COVID-19 Update from an Infectious Diseases Perspective

Patricia Saunders-Hao, PharmD, BCIDP, BCPS (AQ-ID)
Clinical Pharmacy Specialist, Infectious Diseases
North Shore University Hospital

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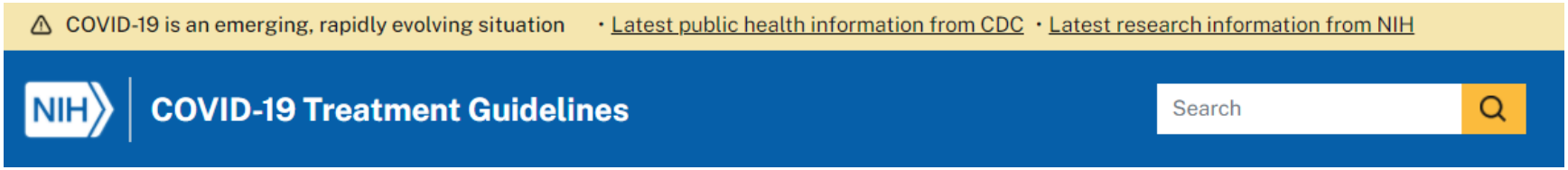
North Shore University Hospital
Northwell Health

Disclaimers

- No conflicts of interest to disclose
- Data/knowledge on COVID-19 constantly evolving so information presented today as current as possible



- Too much data/information!
  - Focus will be highlights, key studies (mostly peer-reviewed), and recent updates regarding ID-related management in adults and vaccines

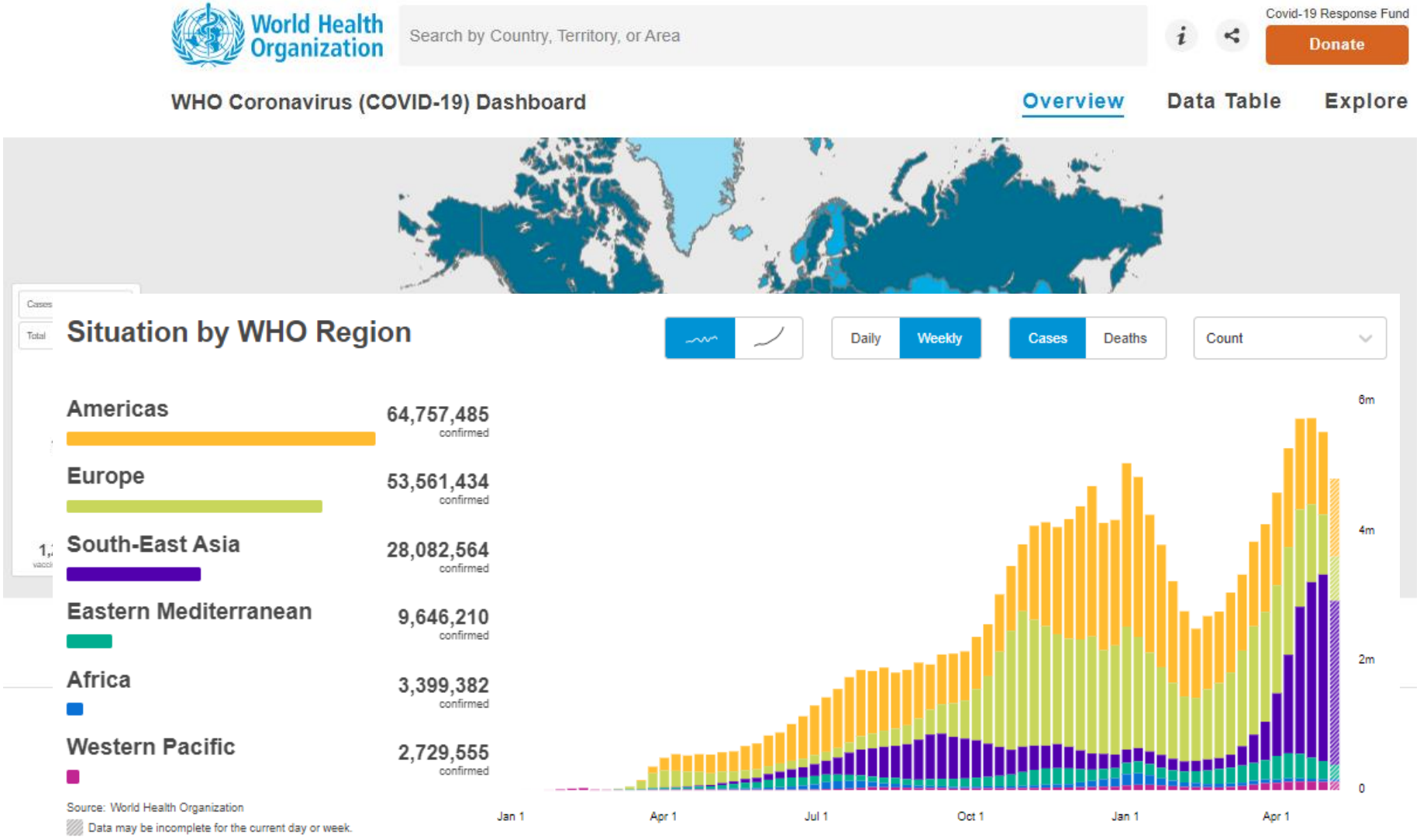
Objectives

- Understand how SARS-CoV-2 and the pathophysiology of COVID-19 may affect our prevention and treatment strategies
- Evaluate the role of monoclonal antibodies for COVID-19
- Discuss the current guidelines and evidence-based treatment options for hospitalized patients with COVID-19
- Review the available COVID-19 vaccines and their safety and efficacy updates

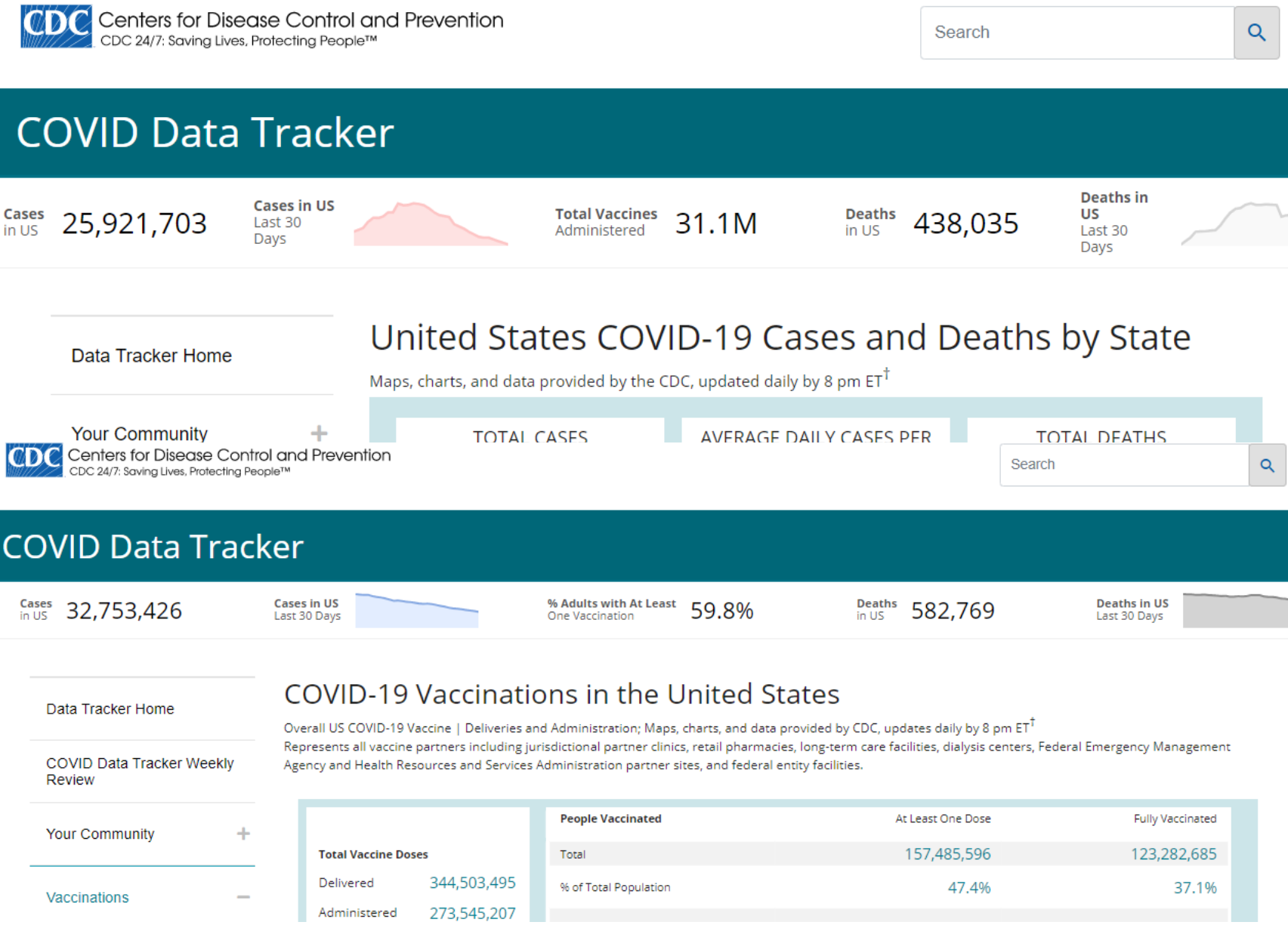
Introduction

- COVID-19 – disease caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
  - Single-stranded RNA virus
  - Most common coronaviruses in clinical practice before this caused common colds
  - SARS-CoV-2 – 3rd coronavirus to cause severe disease
    - Severe acute respiratory syndrome (SARS) – 2002-2003
    - Middle East respiratory syndrome (MERS) – 2012

Statistics

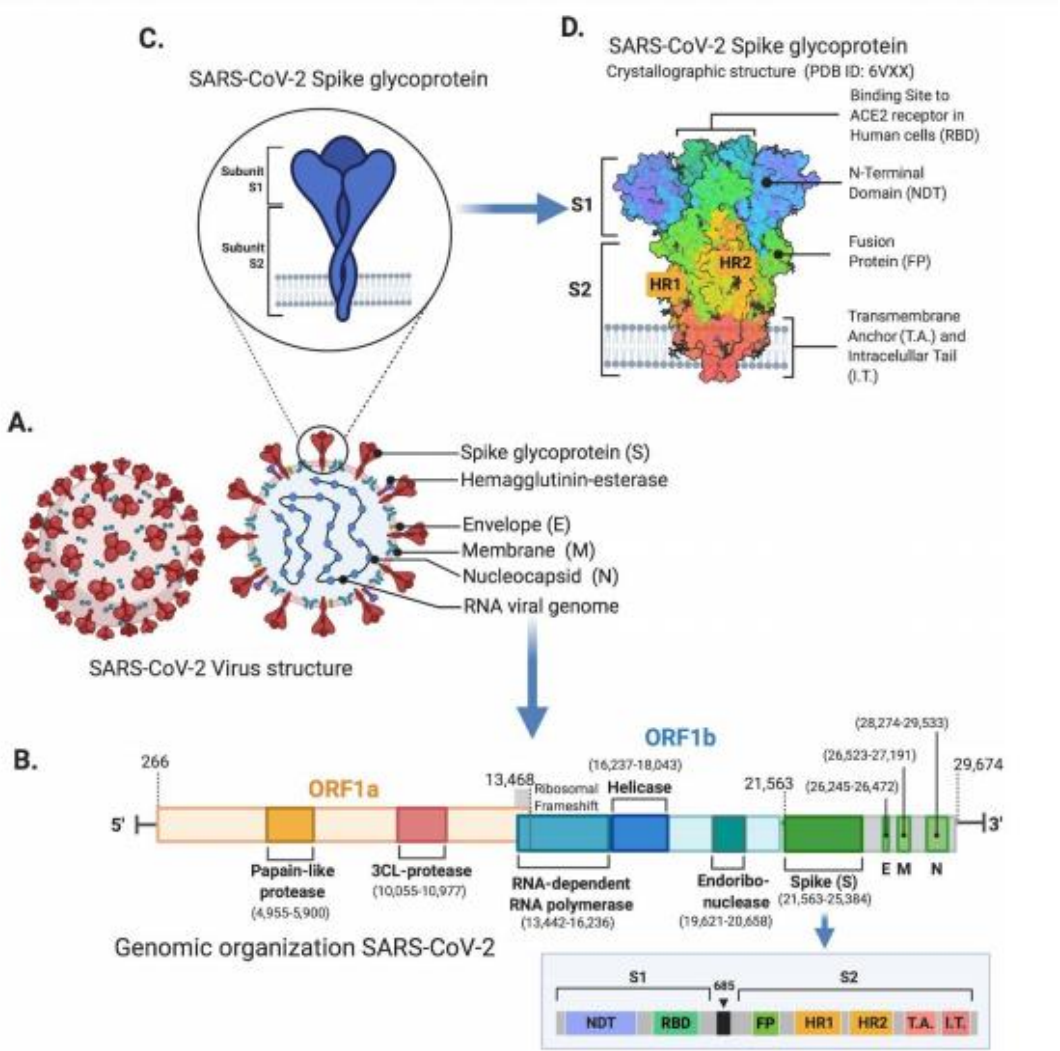


WHO. https://covid19.who.int/ Accessed 5/16/21.



CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker. Accessed 5/16/21.

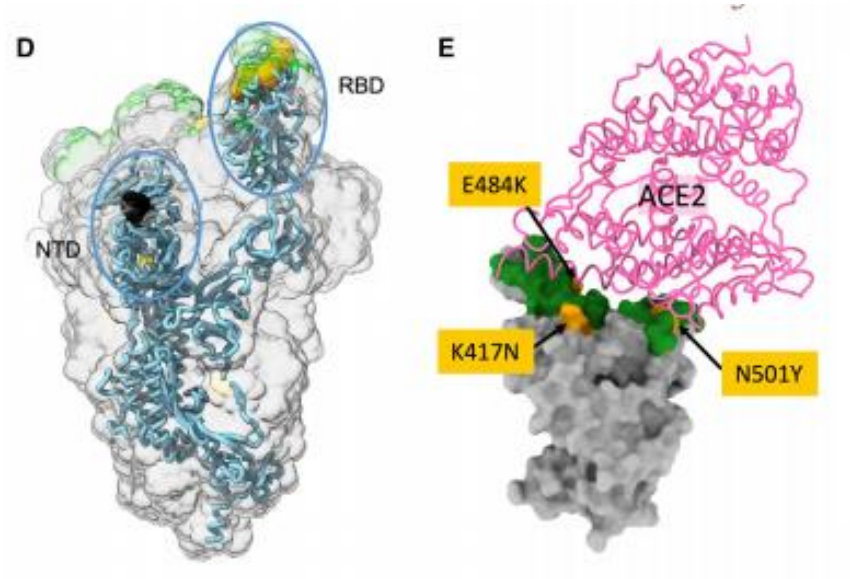
SARS-CoV-2



Chilamakuri R, Agarwal S. *Cells.* 2021.

Spike protein mutations

- Mutations to RBD of spike protein may:
  - Increase affinity to ACE2 → increased transmissibility?
  - Reduce protection from natural infection, vaccine, or monoclonal antibodies



Zhou, et al. *Cell.* 2021.

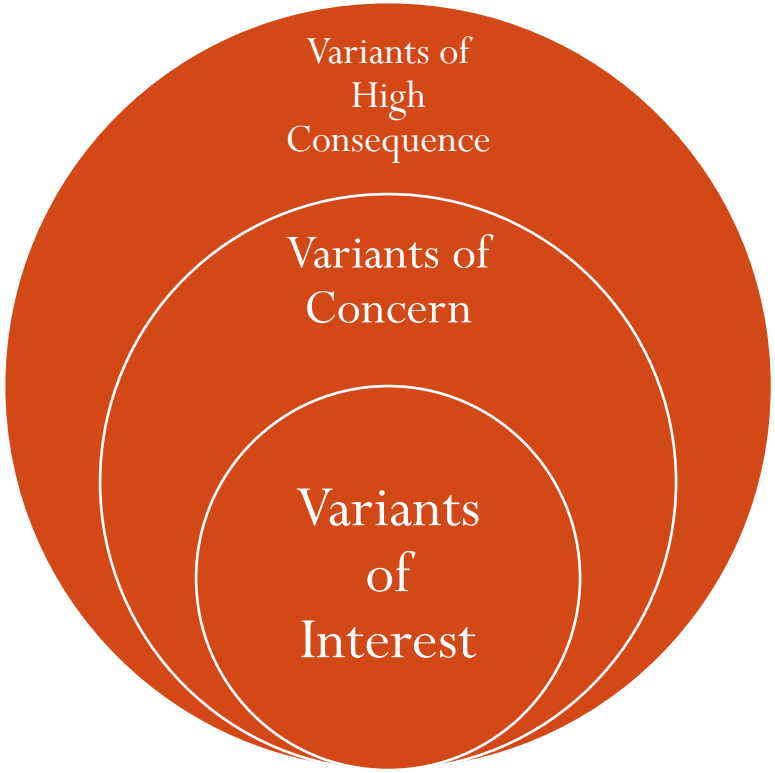
Mutations that may help the coronavirus spread

Lineage	Mutation	Status
B.1	D614G	Appeared in early 2020 and spread around the world.
Several	N501Y	A defining mutation in several lineages, including B.1.1.7, B.1.351 and P.1. Helps the virus bind more tightly to human cells.
Several	E484K or "Eek"	Appears in several lineages. May help the virus avoid some kinds of antibodies.
Several	K417	Appears in several lineages, including B.1.351 and P.1. May help the virus bind more tightly to cells.
Several	L452R	Increasingly common in California, but not yet shown to be more infectious.
Several	Q677	Found in seven U.S. lineages, but not yet shown to be more infectious.

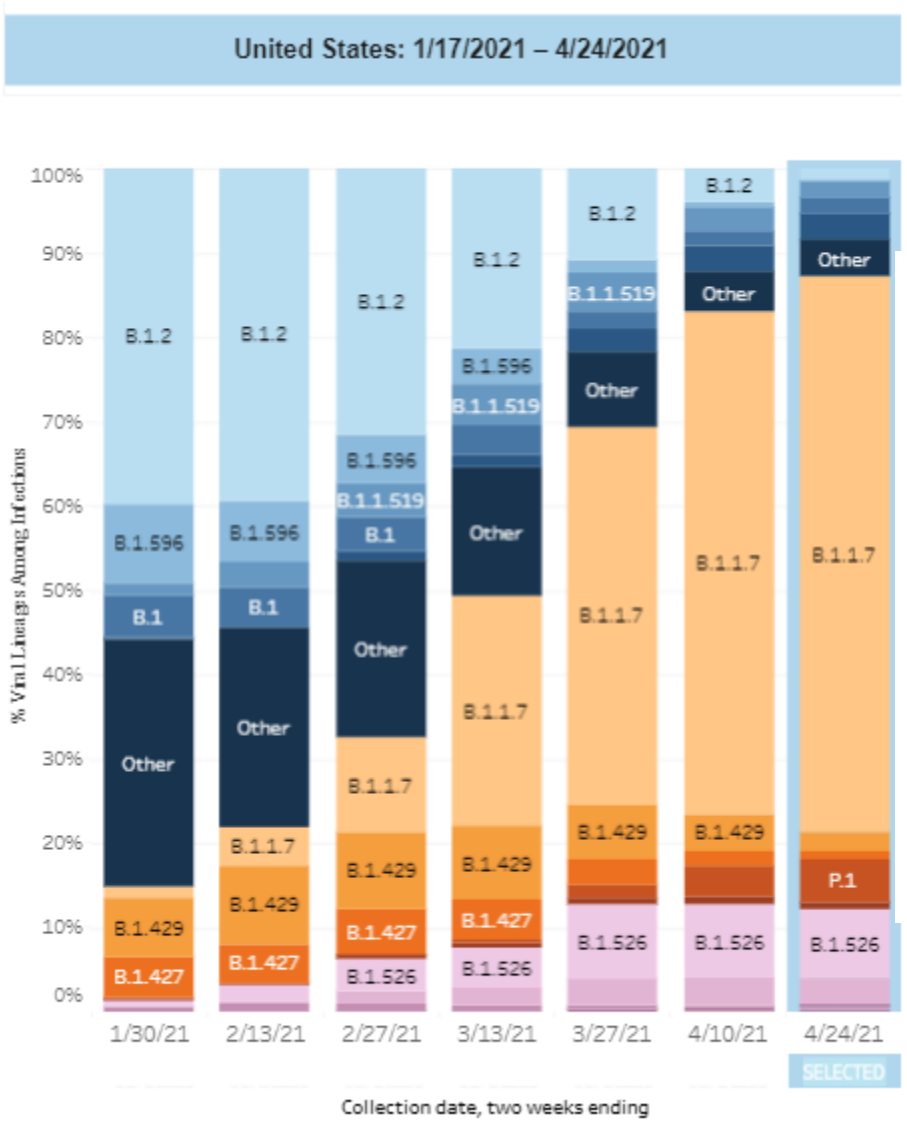
NY Times. https://www.nytimes.com/interactive/2021/health/coronavirus-variant-tracker.html. Accessed 5/16/21.

SARS-CoV-2 Variants

- CDC established classification with 3 classes of variants:



- WHO has similar classifications but may differ from US due to regional variants



Variants of concern

Lineage	Variant name	Status
B.1.1.7	Variant of Concern 202012/01, or 501Y.V1	Emerged in Britain in December and thought to be roughly 50 percent more infectious. Now dominant in the U.S.
B.1.351	501Y.V2	Emerged in South Africa in December. Reduces the effectiveness of some vaccines.
P.1	501Y.V3	Emerged in Brazil in late 2020. Has mutations similar to B.1.351.
B.1.427, B.1.429	CAL.20C	Common in California and thought to be about 20 percent more infectious. Carries the L452R mutation.

Variants of interest

Lineage	Variant name	Status
B.1.525	—	Spreading in New York. Carries some of the same mutations as B.1.1.7.
B.1.526	—	Spreading in New York. One version carries the E484K mutation, another carries S477N.
B.1.617	—	Prevalent in India. Carries the L452R spike mutation, among others.

CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#variant-proportions. Accessed 5/16/21.
NY Times. https://www.nytimes.com/interactive/2021/health/coronavirus-variant-tracker.html. Accessed 5/16/21.

Unweighted Proportions of SARS-CoV-2 Substitutions of Therapeutic Concern

Spike Protein Substitution	National Proportion[a]	Regional Proportions[b]		Common Pango Lineages with Spike Protein Substitutions[c]
L452R	7.6%	Region 1	6.0%	B.1.526.1 B.1.429 B.1.427 B.1.617.2 B.1.617.1 B.1 C.36 A.2.5
		Region 2	8.0%	
		Region 3	7.6%	
		Region 4	4.4%	
		Region 5	6.7%	
		Region 6	4.1%	
		Region 7	6.5%	
		Region 8	14.5%	
		Region 9	16.6%	
		Region 10	18.0%	
E484K	15.8%	Region 1	19.5%	P.1 B.1.526 B.1.1.318 B.1.351 B.1.525 R.1 B.1.1 B.1.621 B.1 B.1.1.7
		Region 2	22.8%	
		Region 3	15.5%	
		Region 4	15.1%	
		Region 5	13.1%	
		Region 6	11.4%	
		Region 7	11.8%	
		Region 8	12.0%	
		Region 9	15.7%	
		Region 10	10.4%	

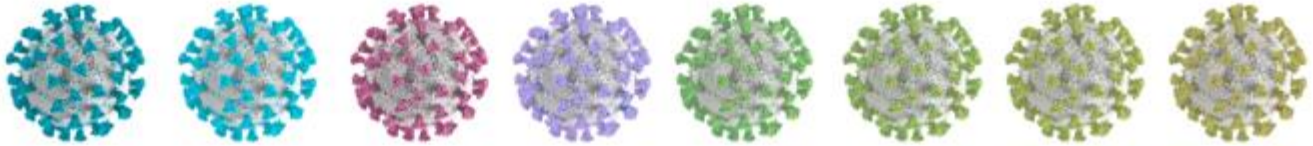
a – The unweighted proportion of SARS-CoV-2 circulating in the United States that contain the designated substitution, based on >20,000 sequences collected through CDC's national genomic surveillance during the two-week period ending April 24, 2021.

b – The unweighted regional proportion of SARS-CoV-2 circulating in each HHS region that contain the designated substitution, based on >20,000 sequences collected through CDC's national genomic surveillance during the two-week period ending April 24, 2021.

c – The lineages listed are the most common lineages within CDC's national genomic surveillance with these substitutions, but this list is not intended to be a complete list of the lineages that contain the spike protein substitutions.

CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#variant-proportions. Accessed 5/16/21.

Variants of Interest

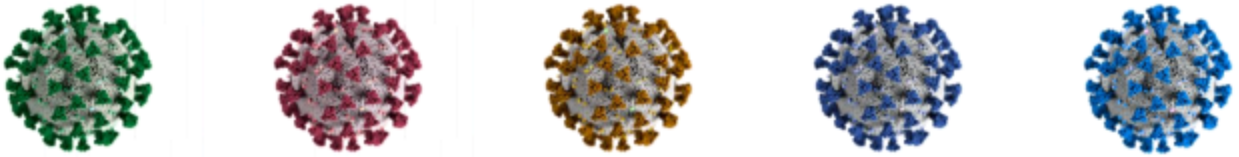


	B.1.526	B.1.526.1	B.1.525	P.2	B.1.617	B.1.617.1	B.1.617.2	B.1.617.3
First detected	New York	New York	UK/Nigeria	Brazil	India	India	India	India
No. of spike mutations	3-7	6-8	8	3-4	3	7-8	9-10	7
Receptor binding domain mutations	(S477N*) (E484K*)	L452R	E484K	E484K	L452R E484Q	L452R E484Q	L452R T478K	L452R E484Q
Attributes	• **Reduced** antibody efficacy • **Reduced** neutralization convalescent or vaccine sera	• Potential reduced antibody efficacy • Potential reduced neutralization by vaccine sera		• Potential reduced antibody efficacy • **Reduced** neutralization by vaccine sera	• Potential reduced antibody efficacy • **Reduced** neutralization by vaccine sera	• Potential reduced antibody efficacy • Potential reduced neutralization by vaccine sera		

SARS-CoV-2 Variants Classifications & Definitions | CDC (*) = detected in some sequences but not all

Scobie H. ACIP meeting. May 12, 2021.
https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-05-12/10-COVID-Scobie-508.pdf

Variants of Concern



	B.1.1.7	B.1.351	P.1	B.1.427	B.1.429
First detected	United Kingdom	South Africa	Japan / Brazil	California	California
No. of spike mutations	10-13	10	11	4	4
Receptor binding domain mutations	N501Y	K417N E484K N501Y	K417T E484K N501Y	L452R	L452R
Attributes	• **50%** increased transmission • **Minimal** impact on neutralization by antibody therapies, convalescent or vaccine sera	• **50%** increased transmission • **Reduced** efficacy of some antibodies • **Reduced** neutralization by convalescent or vaccine sera	• **Reduced** efficacy of some antibodies • **Reduced** neutralization by convalescent or vaccine sera	• **20%** increased transmission • **Modest** decrease in efficacy of some antibodies • **Reduced** neutralization by convalescent or vaccine sera	• **20%** increased transmission • **Modest** decrease in efficacy of some antibodies • **Reduced** neutralization by convalescent or vaccine sera

SARS-CoV-2 Variants Classifications & Definitions | CDC

Scobie H. ACIP meeting. May 12, 2021.
https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-05-12/10-COVID-Scobie-508.pdf

Pathophysiology

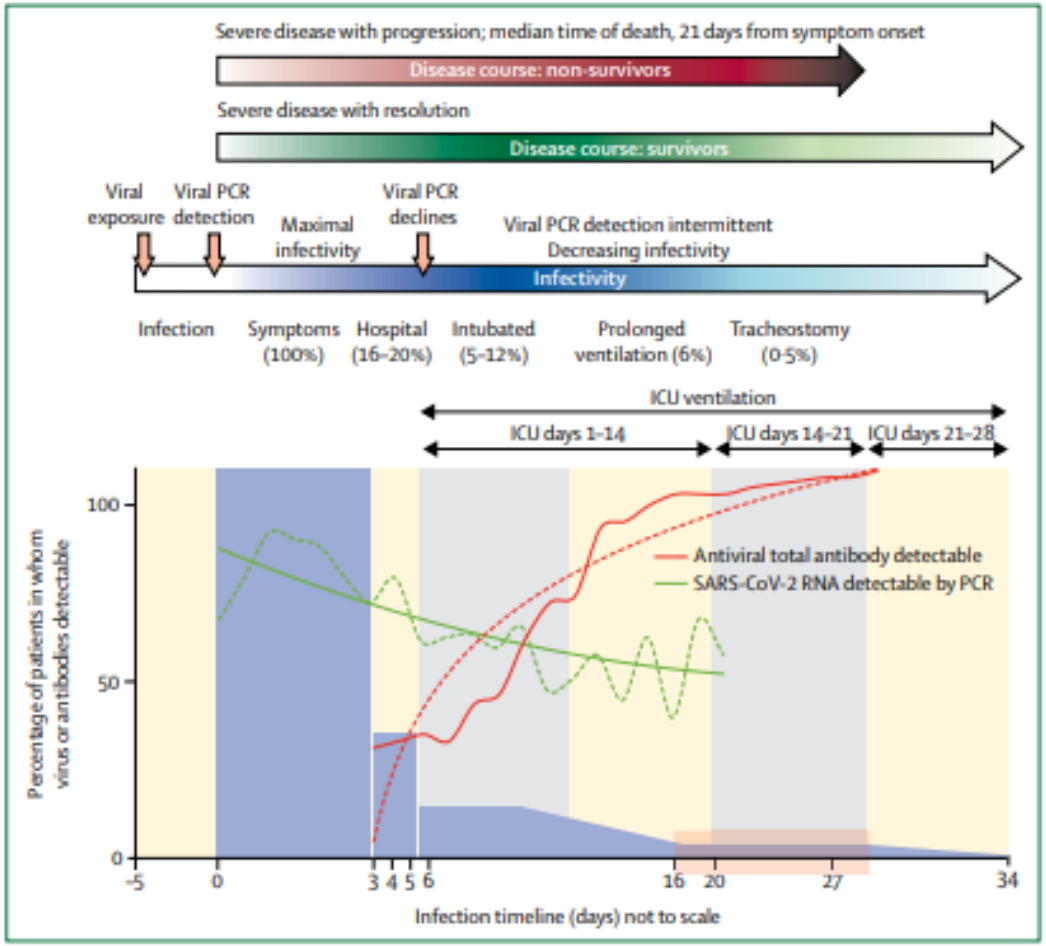
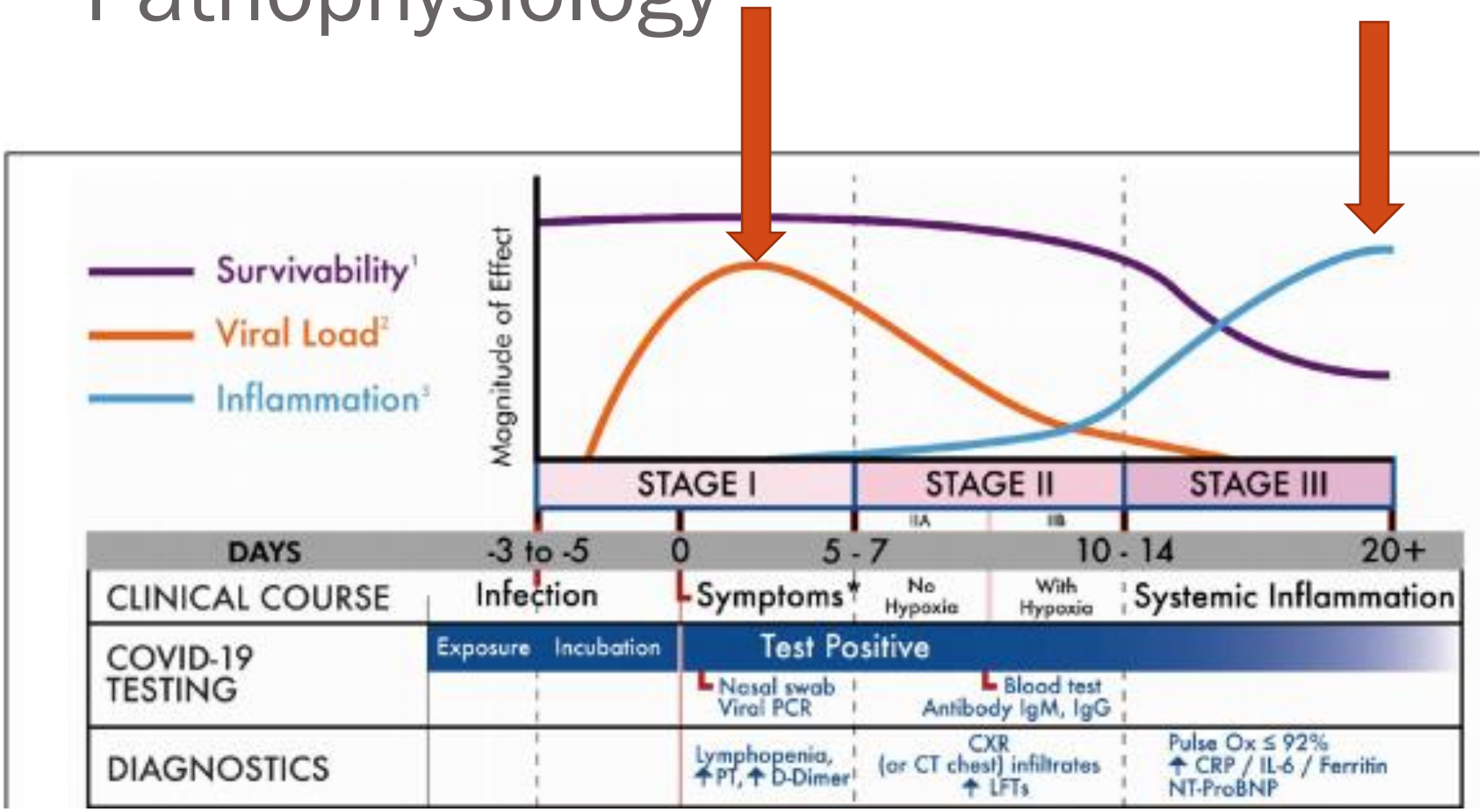


Figure 1: **Typical clinical course, viral PCR, and antiviral antibody detection and infectivity of severe SARS-CoV-2 infection**

McGrath, et al. *Lancet Resp Med.* July 2020.

Pathophysiology



Parasher. *Postgrad Med J.* Sept 2020.

Outline

- Treatment of COVID-19
  - Monoclonal antibodies
  - Remdesivir
  - Treatments aimed at inflammatory/immune response to virus
- Prevention of COVID-19
  - Vaccines
    - Safety concerns
    - Special populations

Assessment Question #1

- Which of the following is the only medication to be recommended as a AI recommendation in current NIH COVID-19 treatment guidelines?

  A. Remdesivir

  B. Dexamethasone

  C. Tocilizumab

  D. Casirivimab/imdevimab

  E. Hydroxychloroquine

Monoclonal Antibodies

- Neutralizing monoclonal antibodies target receptor-binding domain (RBD) of spike protein of SARS-CoV-2
  - Each antibody binds to different epitope of RBD
  - Available antibodies derived from serum of patients early in pandemic and humanized mice exposed to SARS-CoV-2

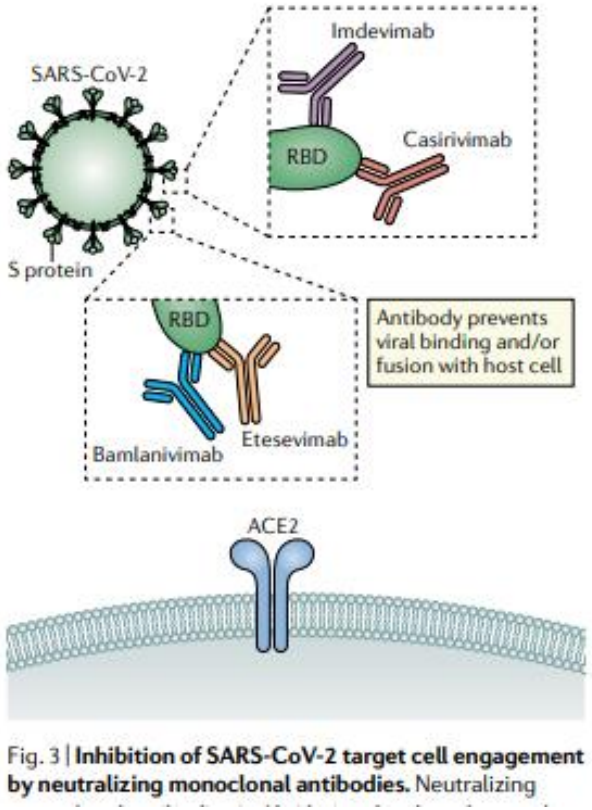


Fig. 3 | **Inhibition of SARS-CoV-2 target cell engagement by neutralizing monoclonal antibodies.** Neutralizing

Taylor, et al. *Nature*. April 2021.

Monoclonal Antibodies

- Being evaluated for treatment and prophylaxis in early disease
  - ACTIV-3 trial in hospitalized patients stopped early for futility[1]
- EUAs
  - Bamlanivimab 700mg – 11/9/2020
  - Casirivimab/imdevimab (REGN10933) 1200mg/1200mg – 11/21/2020
  - Bamlanivimab /etesevimab 700mg/1400mg – 2/9/2021
  - Treatment of non-hospitalized patients with mild-mod COVID-19 at high risk of severe dx or hospitalization
  - Administered ASAP after positive test and w/in 10 days of symptom onset

1. ACTIV-3/TICO LY-CoV555 Study Group. *NEJM.* 2020.

FDA NEWS RELEASE

Coronavirus (COVID-19) Update: FDA Revokes Emergency Use Authorization for Monoclonal Antibody Bamlanivimab

Alternative monoclonal antibody therapies authorized to treat patients with COVID-19 remain available

Share Tweet LinkedIn Email Print

For Immediate Release: April 16, 2021

Español

Today, the U.S. Food and Drug Administration revoked the emergency use authorization (EUA) that allowed for the investigational monoclonal antibody therapy bamlanivimab, *when administered alone*, to be used for the treatment of mild-to-moderate COVID-19 in adults and certain pediatric patients. Based on its ongoing analysis of emerging scientific data, specifically the sustained increase of SARS-CoV-2 viral variants that are resistant to bamlanivimab alone resulting in the increased risk for treatment failure, the FDA has determined that the known and potential benefits of bamlanivimab, when administered alone, no longer outweigh the known and potential risks for its authorized use. Therefore, the agency determined that the criteria for issuance of an authorization are no longer met and has revoked the EUA.

FDA news release. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-monoclonal-antibody-bamlanivimab

Monoclonal Antibodies

- EUAs
  - Casirivimab/imdevimab (REGN10933) 1200mg/1200mg
  - Bamlanivimab /etesevimab 700mg/1400mg
  - Treatment of non-hospitalized patients with mild-mod COVID-19 at high risk of severe disease or hospitalization
    - Body mass index (BMI) ≥35
    - Chronic kidney disease
    - Diabetes mellitus
    - Immunocompromising condition
    - Currently receiving immunosuppressive treatment
    - Aged ≥65 years
    - Aged ≥55 years and have: CV disease, HTN, or COPD/chronic resp disease

Evidence for Monoclonal Antibodies

- Limited published, peer-reviewed literature
- BLAZE-1 – Bam vs. bam/ete (2800/2800mg) vs. placebo
  - Interim results published[1]
    - Bam/ete group had significant change of viral load (p=0.01) and lower proportion of hospitalizations/ER visits (1/109 vs. 9/152, p=0.049)
  - Unpublished[2]
    - Reduction in hospitalization/death by any cause by day 29 (11/518 (2.1%) vs. 36/517 (7.0%); p=0.0004)

1. Gottlieb, et al. *JAMA.* 2021.
2. NIH COVID-19 guidelines. Updated 4/21/21.

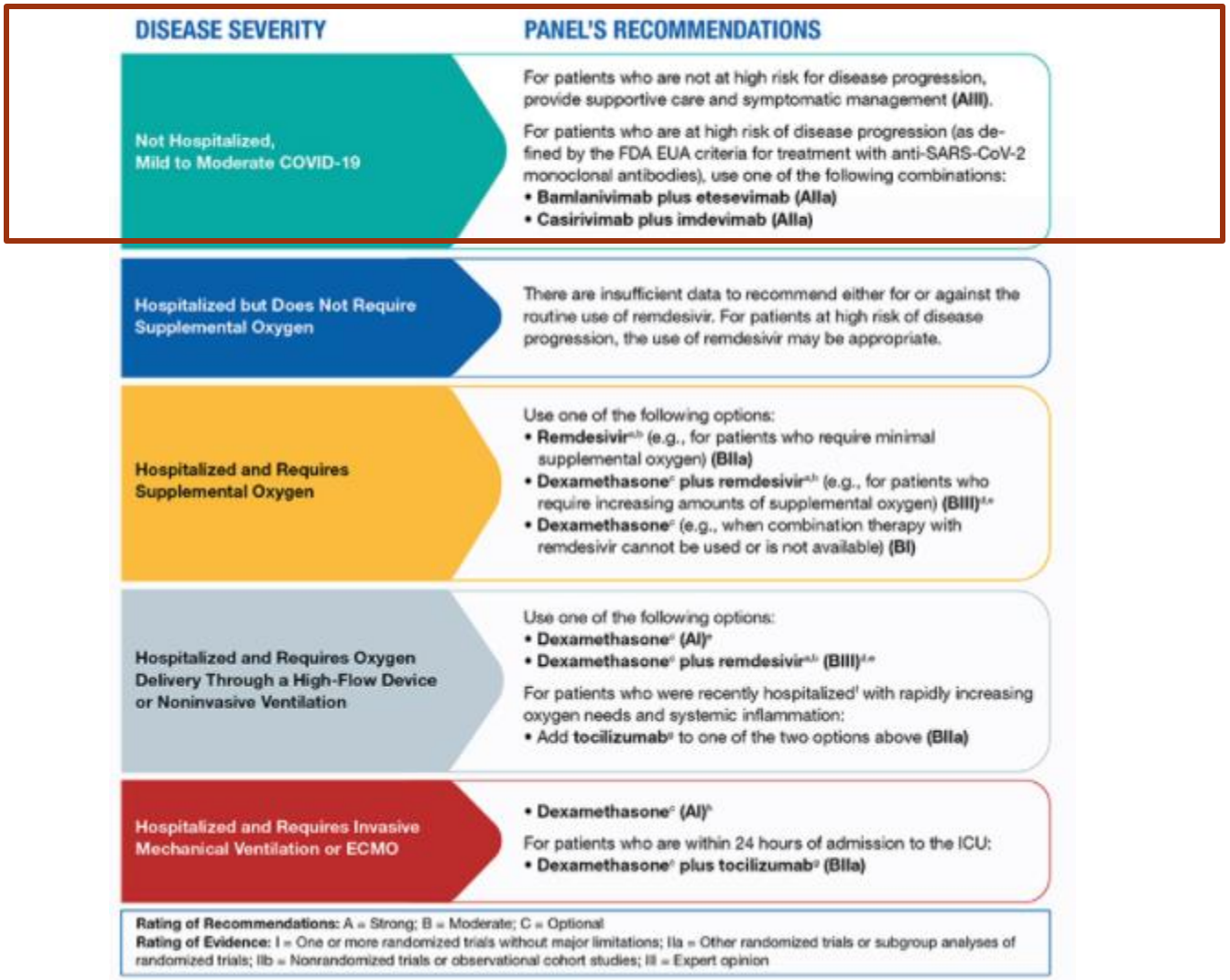
Evidence for Monoclonal Antibodies

- Limited published, peer-reviewed literature
- Casi/imdevi
  - Interim results published[1]
    - Reduction in viral load, numerically lower medically attended visits, esp Ab-
  - Unpublished[2]
    - Reduction in hospitalization/death by any cause by day 29 (18/1355 (1.3%) vs. 62/1341 (4.6%); $p<0.0001$)
- NIH guidelines – recommends either product for use as outlined in EUA
  - Advises to start ASAP positive result and w/in 10 days of symptom onset; may need to consider regional variants

1. Weinreich, et al. *NEJM.* 2021.
2. NIH COVID-19 guidelines. Updated 4/21/21.

Figure 1. Pharmacologic Management of Patients with COVID-19 Based on Disease Severity

Doses and durations are listed in the footnotes.



NIH COVID-19 Treatment Guidelines. Last update April 21, 2021.

Remdesivir

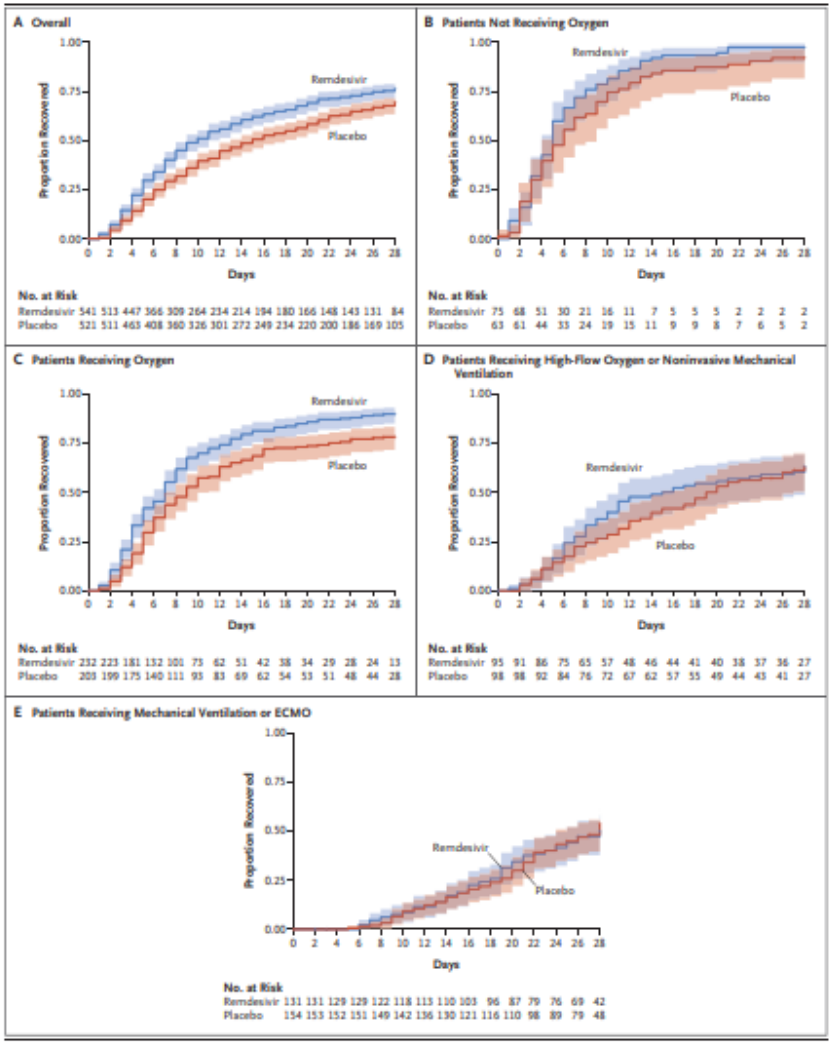
- Inhibitor of viral RNA-dependent, RNA polymerase – affects viral replication
- Repurposed drug – did not work well for Ebola but in vitro activity against SARS-CoV2 and animal studies suggested lower viral loads and less lung damage when given early
- Several clinical trials
  - ACTT-1
  - SOLIDARITY

ACTT-1 Trial

- Randomized, placebo-controlled, double-blind
- Enrolled 1062 hospitalized patients with COVID-19 and evidence of LRTI in 60 international trial sites (45 in US) from Feb 21 – April 19, 2020
- Patients clinical status assessed daily with 8-category ordinal scale for 28 days
- Outcomes
  - Primary – Time to recovery (category 1-3 – not hospitalized or hospitalized but not for COVID-19 treatment)
  - Key secondary
    - Clinical status at day 15
    - Mortality at 15 and 29 days

Beigel, et al. *NEJM.* 2020.

ACTT-1 Trial



Beigel, et al. *NEJM.* 2020.

ACTT-1 Trial

Table 2. Outcomes Overall and According to Score on the Ordinal Scale in the Intention-to-Treat Population.*

	Overall		Ordinal Score at Baseline							
			4		5		6		7	
	Remdesivir (N=541)	Placebo (N=521)	Remdesivir (N=75)	Placebo (N=63)	Remdesivir (N=232)	Placebo (N=203)	Remdesivir (N=95)	Placebo (N=98)	Remdesivir (N=131)	Placebo (N=154)
Recovery										
No. of recoveries	399	352	73	58	206	156	57	61	63	77
Median time to recovery (95% CI) — days	10 (9–11)	15 (13–18)	5 (4–6)	6 (4–7)	7 (6–8)	9 (7–10)	15 (10–27)	20 (14–26)	29 (24–NE)	28 (24–NE)
Rate ratio (95% CI)†	1.29 (1.12–1.49 [P<0.001])		1.29 (0.91–1.83)		1.45 (1.18–1.79)		1.09 (0.76–1.57)		0.98 (0.70–1.36)	
Mortality through day 14‡										
Hazard ratio for data through day 15 (95% CI)	0.55 (0.36–0.83)		0.42 (0.04–4.67)		0.28 (0.12–0.66)		0.82 (0.40–1.69)		0.76 (0.39–1.50)	
No. of deaths by day 15	35	61	1	2	7	21	13	17	14	21
Kaplan–Meier estimate of mortality by day 15 — % (95% CI)	6.7 (4.8–9.2)	11.9 (9.4–15.0)	1.3 (0.2–9.1)	3.2 (0.8–12.1)	3.1 (1.5–6.4)	10.5 (7.0–15.7)	14.2 (8.5–23.2)	17.3 (11.2–26.4)	10.9 (6.6–17.6)	13.8 (9.2–20.4)
Mortality over entire study period‡										
Hazard ratio (95% CI)	0.73 (0.52–1.03)		0.82 (0.17–4.07)		0.30 (0.14–0.64)		1.02 (0.54–1.91)		1.13 (0.67–1.89)	
No. of deaths by day 29	59	77	3	3	9	25	19	20	28	29
Kaplan–Meier estimate of mortality by day 29 — % (95% CI)	11.4 (9.0–14.5)	15.2 (12.3–18.6)	4.1 (1.3–12.1)	4.8 (1.6–14.3)	4.0 (2.1–7.5)	12.7 (8.8–18.3)	21.2 (14.0–31.2)	20.4 (13.7–29.8)	21.9 (15.7–30.1)	19.3 (13.8–26.5)
Ordinal score at day 15 (±2 days) — no. (%)§										
1	157 (29.0)	115 (22.1)	38 (50.7)	28 (44.4)	90 (38.8)	62 (30.5)	18 (18.9)	14 (14.3)	11 (8.4)	11 (7.1)
2	117 (21.6)	102 (19.6)	20 (26.7)	15 (23.8)	70 (30.2)	58 (28.6)	22 (23.2)	19 (19.4)	5 (3.8)	10 (6.5)
3	14 (2.6)	8 (1.5)	8 (10.7)	4 (6.3)	6 (2.6)	4 (2.0)	0	0	0	0
4	38 (7.0)	33 (6.3)	3 (4.0)	7 (11.1)	17 (7.3)	13 (6.4)	12 (12.6)	4 (4.1)	6 (4.6)	9 (5.8)
5	58 (10.7)	60 (11.5)	3 (4.0)	5 (7.9)	25 (10.8)	18 (8.9)	2 (2.1)	14 (14.3)	28 (21.4)	23 (14.9)
6	28 (5.2)	24 (4.6)	1 (1.3)	0	5 (2.2)	7 (3.4)	12 (12.6)	11 (11.2)	10 (7.6)	6 (3.9)
7	95 (17.6)	121 (23.2)	1 (1.3)	3 (4.8)	13 (5.6)	21 (10.3)	16 (16.8)	20 (20.4)	57 (43.5)	74 (48.1)
8	34 (6.3)	58 (11.1)	1 (1.3)	1 (1.6)	6 (2.6)	20 (9.9)	13 (13.7)	16 (16.3)	14 (10.7)	21 (13.6)
Odds ratio (95% CI)	1.5 (1.2–1.9)		1.5 (0.8–2.7)		1.6 (1.2–2.3)		1.4 (0.9–2.3)		1.2 (0.8–1.9)	

Beigel, et al. *NEJM.* 2020.

ACTT-1 Trial

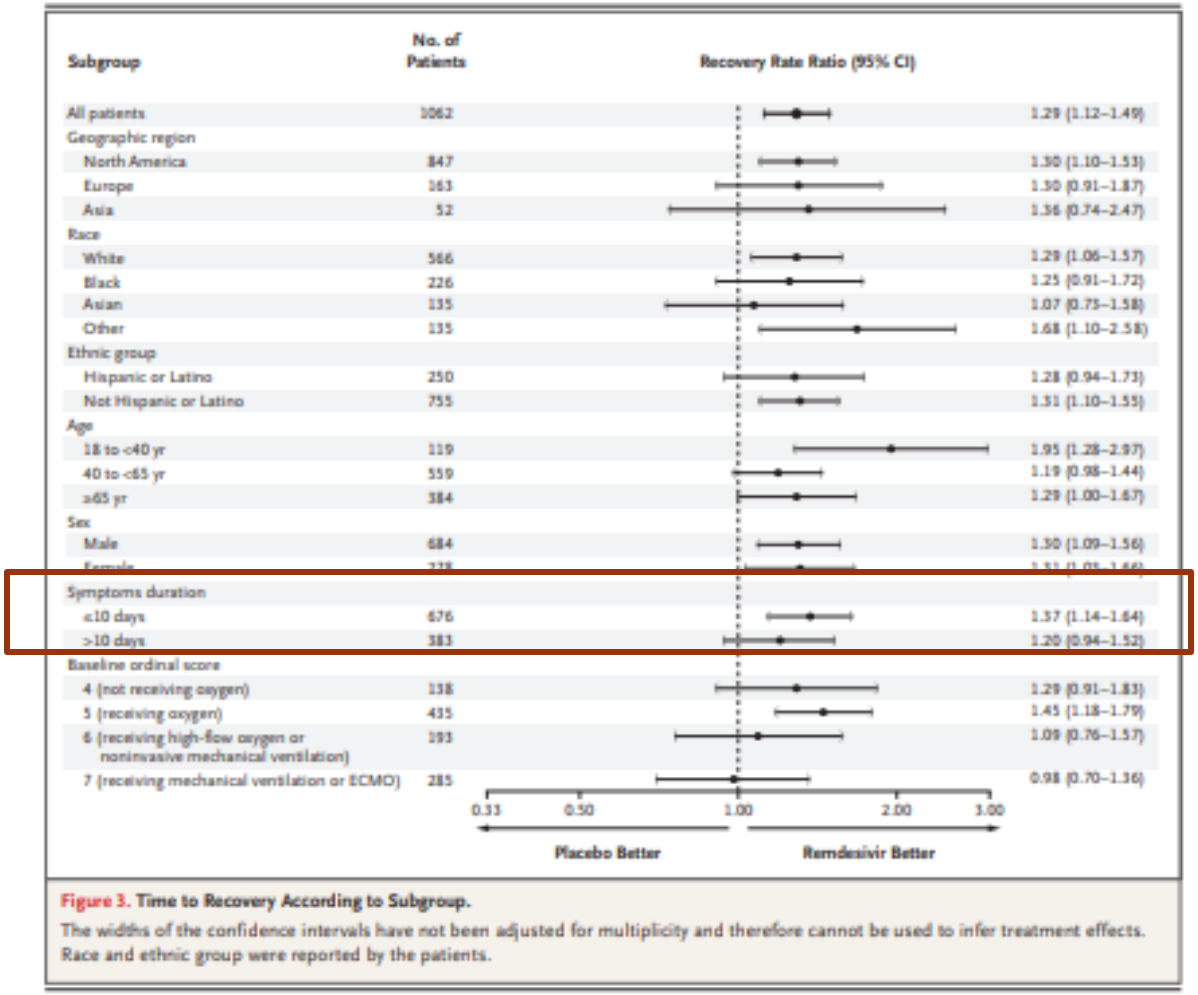


Figure 3. Time to Recovery According to Subgroup.

The widths of the confidence intervals have not been adjusted for multiplicity and therefore cannot be used to infer treatment effects. Race and ethnic group were reported by the patients.

Beigel, et al. *NEJM.* 2020.

Remdesivir

- ACTT-1 trial led to FDA approval on Oct 22 for treatment of adults and pediatric patients ≥12 years old and weighing ≥40 kg requiring hospitalization for COVID-19

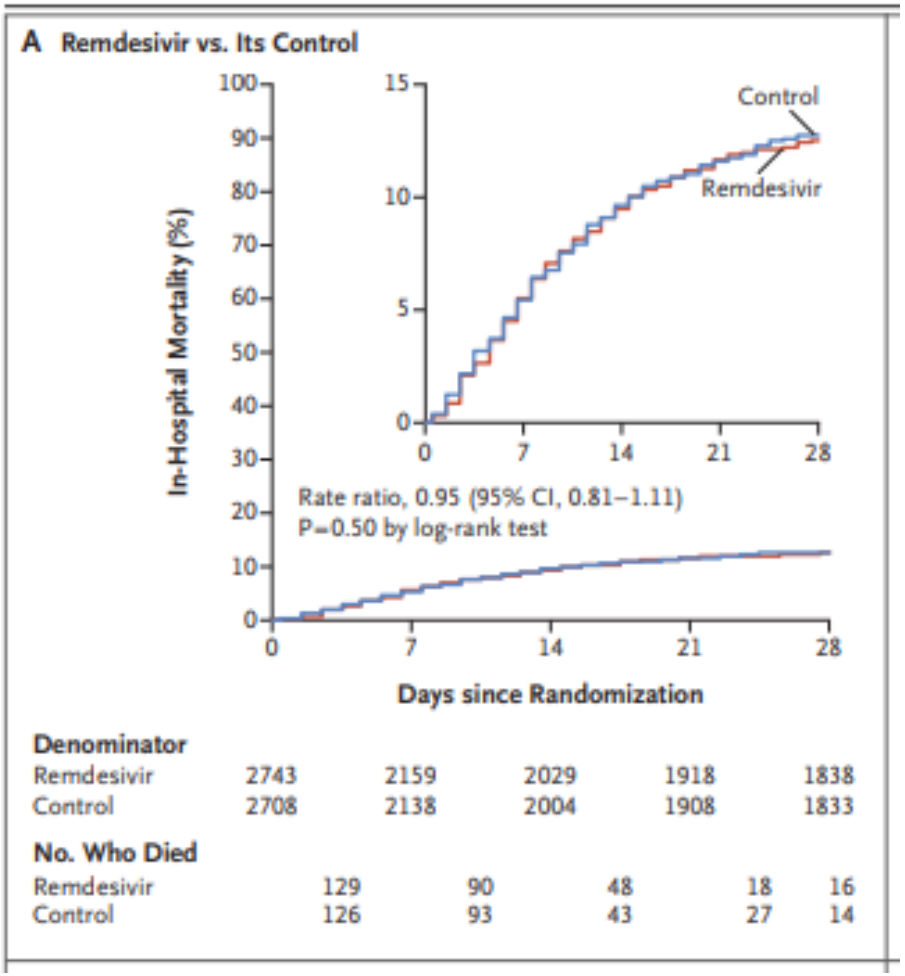
- However, SOLIDARITY trial…

SOLIDARITY Trial

- Randomized, open-label, adaptive
- Enrolled 11,330 hospitalized patients with COVID-19 in 30 countries (405 hospitals) from March 22 – October 4, 2020
  - 2743 randomized to remdesivir, 2708 to standard of care
    - ~48% in each group received corticosteroids
- Outcomes
  - Primary – In-hospital mortality – 11% vs. 11.1% (p=0.50)
  - Secondary
    - Initiation of mechanical ventilation – 10.8 vs. 10.5%
    - Duration of hospitalization – no difference

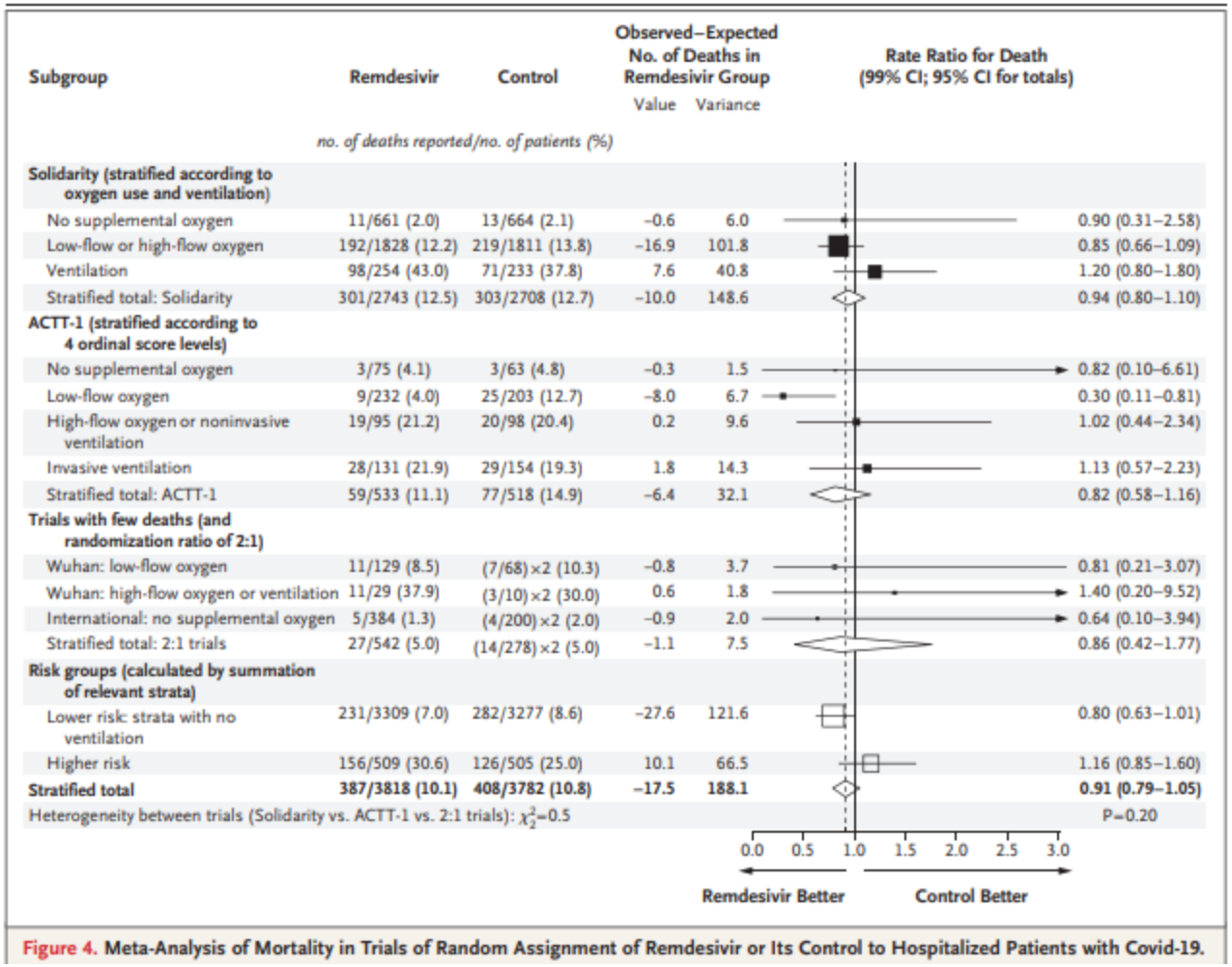
WHO Solidarity Trial Consortium. *NEJM.* 2020.

SOLIDARITY Trial



WHO Solidarity Trial Consortium. *NEJM.* 2020.

SOLIDARITY Trial



Subgroup	Remdesivir	Control	Observed−Expected No. of Deaths in Remdesivir Group: Value	Observed−Expected No. of Deaths in Remdesivir Group: Variance	Rate Ratio for Death (99% CI; 95% CI for totals)
	no. of deaths reported/no. of patients (%)				
Solidarity (stratified according to oxygen use and ventilation)					
No supplemental oxygen	11/661 (2.0)	13/664 (2.1)	−0.6	6.0	0.90 (0.31–2.58)
Low-flow or high-flow oxygen	192/1828 (12.2)	219/1811 (13.8)	−16.9	101.8	0.85 (0.66–1.09)
Ventilation	98/254 (43.0)	71/233 (37.8)	7.6	40.8	1.20 (0.80–1.80)
Stratified total: Solidarity	301/2743 (12.5)	303/2708 (12.7)	−10.0	148.6	0.94 (0.80–1.10)
ACTT-1 (stratified according to 4 ordinal score levels)					
No supplemental oxygen	3/75 (4.1)	3/63 (4.8)	−0.3	1.5	0.82 (0.10–6.61)
Low-flow oxygen	9/232 (4.0)	25/203 (12.7)	−8.0	6.7	0.30 (0.11–0.81)
High-flow oxygen or noninvasive ventilation	19/95 (21.2)	20/98 (20.4)	0.2	9.6	1.02 (0.44–2.34)
Invasive ventilation	28/131 (21.9)	29/154 (19.3)	1.8	14.3	1.13 (0.57–2.23)
Stratified total: ACTT-1	59/533 (11.1)	77/518 (14.9)	−6.4	32.1	0.82 (0.58–1.16)
Trials with few deaths (and randomization ratio of 2:1)					
Wuhan: low-flow oxygen	11/129 (8.5)	(7/68)×2 (10.3)	−0.8	3.7	0.81 (0.21–3.07)
Wuhan: high-flow oxygen or ventilation	11/29 (37.9)	(3/10)×2 (30.0)	0.6	1.8	1.40 (0.20–9.52)
International: no supplemental oxygen	5/384 (1.3)	(4/200)×2 (2.0)	−0.9	2.0	0.64 (0.10–3.94)
Stratified total: 2:1 trials	27/542 (5.0)	(14/278)×2 (5.0)	−1.1	7.5	0.86 (0.42–1.77)
Risk groups (calculated by summation of relevant strata)					
Lower risk: strata with no ventilation	231/3309 (7.0)	282/3277 (8.6)	−27.6	121.6	0.80 (0.63–1.01)
Higher risk	156/509 (30.6)	126/505 (25.0)	10.1	66.5	1.16 (0.85–1.60)
Stratified total	**387/3818 (10.1)**	**408/3782 (10.8)**	**−17.5**	**188.1**	**0.91 (0.79–1.05)**
Heterogeneity between trials (Solidarity vs. ACTT-1 vs. 2:1 trials): χ^2_2=0.5					P=0.20

Figure 4. Meta-Analysis of Mortality in Trials of Random Assignment of Remdesivir or Its Control to Hospitalized Patients with Covid-19.

WHO Solidarity Trial Consortium. *NEJM.* 2020.

Figure 1. Pharmacologic Management of Patients with COVID-19 Based on Disease Severity

Doses and durations are listed in the footnotes.

NIH COVID-19 Treatment Guidelines. Last update April 21, 2021.

Remdesivir Safety

- Adverse effect profile similar in ACTT-1 trial
- Transaminase elevations (2-8%)
  - Per package insert, consider discontinuing if ALT > 10x ULN or if any s/sx of liver failure
  - Monitoring at baseline and throughout therapy

Remdesivir Safety

- Renal disease/failure
  - Concern of accumulation of excipient SBECD[1]
    - Safety threshold 250mg/kg/day of SBECD
    - 100mg remdesivir powder, solution contains 3 and 6g of SBECD
  - Small case series in AKI/CKD
    - 20 patients[2], 18 patients[3], 46 patients[4], 40 patients[5]– no difference in ALT or SCr elevations
- Pregnancy
  - Compassionate use in 86 pregnant women[6] – well tolerated
  - NIH guidelines – Remdesivir should not be withheld from pregnant patients if it is otherwise indicated

1. Adamsick, et al. *JASN.* 2020.
2. Pettit, et al. *CID.* 2020.
3. Estiverne, et al. *Kidney Int Rep.* 2020.
4. Thakare, et al. *Kidney Int Rep.* 2021.
5. Ackley, et al. *AAC.* 2021.
6. Burwick, et al. *CID.* 2020.

Dexamethasone – RECOVERY Trial

- Multicenter, randomized, open-label trial in hospitalized patients with COVID-19 in UK
- Enrolled 2104 patients to receive dexamethasone (6mg IV/PO daily) vs. 4321 standard of care
- Outcomes
  - Primary – all-cause mortality within 28 days of randomization
  - Secondary
    - Time to discharge
    - Progression to mechanical ventilation or death

RECOVERY Collaborative Group. *NEJM.* 2020.

RECOVERY Trial

Table 2. Primary and Secondary Outcomes.

Outcome	Dexamethasone (N=2104)	Usual Care (N=4321)	Rate or Risk Ratio (95% CI)*
	no./total no. of patients (%)		
Primary outcome			
Mortality at 28 days	482/2104 (22.9)	1110/4321 (25.7)	0.83 (0.75–0.93)
Secondary outcomes			
Discharged from hospital within 28 days	1413/2104 (67.2)	2745/4321 (63.5)	1.10 (1.03–1.17)
Invasive mechanical ventilation or death†	456/1780 (25.6)	994/3638 (27.3)	0.92 (0.84–1.01)
Invasive mechanical ventilation	102/1780 (5.7)	285/3638 (7.8)	0.77 (0.62–0.95)
Death	387/1780 (21.7)	827/3638 (22.7)	0.93 (0.84–1.03)

* Rate ratios have been adjusted for age with respect to the outcomes of 28-day mortality and hospital discharge. Risk ratios have been adjusted for age with respect to the outcome of receipt of invasive mechanical ventilation or death and its subcomponents.

† Excluded from this category are patients who were receiving invasive mechanical ventilation at randomization.

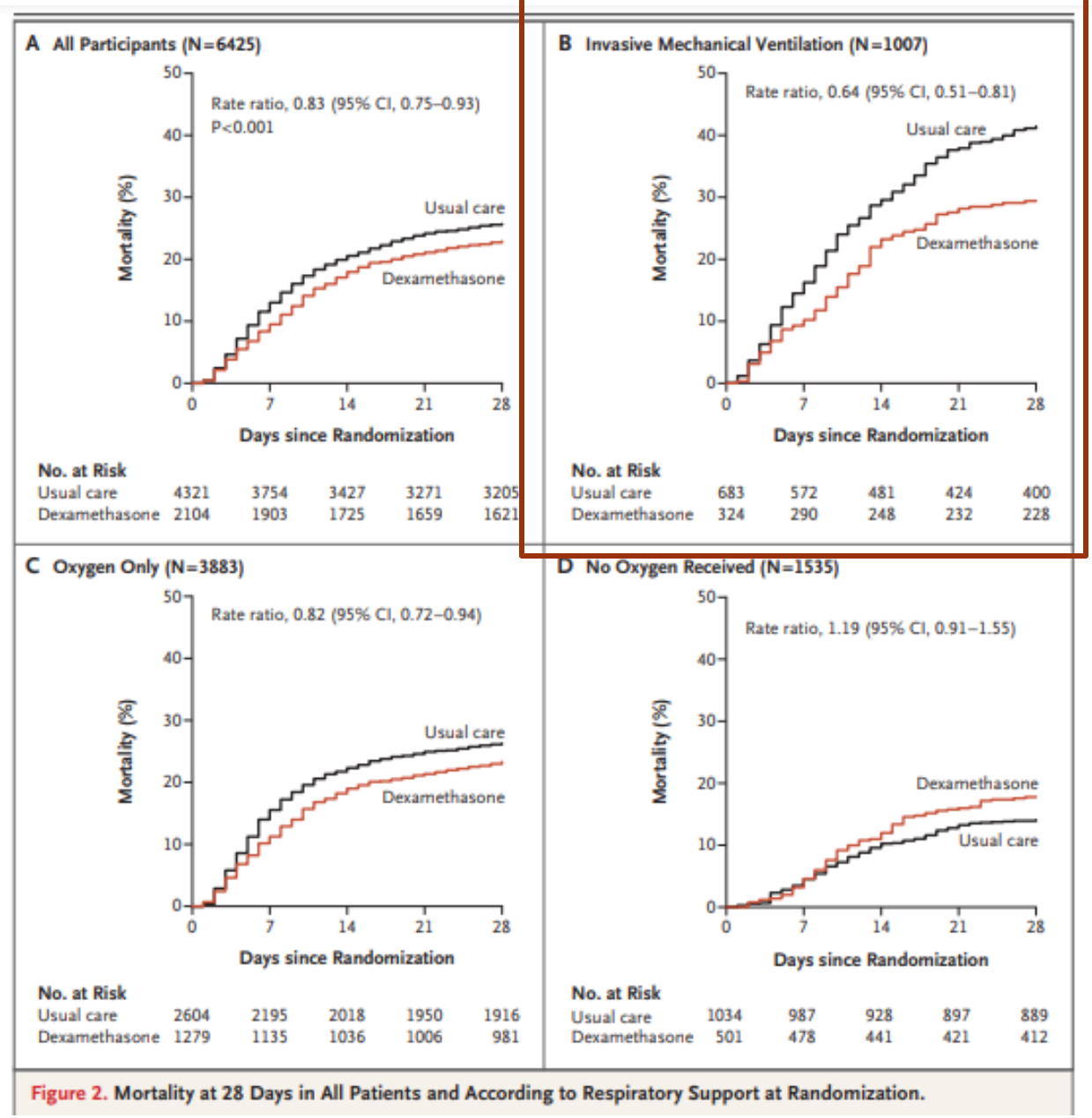


Figure 2. Mortality at 28 Days in All Patients and According to Respiratory Support at Randomization.

RECOVERY Trial

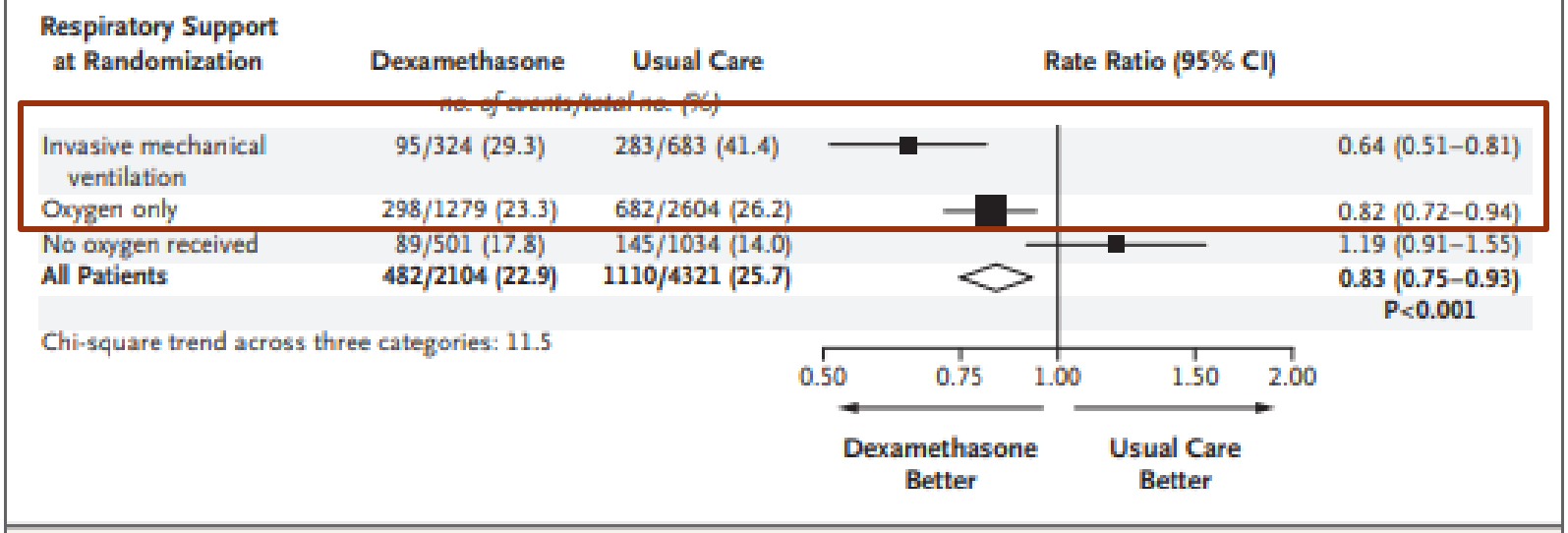
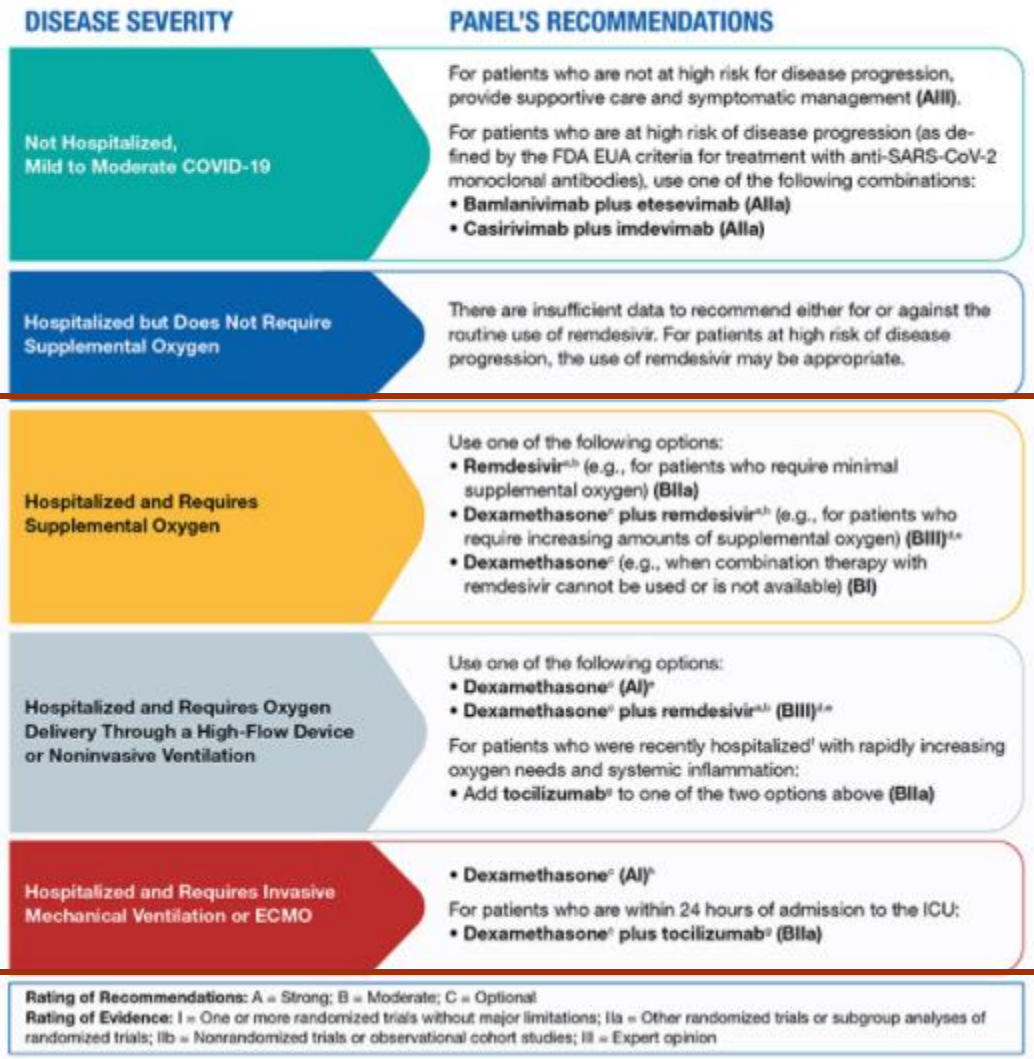


Figure 3. Effect of Dexamethasone on 28-Day Mortality, According to Respiratory Support at Randomization.

Shown are subgroup-specific rate ratios for all the patients and for those who were receiving no oxygen, receiving oxygen only, or undergoing invasive mechanical ventilation at the time of randomization. Rate ratios are plotted as squares, with the size of each square proportional to the amount of statistical information that was available; the horizontal lines represent 95% confidence intervals.

Figure 1. Pharmacologic Management of Patients with COVID-19 Based on Disease Severity

Doses and durations are listed in the footnotes.



NIH COVID-19 Treatment Guidelines. Last update April 21, 2021.

Immunomodulators – IL-6 Inhibitors ☹

- COVACTA[1] – severe COVID-19 w oxygen sat ≤ 93%
  - Enrolled 294 toci vs. 144 placebo from April 13 – May 28, 2020
    - No difference in clinical status or mortality
- Veiga, et al[2] – severe or critical COVID-19 – supp O2 or mech vent
  - Enrolled 129 patients from May 8 – July 17, 2020
    - Stopped early for excess deaths at 15 days in tocilizumab group (17 vs. 3%); in-hospital mortality 21 vs. 9% (p=0.02)
- EMPACTA[3] – hospitalized w COVID-19 PNA not on mech vent
  - Modified Intention-to-Treat – 249 tocilizumab vs. 128 placebo
    - Primary outcome – combined mechanical ventilation or death 12% vs. 19.3% (p=0.04)
    - Secondary outcome – no difference in death from any cause

1. Rosas, et al. *NEJM.* 2021.
2. 2. Veiga, et a. l*BMJ.* 2021.
3. Salama, et al. *NEJM.* 2021.

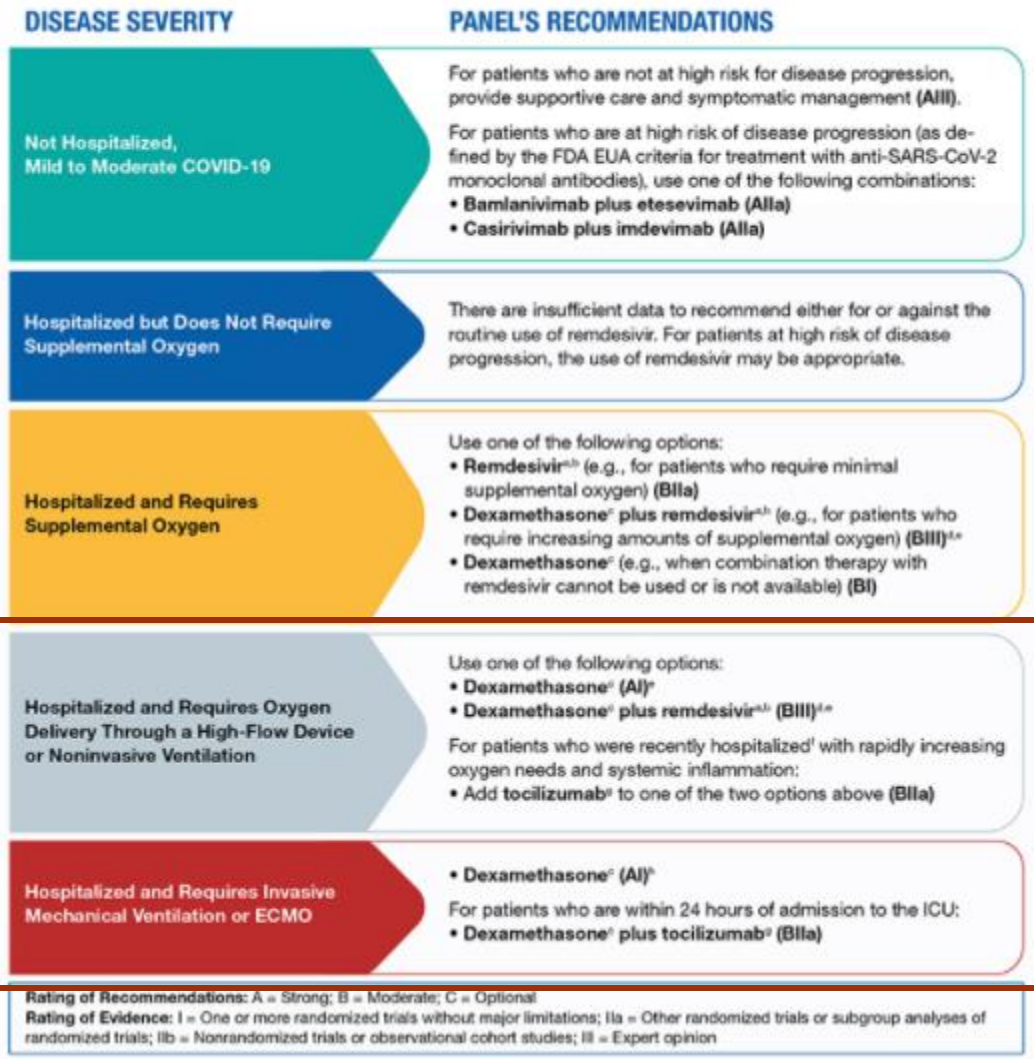
IL-6 Inhibitors – Mostly Tocilizumab ☺

- REMAP-CAP – ICU patients within 24 hours of resp support – April 19 – Nov 19, 2020
  - 353 tocilizumab, 48 sarilumab, 402 control
    - 93% treated with steroids; 33% with remdesivir; median 1.2 days from hospital admission to enrollment
    - Organ support-free days (10, 11 vs. 0) – toci median adjusted OR 1.64 (95% credible interval 1.25 – 2.14)
    - In-hospital mortality 27% (pooled) vs. 36% – toci median adjusted OR 1.64 (95% credible interval 1.14 – 2.35)
- RECOVERY – pts w oxygen sat <92% or requiring O2 and CRP ≥ 75 mg/L – April 23, 2020 – Jan 24, 2021
  - 621 toci vs. 729 control – 82% steroids
    - Mortality at 28 days (31 vs. 35%; p=0.0028)
    - Discharge w/in 28 days (57% vs 50%; p<0·0001)

1. REMAP-CAP. *NEJM.* February 25, 2021.
2. RECOVERY. *Lancet.* May 1, 2021.

Figure 1. Pharmacologic Management of Patients with COVID-19 Based on Disease Severity

Doses and durations are listed in the footnotes.



NIH COVID-19 Treatment Guidelines. Last update April 21, 2021.

Immunomodulators

- JAK inhibitors – baricitinib
  - EUA on Nov 19, 2020
    - Baricitinib + remdesivir in hospitalized patients with COVID-19 who require supplemental oxygen, mechanical ventilation, or ECMO
    - Primarily due to ACTT-2 results
      - Double-blind, placebo-controlled in 8 countries from May 8 – July 1
      - Baricitinib (4mg daily x 14 days) + remdesivir (10 days) (n=515) vs. remdesivir alone (n=518)
      - Combination group recovered 1 day faster (7 vs. 8 days; p=0.03)
      - High flow or non-invasive ventilation most benefit (10 vs. 18 days)
      - No difference in mortality

Kalil, et al. *NEJM.* 2020.

Immunomodulators

- JAK inhibitors – baricitinib
  - ACTT-4 – baricitinib + remdesivir vs. dexamethasone + remdesivir
    - NIH enrollment closed April 13, 2021 for pre-defined futility criteria indicating neither treatment regimen studied likely significantly better than the other[1]
  - NIH guidelines[2]
    - Insufficient data to recommend either for or against use of baricitinib + remdesivir for the treatment of COVID-19 in hospitalized patients, when corticosteroids can be used
    - In rare circumstance when corticosteroids cannot be used, recommends baricitinib + remdesivir for the treatment of COVID-19 in hospitalized, non-intubated patients who require oxygen supplementation

1. Press release: https://www.nih.gov/news-events/news-releases/nih-closes-enrollment-trial-comparing-covid-19-treatment-regimens. April 15, 2021.
2. NIH COVID-19 guidelines. Updated April 21, 2021.

Assessment Question #1

- Which of the following is the only medication to be recommended as a AI recommendation in current NIH COVID-19 treatment guidelines?

  A. Remdesivir

  B. Dexamethasone

  C. Tocilizumab

  D. Casirivimab/imdevimab

  E. Hydroxychloroquine

More to Come on Monoclonal Antibodies – Prophylaxis?

- BLAZE-2 – unpublished[1]
  - Efficacy, safety of bam 4200mg vs placebo in preventing COVID-19 in skilled nursing and assisted living facility residents and staff
  - 80% reduced risk?

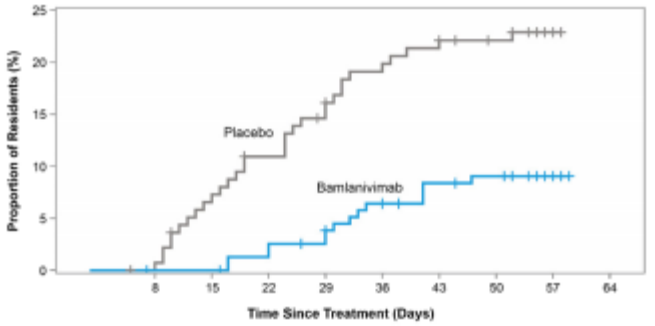
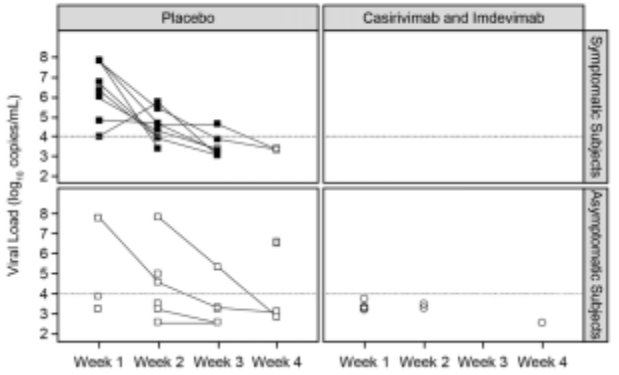


Figure. Time since treatment to development of mild or worse COVID-19 with bamlanivimab versus placebo in residents. Residents were SARS-CoV-2 RT-PCR negative and serology negative at baseline. Mild or worse COVID-19 was defined as positive for SARS-CoV-2 by RT-PCR and reporting of mild or worse symptoms and signs associated with COVID-19 within 21 days of detection.

- Cas/imdev 600/600mg – unpublished[2]
  - Asymptomatic participants exposed to a COVID-19–infected household member w/in 96 hours
  - Interim results – 100% reduction in symptomatic disease; 48% reduction in asymptomatic disease

Figure 1. Weekly viral load for individual symptomatic subjects (filled symbol) and asymptomatic subjects (open symbol) in the two treatment groups.



1. Cohen, et al. CROI abstracts. 2021.
2. O'Brien, et al. CROI abstracts. 2021.

Antibiotic Stewardship and COVID-19

Co-infection and Use of Antibiotics

- NIH guidelines:

  Empiric Broad-Spectrum Antimicrobial Therapy

  Recommendations

  - In patients with COVID-19 and severe or critical illness, there are insufficient data to recommend empiric broad-spectrum antimicrobial therapy in the absence of another indication.
  - If antimicrobials are initiated, the Panel recommends that their use should be reassessed daily in order to minimize the adverse consequences of unnecessary antimicrobial therapy **(AIII)**.

  Rationale

  There are no reliable estimates of the incidence or prevalence of copathogens with severe acute respiratory syndrome coronavirus 2 at this time.

- IDSA guidelines:
  - Bacterial coinfections with SARS-CoV-2 relatively infrequent (likely occurring in <10% of hospitalized COVID-19 patients) – literature does not support routine use of empiric antibiotics
  - Recent studies in COVID-19 patients
    - Antibiotics administered in 56 – 74.6%
    - Bacterial co-infection 3.5 – 31%

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September 9,

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The New York Times

With All Eyes on Covid-19, Drug-Resistant Infections Crept In

The spread of other dangerous germs is surging — a result, in part, of the chaotic response to the pandemic.

A hospital worker disinfecting a room where a Covid patient had died. Focus on the coronavirus has helped a different set of germs spread. Shannon Stapleton/Reuters

By Matt Richtel

Jan. 27, 2021

Procalcitonin in COVID-19

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

Clinical Therapeutics

Limited Utility of Procalcitonin in Identifying Community-Associated Bacterial Infections in Patients Presenting with Coronavirus Disease 2019

Michael May, Michelle Chang, Donald Dietz, Sherif Shoucri, Justin Laracy, Magdalena E. Sobieszczyk, Anne-Catrin Uhlemann, Jason Zucker, Christine J. Kubin

Infection Control & Hospital Epidemiology

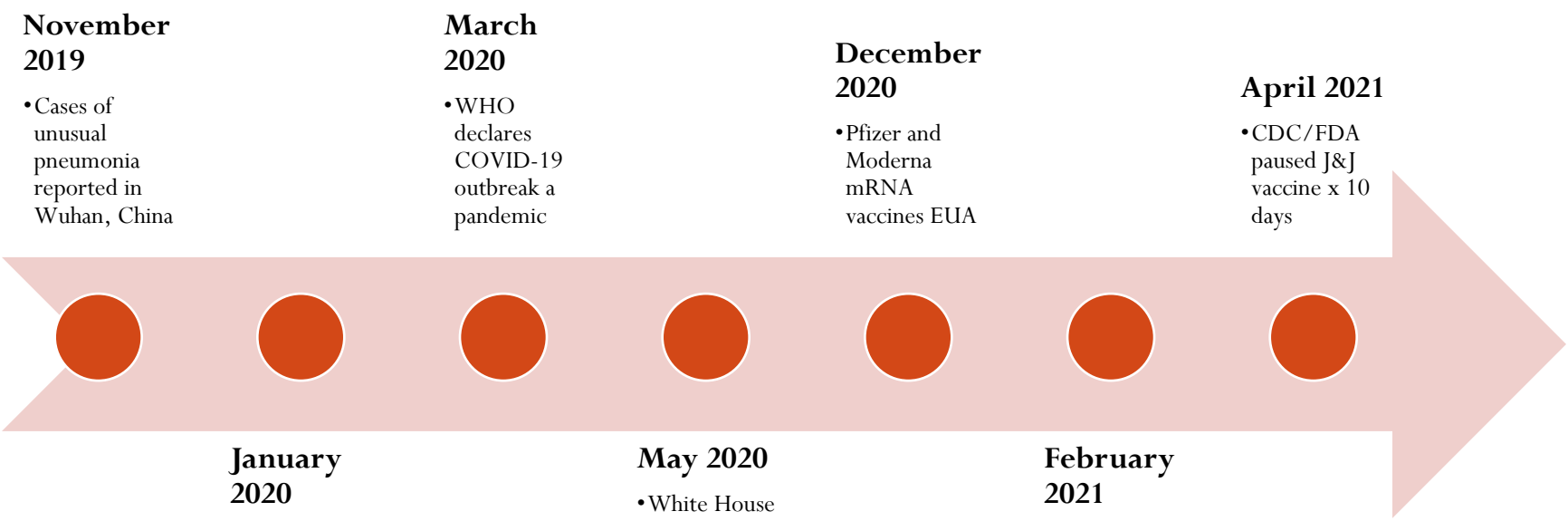
The Role of Procalcitonin in Antibiotic Decision-Making in Covid-19 Infection

Published online by Cambridge University Press: **19 April 2021**

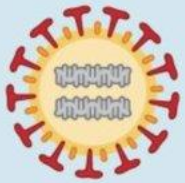
Valeria Fabre, Sara Karaba, Joe Amoah, Matthew Robinson, George Jones, Kathryn Dzintars, Morgan Katz, B. Mark Landrum, Sarojini Qasba, Pooja Gupta, Eili Klein and Sara E. Cosgrove Show author details

COVID-19 Vaccines

Timeline


November 2019
•Cases of unusual pneumonia reported in Wuhan, China
January 2020
•China isolates novel coronavirus and shares genetic sequence world-wide
March 2020
•WHO declares COVID-19 outbreak a pandemic
May 2020
•White House announces Operation Warp Speed
December 2020
•Pfizer and Moderna mRNA vaccines EUA
February 2021
•J&J/Janssen vaccine EUA
April 2021
•CDC/FDA paused J&J vaccine x 10 days

Vaccine Platforms

Types of vaccines	DNA and RNA	Live attenuated	Inactivated	Subunit	Viral vector
					
How it works	This vaccine uses DNA or RNA molecules to teach the immune system to target key viral proteins.	This is a weakened version of the actual virus.	An inactivated vaccine uses the whole virus after it has been killed with heat or chemicals.	This vaccine uses a piece of a virus' surface to focus your immune system on a single target.	This approach takes a harmless virus and uses it to deliver viral genes to build immunity.
Advantages	Easy and quick to design.	Stimulates a robust immune response without causing serious disease.	Safe because the virus is already dead and is easy to make.	Focuses the immune response on the most important part of the virus for protection and cannot cause infection.	Live viruses tend to elicit stronger immune responses than dead viruses or subunit vaccines.
Disadvantages	Never been done before. There are no licensed DNA or RNA vaccines currently in use.	May not be safe for those with compromised immune systems.	Not as effective as a live virus. Some previous inactivated vaccines have made the disease worse; safety for the novel coronavirus needs to be shown in clinical trials.	May not stimulate a strong response, other chemicals may need to be added to boost long-term immunity.	Important to pick a viral vector that is truly safe. An immune response to the viral vector could make the vaccine less effective.
Existing examples	• None	• Measles, Mumps and Rubella • Chickenpox	• Polio	• Pertussis • Hepatitis C • Human Human papillomavirus (HPV)	• Ebola • Veterinary medicine
Group testing this approach for COVID-19	• Moderna (RNA) • Inovio (DNA)	• Codagenix • Indian Immunologicals Ltd.	• Sinovac • Sinopharm	• Novavax • AdaptVac	• University of Oxford & AstraZeneca • CanSino Biologics • Johnson & Johnson

Sources: CDC; NIAID; FDA

MICHELLE GUERRERO and JONATHAN WOSEN U-T

Vaccine Tracker

Covid-19 Vaccine Candidates

Vaccine		Trial		Efficacy					Variants			Specifics					
Type	Developer (Name)	Investigational Status (Participants)	EUA Submission	First dose efficacy	Second dose efficacy	Prevention of moderate to severe disease	Prevention of severe disease	Prevention of death	B1.1.7 (United Kingdom)	P.135 (South Africa)	P.1 (Brazil)	Route/# of doses	Timing of Doses	Presentation [2]	Storage requirements	Preparation & Handling	S
mRNA How it works	Pfizer/BioNTech (BNT162b2)	Phase 2 & 3 with EUA (44,000)	EUA approved 12/11 for ages 16 and older	52%	95%	Not quantified	95%	100%	No impact	100%	No data	IM/ 2 doses	0, 21 days[2]	MDV (5 doses) / 30 mcg/0.3mL[13]	• Ultra-cold storage (-80 to -60°C) until expiration date •Thermal shippers replenished with dry ice for 30 days• Freezer (-25 to -15°C) for up to 2 weeks •Refrigeration (2-8°C) for 5 days. If not used, discard. •Room Temp: thawed vials must be used within 2 hours	•Thawing and reconstitution required. •Reconstitute with 1.8 mL of 0.9% sodium chloride	Sta ho
	Moderna (mRNA-1273)	Phase 3 with EUA (30,000)	EUA approved 12/20 for ages 18 and above	80%	94%	Not quantified	92%	100% (Inferred)	No impact	6-fold reduction in antibodies (unclear impact on efficacy)	No data	IM/ 2 doses	0, 28 days[2]	MDV (10 doses) / 100 mcg/0.5 mL[13]	•Freezer (-50 to -15°C) for 7 months NEW! •Refrigeration (2-8°C) for 3 months •Room Temp: 24 hours (unpunctured)	Thawing required. Vaccine may be thawed in the refrigerator or at room temperature •Refrigerator: 2.5 hours •Room temperature: 1 hour •Vials that have not been punctured may be kept between 8°C and 25°C for up to 24 hours	Sta 12 h
Viral Vector How it works	Johnson & Johnson (Ad26.COV2.S)	Phase 3 (44,325)	Administration resumed on 4/23 EUA approved 2/27 for 18 years and older	66%	N/A	72%	66%	100%	No data	57% efficacy	No data	IM/ 1 dose	0 day[6]	MDV (5 doses)	2 years at -20°C and at least 3 months at 2-8°C.[2,7]	Mix contents of vial gently by swirling before withdrawing. DO NOT SHAKE.	2 tem or 6
	Oxford/AstraZeneca (AZD1222)	Phase 3 (30,000)	Not likely to receive authorization until April/May 2021	76%	82%	(Severe) 100%	100%	Pending	Pending	Pending	Pending	IM/ 2 doses	0, 28 days [6]	MDV (10 doses)[6]	Refrigerator (2-8°C) for up to 6 months **may be longer, pending stability testing*	N/A	

ASHP vaccine tracker. https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/Coronavirus/docs/Vaccine-candidate-tracking-table. Updated 5/3/21.

Real world vaccine effectiveness

- MMWR May 7, 2021 – USA
  - Evaluation at 24 hospitals in 14 states during Jan – March 2021
  - Effectiveness of Pfizer-BioNTech or Moderna vaccines against COVID-19–associated hospitalization among adults aged ≥65 years
  - Vaccine effectiveness
    - 94% - fully vaccinated
    - 64% - partially vaccinated

CDC MMWR. May 7, 2021 / 70(18);674–679.

Vaccine Efficacy or Effectiveness (VE) Against Variants

Vaccine	Study type	VE	
Pfizer	Post-EUA	• 90% against B.1.1.7 in Qatar* • 75% against B.1.351 in Qatar	100% for severe/ critical disease
Janssen	Pre-EUA	• 74% in U.S. • 66% in Brazil • 52% in S. Africa	73-82% for severe/critical disease in each country
Novavax	Pre-EUA Pre-EUA	• 96% against non-B.1.1.7 in UK • 86% against B.1.1.7 in UK • 51% against B.1.351 in S. Africa	
AstraZeneca	Pre-EUA Pre-EUA	• 84% against non-B.1.1.7 in UK • 75% against B.1.1.7 in UK • 10% against B.1.351 in South Africa*	

* >85% in UK & Israel (predominate B.1.1.7): https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-people.html
Abu-Radad and Butt. Effectiveness of the BNT162b2 Covid-19 Vaccine against the B.1.1.7 and B.1.351 Variants | NEJM
https://www.fda.gov/media/146217/download
Novavax.: https://ir.novavax.com/news-releases/news-release-details/novavax-covid-19-vaccine-demonstrates-893-efficacy-uk-phase-3
Shinde et al. Efficacy of NVX-CoV2373 Covid-19 Vaccine against the B.1.351 Variant | NEJM
Madhi et al. Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant | NEJM
Emary et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): The Lancet **mild/moderate illness

Scobie H. ACIP meeting. May 12, 2021. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-05-12/10-COVID-Scobie-508.pdf

Summary of Preliminary Data: Implications of SARS-CoV-2 Variants of Concern on Vaccine Effectiveness

- **B.1.1.7**
  - Exponential increase in prevalence in United States
  - Minimal impact on VE; attention needed for additional substitutions in receptor binding domain (RBD), such as E484K
- **B.1.351**
  - Currently low prevalence in United States
  - Moderate impact on VE for some vaccines, though may still provide protection against severe disease
- **P.1**
  - Increasing prevalence in United States; same 3 RBD mutations as B.1.351
  - Additional data needed on potential impact on VE

Scobie H. ACIP meeting. May 12, 2021.
https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-05-12/10-COVID-Scobie-508.pdf

Johnson & Johnson Vaccine EUA

- EUA 2/27/21
- Based on data from 1 international Phase III clinical trial started in 9/2020 – enrolled ~ 40,000 adults ≥ 18 years
  - Interim findings on vaccine efficacy:
    - Against symptomatic, laboratory confirmed COVID-19
      - 66.3% (95% CI = 59.9%–71.8%) ≥14 days after vaccination
      - 65.5% (95% CI = 57.2%–72.4%) ≥28 days after vaccination
      - Efficacy varied by location
        - Highest in the United States (74.4%; 95% CI = 65.0%–81.6%)
        - Latin America (64.7%; 95% CI = 54.1%–73.0%)
        - South Africa (52.0%; 95% CI = 30.3%–67.4%)
    - Prevention of COVID-19–associated hospitalization
      - ≥14 days (2 vs. 29 – efficacy = 93.1%; 95% CI = 71.1%–98.4%)
      - ≥28 days (0 vs. 16 – efficacy = 100%; 95% CI = 74.3%– 100.0%)

CDC MMWR. March 5, 2021 / 70(9);329–332.

Adverse Event Reporting

CDC

VSD

Vaccine Safety Datalink

CDC + FDA

VAERS

Vaccine Adverse Event Reporting System

CDC

CISA

Clinical Immunization Safety Assessment (CISA) Project

J&J Safety

- CDC/FDA recommended pause on 4/13/21 due to 15 cases of thrombosis with thrombocytopenia syndrome (TTS)
  - TTS – rare syndrome appears similar to HIT and involves acute venous or arterial thrombosis and new onset thrombocytopenia in patients with no recent known exposure to heparin
- Similar to recently reported cases from Europe after AstraZeneca COVID-19 vaccine

J&J/Janssen Safety

- Based on risk-benefit assessment on 4/23/21 – ACIP reaffirmed interim recommendation for the use of the Janssen COVID-19 vaccine in all persons aged ≥18 years

Summary of population-level risks and benefits by recommendation, all scenarios

Recommendation for all persons aged 18+

- **Risks:** Expect **26–45 TTS** cases, depending on uptake
- **Benefits:** Depend on uptake, amount of transmission
  - **800–3,500 fewer ICU** admissions
  - **600–1,400 fewer deaths**

Recommendation for all persons aged 50+

- **Risks:** Expect 2–3 TTS cases, depending on uptake
- **Benefits:** Depend on uptake, amount of transmission
  - **300–1000 fewer ICU** admissions
  - **40–250 fewer deaths**

Note: Benefits of vaccination apply to the whole population over a 6-month period, and result from direct and indirect effects

Acronyms: Thrombosis with Thrombocytopenia Syndrome (TTS)

Brooks JT. CDC COVID Clinician Call. April 24, 2021.

J&J EUA Fact Sheet Warnings

- Providers

Thrombosis with Thrombocytopenia

Reports of adverse events following use of the Janssen COVID-19 Vaccine under emergency use authorization suggest an increased risk of thrombosis involving the cerebral venous sinuses and other sites (including but not limited to the large blood vessels of the abdomen and the veins of the lower extremities) combined with thrombocytopenia and with onset of symptoms approximately one to two weeks after vaccination. Most cases of thrombosis with thrombocytopenia reported following the Janssen COVID-19 Vaccine have occurred in females ages 18 through 49 years; some have been fatal. The clinical course of these events shares features with autoimmune heparin-induced thrombocytopenia. In individuals with suspected thrombosis with thrombocytopenia following the Janssen COVID-19 Vaccine, the use of heparin may be harmful and alternative treatments may be needed. Consultation with hematology specialists is strongly recommended. The American Society of Hematology has published considerations relevant to the diagnosis and treatment of thrombosis with thrombocytopenia following the Janssen COVID-19 Vaccine (*https://www.hematology.org/covid-19/vaccine-induced-immune-thrombotic-thrombocytopenia*). (*see Full EUA Prescribing Information*).

- Patients

Blood clots involving blood vessels in the brain, abdomen, and legs along with low levels of platelets (blood cells that help your body stop bleeding), have occurred in some people who have received the Janssen COVID-19 Vaccine. In people who developed these blood clots and low levels of platelets, symptoms began approximately one to two-weeks following vaccination. Most people who developed these blood clots and low levels of platelets were females ages 18 through 49 years. The chance of having this occur is remote. You should seek medical attention right away if you have any of the following symptoms after receiving Janssen COVID-19 Vaccine:

Revised 4/23/21.

U.S. reporting rates of TTS after Janssen COVID-19 vaccination (as of May 7, 2021)

- 8.73 million total Janssen COVID-19 Vaccine doses administered*

	Females			Males		
Age group	TTS cases	Doses admin	Reporting rate† (per million)	TTS cases	Doses admin	Reporting rate† (per million)
18-29 yrs old	**3**	641,510	4.7	**2**	714,458	2.8
30-39 yrs old	**8**	642,745	12.4	**1**	728,699	1.4
40-49 yrs old	**7**	743,256	9.4	**1**	775,390	1.3
50-64 yrs old	**4**	1,463,416	2.7	**2**	1,505,505	1.3
65+ yrs old	**0**	814,947	0	**0**	697,925	0

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* Source of doses administered: https://covid.cdc.gov/covid-data-tracker/#vaccinations; † Reporting rate = TTS cases per 1 million Janssen COVID-19 vaccine doses administered

Shimabukuro T. ACIP meeting. May 12, 2021.
https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-05-12/07-COVID-Shimabukuro-508.pdf

Special Populations

- Pregnancy
  - Preliminary safety of mRNA vaccines in 35,691 V-Safe participants identified as pregnant (12/14/20 – 2/28/21)[1]
    - Calculated proportions of adverse pregnancy and neonatal outcomes in vaccinated similar to before Covid-19 pandemic
  - Studies demonstrate:
    - Antibody transfer from mother to fetus[2,3]
    - Immunogenic in pregnant women and vaccine-elicited antibodies were transported to infant cord blood and breast milk[4]
  - ACOG recommends vaccine access and clinical decision making[5]

1. Shimabukuro, et al. *NEJM.* April 21, 2021.
2. Rottenstreich, et al. *CID.* April 3, 2021.
3. Mithal, et al. *AJOG.* 2021.
4. Collier, et al. *JAMA.* May 13, 2021.
5. ACOG Practice Advisory. Updated 4/28/21.

Special Populations

- Immunocompromised
  - Patients with rheumatic and musculoskeletal diseases
    - American College of Rheumatology task force recommendations[1]
  - Solid organ transplant patients
    - Prelim data of immunogenicity of 2-dose mRNA vaccine in 658 patients vaccinated between 12/16/20 – 3/13/21[2]
      - At median of 21 days (IQR, 18-25 days) after first dose, antibody detectable in 98 participants (15%; 95% CI, 12%-18%)
      - At median of 29 days (IQR, 18-25 days) after second dose, antibody detectable in 357 participants (54%; 95% CI, 50%-58%)
      - Those receiving mycophenolate or azathioprine less likely to develop an antibody response than those not (43% vs 82%, $P < .001$)

1. ACR COVID-19 Vaccine Clinical Guidance Task Force. https://www.rheumatology.org/Portals/0/Files/COVID-19-Vaccine-Clinical-Guidance-Rheumatic-Diseases-Summary.pdf. Updated 4/28/21.
2. Boyarsky, et al. *JAMA.* May 5, 2021.

AST Recommendations

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STATEMENT ON COVID-19 VACCINATION IN SOLID ORGAN TRANSPLANT RECIPIENTS

Friday, May 7, 2021

Recently, multiple studies have been published examining the response to SARS-CoV-2 mRNA-based vaccines in solid organ transplant (SOT) recipients.(1-7) Overall, these have demonstrated reduced antibody responses to vaccine when compared with reports involving the general public.

The low antibody response rate is concerning but not unexpected as SOT recipients have lower rates of immune responses to other vaccines as well.(8) Further data are needed to evaluate B- and T- cellular responses in SOT recipients after SARS-CoV-2 vaccination and to assess vaccine effectiveness particularly for protection against severe COVID-19 as a clinical end-point. Previous experience with influenza vaccination in transplant patients has demonstrated reduced influenza-related lower respiratory tract disease and hospitalization despite low antibody response.(9, 10). While breakthrough cases of COVID-19 after partial or full vaccination in SOT recipients may occur, it is important to recognize that we may be preventing more cases or reducing severity through vaccination.(11, 12) Thus, we strongly caution against concluding that low antibody response rate to SARS-CoV-2 vaccination will lead to reduced clinical effectiveness until more information is available. These results should not prompt or encourage vaccine hesitancy in SOT recipients.

Until more complete data are available, we urge:

- **Pre-transplant vaccination of all SOT candidates as a priority whenever feasible.**
- **Continued SARS-CoV-2 vaccination in SOT recipients and priority for vaccination of their household members and caregivers to reduce exposure risk for these vulnerable patients.**
- **Continuation of a stable immunosuppression regimen at the time of vaccination to avoid the risk of organ rejection until more comprehensive data are available.**
- **Continued adherence of all transplant recipients to protective measures including masking and social distancing regardless of vaccination status.**

Key Things to Know About COVID-19 Vaccines

Updated Apr. 28, 2021 Languages Print

Key Things to Know

- COVID-19 vaccines are safe and effective.
- You may have side effects after vaccination, but these are normal.
- It typically takes two weeks after vaccination for the body to build protection (immunity) against the virus that causes COVID-19. You are not fully vaccinated until 2 weeks after the 2nd dose of a two-dose vaccine or two weeks after a one-dose vaccine.
- COVID-19 vaccines are more widely accessible. Everyone 16 years and older is now eligible for a COVID-19 vaccination. Find a COVID-19 vaccine.
- People who have been fully vaccinated can start to do some things that they had stopped doing because of the pandemic.

What We are Still Learning

- We are still learning how well vaccines prevent you from spreading the virus that causes COVID-19 to others, even if you do not have symptoms.
- We're also still learning how long COVID-19 vaccines protect people.
- We are still learning how many people have to be vaccinated against COVID-19 before most people can be considered protected (population immunity).
- We are still learning how effective the vaccines are against new variants of the virus that causes COVID-19.

CDC. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/keythingstoknow.html. Accessed 5/8/21.

Other Recent Vaccine Updates

- COVID-19 vaccines and other vaccines **may now be administered without regard to timing**
  - If multiple vaccines are administered at a single visit, administer each injection in a different injection site
- Ideally COVID-19 vaccination should be completed ≥ 14 days before initiation of immunosuppressive therapies
- Antibody testing not recommended to assess for immunity to SARS-CoV-2 following COVID-19 vaccination
  - Revaccination not recommended after people who received COVID-19 vaccines during chemotherapy or treatment with other immunosuppressive drugs

CDC. https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html#janssen-vaccine-certain-populations. Updated May 14, 2021.

Boosters and Second-Generation Vaccines Against SARS-CoV-2 Variants

- Manufacturers launching booster studies of current vaccines and/or developing second-generation vaccines against B.1.351
- Moderna — preliminary phase 2 results of single 50 µg booster of authorized (mRNA-1273) and variant-specific vaccine (mRNA-1273.351)
  - 6-8 months after primary series (pre-booster), low/undetectable neutralizing antibody titers for B.1.351 and P.1, but titers against wild-type still likely protective
  - Both vaccines — acceptable safety; boosted immunity to all types (wild-type, B.1.351, P.1)
  - mRNA-1273.351 booster more effective than mRNA-1273 at neutralizing B.1.351
  - In progress — bivalent vaccine with 1:1 mix of original & variant vaccine (mRNA-1273.211)

Wu et al. medRxiv preprint (May 6, 2021): https://doi.org/10.1101/2021.05.05.21256716
https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-positive-initial-booster-data-against-sars-cov/
https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-initiate-study-part-broad-development

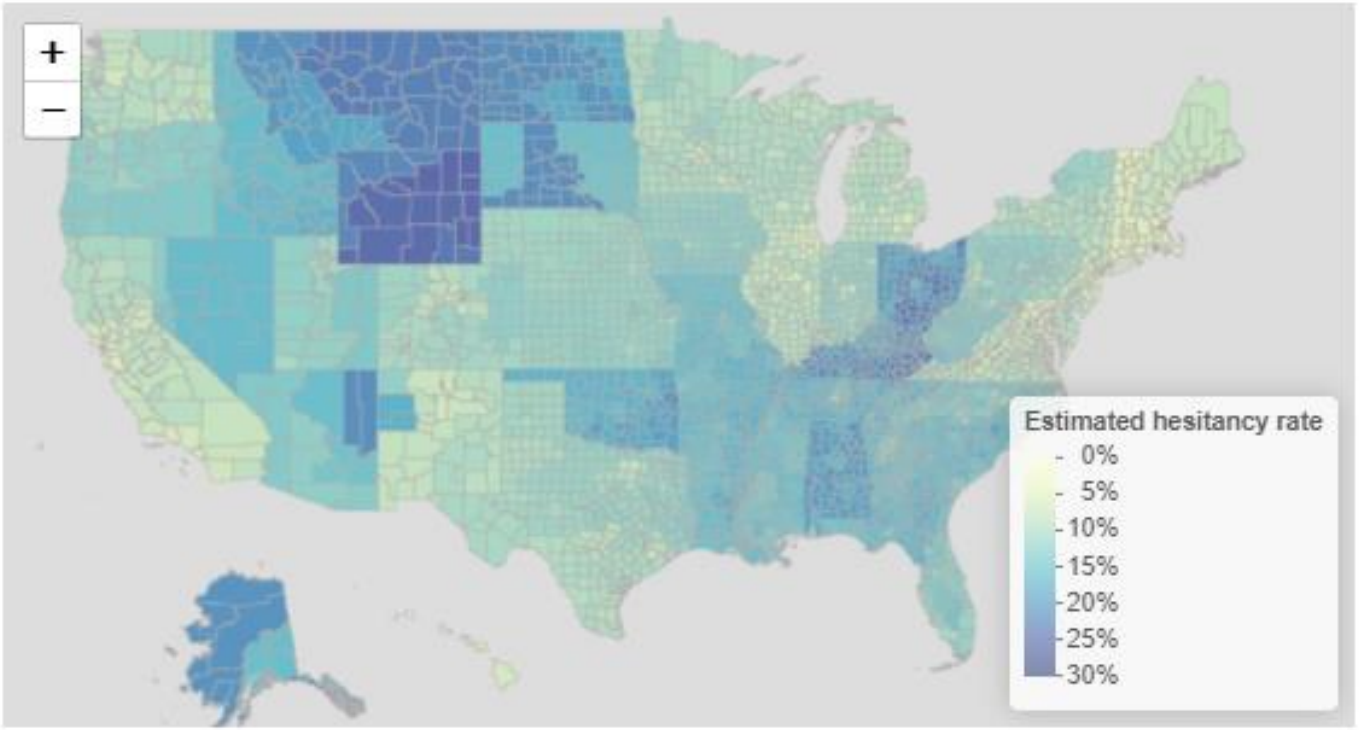
Scobie H. ACIP meeting. May 12, 2021.
https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-05-12/10-COVID-Scobie-508.pdf

COVID-19 Vaccine Hesitancy in Your Community

To make your COVID-19 vaccination outreach more efficient, you can use this map to see where people may be more hesitant about getting vaccinated.

COVID-19 Vaccine Hesitancy Data in the United States, by County

The map shows COVID-19 vaccination hesitancy estimates by county, plus additional facts to help you understand your outreach areas. Zoom in on an area and click on a county to see the information.



US Dept of Health and Human Services. COVID-19 Public Education Campaign. https://wecandothis.hhs.gov/vaccine-hesitancy-your-community. Accessed May 16, 2021.

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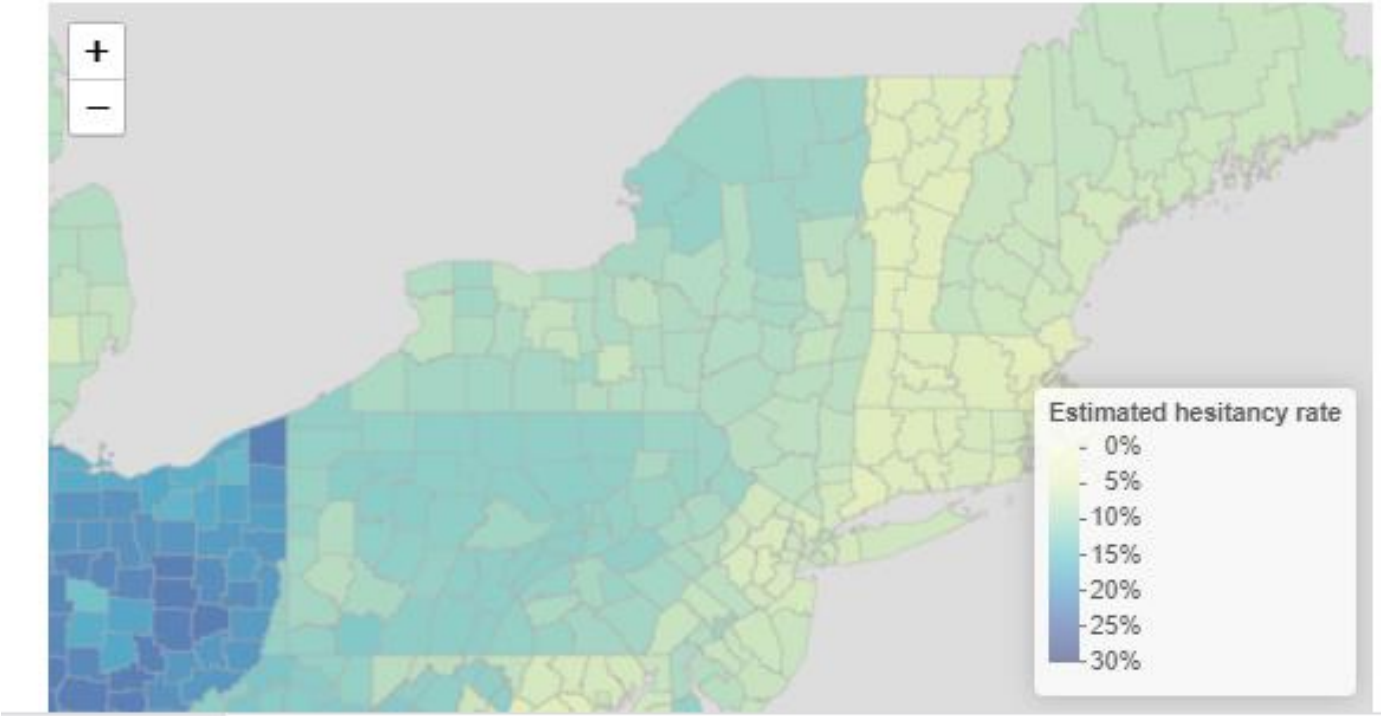
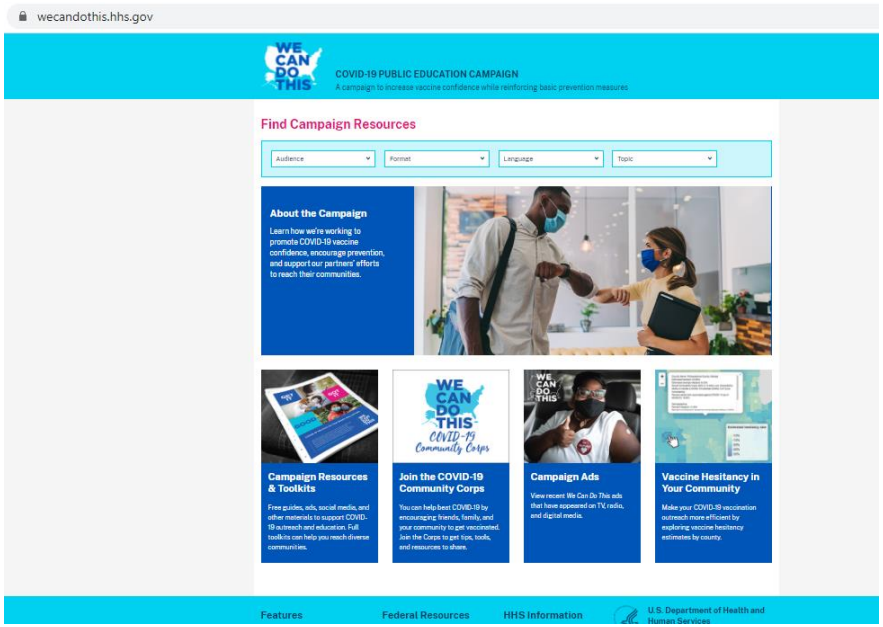


US Dept of Health and Human Services. COVID-19 Public Education Campaign. https://wecandothis.hhs.gov/vaccine-hesitancy-your-community. Accessed May 16, 2021.

Resources

- Treatment
  - NIH guidelines
  - IDSA guidelines
  - SIDP
- Vaccine information/education
  - CDC
  - APIC
  - NYC DOH
  - ASHP
  - HHS -Wecandothis.hhs.org



Thank you!

Patricia Saunders-Hao, PharmD, BCIDP, BCPS (AQ-ID)

Email: psaundershao@northwell.edu