CDC/IDSA COVID-19 Clinician Call

March 20, 2021

Welcome & Introduction

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Vice President, Clinical Affairs & Guidelines
IDSA

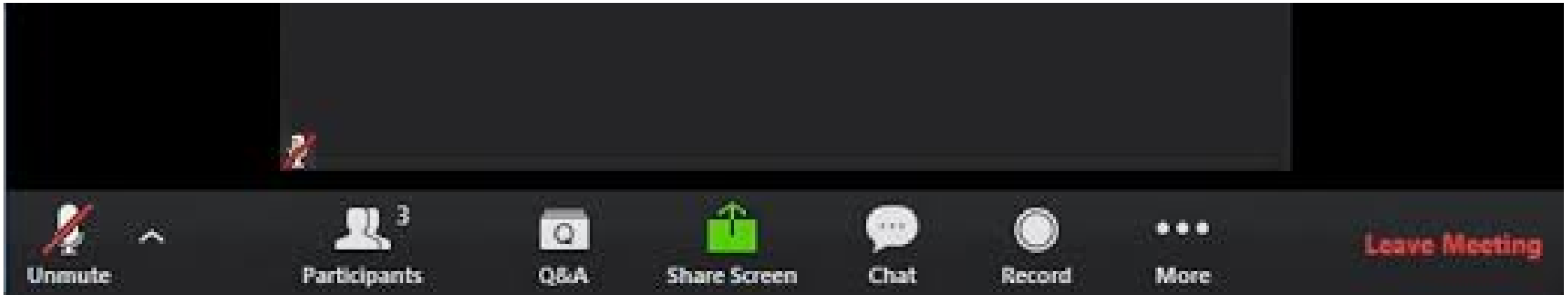
- 59th in a series of weekly calls, initiated by CDC as a forum for information sharing among frontline clinicians caring for patients with COVID-19
- The views and opinions expressed here are those of the presenters and do not necessarily reflect the official policy or position of the CDC or IDSA. Involvement of CDC and IDSA should not be viewed as endorsement of any entity or individual involved.
- This webinar is being recorded and can be found online at www.idsociety.org/cliniciancalls.

TODAY'S TOPICS

- COVID-19 Treatment Updates: Focus on Monoclonal Antibodies and Tocilizumab
- Extended Time: COVID-19 Vaccine Q&A

Question?
Use the “Q&A” Button

Comment?
Use the “Chat” Button



COVID-19 Treatment Updates: Focus on Monoclonal Antibodies and Tocilizumab

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John Farley, MD, MPH
Director of the Office of Infectious Diseases
Center for Drug Evaluation and Research
US Food and Drug Administration

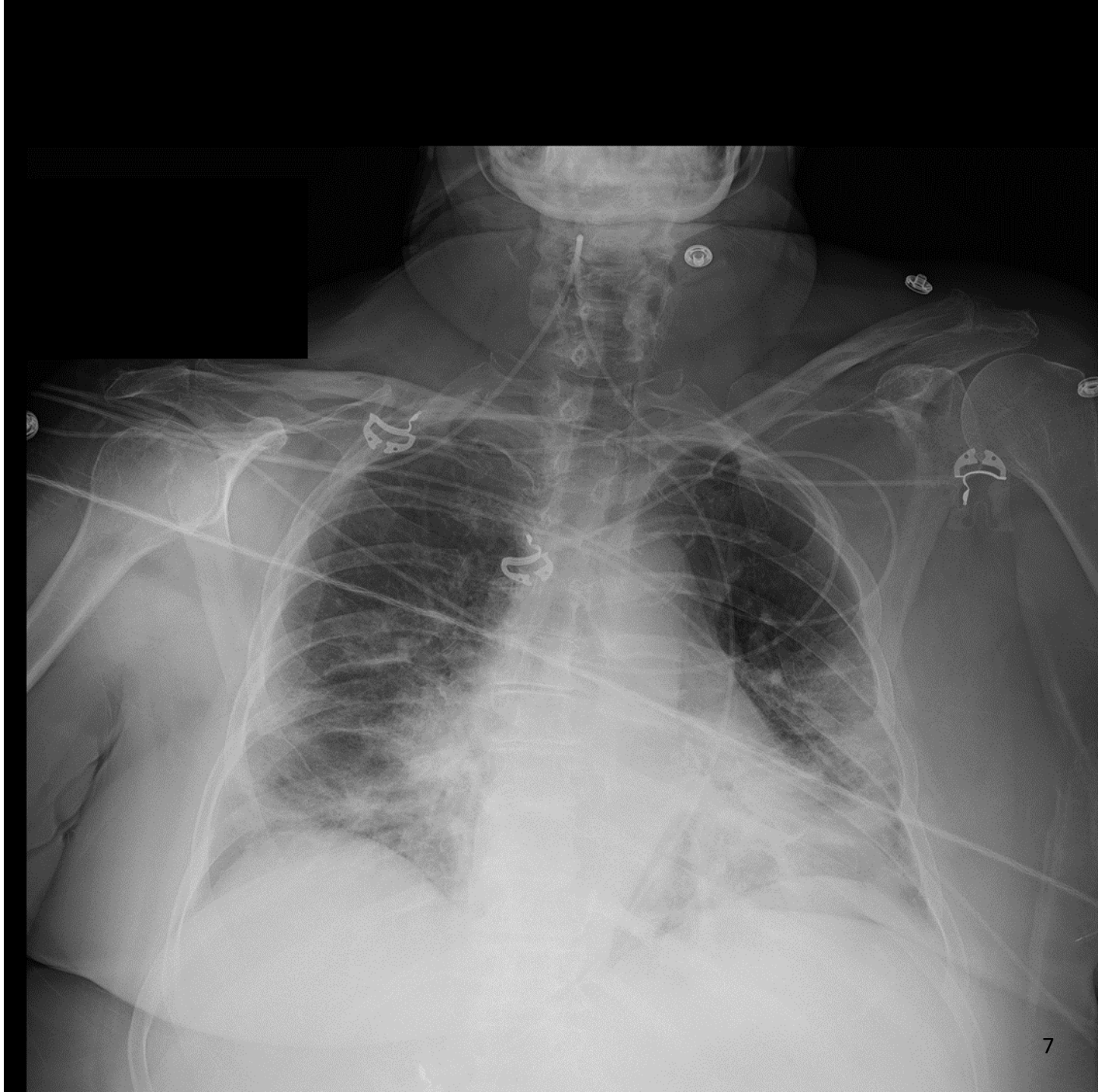
Disclosures

- **Lindsey R. Baden, MD** has no financial relationships with commercial interests to disclose.
- **Rajesh Gandhi, MD, FIDSA** was on scientific advisory boards for Merck (>1 year ago) and Gilead (>2 years ago).
- **John O'Horo, MD, MPH, FACP** has received fees from Bates College and Elsevier, Inc. not directly related to these subjects, as well as small grants from Nference, inc. He is also on the editorial board of BMC infectious diseases.
- **John Farley, MD, MPH** has nothing to disclose.

TOCILIZUMAB

Case #1

- 73 year diabetic female with symptom onset ten days ago
- Admitted six days ago with hypoxia and fever
- Oxygenation worsened from needing supplemental O2
- Now saturating 91% on 50 LPM HFNC FiO2 90%
- CBC entirely normal, CRP 79.0 mg/L, chemistry unremarkable



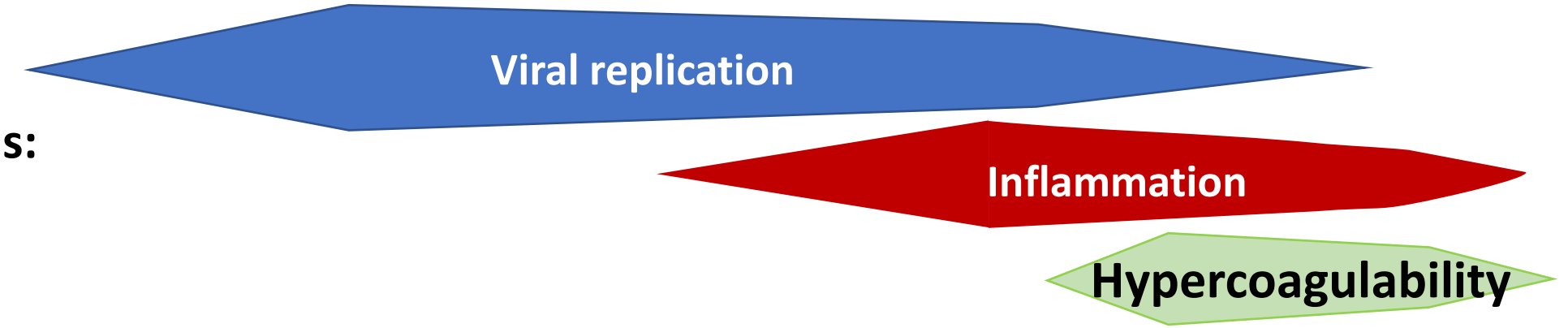
ID consulted

- Finished remdesivir
- Given dexamethasone through the present
- Would you use tocilizumab in this patient?

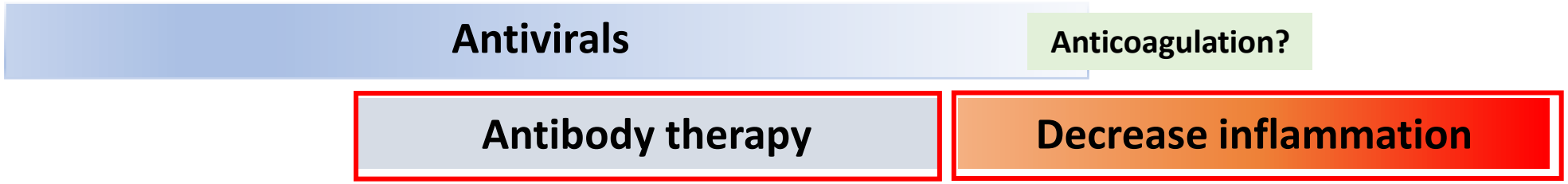
Treatment Across the COVID-19 Spectrum

Stage/ Severity:	Asymptomatic/ Presymptomatic	Mild Illness	Moderate Illness	Severe Illness	Critical illness
	+ SARS-CoV-2 test but no symptoms	Mild symptoms (eg fever, cough, taste/smell changes); no dyspnea	O_2 saturation >=94%, lower respiratory tract disease	O_2 saturation <94%, respiratory rate >30/min; lung infiltrates >50%	Respiratory failure, shock, multi-organ dysfunction/failure

Disease Pathogenesis:



Potential treatment:



Gandhi RT, CID, 2020
Gandhi RT, Lynch J, del Rio C. NEJM 2020

Interleukin-6 Receptor Antagonists: Recent Updates

IDSA Guidelines on the Treatment and Management of Patients with COVID-19

Published by IDSA on 4/11/2020. Last updated, 3/18/2021

COVID-19 Guideline, Part 2: Infection Prevention

COVID-19 Guideline, Part 3: Diagnostics

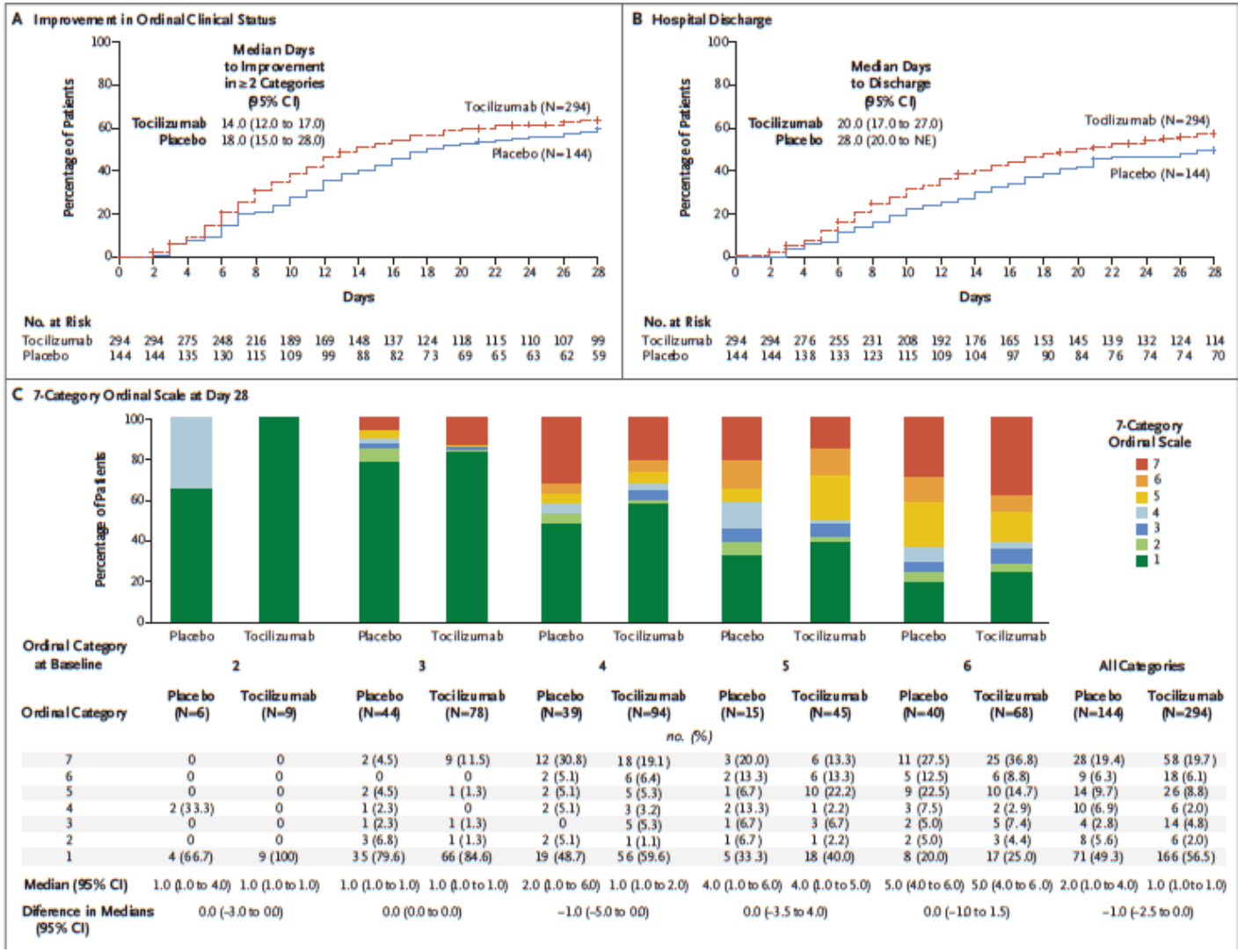
COVID-19 Guideline, Part 4: Serology

Adarsh Bhimraj*, Rebecca L. Morgan**, Amy Hirsch Shumaker, Valery Lavergne**, Lindsey Baden, Vincent Chi-Chung Cheng, Kathryn M. Edwards, Rajesh Gandhi, Jason Gallagher, William J. Muller, John C. O'Horo, Shmuel Shoham, M. Hassan Murad**, Reem A. Mustafa**, Shahnaz Sultan**, Yngve Falck-Ytter**

**Corresponding Author* ***Methodologist*

Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia (COVACTA)

- Phase 3 trial, RCT (2:1) tocilizumab (8mg/kg) vs pbo
  - ~25% received a 2nd dose
- 1ary outcome – clinical status d28 in mITT
  - WHO ordinal scale (1-7)
- N=452 with 438 analyzed
  - 294 toci, 144 pbo
  - April-May 2020
    - Glucocorticoid use 19.4vs28.5%
- D28
  - Toci vs pbo– ordinal 1vs2 p=0.31
  - Mortality – 19.7vs19.4% p=0.94

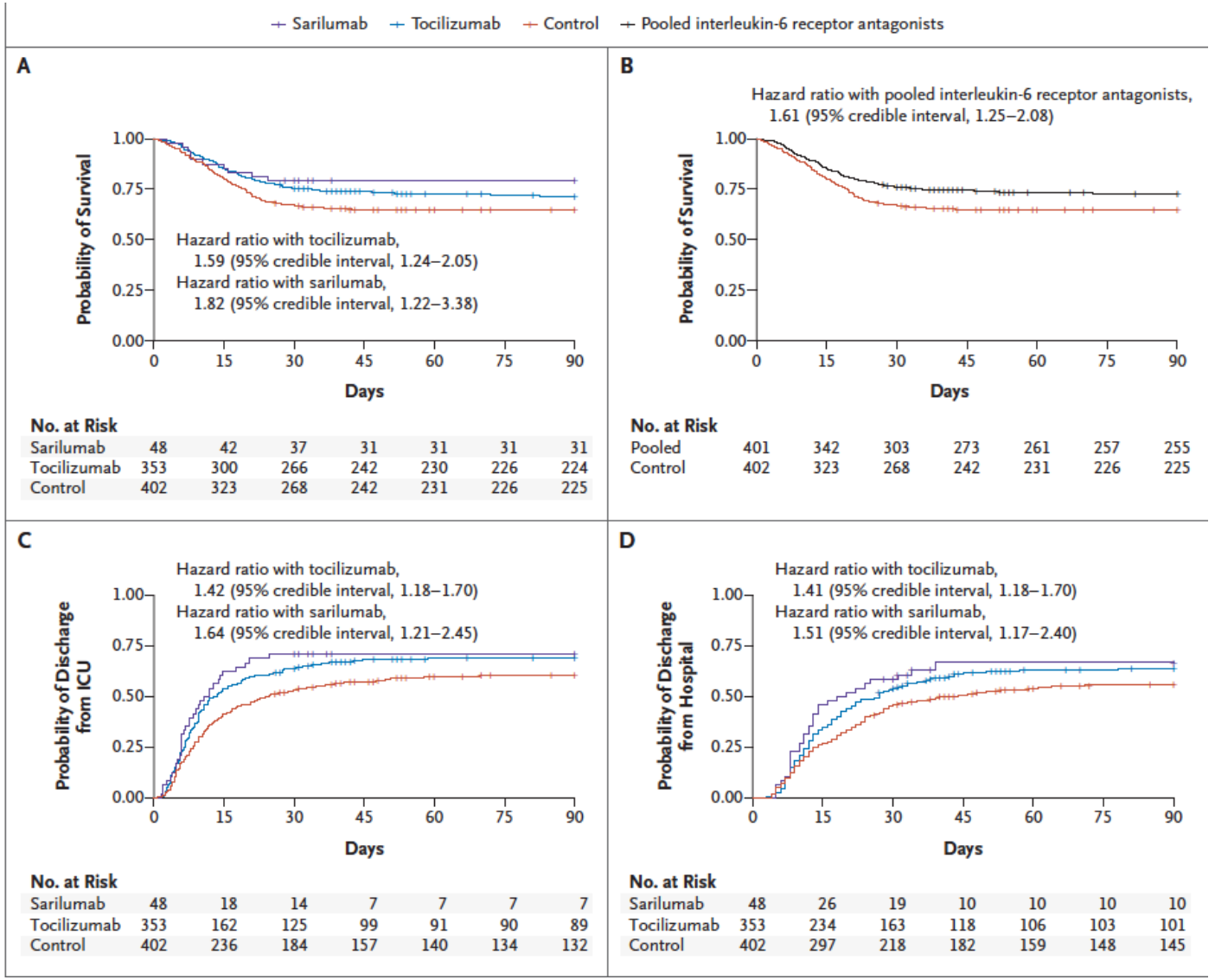


Ordinal Category at Baseline	2		3		4		5		6		All Categories	
Ordinal Category	Placebo (N=6)	Tocilizumab (N=9)	Placebo (N=44)	Tocilizumab (N=78)	Placebo (N=39)	Tocilizumab (N=94)	Placebo (N=15)	Tocilizumab (N=45)	Placebo (N=40)	Tocilizumab (N=68)	Placebo (N=144)	Tocilizumab (N=294)
					no. (%)							
7	0	0	2 (4.5)	9 (11.5)	12 (30.8)	18 (19.1)	3 (20.0)	6 (13.3)	11 (27.5)	25 (36.8)	28 (19.4)	58 (19.7)
6	0	0	0	0	2 (5.1)	6 (6.4)	2 (13.3)	6 (13.3)	5 (12.5)	6 (8.8)	9 (6.3)	18 (6.1)
5	0	0	2 (4.5)	1 (1.3)	2 (5.1)	5 (5.3)	1 (6.7)	10 (22.2)	9 (22.5)	10 (14.7)	14 (9.7)	26 (8.8)
4	2 (33.3)	0	1 (2.3)	0	2 (5.1)	3 (3.2)	2 (13.3)	1 (2.2)	3 (7.5)	2 (2.9)	10 (6.9)	6 (2.0)
3	0	0	1 (2.3)	1 (1.3)	0	5 (5.3)	1 (6.7)	3 (6.7)	2 (5.0)	5 (7.4)	4 (2.8)	14 (4.8)
2	0	0	3 (6.8)	1 (1.3)	2 (5.1)	1 (1.1)	1 (6.7)	1 (2.2)	2 (5.0)	3 (4.4)	8 (5.6)	6 (2.0)
1	4 (66.7)	9 (100)	35 (79.6)	66 (84.6)	19 (48.7)	56 (59.6)	5 (33.3)	18 (40.0)	8 (20.0)	17 (25.0)	71 (49.3)	166 (56.5)
Median (95% CI)	1.0 (1.0 to 4.0)	1.0 (1.0 to 1.0)	1.0 (1.0 to 1.0)	1.0 (1.0 to 1.0)	2.0 (1.0 to 6.0)	1.0 (1.0 to 2.0)	4.0 (1.0 to 6.0)	4.0 (1.0 to 5.0)	5.0 (4.0 to 6.0)	5.0 (4.0 to 6.0)	2.0 (1.0 to 4.0)	1.0 (1.0 to 1.0)
Difference in Medians (95% CI)	0.0 (-3.0 to 0.0)		0.0 (0.0 to 0.0)		-1.0 (-5.0 to 0.0)		0.0 (-3.5 to 4.0)		0.0 (-1.0 to 1.5)		-1.0 (-2.5 to 0.0)	

Rosas IO, et al. NEJM Feb 25, 2021

Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19

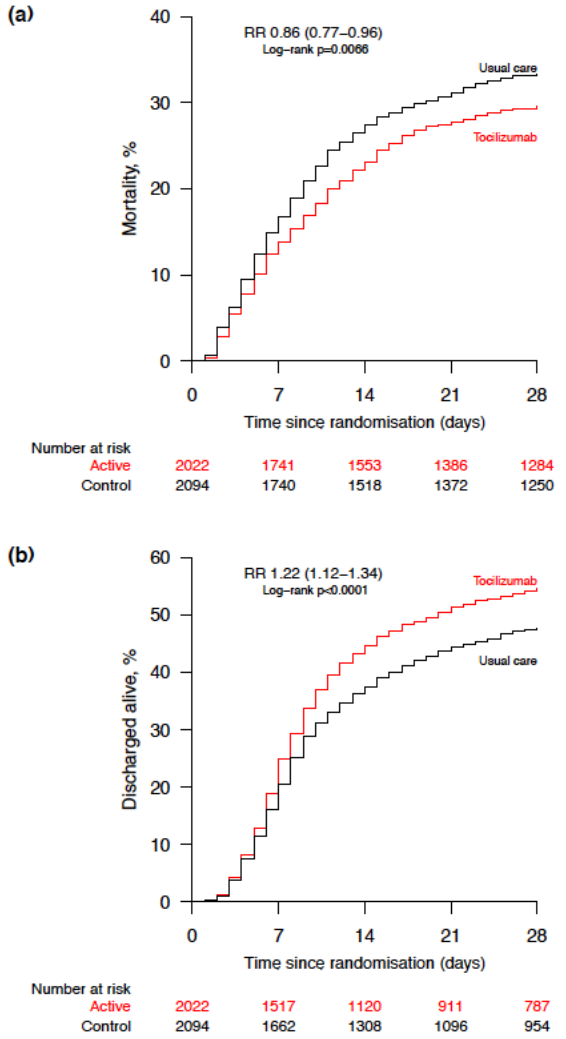
- Adaptive platform trial
  - 1st pt enrolled 9Mar20
    - 113 sites across 6 countries
  - 1st pt Immune Modulation Therapy domain 19Apr20
  - Pts through 19Nov20 w/complete f/u
- Admit ICU w/i 24 hours
- Open-label toci (8mg/kg), sarilumab (400mg) or SOC
  - 93% post 17June20 glucocorticoids (~80%), remdesivir in 33%
  - 92% toci group 1 dose, 29% a second dose
  - 90% sari received dose
  - 2% SOC received an immunomodulating drug
- 1ary – resp/cardio organ support-free days and days free organ support by d21
- N=895 (366 toci, 48 sari, 412 SOC, 69 other)
- Median time from admission 1.2-1.4 days, ICU admit 13-16 hours, CRP 130-150ug/ml
- Median organ support free days 10(T) vs 11(S) vs 0(SOC)
  - Median OR 1.64(T) and 1.76(S) vs SOC
  - Survival at d90 HR 1.61 (T/S) vs SOC
  - Benefit IL-6 antagonists greater in those receiving glucocorticoids



REMAP-CAP. NEJM Feb 25, 2021

Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomized, controlled, open-label platform trial

- UK: 23Apr20 – 24Jan21
  - 4,116 of 21,550 enrolled in toci comparison at 131 sites
- Patients O2sat<92%, CRP ≥75 mg/L
- Toci 400-800mg by weight
- 1ary outcome 28d mortality
- N=4,116
  - 14% IMV, 41% Non-invasive, 45% supp O2
  - 82% on corticosteroids
- D28 mort: 29%T, 33%SOC (Rate ratio-0.86, p=0.007)



Horby P, RECOVERY medRxiv 11Feb21

Challenging Area to Decipher

- Population understudy
  - Background care, placebo group mortality
- When study done
  - Evolving standard of care
- Precise understanding of clinical phenotype
  - Timing of intervention (inflammatory flare), subgroup effects
- Outcome of value
  - Mortality, LOS, disease progression, time to recovery
- Effect modifiers
  - Glucocorticoid or other anti-inflammatory use
- Study design
  - Platform trials, blinding

Table s10. Risk of bias for randomized controlled studies (tocilizumab vs. no tocilizumab)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Gordon 2021							
Hermine 2020							
Horby 2021							
Rosas 2020							
Salama 2020							
Salvarani 2020							
Stone 2020							
Veiga 2021							

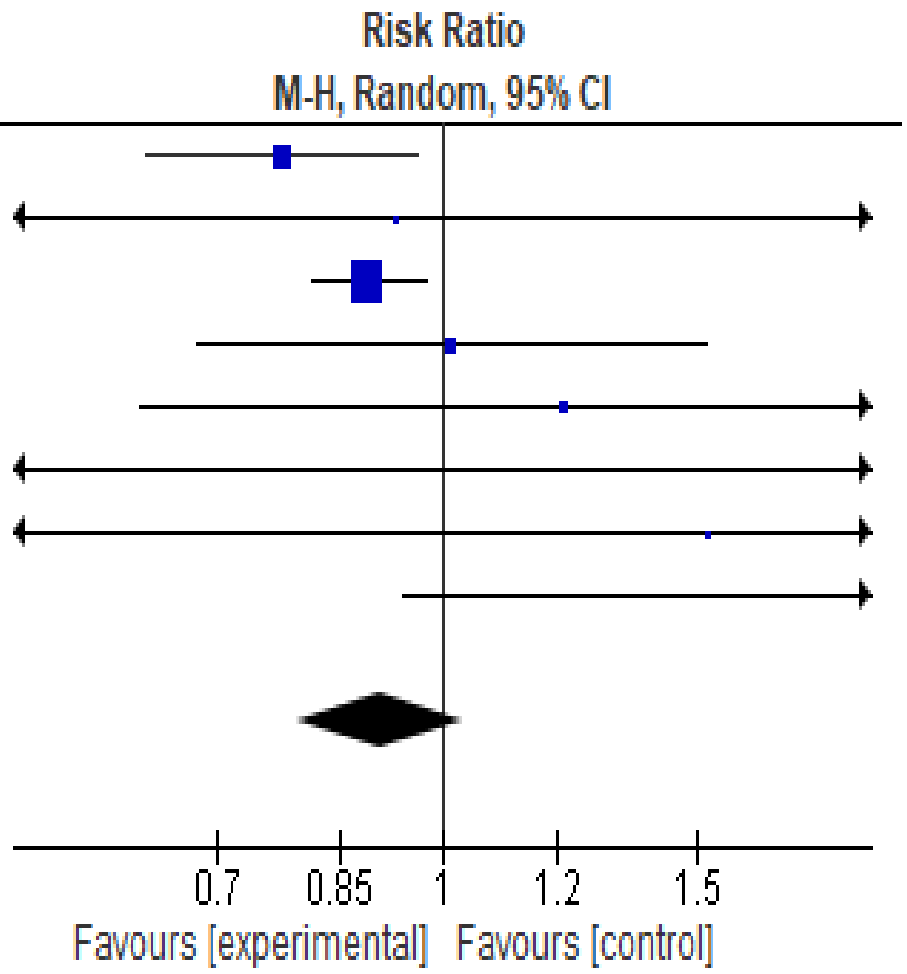
Low	High	Unclear

Figure s4a. Forest plot for the outcome of mortality for tocilizumab vs. no tocilizumab

Study or Subgroup	Tocilizumab Events	Tocilizumab Total	No tocilizumab Events	No tocilizumab Total	Weight	Risk Ratio M-H, Random, 95% CI
Gordon 2021	98	366	142	412	25.4%	0.78 [0.63, 0.96]
Hermine 2020	7	63	8	67	1.9%	0.93 [0.36, 2.42]
Horby 2021	596	2022	694	2094	55.8%	0.89 [0.81, 0.97]
Rosas 2020	58	294	28	144	9.5%	1.01 [0.68, 1.52]
Salama 2020	26	249	11	128	3.8%	1.22 [0.62, 2.38]
Salvarani 2020	2	60	1	63	0.3%	2.10 [0.20, 22.56]
Stone 2020	9	161	3	82	1.1%	1.53 [0.43, 5.49]
Veiga 2021	14	65	6	64	2.2%	2.30 [0.94, 5.61]
Total (95% CI)		**3280**		**3054**	**100.0%**	**0.91 [0.79, 1.04]**
Total events	810		893			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 8.32$, df = 7 (P = 0.31); $I^2 = 16\%$

Test for overall effect: Z = 1.43 (P = 0.15)



Tocilizumab

Section last reviewed and updated on 2/17/2021

Last literature search conducted 2/11/2021

Recommendation 7: Among hospitalized adults with progressive severe* or critical COVID-19 who have elevated markers of systemic inflammation, the IDSA guideline panel suggests tocilizumab in addition to standard of care (i.e., steroids) rather than standard of care alone. (Conditional recommendation, Low certainty of evidence)**

- **Remarks:**
  - Patients, particularly those who respond to steroids alone, who put a high value on avoiding possible adverse events of tocilizumab and a low value on the uncertain mortality reduction, would reasonably decline tocilizumab.
  - In the largest trial on the treatment of tocilizumab, criterion for systemic inflammation was defined as CRP ≥75 mg/L.

Severity definitions:

*Severe illness is defined as patients with SpO_2 ≤94% on room air, including patients on supplemental oxygen.

**Critical illness is defined as patients on mechanical ventilation and ECMO. Critical illness includes end organ dysfunction as is seen in sepsis/septic shock. In COVID-19, the most commonly reported form of end organ dysfunction is ARDS.

References

Table 7. GRADE evidence profile, Recommendation 7

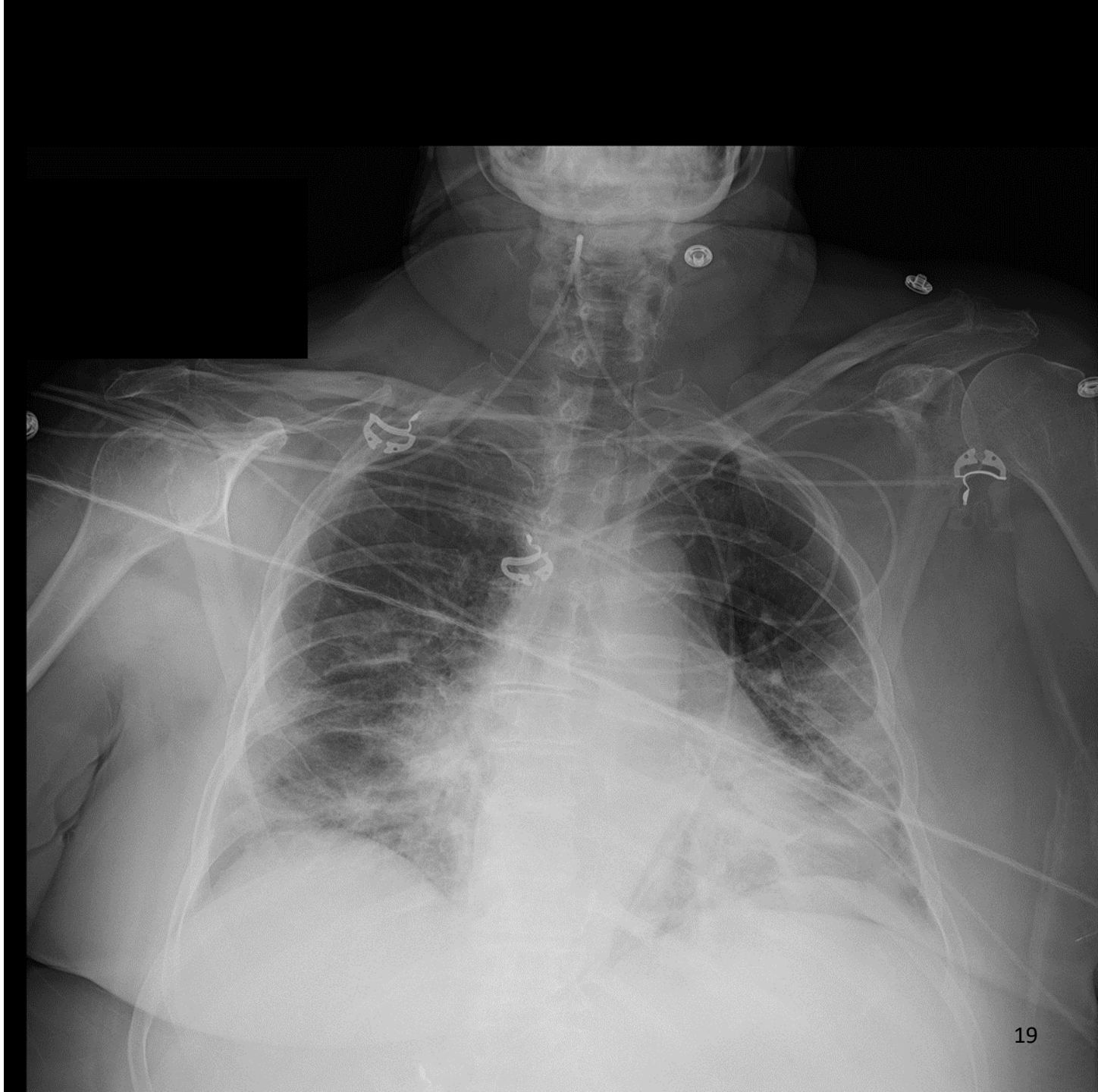
Question: Tocilizumab compared to no tocilizumab for hospitalized patients with COVID-19

Last reviewed and updated 2/17/2021

1. Gordon AC, Mouncey PR, Al-Beidh F, et al. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 – Preliminary report. medRxiv **2021**: Available at: https://www.medrxiv.org/content/10.1101/2021.01.07.21249390v2.full [Preprint 9 January 2021].
2. Rosas I, Bräu N, Waters M, et al. Tocilizumab in hospitalized patients with COVID-19 pneumonia. medRxiv **2020**: Available at: https://doi.org/10.1101/2020.08.27.20183442 [Preprint 12 September 2020].
3. Hermine O, Mariette X, Tharaux PL, et al. Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. JAMA Intern Med **2020**; 181(1): 32-40.
4. Salama C, Han J, Yau L, et al. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med **2021**; 384(1): 20-30.
5. Salvarani C, Dolci G, Massari M, et al. Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia: A Randomized Clinical Trial. JAMA Intern Med **2020**; 181(1): 24-31.
6. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. N Engl J Med **2020**; 383: 2333-44.
7. Veiga VC, Prats J, Farias DLC, et al. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. BMJ **2021**; 372: n84.
8. Horby PW, Pessoa-Amorim G, Peto L, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial. medRxiv **2021**: Available at: https://doi.org/10.1101/2021.02.11.21249258 [Preprint 11 February 2021].

Case #1- revisited

- 73 year diabetic female with symptom onset ten days ago
- Admitted six days ago with hypoxia and fever
- Oxygenation worsened from needing supplemental O2
- Now saturating 91% on 50 LPM HFNC FiO2 90%
- CBC entirely normal, CRP 79.0 mg/L, chemistry unremarkable



ID consulted

- Finished remdesivir
- Given dexamethasone through the present
- Would you do toculizumab in this patient?

Alterations on the scenario

- What if this was time of admission?
- What if symptom onset was three days ago?
- What if patient had been lymphopenic, but CRP was 40 mg/L?

MONOCLONAL ANTIBODIES

Case #2

- 76 YOM with asthma, and hypertension became symptomatic three days ago
- Test is positive today
- Patient has symptoms of fevers, headache and cough, but is not short of breath or hypoxic
- Patient received first dose of mRNA vaccine 1 week ago

Questions

- Would you treat with bamlanivimab/etesevimab?
  - If it wasn't available, would you consider bamlanivimab monotherapy or Casirivimab/imdevimab? Is one preferable?
- Should patient get his second dose of vaccine on time?
- What if this patient was in a car accident on his way to the infusion center and was hospitalized? Could we still give monoclonals?

Monoclonal Antibodies against SARS CoV-2: Recent Updates

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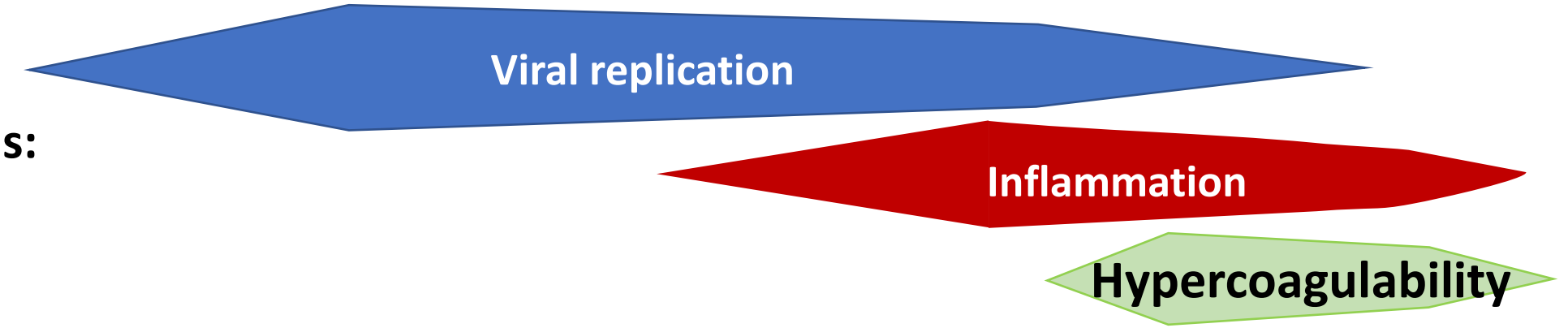
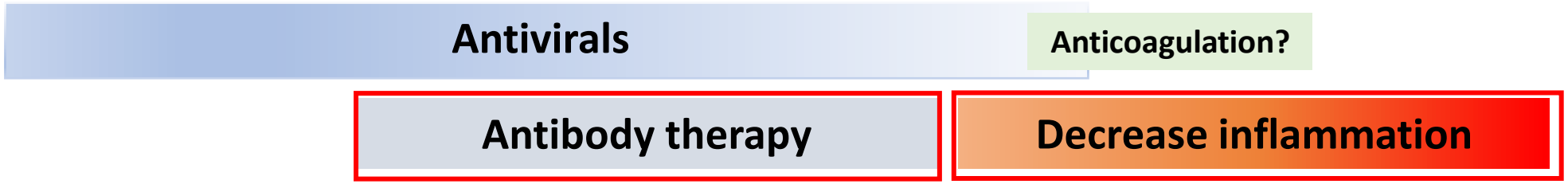
Treatment Across the COVID-19 Spectrum

Stage/ Severity:	Asymptomatic/ Presymptomatic	Mild Illness	Moderate Illness	Severe Illness	Critical illness
	+ SARS-CoV-2 test but no symptoms	Mild symptoms (eg fever, cough, taste/smell changes); no dyspnea	O_2 saturation >=94%, lower respiratory tract disease	O_2 saturation <94%, respiratory rate >30/min; lung infiltrates >50%	Respiratory failure, shock, multi-organ dysfunction/failure

Disease Pathogenesis:



Potential treatment:



Gandhi RT, CID, 2020
Gandhi RT, Lynch J, del Rio C. NEJM 2020

Monoclonal Antibodies

Monoclonal antibodies (mAbs) against SARS-CoV-2 spike protein being studied for treatment and prevention

- Emergency Use Authorizations (EUAs) for treatment of ambulatory patients with mild to moderate COVID-19 at high risk of progression and within 10 days of symptom onset:

  Bamlanivimab (700 mg). Nov 2020

  Casirivimab + Imdevimab (1200/1200 mg). Nov 2020

  Bamlanivimab + Etesevimab (700/1400 mg). Feb 2021

Bamlanivimab

In outpatients with mild to moderate disease (n=452) enrolled within 3 days of positive SARS-CoV-2 test, lower rate of ED visits/hospitalization in those who received bamlanivimab vs. placebo, particularly among high-risk patients

Hospitalization/ED Visit: All Participants			
Treatment	**N**	**Events**	**Proportion**
Placebo	156	9	6%
700 mg	101	1	1%
2800 mg	107	2	2%
7000 mg	101	2	2%
Pooled antibody	309	5	2%

Hospitalization/ED Visit: Participants at Higher Risk of Hospitalization			
Treatment	**N**	**Events**	**Proportion**
Placebo	69	7	10%
700 mg	46	1	2%
2800 mg	46	1	2%
7000 mg	44	2	5%
Pooled antibody	136	4	3%

Chen P et al, NEJM, 2020; http://pi.lilly.com/eua/bamlanivimab-eua-factsheet-hcp.pdf

Casirivimab/Imdevimab

- In outpatients with mild to moderate disease (n=799) enrolled within 3 days of positive SARS-CoV-2 test, lower rate of hospitalization/ED visit in those who received casirivimab/imdevimab vs. placebo, particularly among high-risk patients

Hospitalization/ED Visit: All Participants			
Treatment	**N**	**Events**	**Proportion**
Placebo	231	10	4%
2400 mg	215	4	2%
8000 mg	219	4	2%
Pooled antibody	434	8	2%

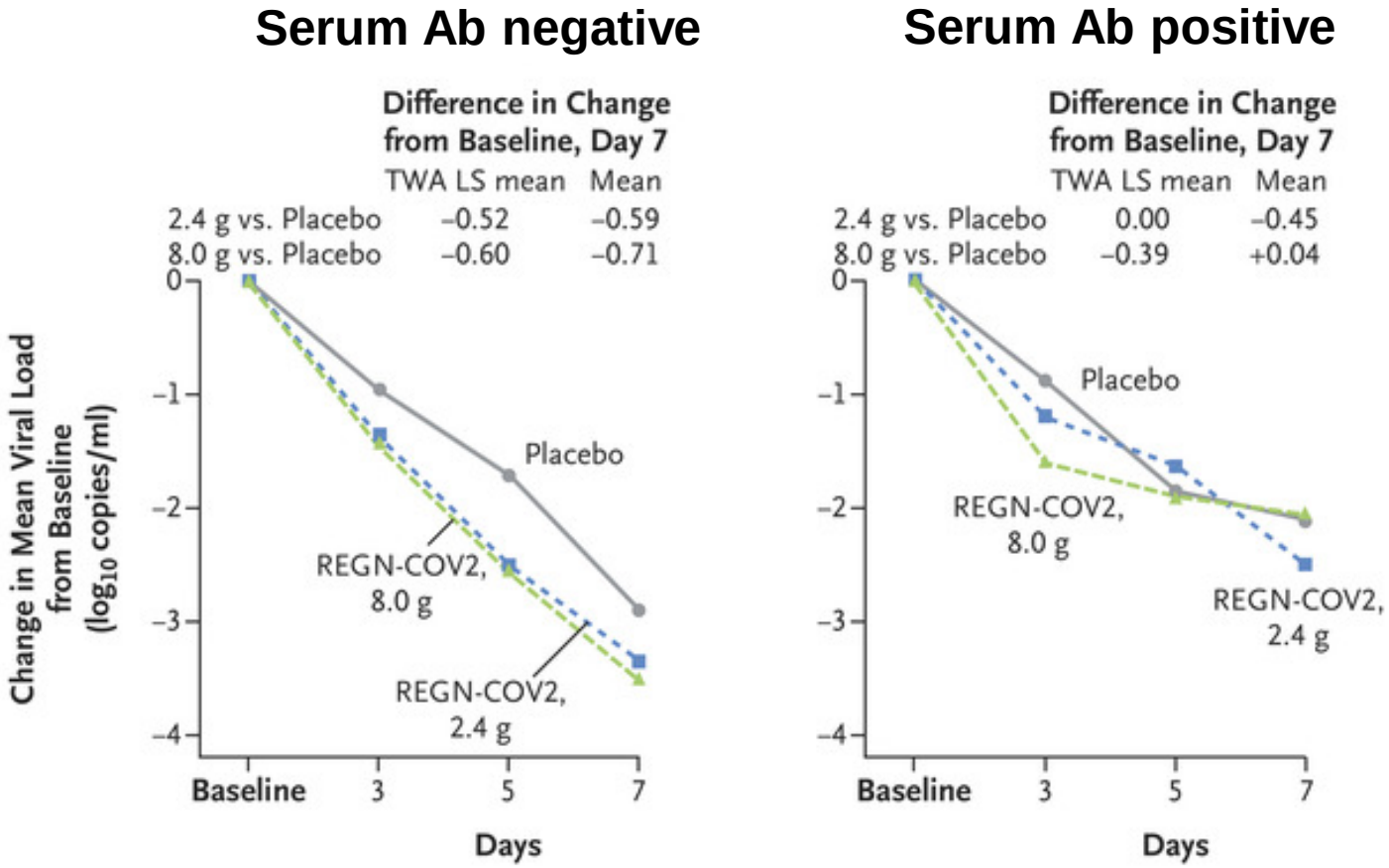
Hospitalization/ED Visit: Participants at Higher Risk of Hospitalization			
Treatment	**N**	**Events**	**Proportion**
Placebo	78	7	9%
2400 mg	70	2	3%
8000 mg	81	2	2%
Pooled antibody	151	4	3%

https://www.regeneron.com/sites/default/files/treatment-covid19-eua-fda-letter.pdf; Weinreich DM et al. N Engl J Med 2020 Dec 17

Casirivimab/Imdevimab

- SARS-CoV-2 Ab negative at baseline (41%):
  - Viral load change greater in antibody than in placebo recipients (difference, -0.56 log_{10} copies/mL)
  - 6% of antibody recipients and 15% of placebo recipients had medically attended visit.

Viral load over time



Weinreich DM et al. N Engl J Med 2020 Dec 17

Bamlanivimab/Etesevimab for Treatment: BLAZE-1

- Outpatients with mild to moderate COVID-19 within 3 days of first positive test; 1 or more risk factors for developing severe COVID-19
- Single iv infusion of bamlanivimab 2800 mg + etesevimab 2800 mg or placebo

COVID-19 RELATED HOSPITALIZATION OR ANY-CAUSE DEATH BY DAY 29

Treatment	N	Events	Rate	*p*
Placebo	517	36	7.0%	-
Bamlanivimab 2800 mg + Etesevimab 2800 mg	518	11	2.1%	0.0004

70% reduction in COVID-19 hospitalization or any-cause death by d 29

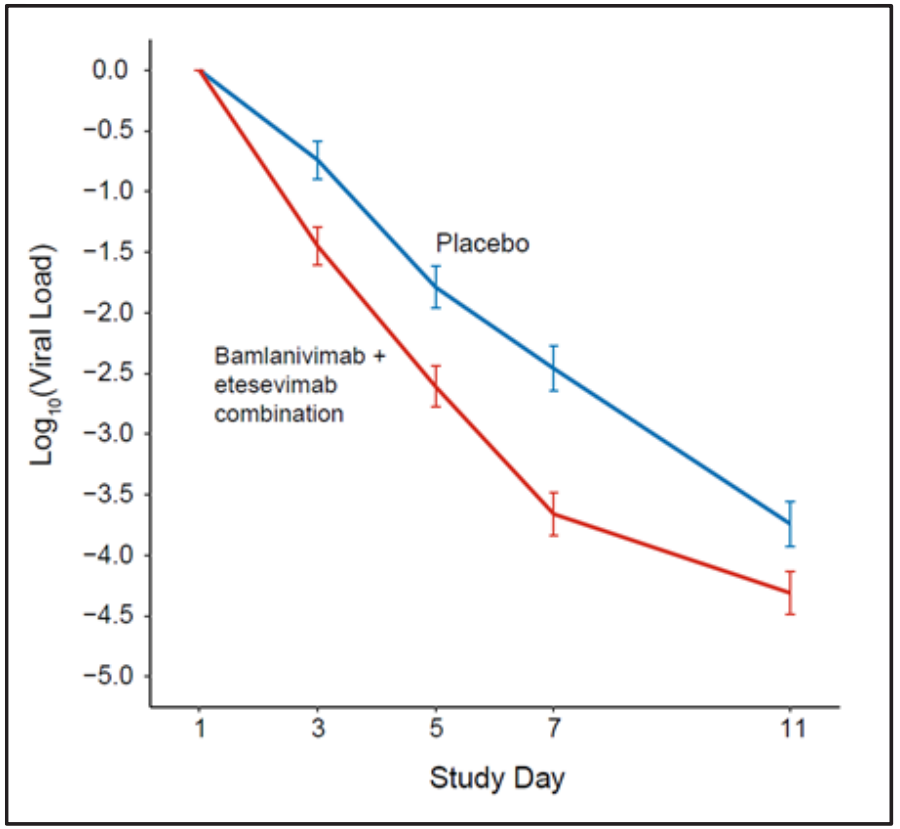
ANY-CAUSE DEATHS

Treatment	N	Events	Rate
Placebo	517	10†	1.9%
Bamlanivimab 2800 mg + Etesevimab 2800 mg	518	0	0%

Dougan M et al, CROI 2021, #122

Bamlanivimab/Etesevimab for Treatment: Effect on VL

VIRAL LOAD CHANGE FROM BASELINE



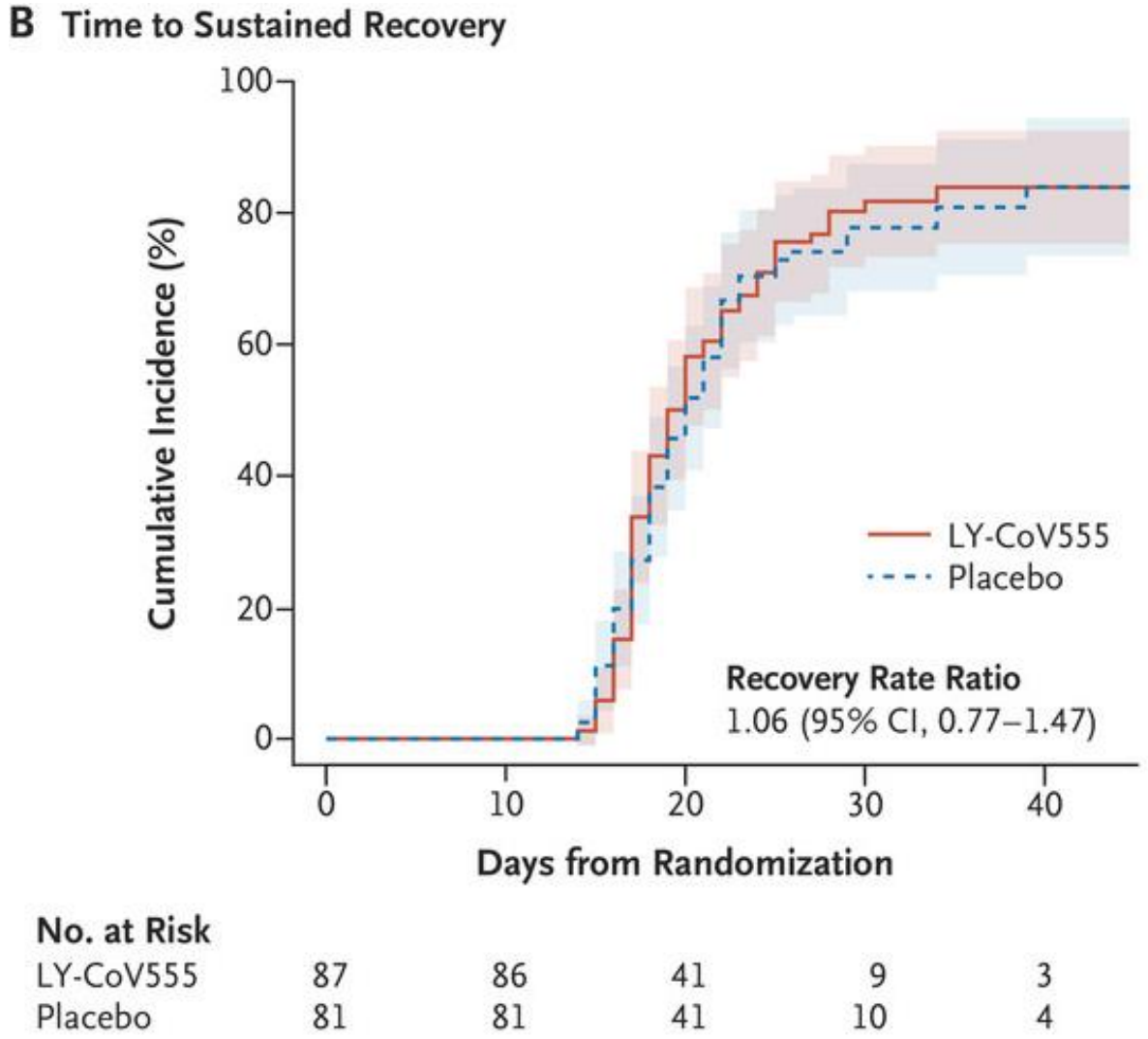
MEAN VIRAL LOAD

	Placebo	Bamlanivimab + Etesevimab	*p*
Day 1	6.52	6.51	-
Day 3	5.74	5.04	<0.001
Day 5	4.68	3.85	<0.001
Day 7	4.05	2.87	<0.001
Day 11	2.69	2.21	<0.001

Dougan M et al, CROI 2021, #122

Bamlanivimab in Hospitalized Patients

- Hospitalized patients with COVID-19 and without end organ failure randomized 1:1 to receive bamlanivimab or placebo (ACTIV-3)
- Stopped for futility after 314 participants enrolled: no evidence for efficacy of the antibody



IDSA Guidelines: Neutralizing Antibodies

Section last reviewed and updated on 3/2/2021. Last literature search conducted 2/24/2021

Among ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease, IDSA guideline panel suggests bamlanivimab/etesevimab rather than no bamlanivimab/etesevimab. (Conditional recommendation, low certainty of evidence)

- **Remarks**:
  - Patients with mild to moderate COVID-19 who are at high risk of progression to severe disease admitted to the hospital for reasons other than COVID-19 may also receive bamlanivimab/etesevimab.
  - For patients at high risk for progression to severe disease, the data are strongest for bamlanivimab/etesevimab. Bamlanivimab monotherapy or casirivimab/imdevimab may have similar clinical benefit, but data are more limited.
  - There are limited data on efficacy of bamlanivimab/etesevimab in high-risk patients between 12 and 18 years of age.

IDSA Guidelines: Neutralizing Antibodies

Section last reviewed and updated on 3/2/2021. *Last literature search conducted 2/24/2021*

Among hospitalized patients with severe COVID-19, the IDSA guideline panel recommends against bamlanivimab monotherapy. (Strong recommendation, Moderate certainty of evidence)

Case #2- revisited

- 76 YOM with asthma, and hypertension became symptomatic three days ago
- Test is positive today
- Patient has symptoms of fevers, headache and cough, but is not short of breath or hypoxic
- Patient received first dose of mRNA vaccine 1 week ago

Questions

- Would you treat with bamlanivimab/etesevimab?
  - If it wasn't available, would you consider bamlanivimab monotherapy or Casirivimab/imdevimab? Is one preferable?
- Should patient get his second dose of vaccine on time?
- What if this patient was in a car accident on his way to the infusion center and was hospitalized? Could we still give monoclonals?

U.S. FOOD & DRUG ADMINISTRATION

Brief Update: Emergent Variants of SARS-CoV-2 and Authorized mAbs

John Farley
Director, Office of Infectious Disease, Center for Drug Evaluation and Research

CDC/IDSA COVID-19 Clinician Call
March 20, 2021

Authorized Monoclonal Antibodies (mAbs)

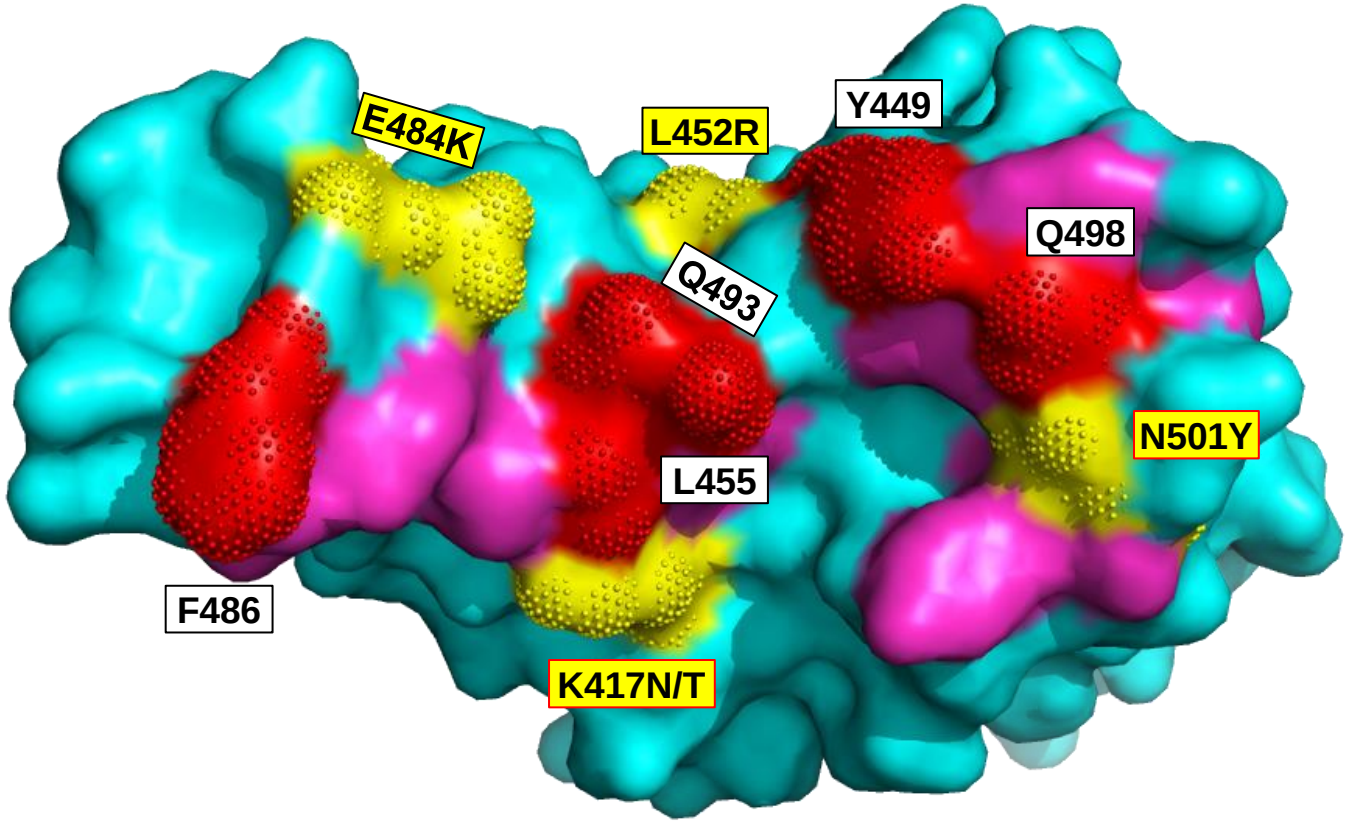
- Neutralizing monoclonal antibodies are designed to block SARS-CoV-2 viral attachment and entry into human cells, thus neutralizing the virus
- Three Authorized Products:
  - Bamlanivimab
  - Bamlanivimab and Etesevimab administered together
  - REGEN-COV: casirivimab and imdevimab administered together

  https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs
- **Authorized use:** treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg), with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progressing to severe COVID-19 and/or hospitalization

Variant Lineages and Substitutions in the Spike Protein Receptor Binding Domain of the Virus

Variant Lineage with Spike Protein Substitution	Key Substitutions with Potential mAb Impact
B.1.1.7 (UK Origin)	N501Y
B.1.351 (South Africa Origin)	K417N, E484K, N501Y
P.1 (Brazil Origin)	K417T, E484K, N501Y
B.1.427/B.1.429 (California Origin)	L452R
B.1.526 (New York Origin)	E484K (not all isolates of the lineage)

RBD- ACE2 Interaction Sites With Variants



RBD

RBM (within 4Å)

Contacts

Variants

Assessing Potential Risk of Treatment Failure of mAbs Due to Substitutions in the RBD

<u>Data we have:</u>

- Neutralization assays using a pseudovirus (e.g. Vesicular stomatitis virus expressing the entire variant spike protein or individual amino acid substitution(s) in the spike protein)

We don't know how pseudovirus data correlate with clinical outcomes.

<u>Data we would like:</u>

- Neutralization assays using authentic virus with the substitutions of interest
- Genotyping in clinical trials with clinical outcome

Pseudovirus Neutralization Data for SARS-CoV-2 Variant Substitutions

Variant Lineage	Key Substitutions Tested	Fold Reduction in Susceptibility		
		Bam	Bam + Ete	REGEN-COV
B.1.1.7 (UK Origin)	N501Y	No change	No change	No change [a]
B.1.351 (South Africa Origin)	E484K	>2,360	>45 [c]	No change [a]
P.1 (Brazil Origin)	E484K	>2,360	>511 [d]	No change [b]
B.1.427/B.1.429 (California Origin)	L452R	>1,020	7.4	No change
B.1.526 (New York Origin)	E484K	>2,360	17	No change

a - Pseudovirus expressing the entire variant spike protein was tested.
b - Also tested K417T
c - Also tested K417N and N501Y
d - Also tested K417T and N501Y
No change: <2-fold reduction in susceptibility for REGN-COV, <5-fold reduction for Bam and Bam+Ete
Red: No activity observed at the highest concentration tested.

Actions This Past Week

- ASPR announced it will limit distribution of bamlanivimab alone to California, Arizona, and Nevada. https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Bamlanivimab/Pages/default.aspx
- CDC updated webpages to provided information regarding variants of concern by State. https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html
- The Fact Sheets for the bamlanivimab, bamlanivimab and etesevimab, and REGEN-COV EUAs were modified to include the following statement and updated virology information regarding variants and the particular mAb(s):

  Circulating SARS-CoV-2 viral variants may be associated with resistance to monoclonal antibodies. Health care providers should review the Antiviral Resistance information in Section 15 of this Fact Sheet for details regarding specific variants and resistance, and refer to the CDC website (https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html) as well as information from state and local health authorities regarding reports of viral variants of importance in their region to guide treatment decisions.

  – Updated Fact Sheets available at: https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs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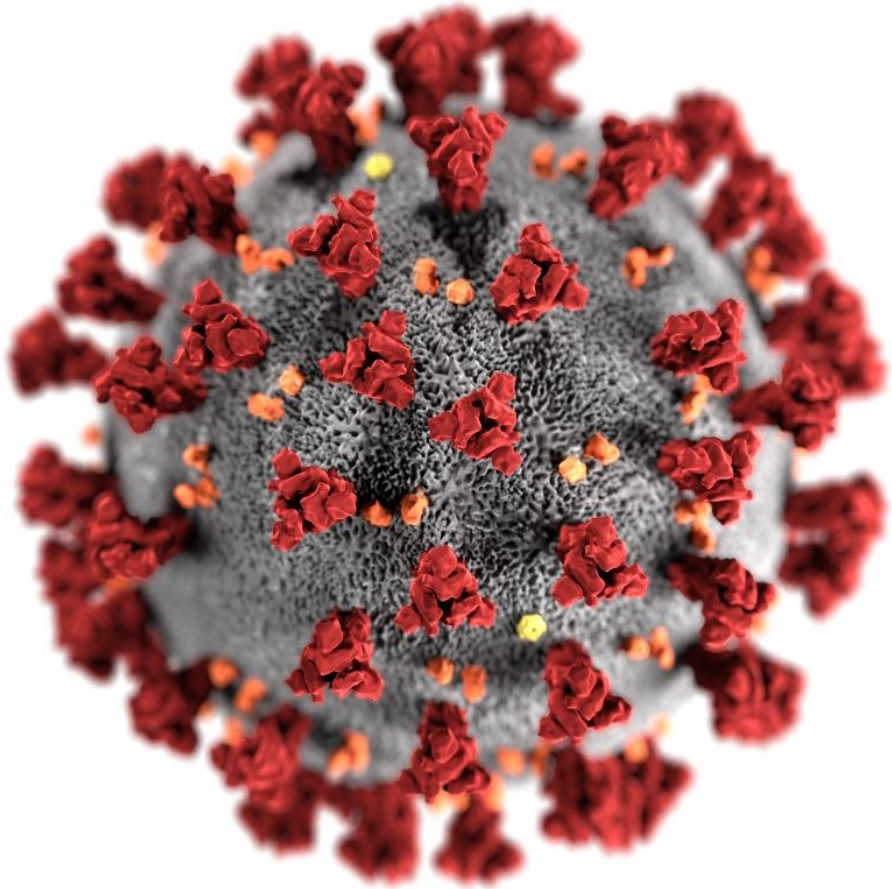
COVID-19 Vaccine Q&A

Sara Oliver, MD, MSPH
LCDR, U.S. Public Health Service
Co-Lead, COVID-19 Work Group of the Advisory Committee on Immunization Practices
Centers for Disease Control and Prevention

Disclosures

- **Sara Oliver, MD, MSPH** - has no disclosures.

Emerging SARS-CoV-2 Variants: Considerations for Vaccine



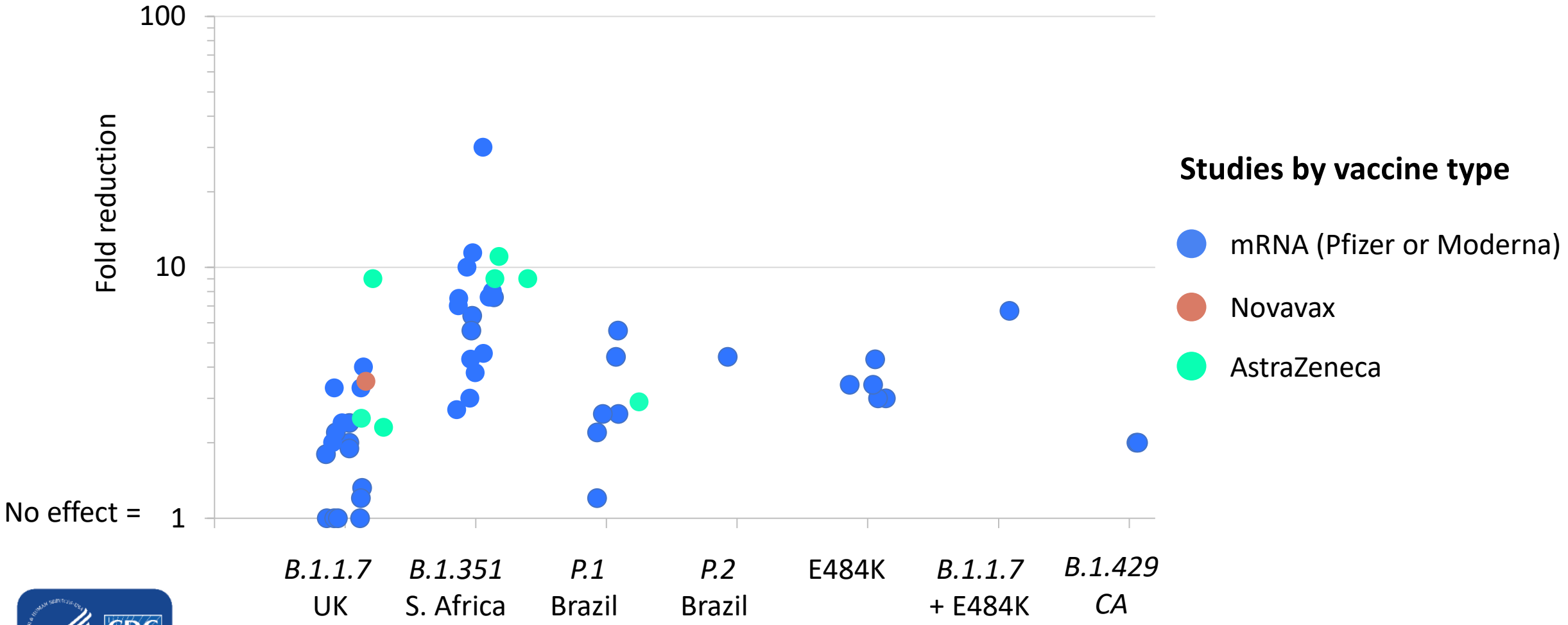
Review of 34 studies: Vaccine sera neutralization of SARS-CoV-2 variants

- 12 published studies and 22 preprint studies; all small sample sizes (n=5−62)
- 18 studies only Pfizer; 3 studies only Moderna; 2 studies on AstraZeneca; 10 studies on ≥1 vaccine; 1 study on unspecified mRNA vaccine
- 8 studies on single/limited sets of mutations – generally minimal impact
  - E484K and E484K-K417N-N501Y larger effects*
- Largest impacts: **B.1.351** (South Africa) > **P.1, P.2** (Brazil) > **B.1.1.7** (UK)
  - B.1.351: median 7.6-fold reduction (IQR: 4.8−9.0, n=18)
  - P.1: median 2.6-fold reduction (IQR: 2.4−3.7, n=7)
  - B.1.1.7: median 2.1-fold reduction (IQR: 1.3−2.7, n=20)

* Mutations found in South Africa (B.1.351) and Brazil (P.1, P.2)

References in Appendix

Reduced neutralization activity of vaccine sera relative to wildtype/dominant strain, by study (n=26)



References in Appendix

Neutralization of variants after 1 & 2 vaccine doses

- Postponing 2nd mRNA dose may leave some less protected against variants
- Minimal/no neutralization of B.1.351 after one dose
  - History of COVID-19 + 1 dose → moderate protection against B.1.351
- Improved neutralization of B.1.1.7 and B.1.351 after 2nd dose
- Delayed antibody response against variants

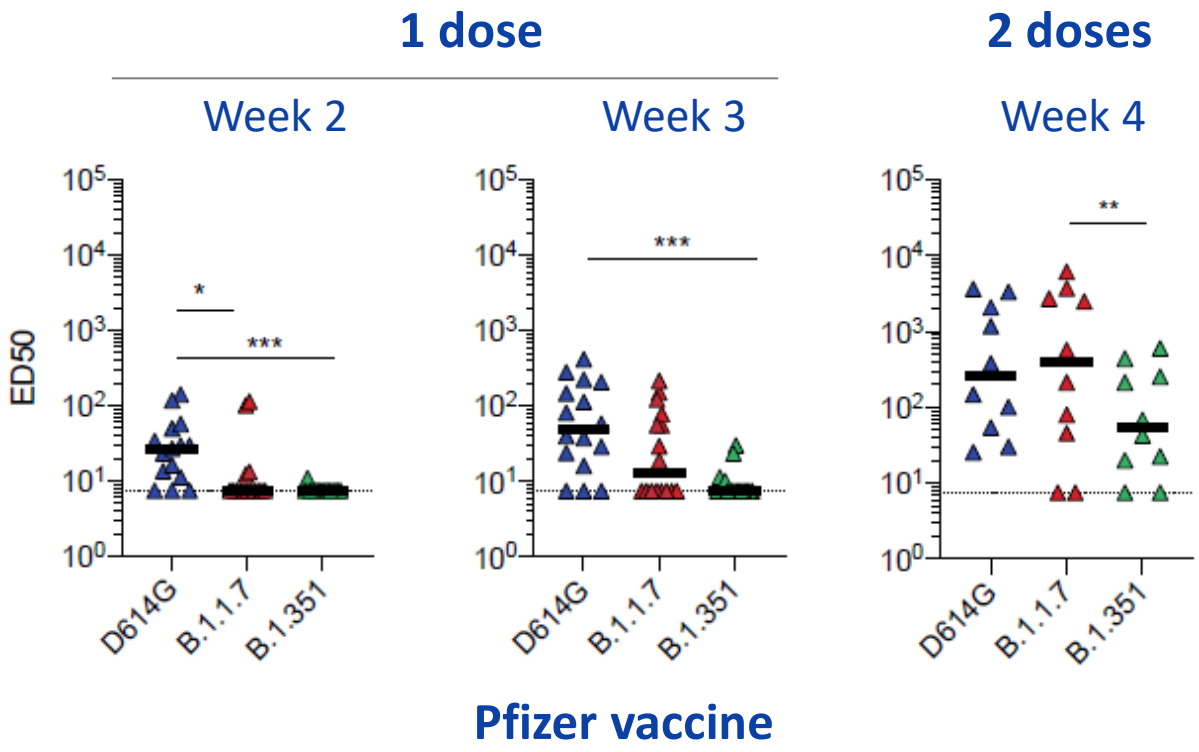


Figure Source: Planas et al. bioRxiv preprint (Feb 12 2021: https://doi.org/10.1101/2021.02.12.430472
Skelly et al. Res square preprint (Feb 9 2021); https://www.researchsquare.com/article/rs-226857/v1
Garcia-Beltran et al. medRxiv preprint (Feb 14 2021): https://doi.org/10.1101/2021.02.14.21251704
Shen et al. bioRxiv preprint (Jan 28 2021); https://doi.org/10.1101/2021.01.27.428516
Collier et al. medRxiv preprint (Feb 15 2021): https://doi.org/10.1101/2021.01.19.21249840
Stamatatos et al. medRxiv preprint (Feb 5 2021): https://doi.org/10.1101/2021.02.05.21251182
Supasa et al.Cell (2021): https://doi.org/10.1016/j.cell.2021.02.033
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Becker et al. medRxiv preprint (Mar 10 2021): https://doi.org/10.1101/2021.03.08.21252958

Discussion of lab studies

- Difficult to estimate how laboratory results might translate to clinical protection
  - No immunological correlate of protection for SARS-CoV-2
- Neutralizing antibodies in sera from mRNA vaccine recipients generally shown to be higher than COVID-19 convalescent sera
- Variation in results may be explained by differences in experimental conditions
  - Neutralization assays — replicating & nonreplicating pseudovirus vs. SARS-CoV-2
  - Sera — time post-vaccination, or population (e.g., age, COVID-19 history)
  - Use of limited or full sets of spike mutations vs. clinical isolates of variants
- AstraZeneca — not prefusion stabilized spike, limited generalizability to other vaccines
- Limitation for all studies — small sample sizes and lack generalizability
  - Many studies are preprints not yet peer-reviewed

Vaccine efficacy or effectiveness (VE) against variants

Vaccine	Study type	VE
Pfizer	Post-EUA	• 86% in UK (predominate B.1.1.7 circulation)* • 94% in Israel (up to 80% of cases from B.1.1.7)
Janssen	Pre-EUA	• 74% in U.S. • 66% in Brazil • 52% in S. Africa
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

73-82% for severe/critical disease in each country

Hall et al. Lancet preprint (Feb 22 2021): https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3790399; *VE for symptomatic & asymptomatic infection
Dagan et al. NEJM (2021). https://www.nejm.org/doi/full/10.1056/NEJMoa2101765?query=TOC
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. medRxiv preprint (Mar 3 2021); doi: https://doi.org/10.1101/2021.02.25.21252477
Madhi et al. medRxiv preprint (Feb 12 2021): https://doi.org/10.1101/2021.02.10.21251247
Emary et al. Lancet preprint (Feb 4 2021): https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3779160

Summary of preliminary data: Implications of SARS-CoV-2 variants of concern on vaccine effectiveness

- **B.1.1.7** (first detected in the United Kingdom)
  - Exponential increase in prevalence in United States
  - Minimal impact on vaccine effectiveness, but attention needed for variants with additional substitutions in RBD, such as E484K
- **B.1.351** (first detected in South Africa)
  - Currently low prevalence in United States
  - Moderate impact on vaccine effectiveness, suggests it's prudent to start evaluating variant vaccines in case prevalence substantially increases
- **P.1** (first detected in Brazil/Japan)
  - Very low prevalence in United States, but same three RBD mutations as B.1.351
  - Additional data needed on potential impact on vaccine effectiveness

Links from Today's call

- **Slide 18 -** Gordon AC, Mouncey PR, Al-Beidh F, et al. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 – Preliminary report. medRxiv **2021**: Available at: https://www.medrxiv.org/content/10.1101/2021.01.07.21249390v2.full [Preprint 9 January 2021].
- **Slide 18 -** Rosas I, Bräu N, Waters M, et al. Tocilizumab in hospitalized patients with COVID-19 pneumonia. medRxiv **2020**: Available at: https://doi.org/10.1101/2020.08.27.20183442 [Preprint 12 September 2020].
- **Slide 18 -** Horby PW, Pessoa-Amorim G, Peto L, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial. medRxiv **2021**: Available at: https://doi.org/10.1101/2021.02.11.21249258 [Preprint 11 February 2021].
- **Slide 27** - Chen P et al, NEJM, 2020; http://pi.lilly.com/eua/bamlanivimab-eua-factsheet-hcp.pdf
- **Slide 28** - REGEN-COV EAU FDA Letter: https://www.regeneron.com/sites/default/files/treatment-covid19-eua-fda-letter.pdf;
- **Slide 37** - REGEN-COV: casirivimab and imdevimab administered together https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#coviddrugs
- **Slide 42** - ASPR announced it will limit distribution of bamlanivimab alone to California, Arizona, and Nevada. https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Bamlanivimab/Pages/default.aspx
- **Slide 42** - CDC updated webpages to provided information regarding variants of concern by State. https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html
- **Slide 42** - The Fact Sheets for the bamlanivimab, bamlanivimab and etesevimab, and REGEN-COV EUAs https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html
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- **Slide 49 -** Shen et al. bioRxiv preprint (Jan 28 2021); https://doi.org/10.1101/2021.01.27.428516
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- **Slide 51 -** Hall et al. Lancet preprint (Feb 22 2021): https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3790399; *VE for symptomatic & asymptomatic infection
- **Slide 51 -** Dagan et al. NEJM (2021). https://www.nejm.org/doi/full/10.1056/NEJMoa2101765?query=TOC
- **Slide 51 -** https://www.fda.gov/media/146217/download
- **Slide 51 -** Novavax.: https://ir.novavax.com/news-releases/news-release-details/novavax-covid-19-vaccine-demonstrates-893-efficacy-uk-phase-3
- **Slide 51 -** Shinde et al. medRxiv preprint (Mar 3 2021); doi: https://doi.org/10.1101/2021.02.25.21252477
- **Slide 51 -** Madhi et al. medRxiv preprint (Feb 12 2021): https://doi.org/10.1101/2021.02.10.21251247

SPECIAL NOTICE - UPCOMING WEBINAR

COVID-19 Vaccine in Transplant & Immunocompromised Populations

Thursday, March 25th - 4 p.m. ET/ 1 p.m. PT

Hosted by the American Society of Transplantation and the Infectious Diseases Society of America

Join us for a panel discussion and Q&A with experts in transplantation and infectious diseases, who will review safety and efficacy data and discuss clinical considerations for administering the COVID-19 vaccines in transplant and immunocompromised patients.

This webinar is not part of the CDC/IDSA COVID-19 Clinician Call series and requires separate registration.

To Register: https://societycentral.zoom.us/webinar/register/2016073861993/WN_hhpFc34TQMGauDsbPfgLxw

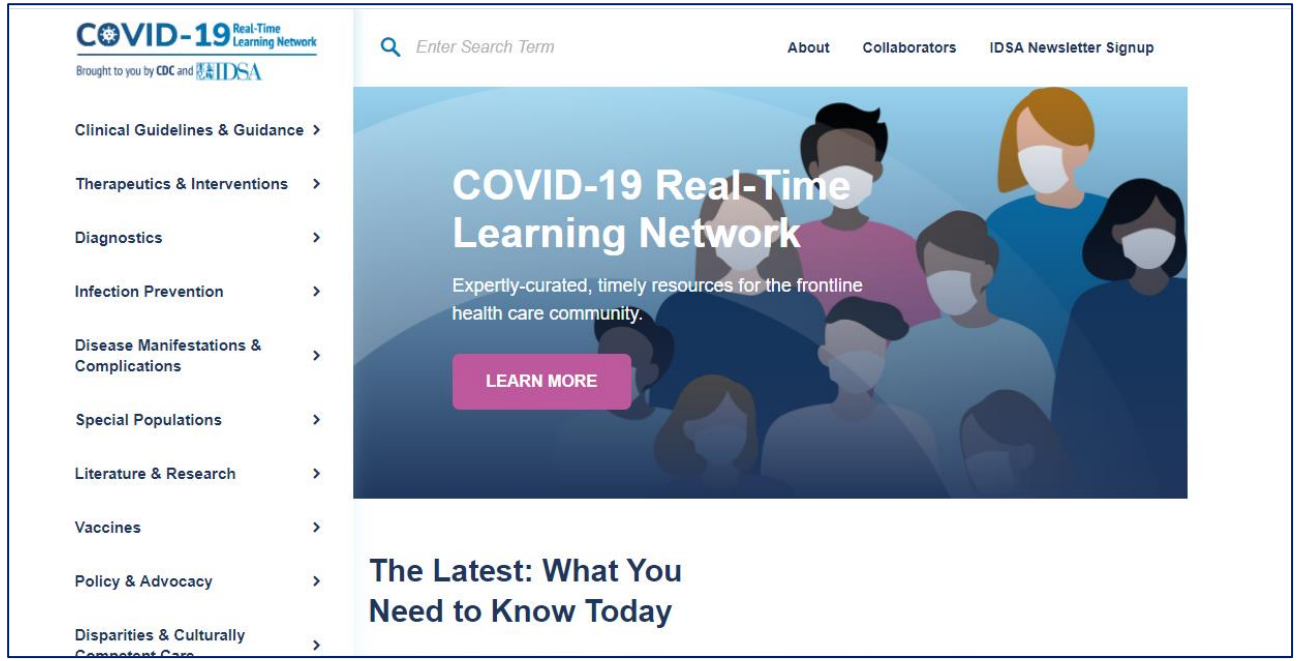
AST | AMERICAN SOCIETY OF TRANSPLANTATION

IDSA
Infectious Diseases Society of America

COVID-19 Real-Time Learning Network

Brought to you by CDC and IDSA

An online community bringing together information and opportunities for discussion on latest research, guidelines, tools and resources from a variety of medical subspecialties around the world.



Specialty Society Collaborators

American Academy of Family Physicians
American Academy of Pediatrics
American College of Emergency Physicians
American College of Physicians
American Geriatrics Society
American Thoracic Society
Pediatric Infectious Diseases Society
Society for Critical Care Medicine
Society for Healthcare Epidemiology of America
Society of Hospital Medicine
Society of Infectious Diseases Pharmacists

www.COVID19LearningNetwork.org
@RealTimeCOVID19
#RealTimeCOVID19

CDC-IDSA Partnership: Clinical Management Call Support

FOR WHOM?

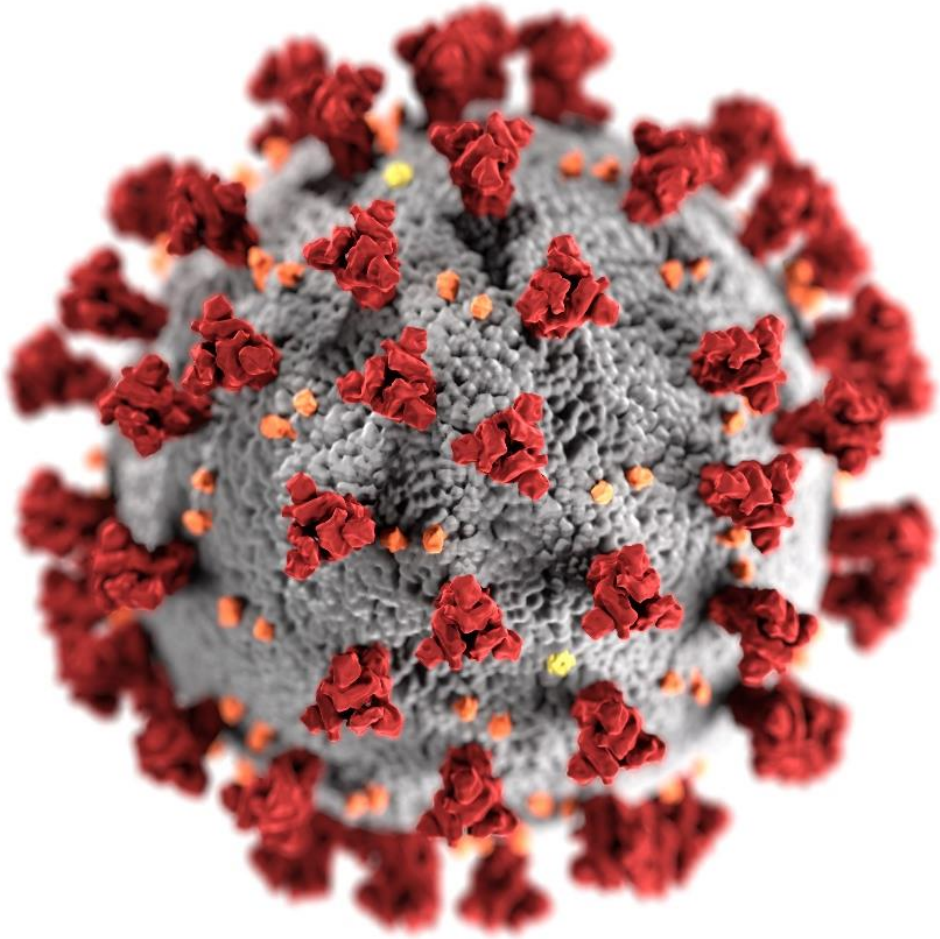
- Clinicians who have questions about the clinical management of COVID-19

WHAT?

- Calls from clinicians will be triaged by CDC to a group of IDSA volunteer clinicians for peer-to-peer support

HOW?

- Clinicians may call the main CDC information line at 800-CDC-INFO (800-232-4636)
- To submit your question in writing, go to www.cdc.gov/cdc-info and click on Contact Form



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Infectious Diseases Society of America

cdc.gov/coronavirus

Continue the conversation on Twitter

@RealTimeCOVID19
#RealTimeCOVID19

We want to hear from you! Please complete the post-call survey.

Next Call: **Saturday, March 27th**

A recording of this call will be posted at **www.idsociety.org/cliniciancalls**

-- library of all past calls now available --

Contact Us:

Dana Wollins (dwollins@idsociety.org)
Deirdre Lewis (dlewis@idsociety.org)