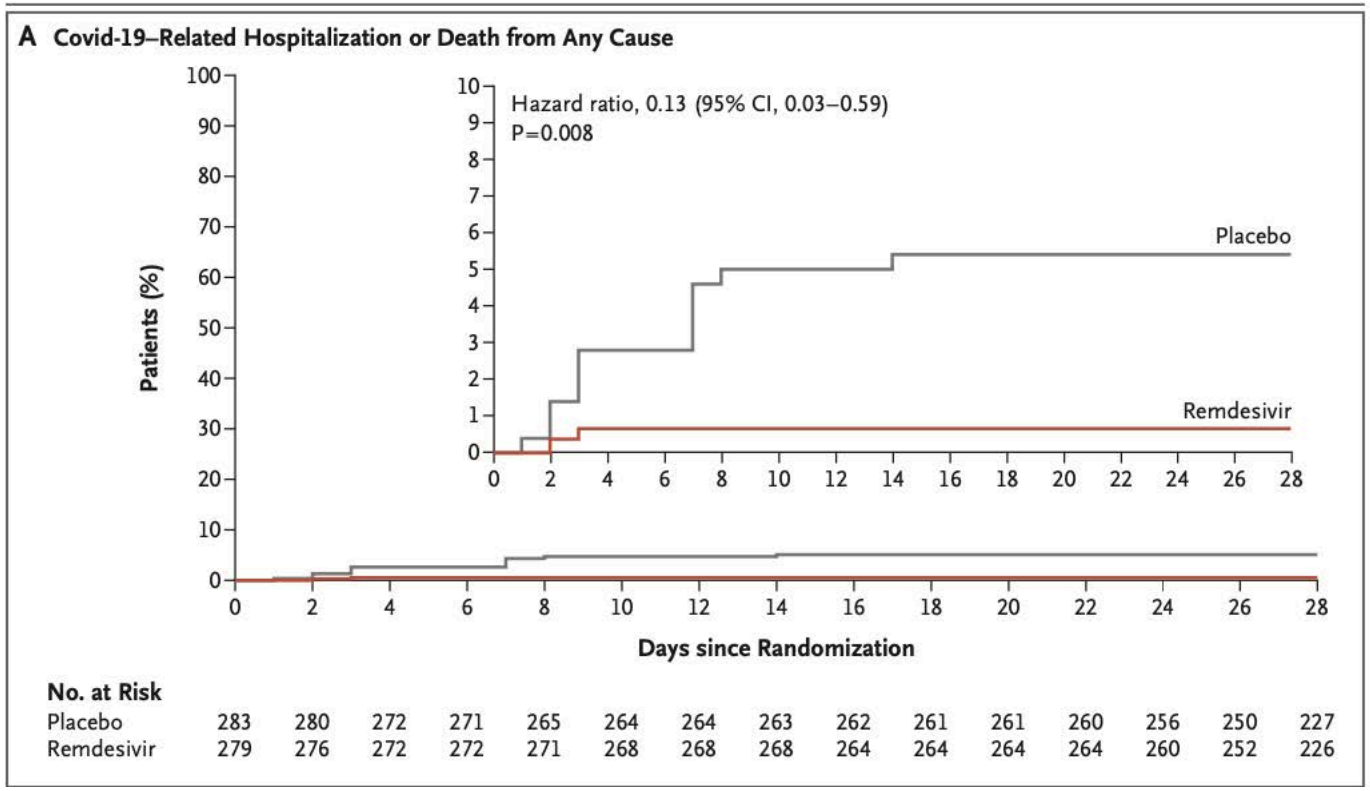
"The trial looked at 1,062 hospitalized subjects with mild, moderate and severe COVID-19 who received Veklury (n=541) or placebo (n=521), plus standard of care. The median time to recovery from COVID-19 was 10 days for the Veklury group compared to 15 days for the placebo group, a statistically significant difference. Overall, the odds of clinical improvement at Day 15 were also statistically significantly higher in the Veklury group when compared to the placebo group."

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 27, 2022 VOL. 386 NO. 4

Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients

R.L. Gottlieb, C.E. Vaca, R. Paredes, J. Mera, B.J. Webb, G. Perez, G. Oguchi, P. Ryan, B.U. Nielsen, M. Brown, A. Hidalgo, Y. Sachdeva, S. Mittal, O. Osiyemi, J. Skarbinski, K. Juneja, R.H. Hyland, A. Osinusi, S. Chen, G. Camus, M. Abdelghany, S. Davies, N. Behenna-Renton, F. Duff, F.M. Marty,* M.J. Katz, A.A. Ginde, S.M. Brown, J.T. Schiffer, and J.A. Hill, for the GS-US-540-9012 (PINETREE) Investigators†



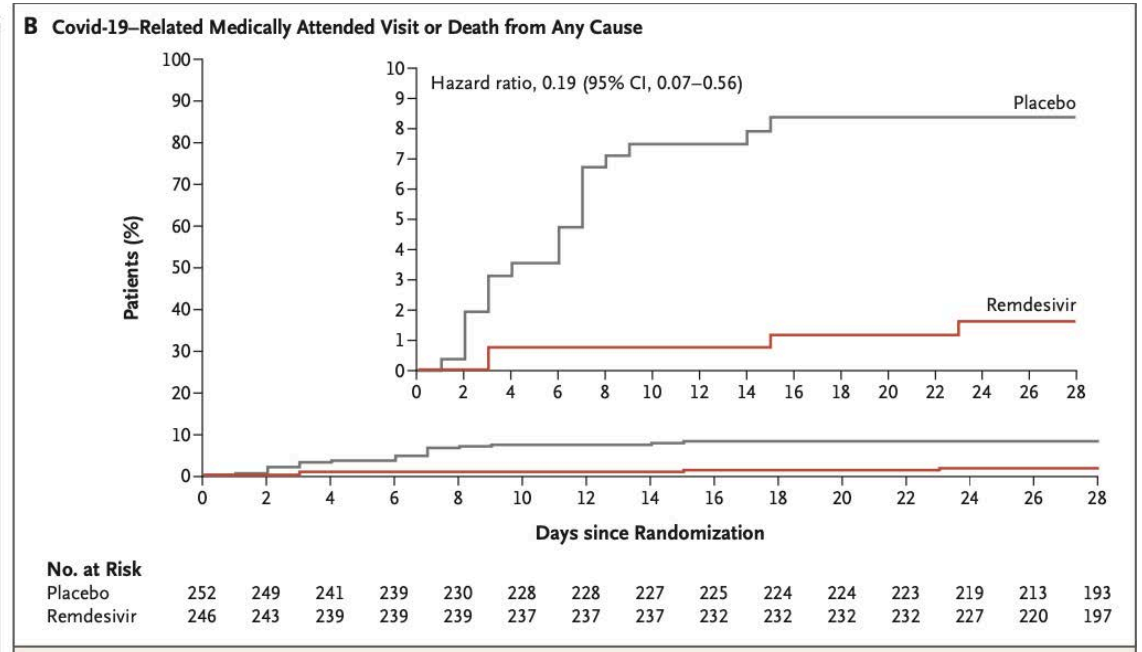


Figure 1. Primary Efficacy and Secondary End Points.

Panel A shows the Kaplan–Meier estimate of the time to hospitalization related to coronavirus disease 2019 (Covid-19) or death from any cause by day 28 (the primary efficacy end point). Panel B shows the Kaplan–Meier estimate of the time to a Covid-19–related medically attended visit or death from any cause by day 28 (a secondary end point); this end point was assessed in the modified full analysis set, which is defined in the statistical analysis plan (available with the protocol at NEJM.org). The hazard ratios, two-sided 95% confidence intervals, and P value were estimated with the use of Cox regression with the baseline stratification factors as covariates: residence in a skilled nursing facility (yes or no), age (<60 years or ≥60 years), and country (United States or outside the United States). Insets show the same data on an enlarged y axis.

Remdesivir

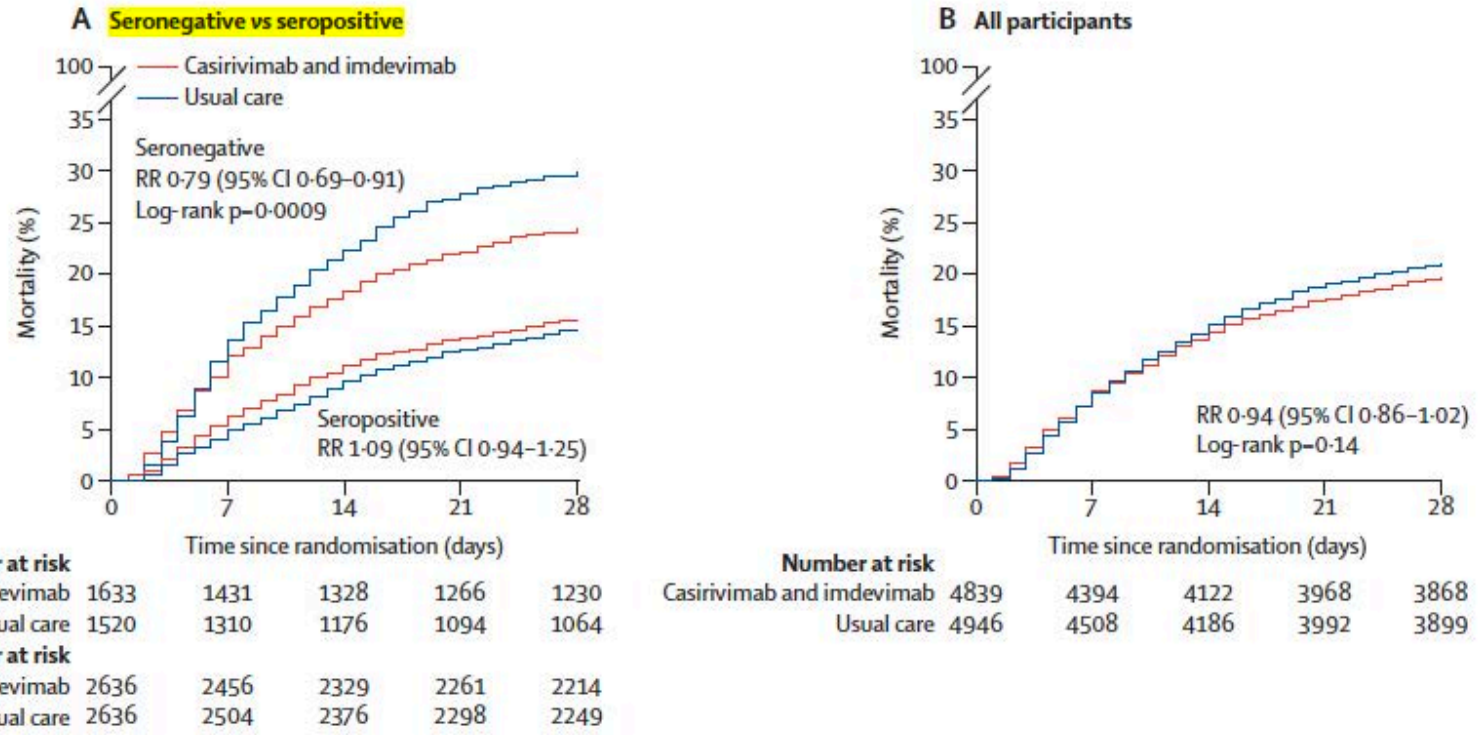
Source: Photographs from Gilead Sciences, Inc. | GAO-21-272

- Demonstrated efficacy for hospitalized patients with acute COVID-19
- Cost is ~$3,000 for a 5-day course
- Only available as once daily infusion
  - Challenging chemistry prevents oral version in near term

Antibody in hospitalized patients

Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

*RECOVERY Collaborative Group**

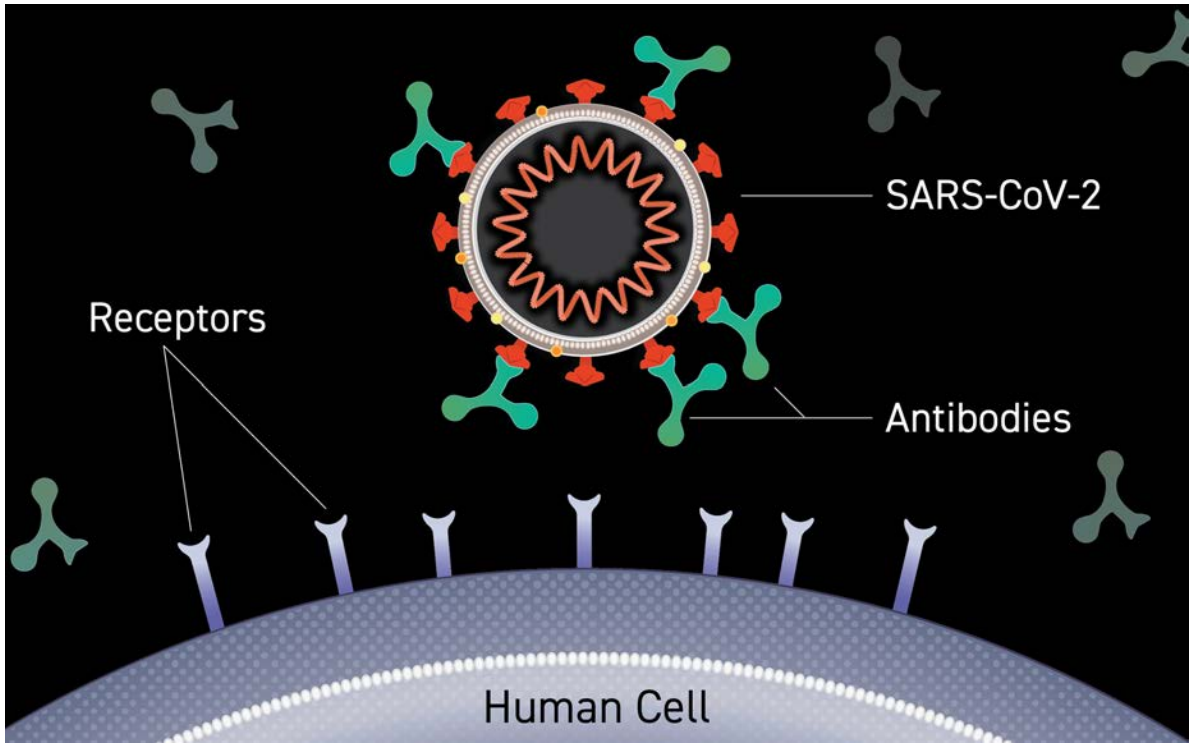


Seronegative number at risk					
Casirivimab and imdevimab	1633	1431	1328	1266	1230
Usual care	1520	1310	1176	1094	1064
Seropositive number at risk					
Casirivimab and imdevimab	2636	2456	2329	2261	2214
Usual care	2636	2504	2376	2298	2249

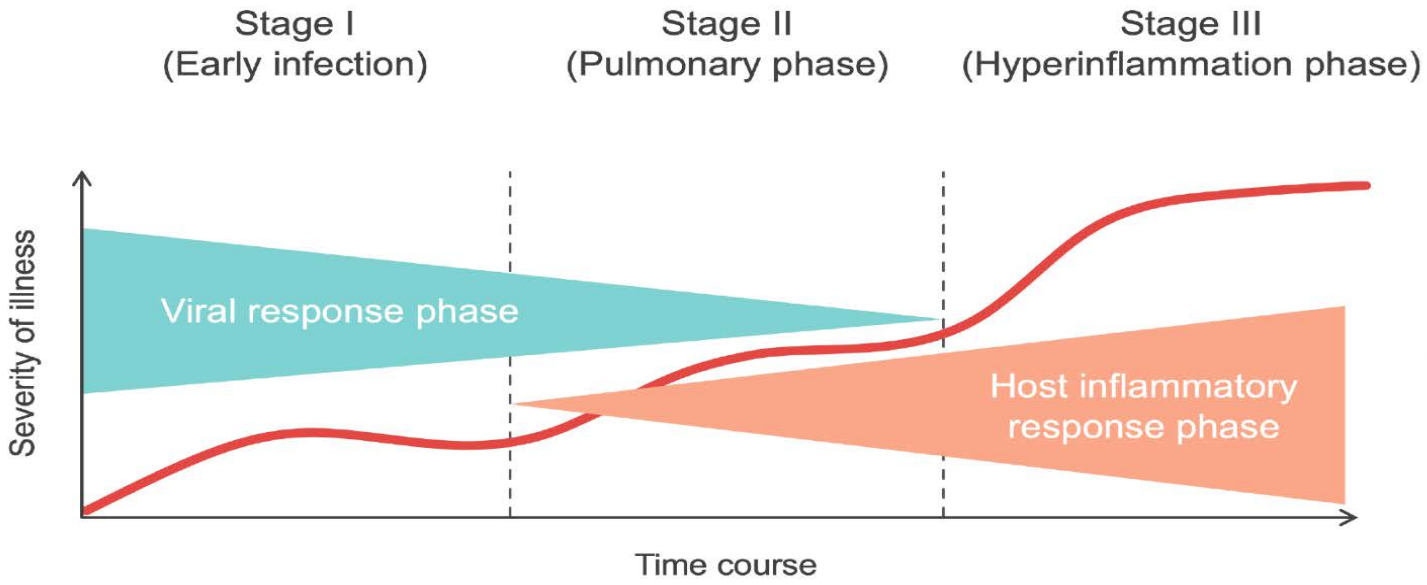
Number at risk					
Casirivimab and imdevimab	4839	4394	4122	3968	3868
Usual care	4946	4508	4186	3992	3899

Antibody in hospitalized patients

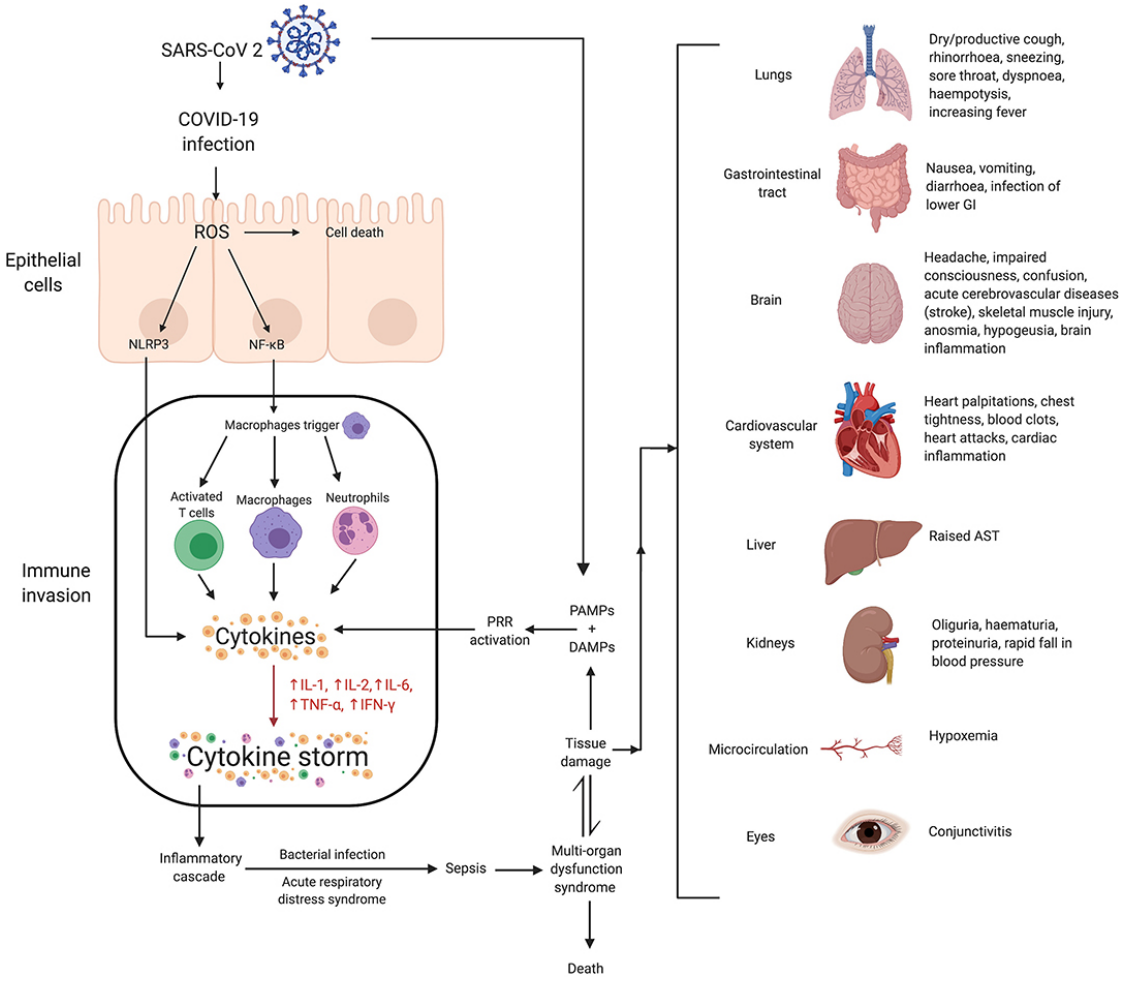
- Antibody (plasma or monoclonal) has benefit if:
  - Product is active against the strain present
  - Patient has not serologically converted at time of intervention
- As shown in Recovery study, minority of inpatients are seronegative
  - that study pre-dates Omicron strain



Immune Modulatory Strategies



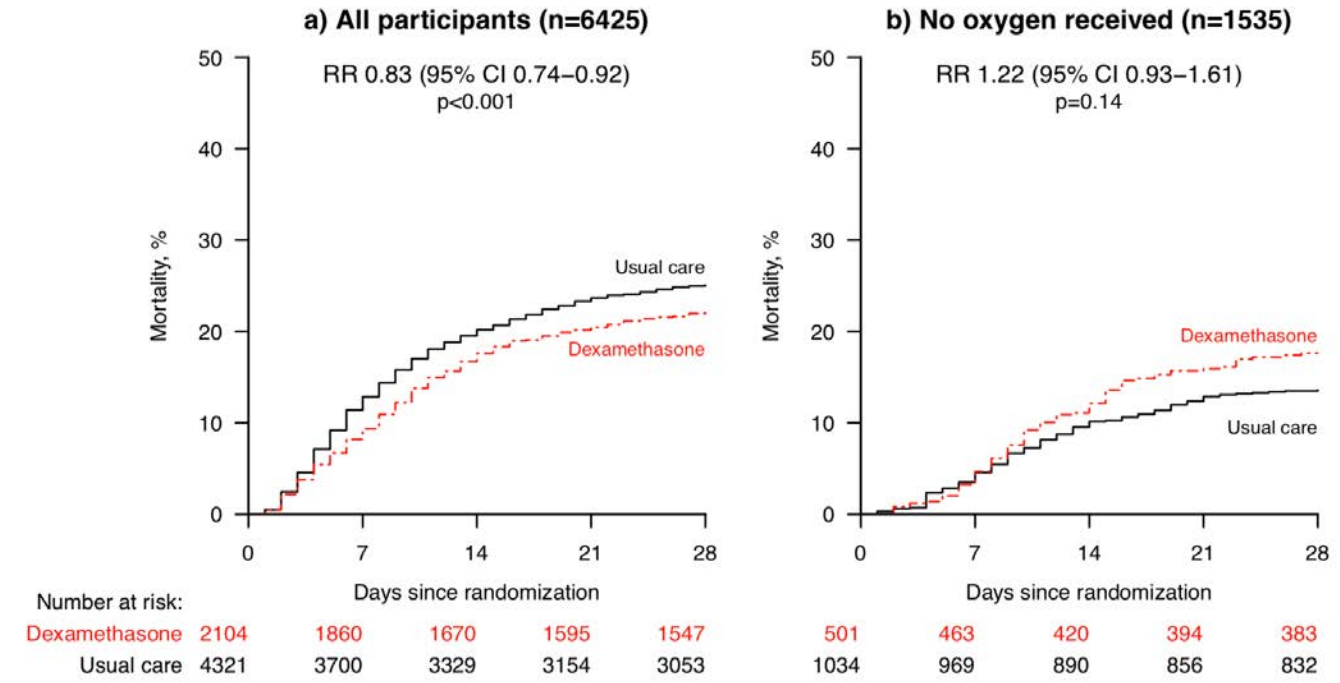
- Corticosteroids
  - dexamethasone
- JAK Inhibitors
  - Baricitinib
- IL-6
  - Tocilizumab
- IL-1
  - Anakinra
- TNF inhibitors



RECOVERY

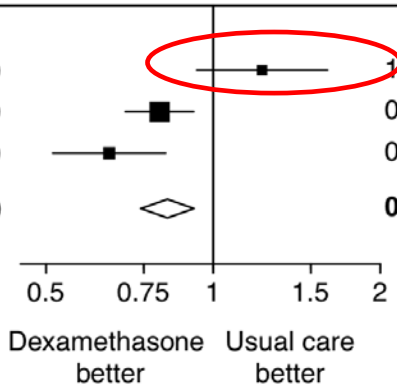
Randomised Evaluation of COVID-19 Therapy

- Dexamethasone reduced deaths by one-third in patients receiving invasive mechanical ventilation (29.0% vs. 40.7%, RR 0.65; p<0.001), by one-fifth in patients receiving oxygen without invasive mechanical ventilation (21.5% vs. 25.0%, RR 0.80; p=0.002)
- Did not reduce mortality in patients not receiving respiratory support at randomization (17.0% vs. 13.2%, RR 1.22; p=0.14).



Respiratory support at randomization	Dexamethasone	Usual care	RR (95% CI)
No oxygen received	85/501 (17.0%)	137/1034 (13.2%)	1.22 (0.93–1.61)
Oxygen only	275/1279 (21.5%)	650/2604 (25.0%)	0.80 (0.70–0.92)
Invasive mechanical ventilation	94/324 (29.0%)	278/683 (40.7%)	0.65 (0.51–0.82)
All participants	**454/2104 (21.6%)**	**1065/4321 (24.6%)**	**0.83 (0.74–0.92) p<0.001**

Trend across three categories: χ^2_1=11.49; p<0.001



ACTT 2

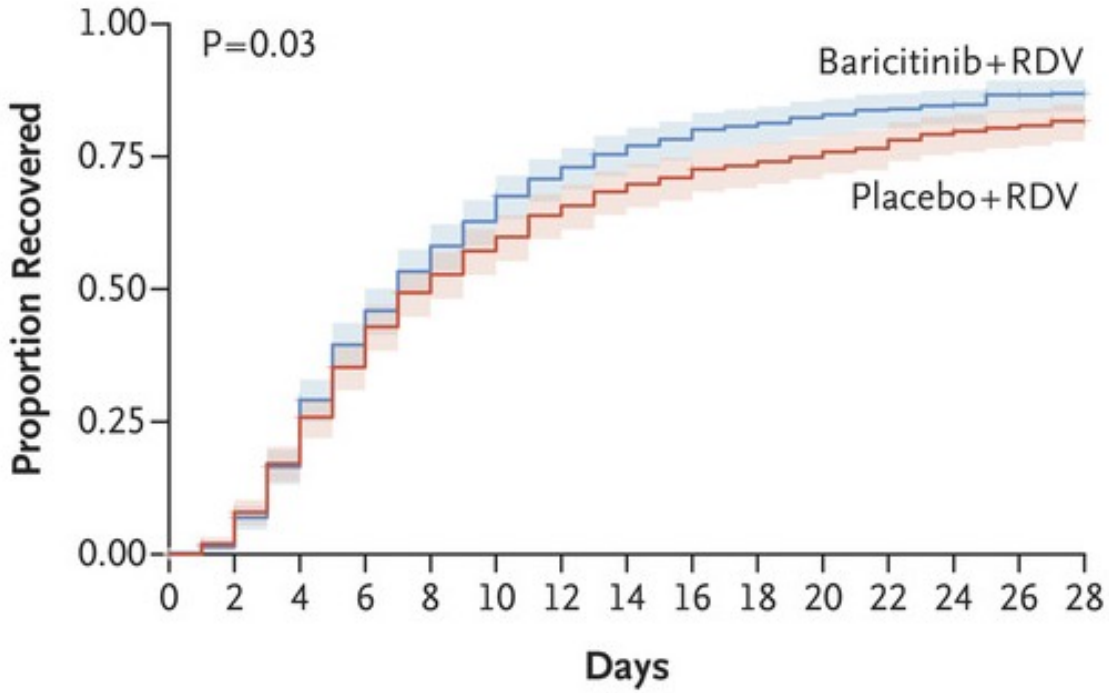
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19

A.C. Kalil, T.F. Patterson, A.K. Mehta, K.M. Tomashek, C.R. Wolfe, V. Ghazaryan, V.C. Marconi, G.M. Ruiz-Palacios, L. Hsieh, S. Kline, V. Tapson, N.M. Iovine, M.K. Jain, D.A. Sweeney, H.M. El Sahly, A.R. Branche, J. Regalado Pineda, D.C. Lye, U. Sandkovsky, A.F. Luetkemeyer, S.H. Cohen, R.W. Finberg, P.E.H. Jackson, B. Taiwo, C.I. Paules, H. Arguinchona, N. Erdmann, N. Ahuja, M. Frank, M. Oh, E.-S. Kim, S.Y. Tan, R.A. Mularski, H. Nielsen, P.O. Ponce, B.S. Taylor, L.A. Larson, N.G. Rouphael, Y. Saklawi, V.D. Cantos, E.R. Ko, J.J. Engemann, A.N. Amin, M. Watanabe, J. Billings, M.-C. Elie, R.T. Davey, T.H. Burgess, J. Ferreira, M. Green, M. Makowski, A. Cardoso, S. de Bono, T. Bonnett, M. Proschan, G.A. Deye, W. Dempsey, S.U. Nayak, L.E. Dodd, and J.H. Beigel, for the ACTT-2 Study Group Members*

A Overall



No. at Risk

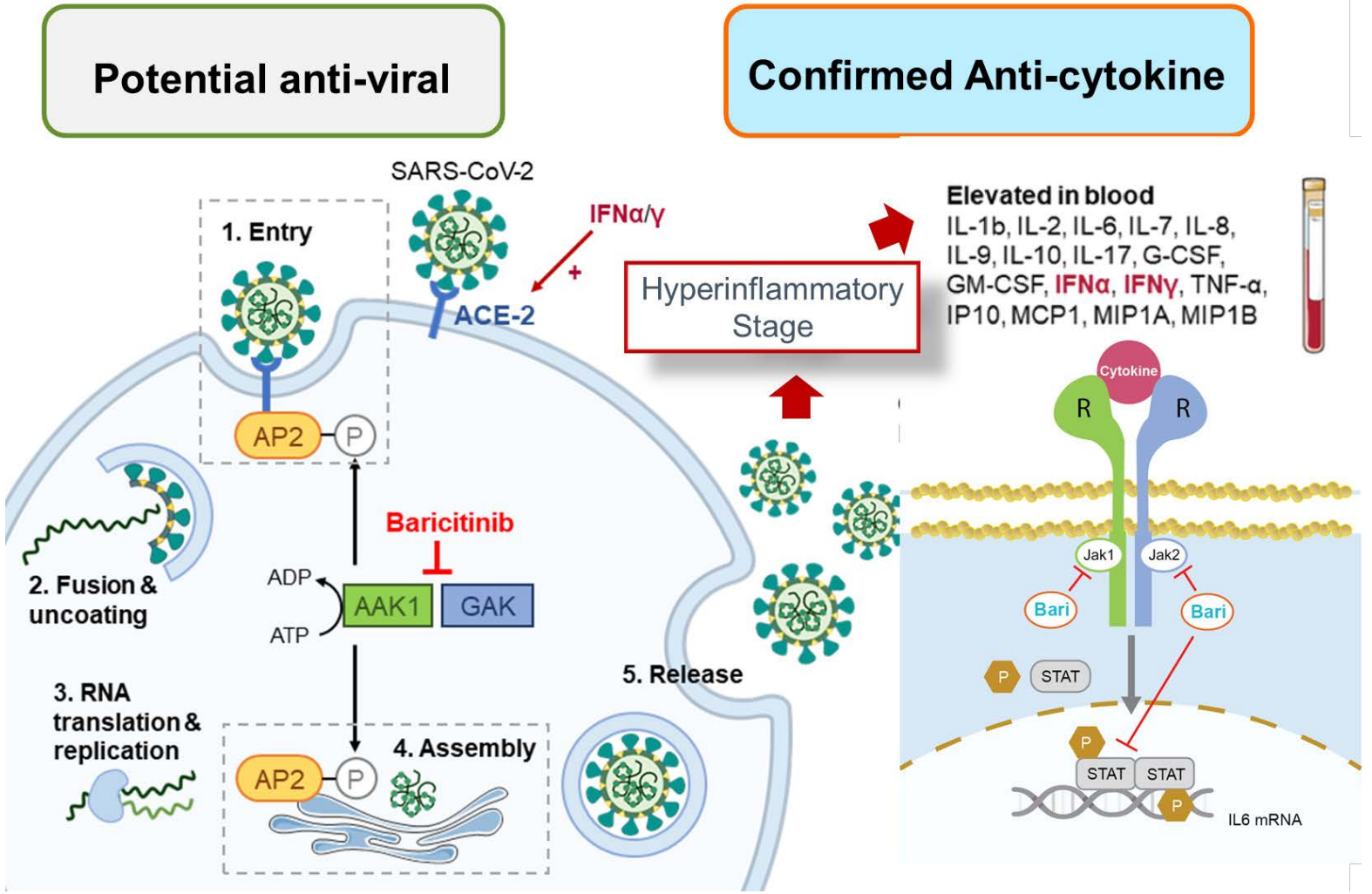
Baricitinib+RDV	515	497	418	302	233	186	145	121	107	95	87	80	76	63	30
Placebo+RDV	518	495	417	322	251	211	178	156	143	131	123	115	102	92	44

Primary Endpoint

	Overall	
	Baricitinib + RDV (n=515)	Placebo + RDV (n=518)
Recovery		
No. of recoveries	433	406
Median time to recovery (95% CI) - days	7 (6, 8)	8 (7, 9)
Rate ratio (95% CI)	1.16 (1.01, 1.32); p=0.035	

Baricitinib – Jak 1, 2 inhibitor

- Short half-life
  - About 10 hours
- Established safety profile
  - Approved for RA since 2017
  - Licensed in > 70 countries, rapidly scalable intervention
- Inhibits signaling of cytokines implicated in COVID-19
- Potential antiviral activities
  - Inhibitor of AP2-associated protein kinase 1



Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis

Running title: Baricitinib for COVID-19

RECOVERY Collaborative Group*

Efficacy and safety of baricitinib plus standard of care for the treatment of critically ill hospitalised adults with COVID-19 on invasive mechanical ventilation or extracorporeal membrane oxygenation: an exploratory, randomised, placebo-controlled trial

E Wesley Ely, Athimalaipet V Ramanan, Cynthia E Kartman, Stephanie de Bono, Ran Liao, Maria Lucia B Piruzeli, Jason D Goldman, José Francisco Kerr Saraiva, Sujatro Chakladar, Vincent C Marconi, on behalf of the COV-BARRIER Study Group*

Baricitinib+RDV	515	497	418	302	233	186	145	121	107	95	87	80	76	63	
Placebo+RDV	518	495	417	322	251	211	178	156	143	131	123	115	102	92	

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tofacitinib in Patients Hospitalized with Covid-19 Pneumonia

Patrícia O. Guimarães, M.D., Ph.D., Daniel Quirk, M.D., M.P.H., Remo H. Furtado, M.D., Ph.D., Lilia N. Maia, M.D., Ph.D., José F. Saraiva, M.D., Ph.D., Murillo O. Antunes, M.D., Ph.D., Roberto Kalil Filho, M.D., Ph.D., Vagner M. Junior, M.D., Alexandre M. Soeiro, M.D., Alexandre P. Tognon, M.D., Ph.D., Viviane C. Veiga, M.D., Ph.D., Priscilla A. Martins, M.D., Diogo D.F. Moia, Pharm.D., Bruna S. Sampaio, B.Sc., Silvia R.L. Assis, M.S., Ronaldo V.P. Soares, Pharm.D., Luciana P.A. Piano, Ph.D., Kleber Castilho, M.B.A., Roberta G.R.A.P. Momesso, Ph.D., Frederico Monfardini, M.Sc., Helio P. Guimarães, M.D., Ph.D., Dario Ponce de Leon, M.D., Majori Dulcine, M.D., Marcia R.T. Pinheiro, M.D., Levent M. Gunay, M.D., J. Jasper Deuring, Ph.D., Luiz V. Rizzo, M.D., Ph.D., Tamas Koncz, M.D., Ph.D., and Otavio Berwanger, M.D., Ph.D., for the STOP-COVID Trial Investigators*

Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial

Vincent C Marconi, Athimalaipet V Ramanan, Stephanie de Bono, Cynthia E Kartman, Venkatesh Krishnan, Ran Liao, Maria Lucia B Piruzeli, Jason D Goldman, Jorge Alatorre-Alexander, Rita de Cassia Pellegrini, Vicente Estrada, Mousumi Som, Anabela Cardoso, Sujatro Chakladar, Brenda Crowe, Paulo Reis, Xin Zhang, David H Adams, E Wesley Ely, on behalf of the COV-BARRIER Study Group*

p=0.035

Immune Modulatory Strategies

JAMA Internal Medicine | **Original Investigation**

Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia

A Rand

Olivier Hermin PhD;
Raphaël Porch

CONCLUSION
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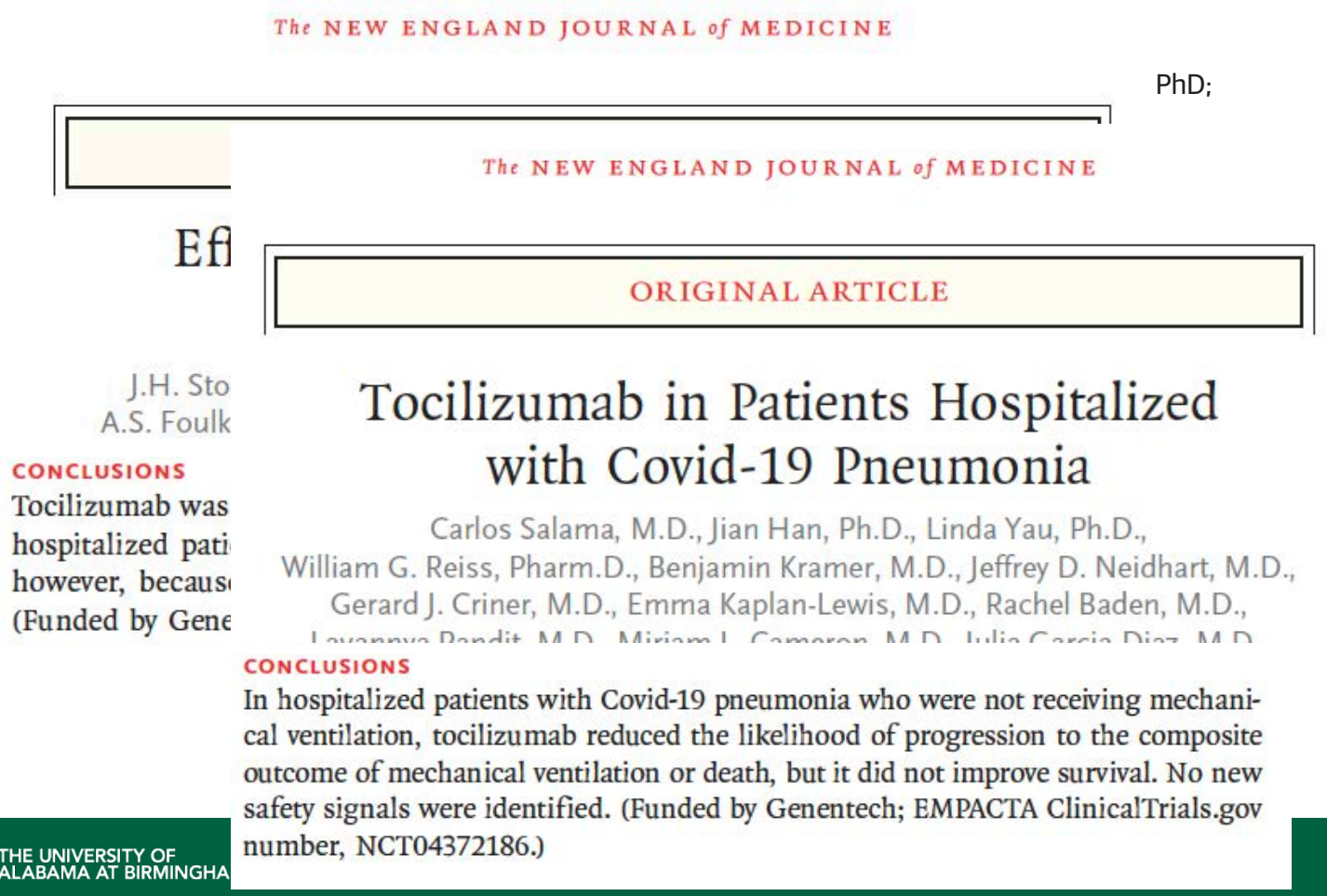
death by day
for confirmi



The NEW ENGLAND JOURNAL of MEDICINE

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CONCLUSIONS
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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia

Carlos Salama, M.D., Jian Han, Ph.D., Linda Yau, Ph.D., William G. Reiss, Pharm.D., Benjamin Kramer, M.D., Jeffrey D. Neidhart, M.D., Gerard J. Criner, M.D., Emma Kaplan-Lewis, M.D., Rachel Baden, M.D.,

CONCLUSIONS

In hospitalized patients with Covid-19 pneumonia who were not receiving mechanical ventilation, tocilizumab reduced the likelihood of progression to the composite outcome of mechanical ventilation or death, but it did not improve survival. No new safety signals were identified. (Funded by Genentech; EMPACTA ClinicalTrials.gov number, NCT04372186.)

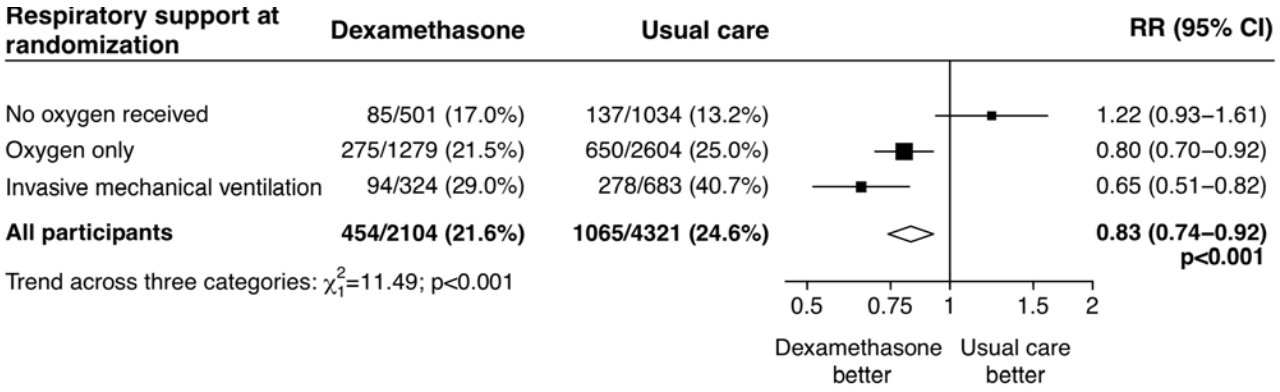
- Given the broad inflammatory response triggered by SARS-CoV 2, targeting a single cytokine may not be sufficient

UAB COVID Therapeutic Committee

- **Representation from: ID, Pulm/Critical Care, Rheumatology, Pharmacy, and Ethics**

NIAID Adaptive Randomized, Controlled Treatment Trial for COVID-19

RECOVERY
Randomised Evaluation of COVID-19 Therapy



FDA NEWS RELEASE

FDA Issues Emergency Use Authorization for Convalescent Plasma as Potential Promising COVID–19 Treatment, Another Achievement in Administration's Fight Against Pandemic

FDA NEWS RELEASE

Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Chloroquine and Hydroxychloroquine

UAB MEDICINE

UAB Treatment Guidance for COVID-19 (SARS-CoV-2). Updated 10/26/2020

Severity	Clinical Presentation	Medication Treatment	Supportive Care/Adjunctive Therapy	Notes
Prophylaxis	• No SARS-CoV-2 infection	No prophylaxis recommended	Follow government recs for hand washing, social distancing, masking	No medication has been shown to prevent COVID-19
Asymptomatic	• Confirmed SARS-CoV-2 without symptoms	None	Isolation for 10 days after positive test Follow CDC guidance	Asymptomatic patients can still transmit the virus
Mild (Outpatients)^	• Confirmed SARS-CoV-2 • Fever (≥100.4°F) • Cough/cold symptoms • No dyspnea or hypoxia • Normal chest imaging°	Observational clinical trial enrollment (e.g. antibody levels), call 205-996-4099 Therapeutic clinical trial enrollment, call 205-934-6777 Steroids not routinely recommended	Isolation until: 10 days since symptoms began, 24 hours since fever resolved, and other symptoms improved Cough and cold meds, rest, hydration Follow CDC guidance	COVID-19 outpatient clinical trials: ACTIV-2 (Lilly Monoclonal Antibody) Convalescent Plasma
Moderate (Hospitalized)	• Confirmed SARS-CoV-2 • Fever (≥100.4°F) • Cough/cold symptoms • Dyspnea • Hypoxia • Pneumonia on chest imaging°	Clinical trial enrollment Remdesivir - see next sheet# If new/increasing O2 needed to maintain sat >94%, consider dexamethasone 6-8 mg PO or 8 mg IV daily x10 days (stop if discharged)	Prefer low-flow NC or Venturi or NRB Cautious use of HFNC (under surgical mask) Pharmacologic DVT prophylaxis Early goals of care discussion	COVID-19 inpatient clinical trials: Adaptive COVID-19 Treatment (ACTT) Anakinra/Cytokine Storm Syndrome I-SPY COVID-19 Inhaled Ensifentrine Regeneron Monoclonal Antibody No limitations on use, specific guidance pending RCT data: Convalescent plasma (order through powerplan) – page 8468 w/ questions
Severe (ICU)	• Confirmed SARS-CoV-2 • Fever (≥100.4°F) • Cough/cold symptoms • Dyspnea • Severe hypoxia • Pneumonia on chest imaging° • Mechanical ventilation/ARDS • Hemodynamic decompensation	Clinical trial enrollment Remdesivir - see next sheet# If new/increasing O2 needed to maintain sat >94%, dexamethasone 6-8 mg PO or 8 mg IV daily x10 days (stop if discharged)	Consider awake proning Cautious use of HFNC (under surgical mask) or BIPAP (viral filter in tubing) Rapid-sequence intubation w/ paralytic If intubated, ARDSnet ventilation with low tidal volumes and plateau <30. -If P/F below 150, prone 16+ hours/day	

^High risk outpatients if any of: Age ≥60, diabetes, obesity, cardiovascular disease, chronic respiratory disease, chronic kidney disease, cirrhosis, sickle cell, or immunosuppressed.

°Chest imaging not mandatory to obtain for outpatients or inpatients.

#Our Remdesivir Prioritization document is on the next page.

This document created by specialists from infectious diseases, pulmonary/critical care, rheumatology, hospitalists and pharmacy. We will update frequently, do not print this document.

Therapeutic Management of Hospitalized Adults With COVID-19

Last Updated: February 24, 2022

Figure 2. Therapeutic Management of Adults Hospitalized for COVID-19 Based on Disease Severity

Dosing regimens for the drugs recommended in this figure are listed in Table A below.

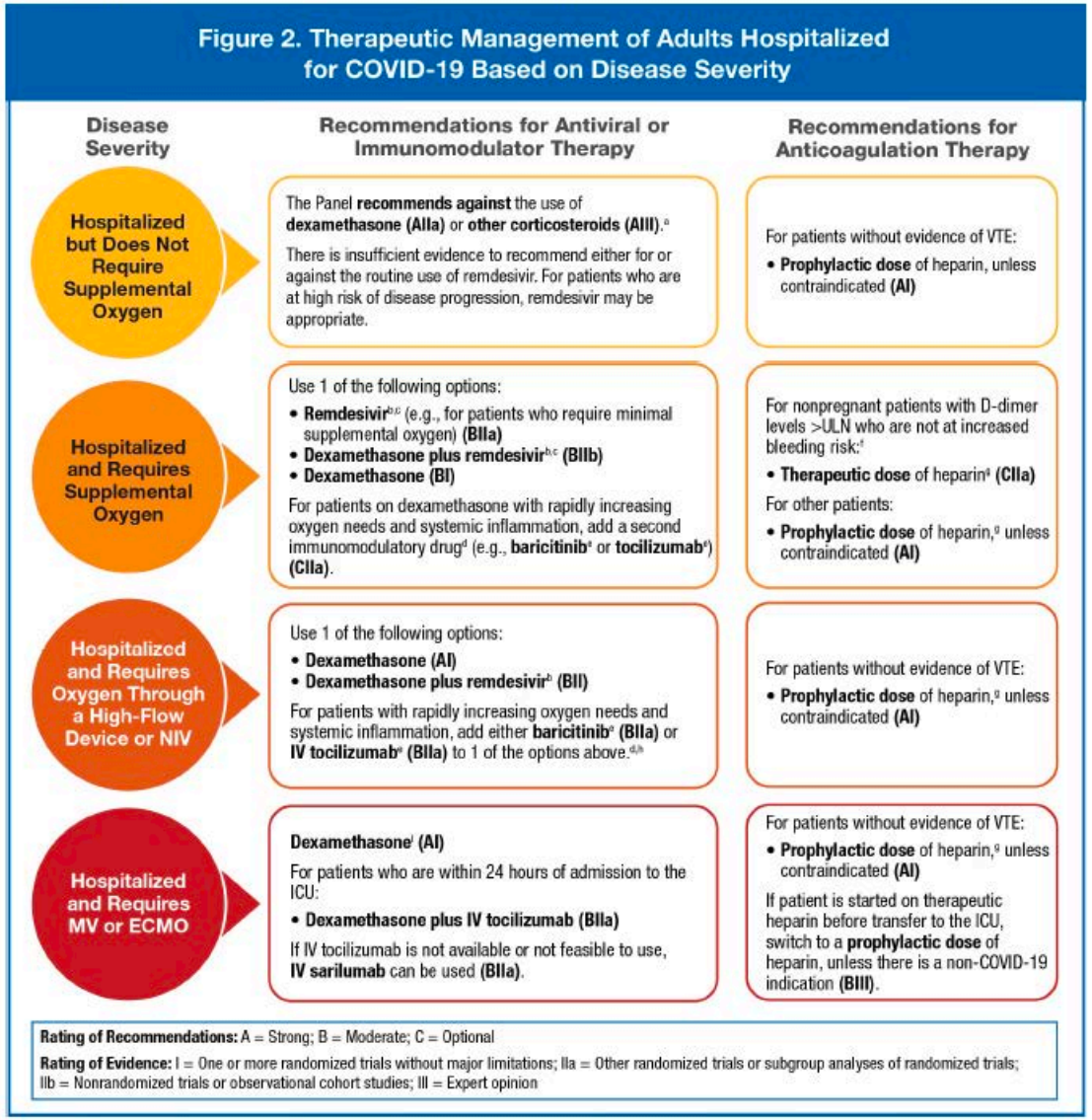


Table A. Dosing Regimens for the Drugs Recommended in Figure 2

Drug Name	Dosing Regimen	Comments
Remdesivir	RDV 200 mg IV once, then RDV 100 mg IV once daily for 4 days or until hospital discharge	• If the patient progresses to more severe illness, complete the course of RDV. • For a discussion on using RDV in patients with renal insufficiency, see Remdesivir.
Dexamethasone	DEX 6 mg IV or PO once daily for up to 10 days or until hospital discharge	• If DEX is not available, an equivalent dose of another corticosteroid may be used. • For more information, see Corticosteroids.
Baricitinib	Baricitinib dose is dependent on eGFR; duration of therapy is up to 14 days or until hospital discharge.	• eGFR ≥60 mL/min/1.73 m^2: Baricitinib 4 mg PO once daily • eGFR 30 to <60 mL/min/1.73 m^2: Baricitinib 2 mg PO once daily • eGFR 15 to <30 mL/min/1.73 m^2: Baricitinib 1 mg PO once daily • eGFR <15 mL/min/1.73 m^2: Baricitinib **is not recommended**.
Heparin	Therapeutic dose of SUBQ LMWH or IV UFH	• Administer for 14 days or until hospital discharge, unless there is a diagnosis of VTE or another indication for therapeutic anticoagulation.
	Prophylactic dose of SUBQ LMWH or SUBQ UFH	• Administer for the duration of the hospital stay.
Tofacitinib	Tofacitinib 10 mg PO twice daily for up to 14 days or until hospital discharge	• Use as an alternative immunomodulatory drug if baricitinib is not available or not feasible to use **(BIIa)**. • eGFR <60 mL/min/1.73 m^2: Tofacitinib 5 mg PO twice daily

Case 1:

- 50 yo patient on rituximab for lymphoma (in remission)
- Received 2 doses of Pfizer vaccine and Pfizer booster 4 months ago
- Admitted for Acute COVID; onset of symptoms 5 days ago

- Temp 101.2, O2 sats at 91%, HR 118, BP 110/62
- Serum Cr 1.5 (baseline 1.0)
- ALT 62 (baseline 24)
- Inflammatory biomarkers are pending

(Omicron BA.2 variant is now circulating in the community)

You recommend:

A. Start **Paxlovid** orally for 5 days
B. Start **Molnupiravir** orally for 5 days
C. Start **Remdesivir** IV daily + **Dexamethasone**
D. Give **Bebtelovimab** IV infusion X1 + **Dexamethaxone**
E. Give Ivermectin + Dexamethasone

https://www.covid19-druginteractions.org

Case 1 (continued):

- Despite initial interventions, hypoxia progresses over next 48hrs to 6L via nasal cannula with imminent transition to HFNC
- GFR now 27, liver enzymes stable
- Inflammatory biomarkers are elevated

Case 1

You now recommend:

A. Continue Remdesivir/dexamethasone, add Convalescent Plasma
B. Continue Remdesivir/dexamethasone, add **Tocilizumab**
C. Continue Remdesivir/dexamethasone, add **Baricitinib**
D. Continue Remdesivir/dexamethasone, add **Tofacitinib**
E. No change

https://www.covid19-druginteractions.org

Atypical Presentations in Immunosuppressed

- Highly variable immune states influenced by prior Coronavirus infections, vaccinations, immunosuppressive drugs
- Acute decompensations can be driven by excessive inflammation, or by rebound viremia
- Difficult to differentiate, but major impact on treatment recommendations
- Ct value and trajectory can provide valuable insight

Case 2

- 56y/o with hx of ESRD s/p DDKT 1987, maintained on CellCept 500 BID, prednisone 5, cyclosporine 100.
- Diagnosed with COVID 12/29 after 1 week of symptoms. Was referred for EUA Bamlanivumab and received 12/30. Started feeling better shortly after therapy, although persistent fatigue. Patient began feeling more tired with new cough and dyspnea and presented back to clinic and was referred for admission.

- Repeat COVID test +positive, placed on supplemental O2 (2L) started on anti-bacterials for possible secondary infection
- CRP – 202, Ferritin 1243

Case 2

- Prolonged COVID with hyperinflammatory response in setting of immunosuppression
- In discussions with Rheumatology, started patient on anakinra

- Rapid improvement in symptoms, weaned oxygen and discharged in few days.

- 12/29 COVID Cycle Threshold-19.8 (High burden of viremia)
- 1/20/21 COVID Cycle Threshold - 33 (very low viremia/residual template)

Case 3

- 58y/o with hx of breast cancer and subsequent AML/HSCT in 2014, now in remission, but receiving rituximab and tacro.
- Diagnosed with COVID 2/4, given Sotrovimab 2/7. Seen 2/28 with some lingering dyspnea/fatigue, COVID PCR (-), but noted to have pulmonary infiltrates. Next day developed new fever and admitted.
  - COVID PCR Ct 35
  - CRP 109, ferritin 899; infectious workup negative
- Given broad spectrum abx and corticosteroids/bari as well as convalescent plasma, discharged on steroid taper

Case 3

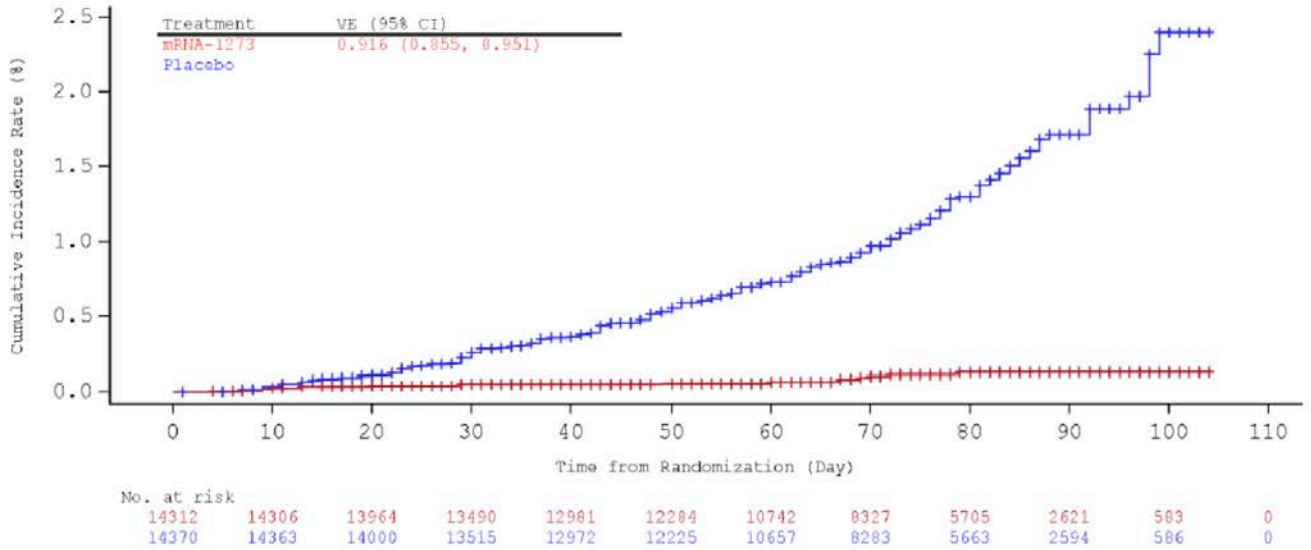
- 1-week later presents with fever, cough and decreased taste; re-admitted
- COVID PCR (+), Ct 16 (Very high viremia)
- Initiated on remdesivir, convalescent plasma, baricitinib

- Clinically improved, Ct appropriately increased to 30
- Plan for discharge and evusheld in a few weeks

Table 17. Final Scheduled Efficacy Analysis, Primary Endpoint, COVID-19 Starting 14 Days After the Second Dose per Adjudication Committee Assessments, Per-Protocol Set

Primary Endpoint: COVID-19 (per adjudication committee assessment)	Vaccine Group N=13934 Cases n (%) (Incidence Rate per 1,000 person-years)*	Placebo Group N=13883 Cases n (%) (Incidence Rate per 1,000 person-years)*	Vaccine Efficacy (VE) % (95% CI)**	Met Predefined Success Criterion***
All participants	11 (<0.1) 3.328	185 (1.3) 56.510	94.1% (89.3%, 96.8%)	Yes
18 to <65 years[1]	7/10551 (<0.1) 2.875	156/10521 (1.5) 64.625	95.6%; (90.6%, 97.9%)	NA
65 years and older[2]	4/3583 (0.1); 4.595	29/3552 (0.8); 33.728	86.4%; (61.4%, 95.5%)	NA

Figure 2. Cumulative Incidence Curves for the First COVID-19 Occurrence After Randomization, mITT Set

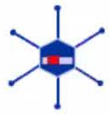
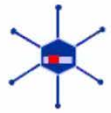


- All 11 cases of severe COVID-19 occurring 14 days after 2nd dose were in placebo group
- Efficacy of a single dose ~80.2%

FDA Briefing Document

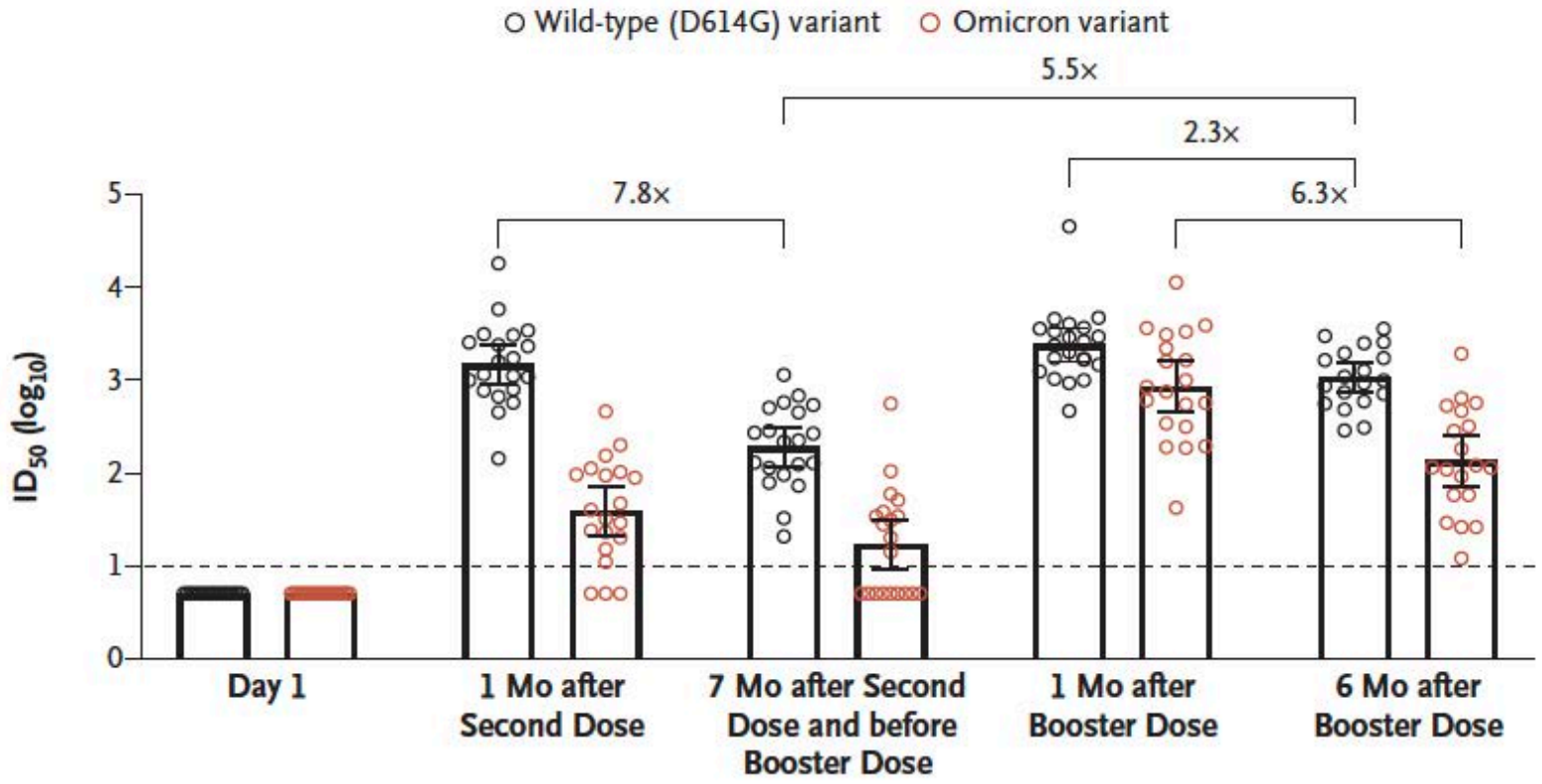
Moderna COVID-19 Vaccine

Update: Efficacy Testing of CoVID-19 Vaccine Candidates

Company	Platform	Product	Dose schedule	Phase 3 Status
moderna	 **mRNA**	Stabilized SARS-CoV-2 Spike	2 doses (0, 28)	VE=94%* BLA 18+; EUA 2 dose+boost; Ph3 ongoing boosts**
BIONTECH Pfizer	 **mRNA**	Stabilized SARS-CoV-2 Spike	2 doses (0, 21)	VE=95%, Final analysis: VE=84% BLA 16+ EUA 2 dose 5-11 yo EUA boost 12+
janssen	 **Ad Vector**	Stabilized SARS-CoV-2 Spike △F; TM	**1 dose**	Overall VE=66%* US 77%, BR 66%, SA 58% EUA issued 18+ Ph3 Ongoing boosts**
UNIVERSITY OF OXFORD AstraZeneca	 **Ad Vector**	ChAdOx1 **wild type Spike**; △F; TM **Ratio 2:1 Vaccine: Placebo**	2 doses (0, 28)	VE=76% Ph3 Closed n=32,427 BLA submission pending
NOVAVAX Creating Tomorrow's Vaccines Today	 **Recombinant protein**	Stabilized trimer Spike, △F; TM; Matrix M Adjuvant **Ratio 2:1 Vaccine: Placebo**	2 doses (0, 21)	US Overall VE=90.4% UK VE 89%, SA 49% EUA submission pending Ph3 ongoing boosts**
gsk SANOFI	 **Recombinant protein**	Stabilized Trimer Spike, △F; TM AS03 Adjuvant	2 doses (0, 21)	Ph3 Stage 1 await interim analysis; Stage 2 enrolling. Monovalent vs bivalent trimer boosts

Booster needed to develop omicron neutralizing antibodies

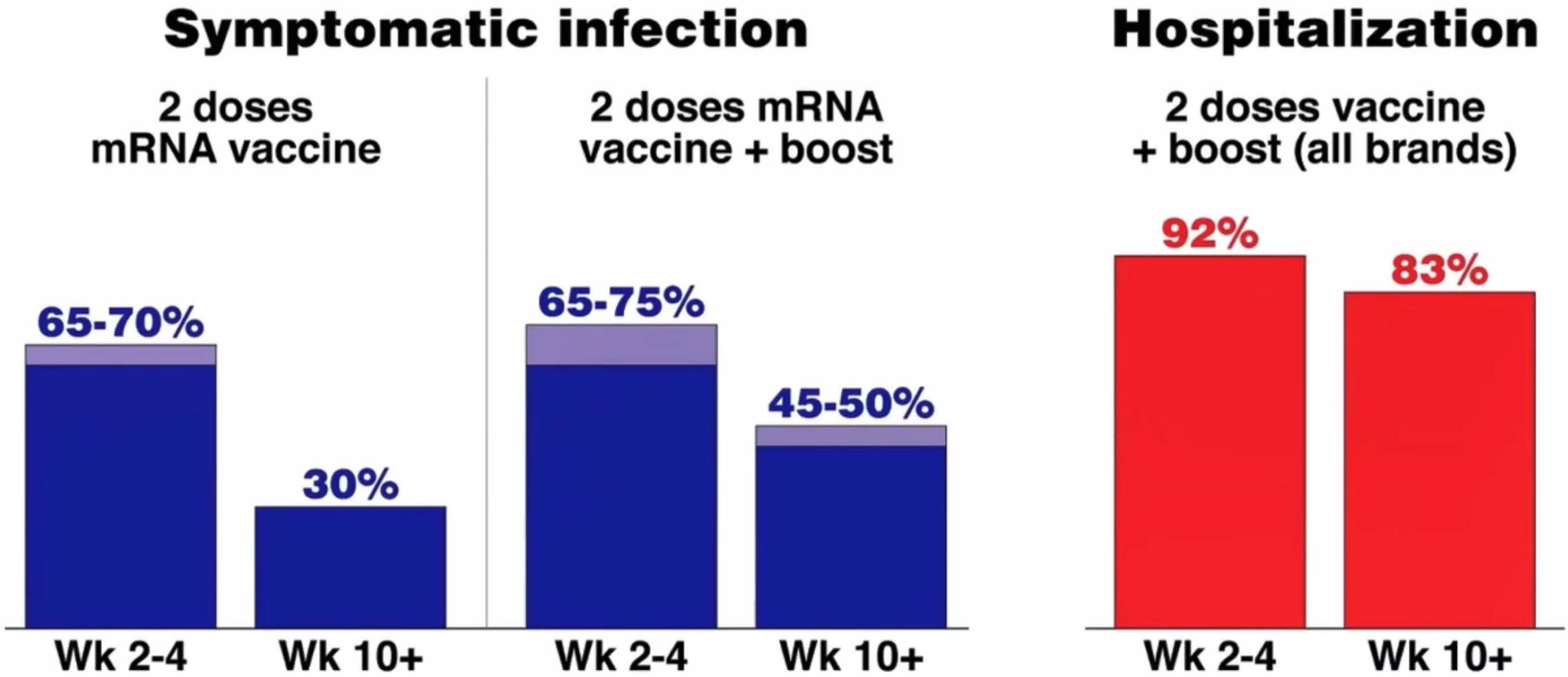
A Neutralizing Antibody Titers over Time



Geometric Mean Titer	1496	43	193	23	2423	850	1067	136
Percentage of Participants with Detectable Neutralizing Antibodies	100	85	100	55	100	100	100	100

Pajon et al. NEJM 2022

COVID-19 Vaccine Effectiveness Against Omicron Variant, UK

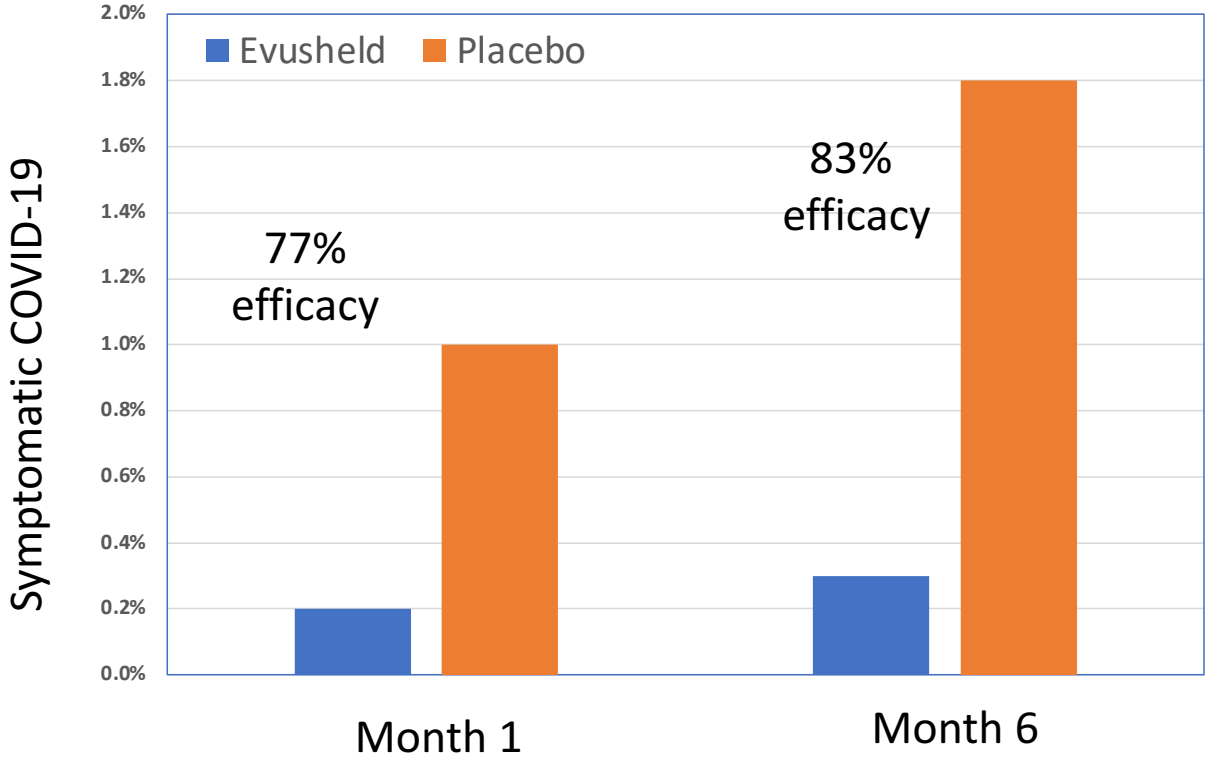


Source: UK Health Security Agency, 1/20/2022

Tixagevimab and Cilgavimab (Evusheld) for Pre-Exposure Prophylaxis of COVID-19

Box. Some Moderately or Severely Immunocompromising Conditions[5]

- Moderate or severe primary immunodeficiency
- Advanced or untreated HIV infection
- Receipt of CAR T-cell therapy or hematopoietic cell transplant within the previous 2 years
- Active treatment for a solid tumor or hematologic malignancy
- Use of immunosuppressive therapy after a solid-organ transplant
- Active treatment with other immunosuppressive or immuno-modulatory drugs, such as high-dose corticosteroids (≥20 mg/d of prednisone or equivalent) and tumor necrosis factor (TNF) inhibitors.



Modified from JAMA 2020

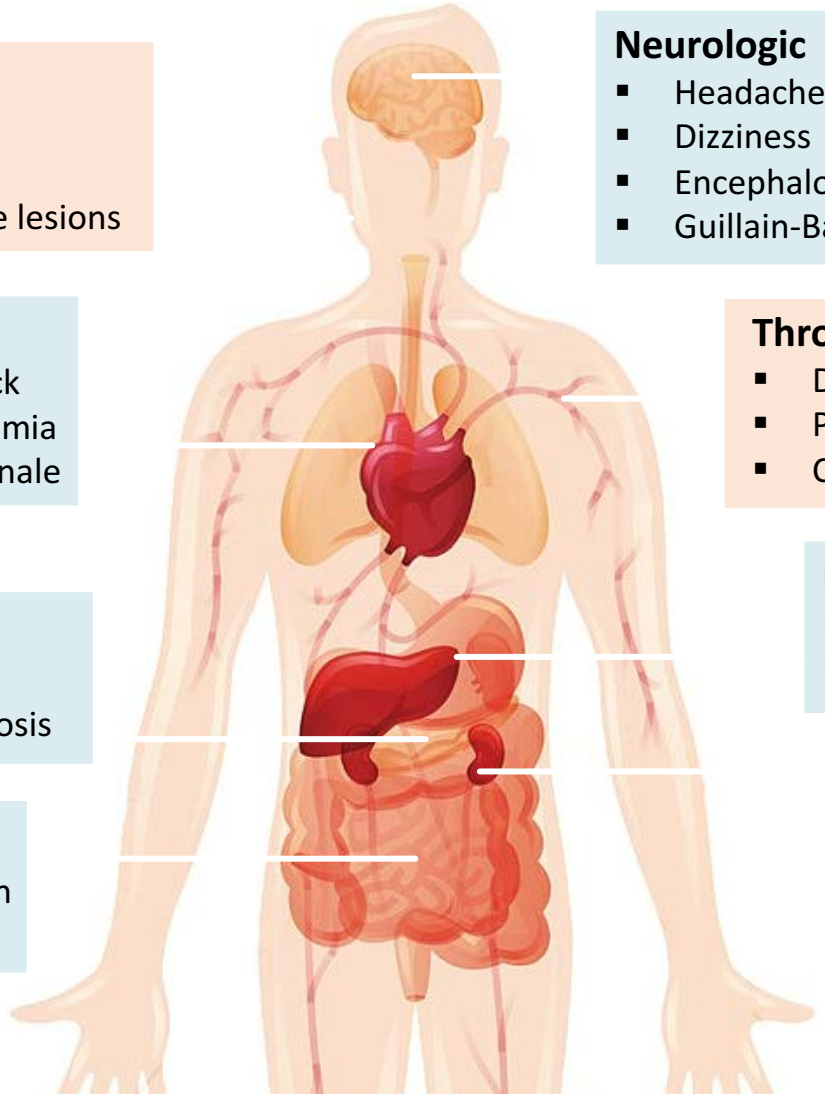
Extrapulmonary Manifestations of COVID-19: Which of These Return or Last?

Dermatologic
- Petechaie
- Livedo reticularis
- Erythematous rash
- Urticaria
- Vesicles
- Pernio-like lesions

Neurologic
- Headaches
- Dizziness
- Encephalopathy
- Guillain-Barré
- Ageusia
- Myalgia
- Anosmia
- Stroke

Cardiac
- Takotsubo cardiomyopathy
- Myocardial injury/myocarditis
- Cardiac arrhythmias
- Cardiogenic shock
- Myocardial ischemia
- Acute cor pulmonale

Thromboembolism
- Deep vein thrombosis
- Pulmonary embolism
- Catheter-related thrombosis



Endocrine
- Hyperglycemia
- Diabetic ketoacidosis

Hepatic
- Elevated ALT/AST
- Elevated bilirubin

Gastrointestinal
- Diarrhea
- Nausea/vomiting
- Abdominal pain
- Anorexia

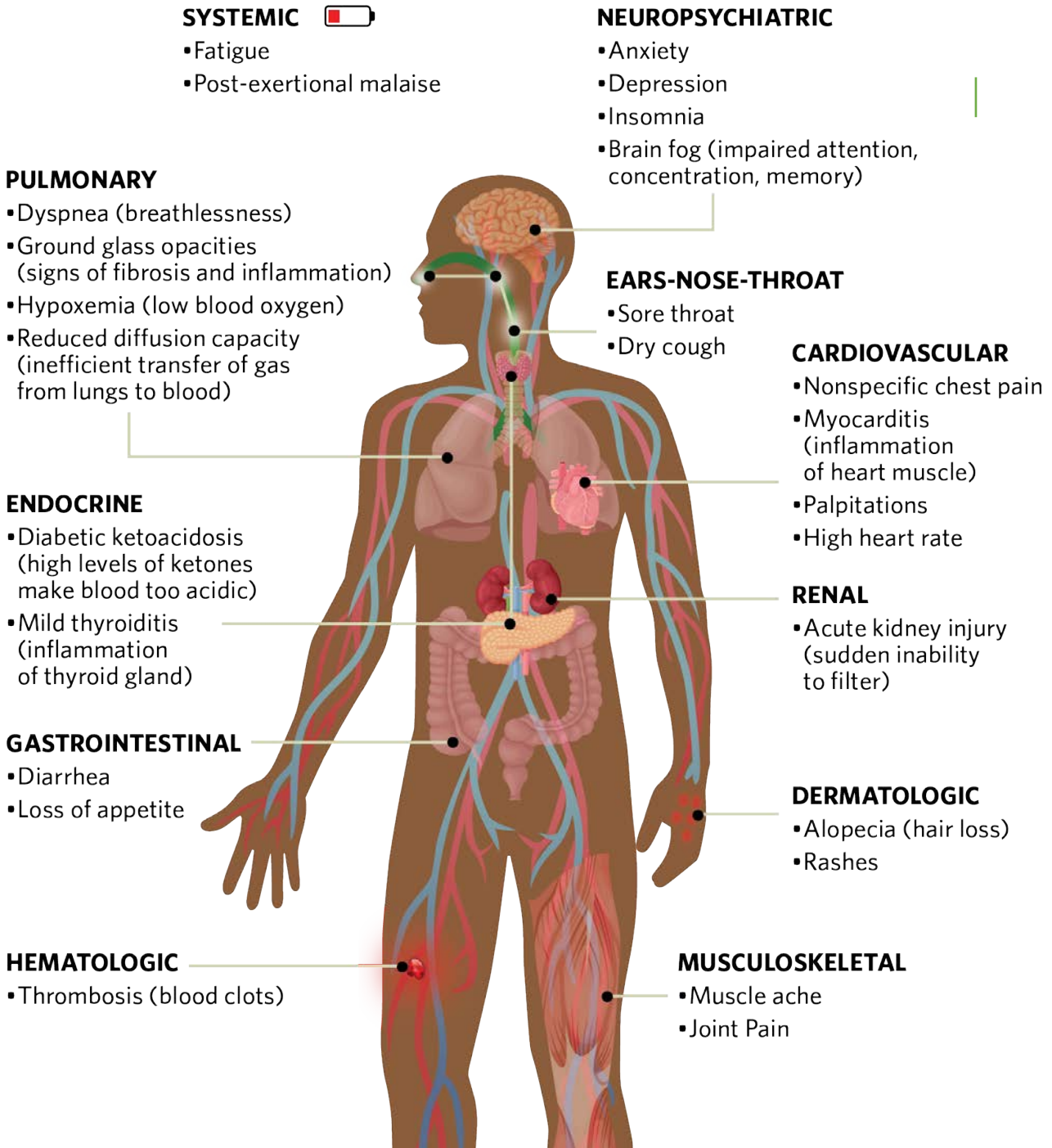
Renal
- Acute kidney injury
- Proteinuria
- Hematuria

Gupta. Nat Med. 2020;26:1017.

Slide credit: clinicaloptions.com

Manifestations of PASC
(**P**ost **A**cute **S**equelae of **C**OVID-19):

A Broad Array of Symptoms/Syndromes



- RECOVER, an initiative from the NIH, seeks to understand, prevent, and treat post-acute sequelae of (SARS-CoV-2 PASC)

What does recovery from SARS-CoV-2 infection look like among different groups?
How many people continue to have symptoms after acute infection?
How many people develop new symptoms after acute infection?
What causes these health effects?
Why do some people develop these health effects while others do not?
Does SARS-CoV-2 infection trigger changes in the body that increase the risk of other conditions, such as chronic lung, heart, or brain disorders?

Deep South COVID-19 Recovery Cohort

- Jeanne Marrazzo MD, cMPI
- Emily Levitan ScD, MPI
- Nathan Erdmann MD, PhD, MPI

Acknowledgments

- **Study Participants!**
- **COVID Care Teams and Clinical Staff**
- **ACTT Team**
  - Paul Goepfert, Alisa Peinhart, Melissa Garner, Chris Chapleau, Christen Press, Rebecca Smith, Jenna Weber, Latasha Vereen, Rachel McMullen, Meagan Whatley, Amber Samuelson, Deborah Lowman, Patrick Frazier,
  - John Beigel, Andre Kalil, Neera Ahuja
- **COVID Therapeutic Committee/CCTC**
  - Dan Kelmenson, Matt Brown, Randy Cron, Derek Russell, Sheetal Gandotra, Brian May, Orlando Turner, Aadia Rana
- **Enterprise Team**
  - **Enrollment –** Leigh Kirkwood, Wanda Hall, Tyler Plumlee, Ainsley Greenstein, MK Moore, Anisha Jackson, Pat McCurdy, Heath Logan
  - **Sample processing –** Tim Fram, Sarah Sterrett, and CFAR Biorepository
  - **Respiratory Samples –** Amit Gaggar, Derek Russell, Sid Patel
  - **Governance Committee –** Paul Goepfert, Fran Lund, Kevin Harrod, Suresh Boppanna, Paul Benson, Jeff Edberg

CCTS

- Robert Kimberly, Jeff Edberg, Jennifer Crocker

- **UAB Collaborators**
  - Paul Goepfert
    - Jake Files
    - Sushma Boppanna
  - Anju Bansal
  - Tim Fram
  - Sonya Heath
    - Lynn Prichard
  - Steffanie Sabbaj
  - James Kobie
  - Olaf Kutsch
  - Rachael Lee

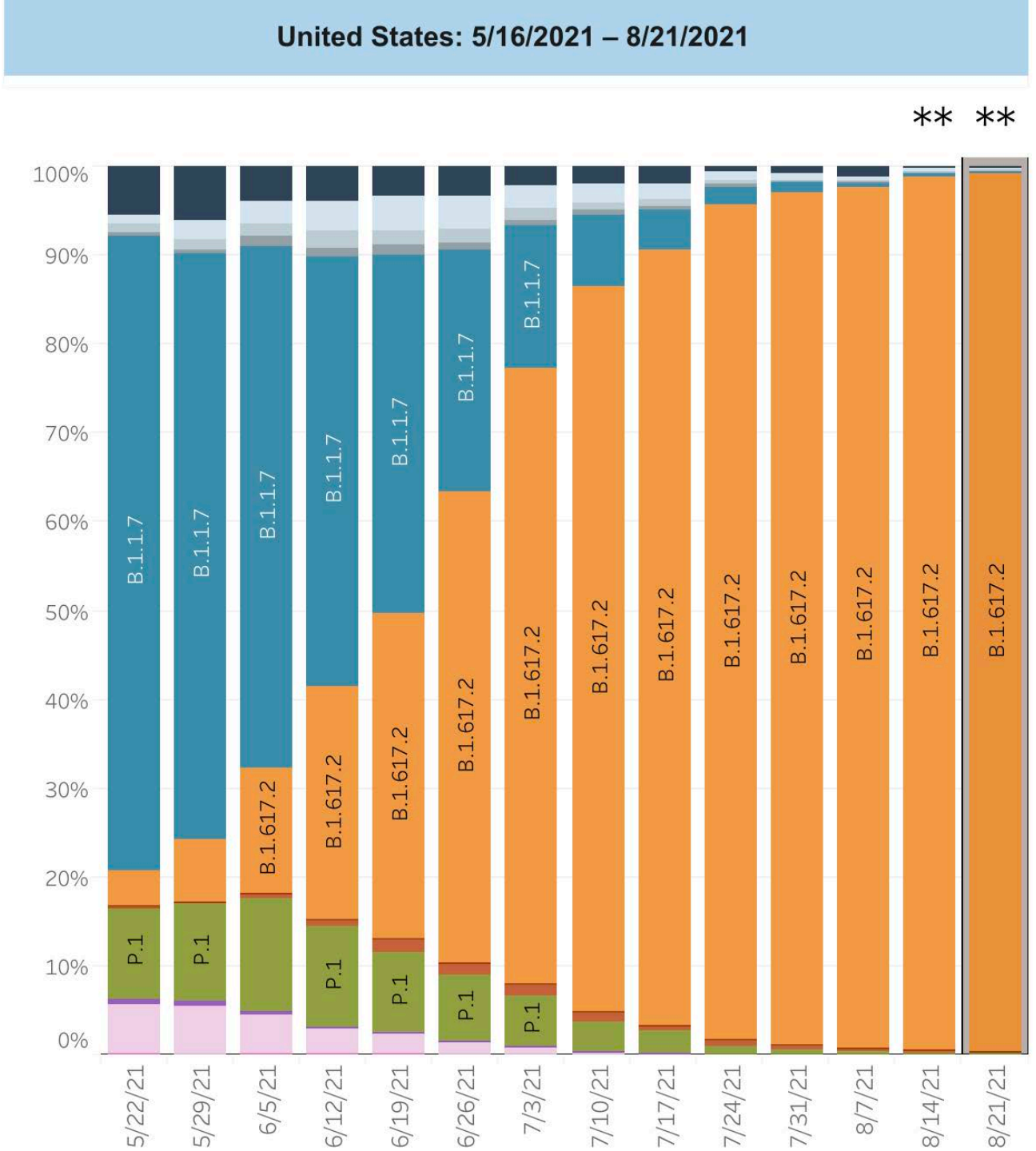
  - Fran Lund
  - Randall Davis
  - Zdenek Hel
  - Kevin Harrod
  - Sixto Leal
    - Drew Freeman

- **COVID Funding**
  - UAB School of Medicine
  - UAB Department of Medicine

Thank you!

Questions?

Delta Variant Dominates



Omicron Variant Dominates