COVID-19
ONLINE EDUCATIONAL PROGRAM

Antibody Therapies for COVID-19

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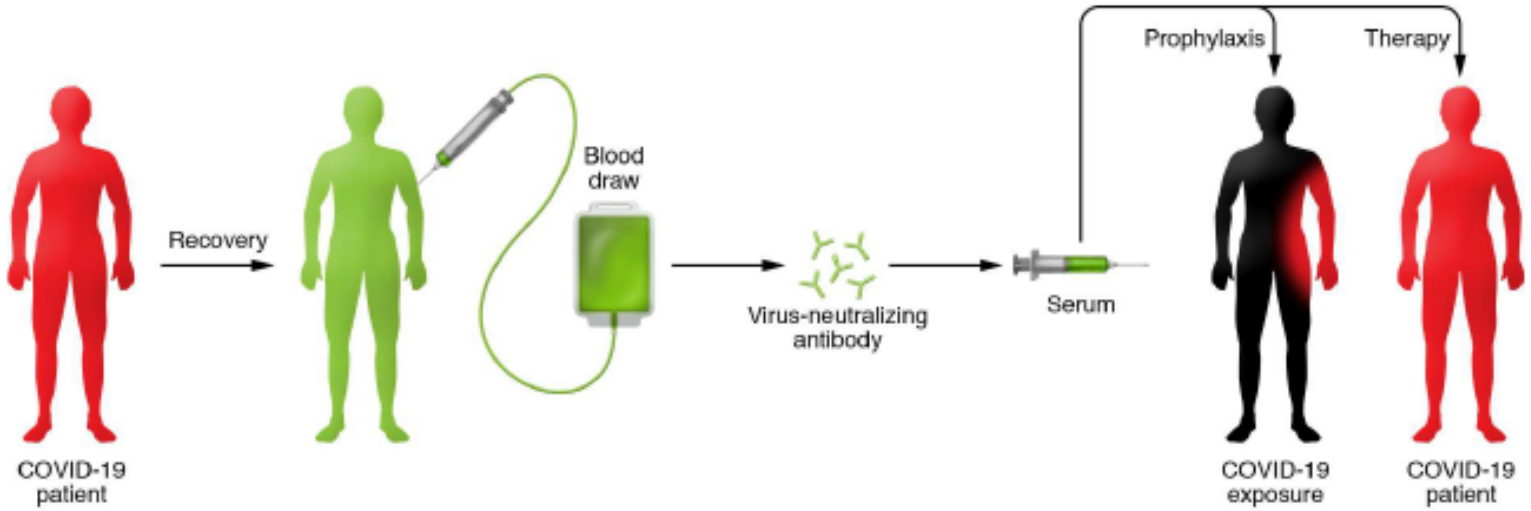
academic medical education

Disclosures

- **The speaker is a consultant to and has received honoraria and/or research support from the following companies:**
  - Abpro
  - Atea
  - Decoy
  - Gilead
  - GlaxoSmithKline
  - Merck
  - Novartis
  - Rigel
  - ViiV

Convalescent plasma

Convalescent COVID-19 Plasma (CCP)

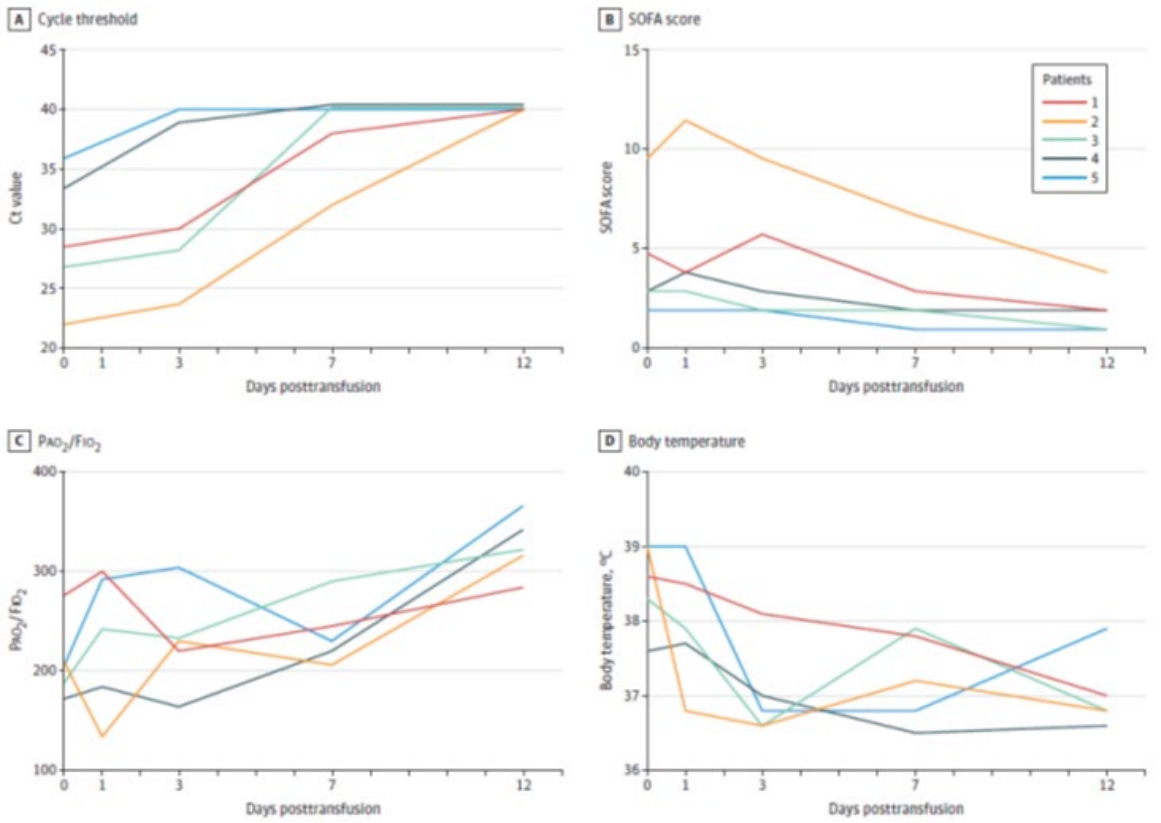


- Convalescent plasma from survivors of COVID-19 infection may contain high titers of neutralizing Ab
- Convalescent plasma has shown some benefit in treatment of avian (H1N5) and H1N1 influenza and MERS
- Pilot studies and uncontrolled trials suggest possible benefit

Casadoval and Pirofsky J Clin Invest 2020

Uncontrolled anecdotal observations

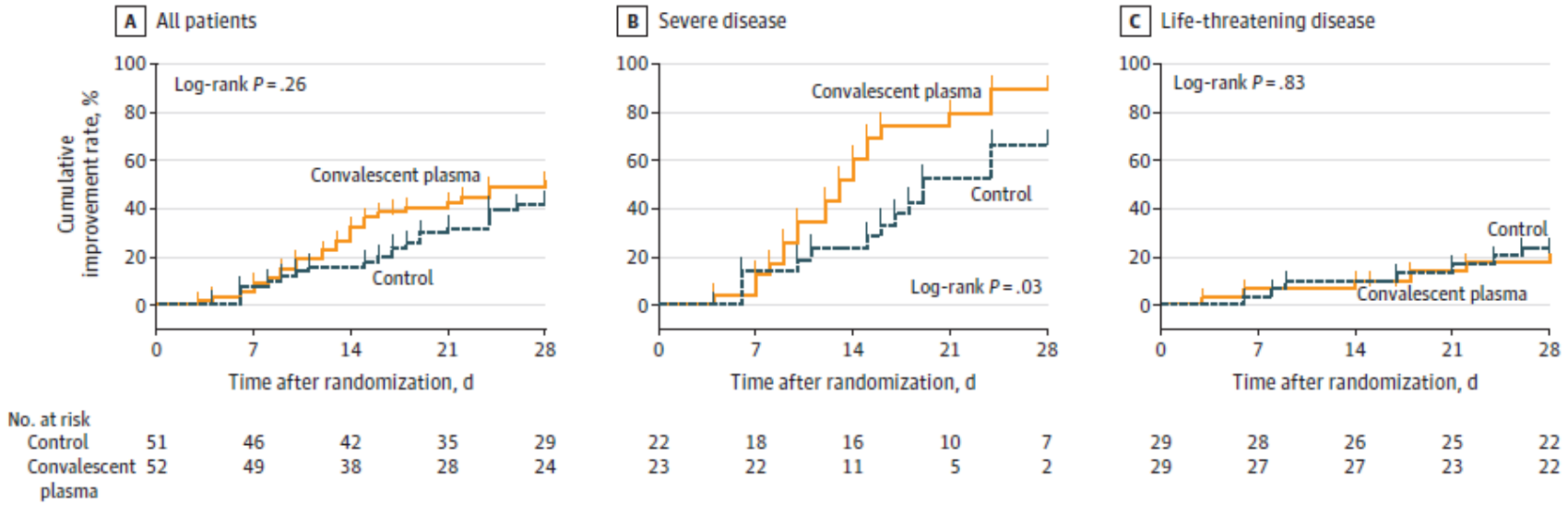
- **Uncontrolled pilot study (N=5) suggested possible benefit of CCP in patients with COVID-19**
  - 4 of 5 weaned from ventilator



Shen C et al JAMA 2020

Phase 2 open-label RCT of convalescent plasma

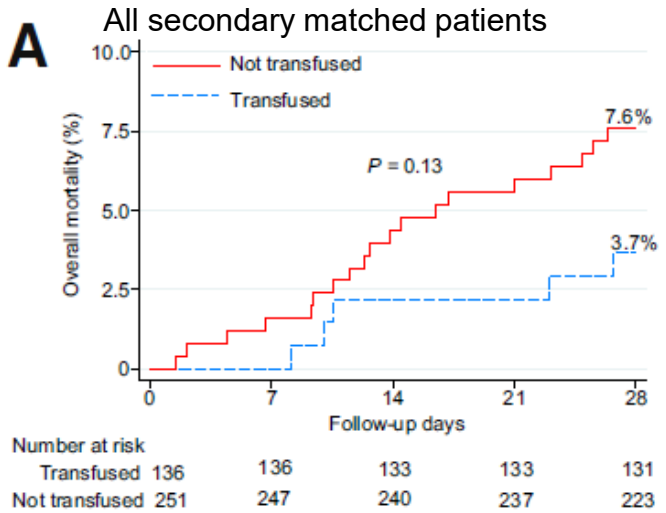
- 7 medical centers in Wuhan
- 103 participants randomized 1:1 to CCP vs SOC
- Plasma units screened for S-RBD-specific IgG titer ≥1:640
- Primary endpoint: time to clinical improvement within 28 days



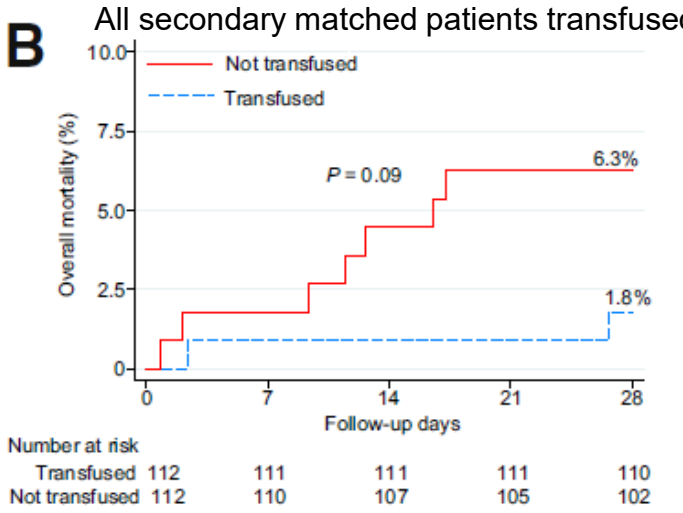
Li L et al JAMA 2020

Interim results of CCP use at Houston Methodist

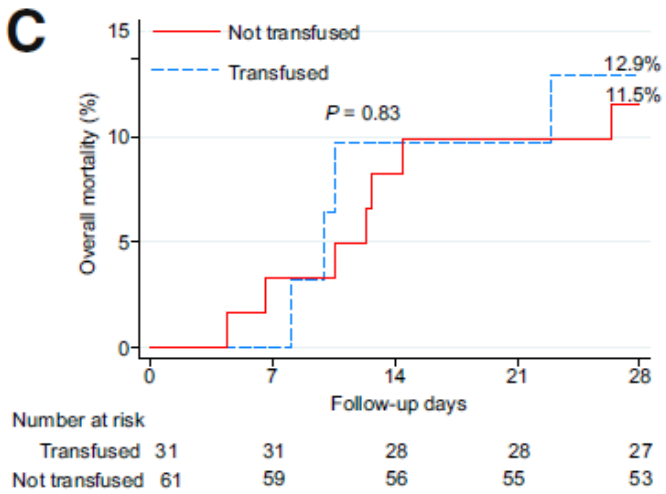
- Patients with severe or life-threatening disease
- Received 1 or 2 units CCP
- Matched to controls by primary and secondary propensity score
- N=136 patients transfused; 251 controls



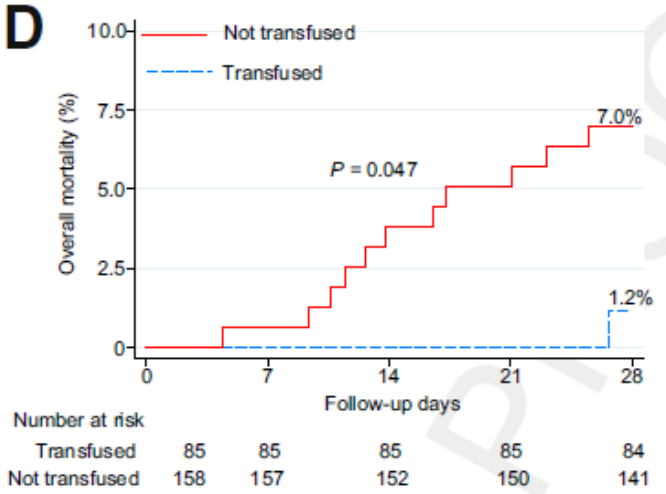
All secondary matched patients



All secondary matched patients transfused ≤72 hr



All secondary matched patients transfused >72 hr

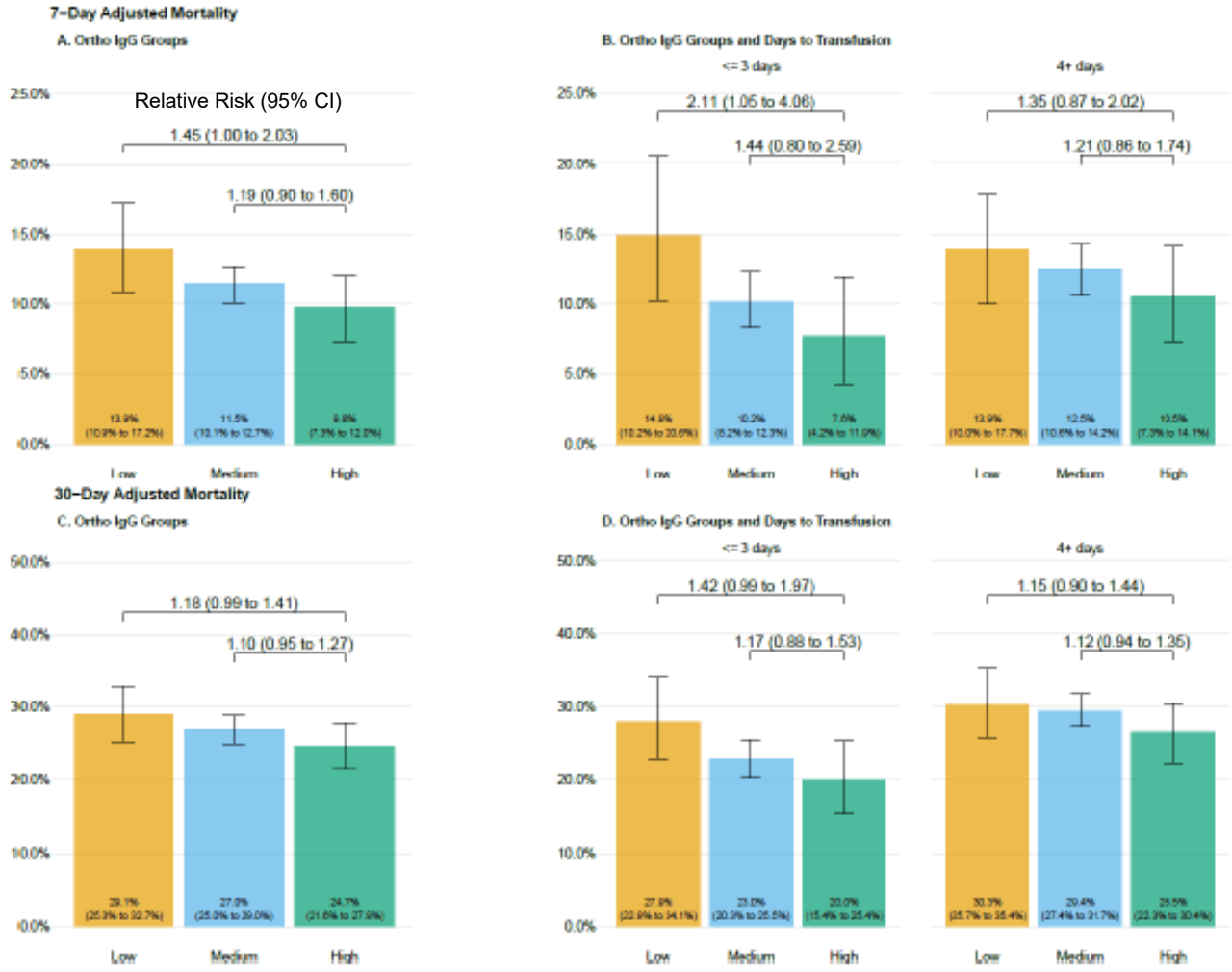


All secondary matched patients transfused ≤72 hr with high-titer plasma

Salazar E et al Am J Pathol 2020

COVID-19 Convalescent Plasma: EAP Results

- N=35,322
- 52.3% in ICU; 27.5% intubated
- 7-day mortality 8.7% vs 11.9% for transfusion within 3 days vs ≥4 days (p<0.001)
- 30-day mortality 21.6% vs. 26.7%, for transfusion within 3 days vs ≥4 days (p<0.0001)



Joyner MJ et al medRxiv accessed 9 Sept 2020

Analysis of Mayo CCP experience based on Broad Institute neutralization data

- No difference in 7-day mortality overall (high vs low titer CCP)
- 21% reduction in 7-day mortality among non-intubated patients who received high vs low titer CCP (14% vs 11%, p=0.03)
- No association between CCP titer and 7-day mortality among intubated patients
- In non-intubated patients under age 80, receipt of high-titer CCP within 72 hr associated with significant reduction in 7-day mortality (11.3% vs 6.3%, p=0.0008)

FDA COVID-19 Convalescent Plasma EUA Clinical Memorandum available at: https://www.fda.gov/media/141480/download accessed 24 August 2020

CCP Summary

- **Anecdotal evidence and uncontrolled trials suggest convalescent plasma may provide benefit in patients with severe COVID-19**
- **Benefit appears related to early administration of high-titer CCP**
- **Little or no benefit in critically ill (intubated) patients**
- **Randomized trials ongoing**
- **IDSA guideline panel recommends COVID-19 convalescent plasma only in the context of a clinical trial**
- **DHHS COVID-19 Treatment Guidelines state:**
  - There are insufficient data to recommend either for or against the use of convalescent plasma for the treatment of COVID-19.
  - Convalescent plasma should not be considered standard of care for the treatment of patients with COVID-19.

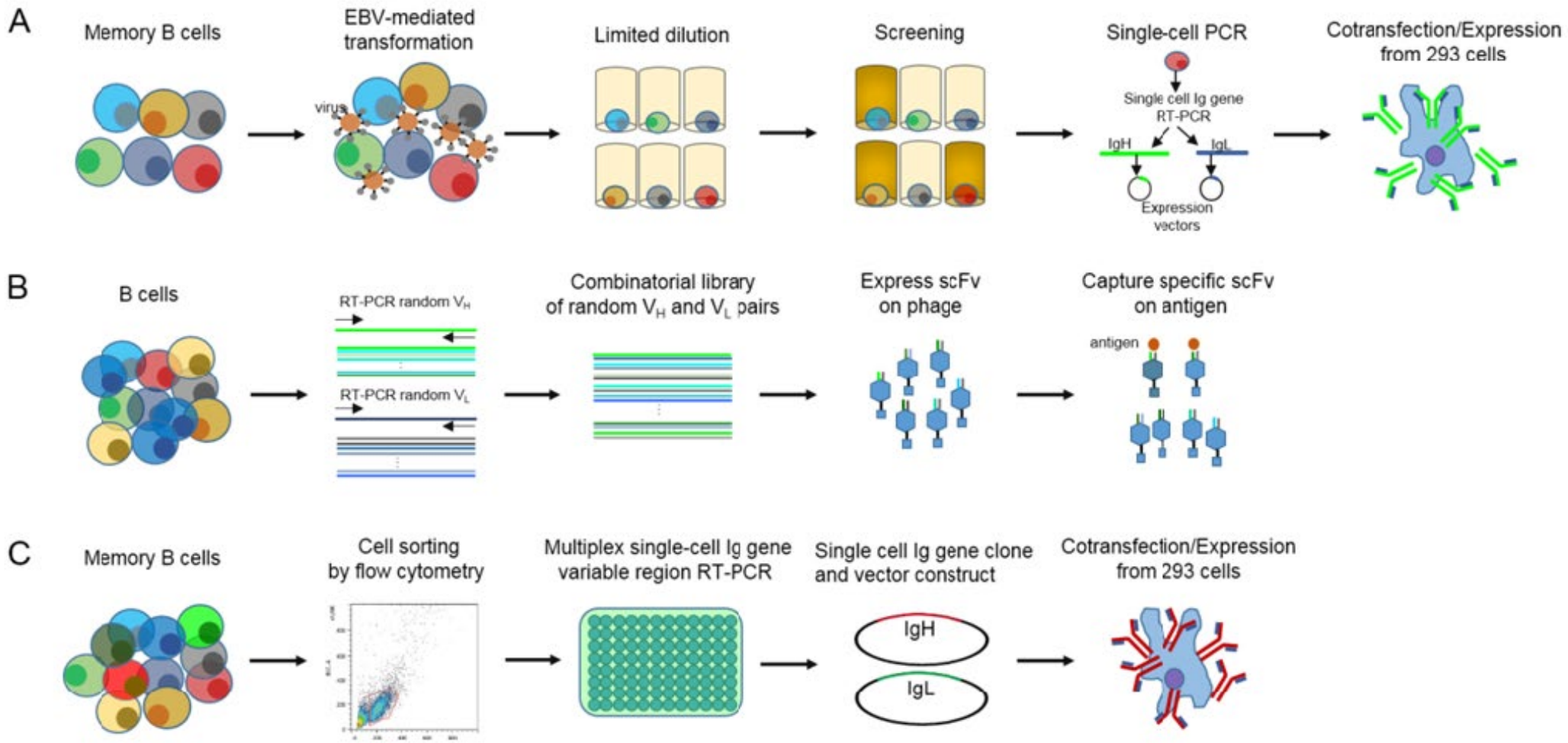
https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/ accessed 6 October 2020
https://www.covid19treatmentguidelines.nih.gov/statement-on-convalescent-plasma-eua/ accessed 6 October 2020

Monoclonal Antibodies

Monoclonal neutralizing antibodies

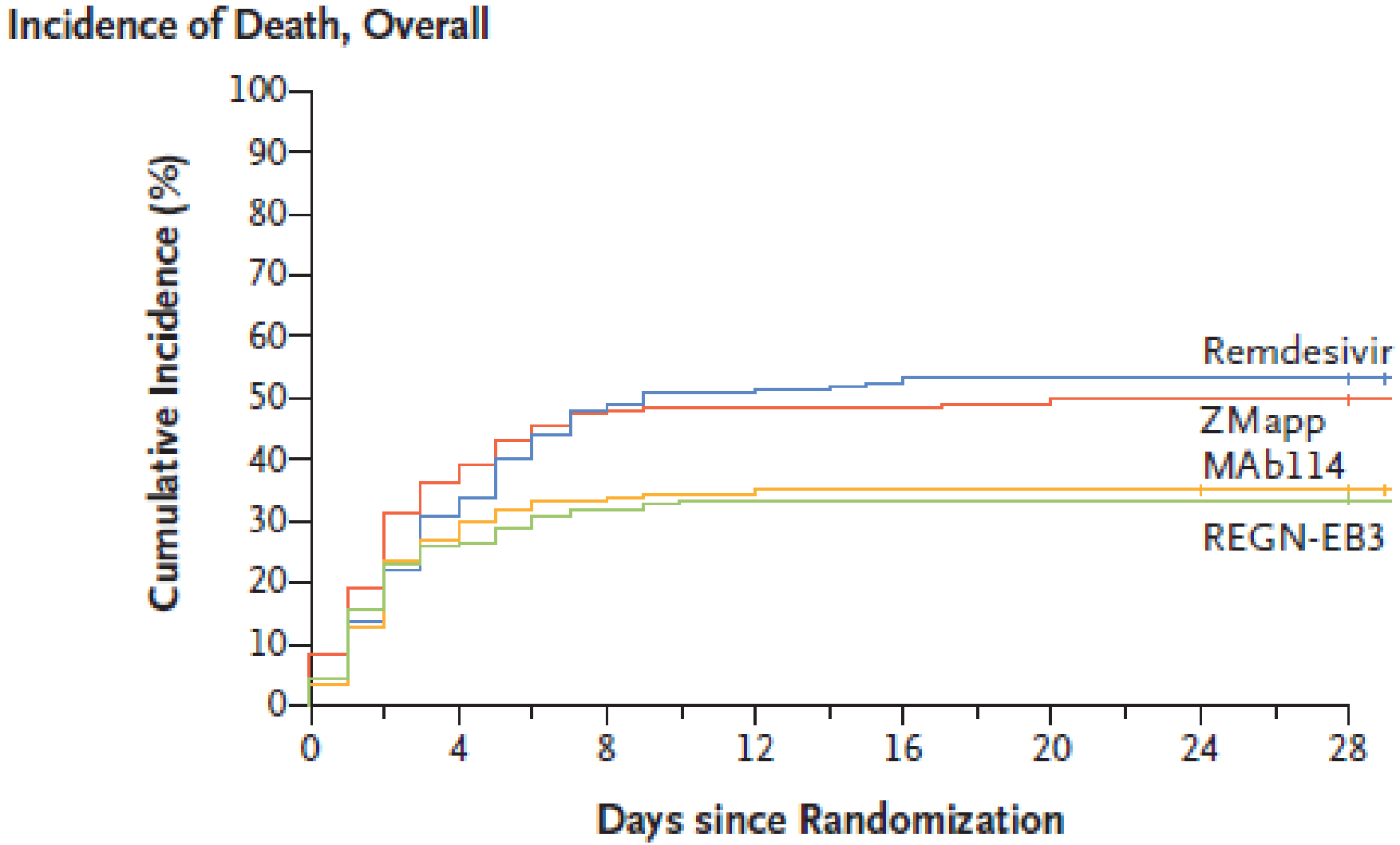
- **Human monoclonal antibodies able to neutralize a wide range of SARS-CoV-2 isolates**
- **Target S protein**
- **May enhance various effector functions**
  - Complement-mediated lysis
  - ADCC, ADCP
- **Can be genetically engineered to combine multiple specificities or extend half-life**
- **Potential utility for treatment or prevention of COVID-19**

Strategies for isolating neutralizing mAbs



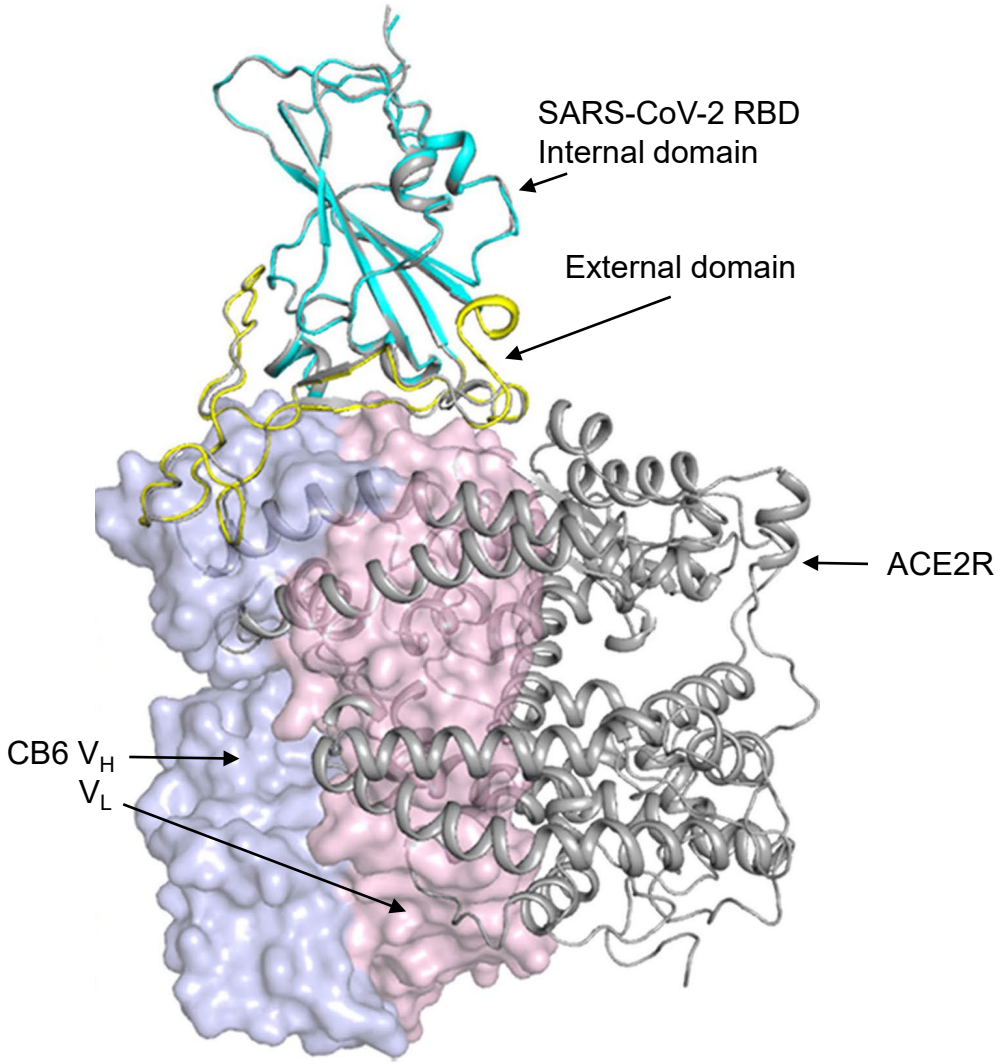
Zhang Z et al J AIDS Clin Res 2016

mAbs more effective than remdesivir against Ebola

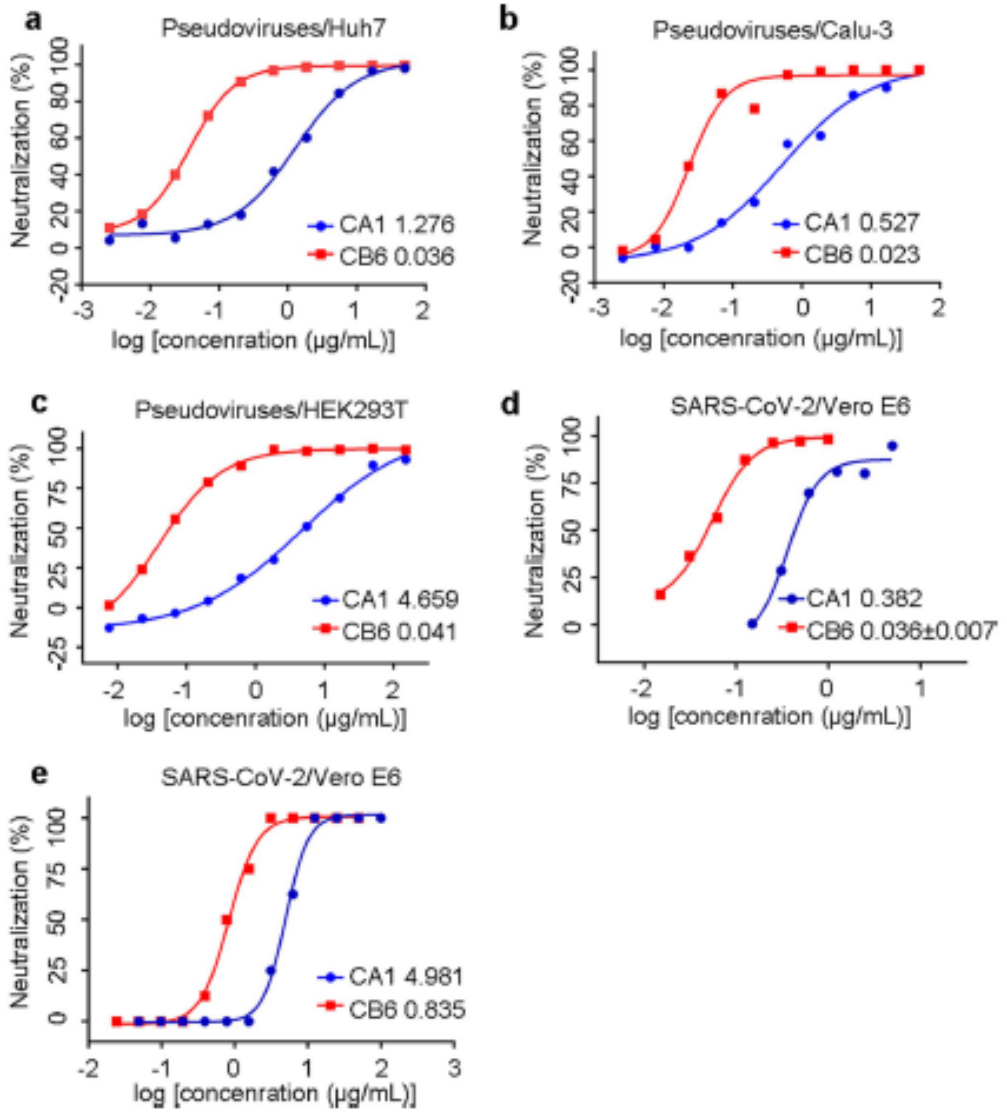


Mulangu S et al N Engl J Med 2019

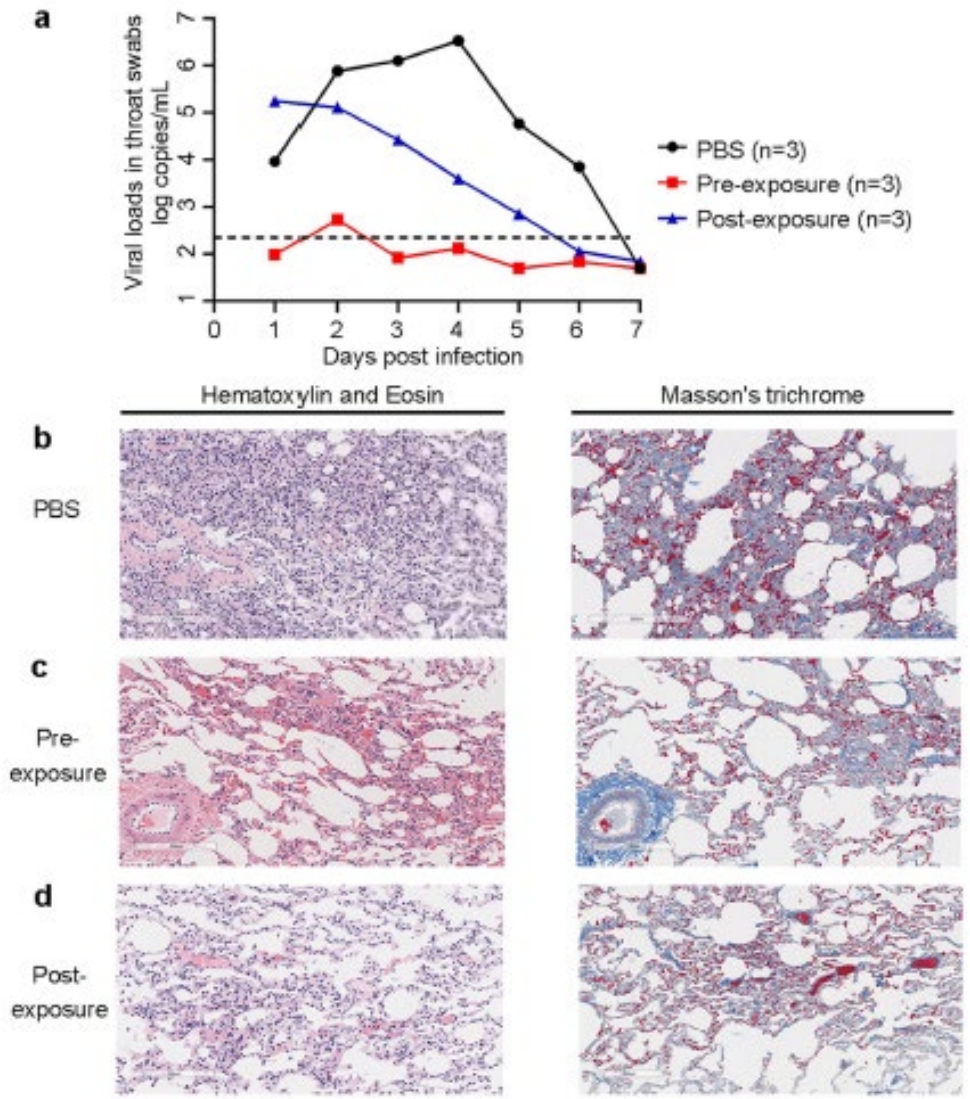
Neutralizing mAbs against SARS-CoV-2



Shi R et al Nature 2020



Effect of SARS-CoV-2 mAbs in rhesus COVID-19



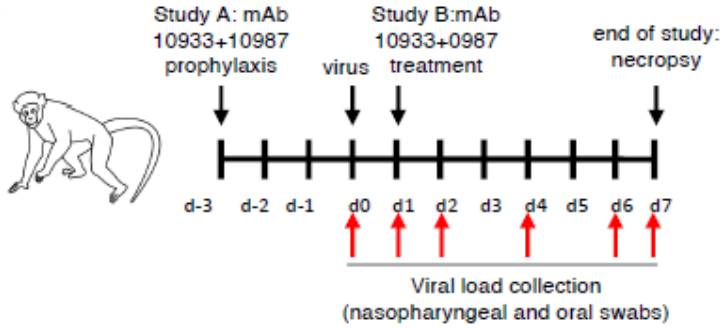
Shi R et al Nature 2020

LY-CoV555 preliminary results

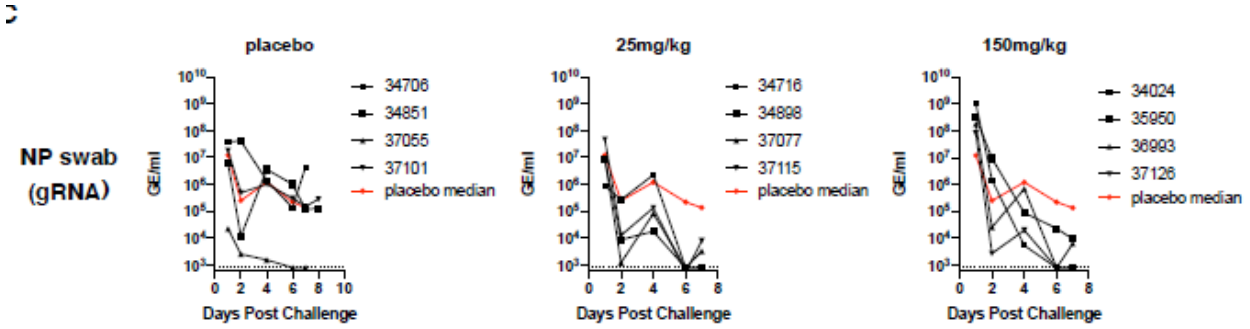
- **BLAZE-1**
  - Placebo-controlled phase 2 trial
  - Symptomatic outpatients with COVID-19
  - 3 dose groups: 700 mg, 2800 mg, 7000 mg
- **Change in virus load endpoint at day 11 met for 2800 mg group (not for lower or higher dose groups)**
- **ER visits/hospitalizations occurred in 5/302 (1.7%) of mAb recipients vs 9/150 (6%) placebo group**
- **No study drug-related SAEs**
- **Viruses with putative resistance mutations emerged in 8 treated and 6 placebo participants**
- **Additional trials (inpatient, outpatient, prophylaxis) are ongoing**

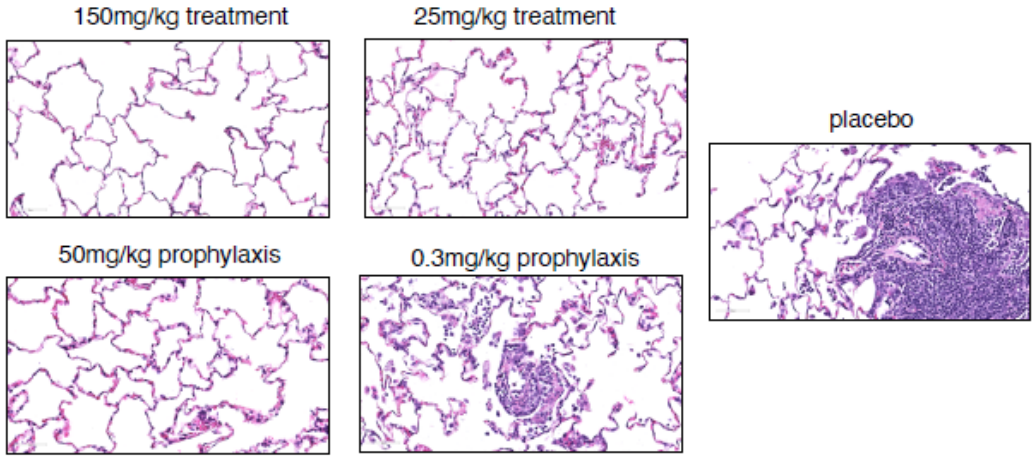
Source: Eli Lilly & Co 16 Sept 2020

SARS-CoV-2 mAb combinations for prevention and treatment in the rhesus macque



Challenge route	intratracheal/ intranasal
Challenge dose	1.05x10^6 PFU
Study A dose groups (prophylaxis)	0.3,50 (mg/kg)
Study B dose groups (treatment)	25,150 (mg/kg)





Baum A et al bioRxiv 2020

REGN-CoV2 mAb cocktail preliminary results

- **“Seamless” phase 1-2-3 trial of REGN-CoV-2 mAb cocktail**
- **275 outpatients with COVID-19 randomized to receive 8 grams or 2.4 grams of REGN-CoV-2 or placebo**
- **Serological status highly correlated with baseline viral load ($p<0.0001$).**
- **There was a 0.51-$\log_{10}$ copies/mL greater reduction ($p=0.0049$) in patients treated with high dose, and a 0.23-$\log_{10}$ copies/mL greater reduction ($p= 0.20$) in patients treated with low dose, compared to placebo**
  - These differences were slightly greater in the seronegative subgroup
- **Among seronegative patients, median time to symptom alleviation was 13 days in placebo, 8 days in high dose ($p=0.22$), and 6 days in low dose ($p=0.09$)**
- **Both doses were well-tolerated**
- **Additional inpatient, outpatient and prophylaxis trials are ongoing**

Source: Regeneron Pharmaceuticals, Inc. 29 Sept 2020

Summary: SARS-CoV-2 mAbs

- Numerous SARS-CoV-2 mAbs have been produced
- These mAbs reduce virus load, protect against infection and/or reduce lung injury in animal models
- Multiple human clinical trials are ongoing for treatment and prevention of COVID-19
- Preliminary results of phase 1-2 trials with LY-CoV555 and REGN-CoV2 cocktail are encouraging
- No safety concerns to date
- Phase 3 data needed to demonstrate clinical efficacy