COVID19

Keeping Up with a Moving Target

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Faculty Disclosures

The faculty reported the following financial relationships or relationships they or their spouse/life partner have with commercial interests related to the content of this continuing education activity:

Name of Faculty or Presenter	Reported Financial Relationship
Charles Vega, MD	None
Aimalohi Ahonkhai, MD, MPH	None

The faculty have indicated that they will be referencing the unlabeled or unapproved use of agents currently being investigated in on-going studies and trials, including COVID-19 convalescent plasma, monoclonal antibody treatments, vaccines, tocilizumab, baricitinib, and dexamethasone

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All activity content and materials have been developed solely by the planning committee members and faculty presenters.

Learning Objectives

1. Assess the impact of COVID-19 on Black, Latinx, and American Indian/Alaska Native communities and the factors contributing to health disparities in these communities.
2. Describe current and potential management strategies for mild to moderate COVID-19
3. Describe current management strategies and identify potential treatments for COVID-19 requiring hospitalization.

Please note that the material presented in this program is current as of November 1, 2021.

For the most up-to-date guidance, please review the following:

NIH COVID-19 Treatment Guidelines:
https://www.covid19treatmentguidelines.nih.gov/

IDSA Guidelines on the Treatment and Management of Patients with COVID-19:
https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

A Lesson Reinforced

"COVID is a funhouse mirror that is amplifying issues that have existed forever. People are not dying of COVID. They are dying of racism, of economic inequality and it is not going to stop with COVID."

Shreya Kangovi, MD, MSHP, Associate Professor of Medicine Perelman School of Medicine at the University of Pennsylvania Executive Director of the Penn Center for Community Health Workers

Clinical Course

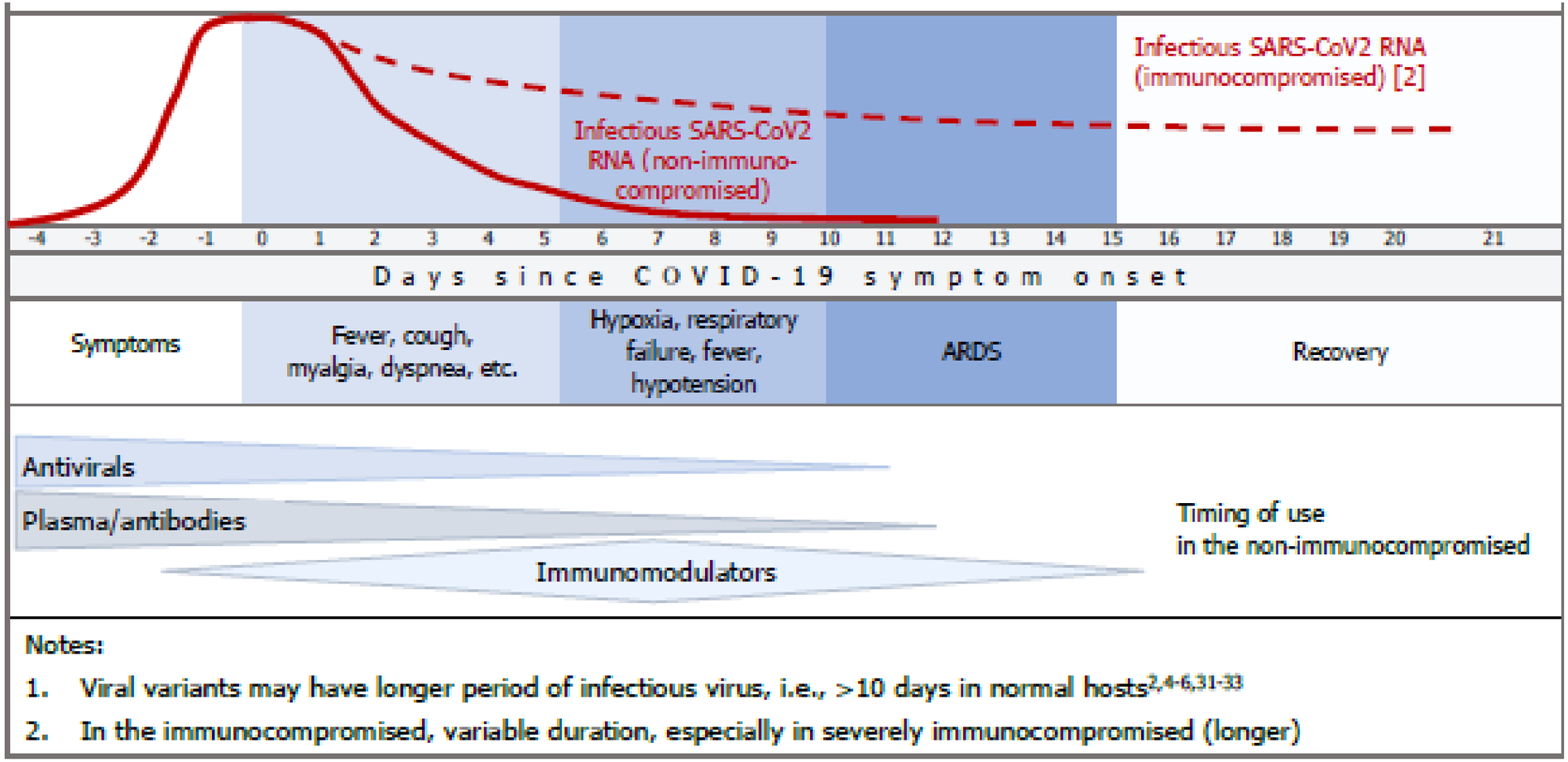
Illness severity:

- Mild to moderate (mild symptoms to mild pneumonia): **81%**
- Severe (dyspnea, hypoxia, or > 50% lung involvement on imaging): **14%**
- Critical (respiratory failure, shock, multiorgan dysfunction): **5%**

https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html

Clinical Progression

Schematic of Clinical Course of Severe COVID-19



JHMI Clinical Recommendations for Available Pharmacologic Therapies for COVID-19
https://www.hopkinsguides.com/hopkins/ub?cmd=repview&type=479-1155&name=14_538747_PDF

CDC: Risk Factors for Severe Illness

Meta-analysis, systematic review	Cohort, case-control, cross-sectional studies	Case series, case reports
• Cancer • Cerebrovascular disease • CKD • COPD • Serious heart conditions (HF, CAD, cardiomyopathies) • Smoking (current/former) • Obesity (BMI ≥ 30) • Pregnancy/recent pregnancy • T1DM • T2DM	• Children with certain underlying conditions • Down syndrome • HIV • Neurologic conditions (AD) • Overweight (BMI>25 but <30) • Other lung disease (PF, pulmonary hypertension) • Sickle cell disease • Solid organ/blood stem cell transplantation • Substance use disorder • Use of steroids or immunosuppressive meds	• Cystic fibrosis • Thalassemia **Mixed evidence** • Asthma • Hypertension • Liver disease • Immune deficiencies

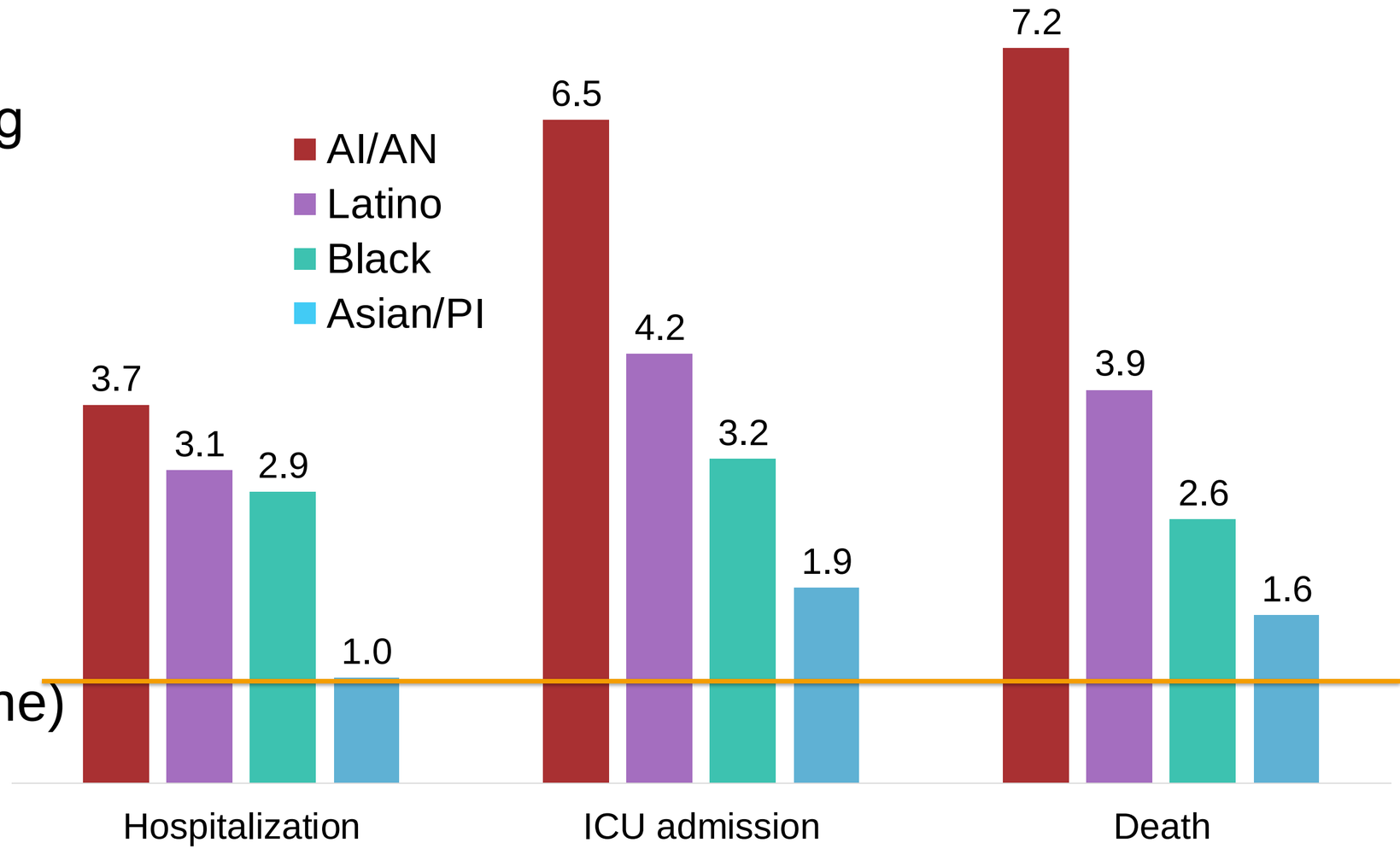
https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlying-evidence-table.html

Disparities in Hospitalization, ICU Admission, & Death - March 2020 to February 2021

COVID-NET surveillance data

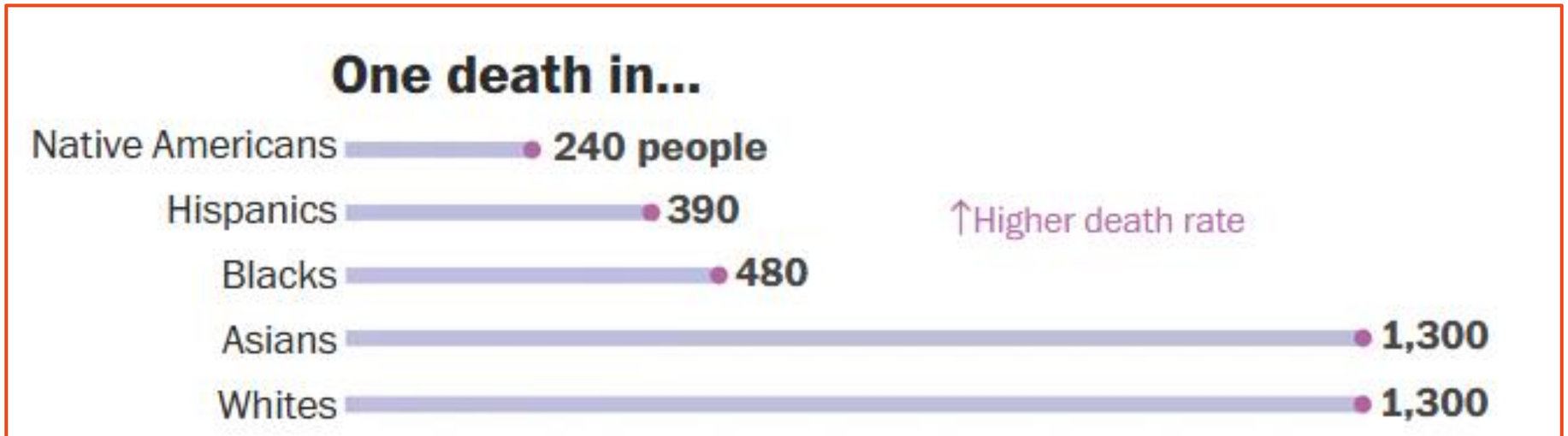
- 143,342 hospitalizations
- Most had ≥ one underlying condition
  - AI/AN: 90%
  - Asian/PI: 88.9%
  - Black: 94.4%
  - Latino: 82.1%
  - White: 94.4%

Risk ratios shown compared with White people (orange line)



Acosta et al. 2021 JAMA Netw Open.

Disparities Simplified



Children of racial and ethnic minorities accounted for 65% of those who lost a primary caregiver from the pandemic

COVID19

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AMBULATORY PATIENTS

Home Care

- Monitor symptoms
- Supportive care
- Infection prevention and control measures

Isolation for People with COVID-19

May be discontinued under these conditions:

- At least 10 days since symptom onset *and*
- At least 24 hours since resolution of fever without fever-reducing meds *and*
- Other symptoms have improved

Quarantine for Close Contacts (not vaccinated)

Recommended for 14 days; but can end:

- After day 10 without testing if no symptoms
- After day 7 if testing is negative and no symptoms

Symptom monitoring and masking through day 14 still required.

https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-in-home-patients.html

COVID19

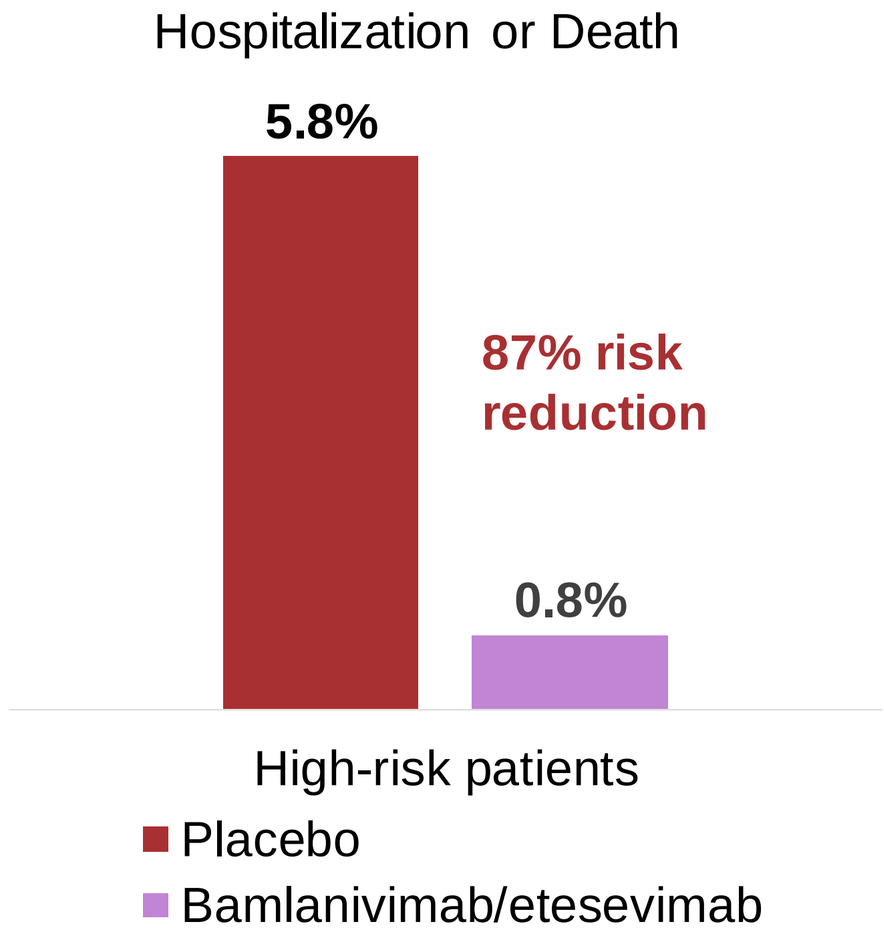
Keeping Up with a Moving Target

They’re really antivirals.

ANTIBODY-BASED THERAPIES

Bamlanivimab/Etesevimab mAb Cocktail

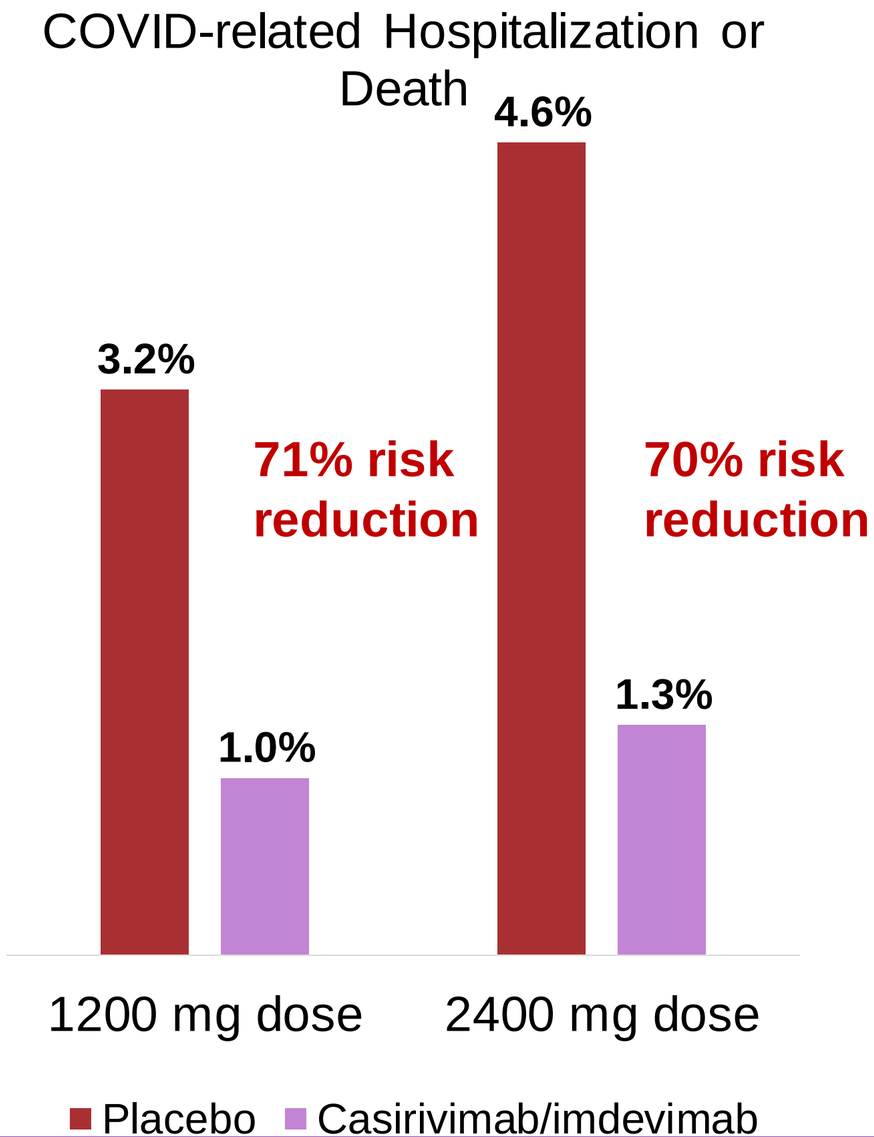
- N = 769, BLAZE-1 RCT, phase 3 cohort, high-risk patients with mild/moderate COVID-19
- Dose 700 mg bamlanivimab/1400 mg etesevimab (authorized dose)
- After distribution was paused in June because the circulating variants were not responsive to the combination, the FDA resumed distribution in early September.



Press release. https://investor.lilly.com/news-releases/news-release-details/lillys-bamlanivimab-and-etesevimab-together-reduced

Casirivimab/Imdevimab mAb Cocktail

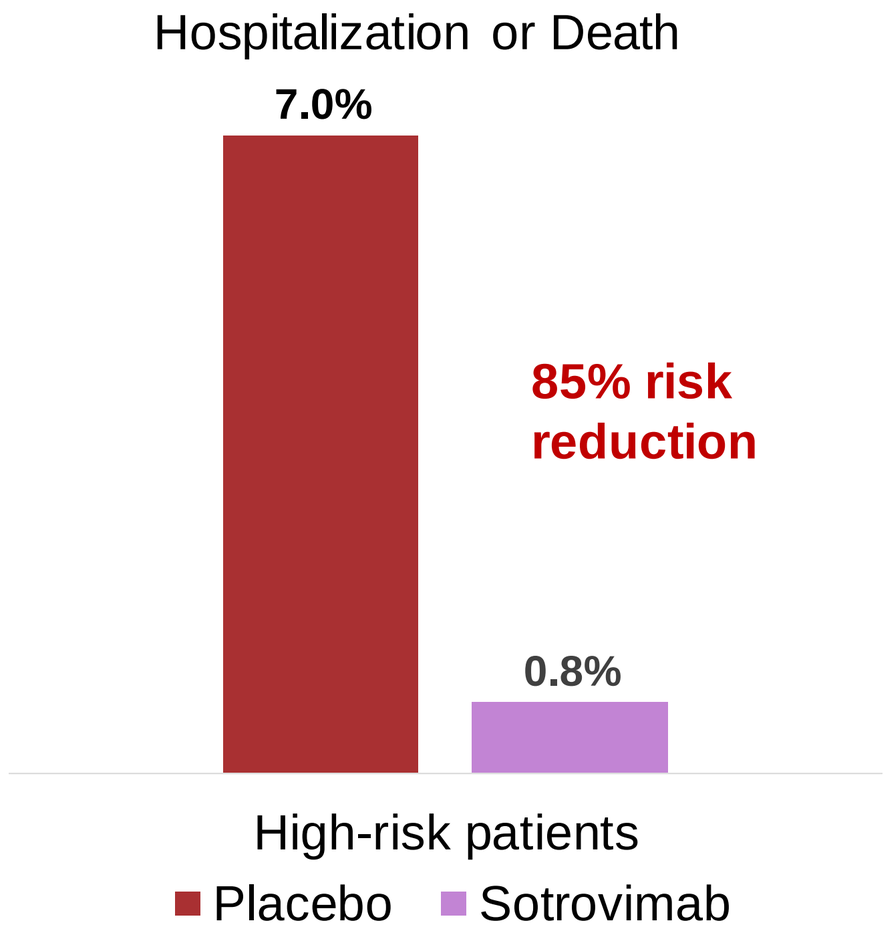
- Phase 3 portion
- N = 4,057 high-risk patients; obesity in 58%, CVD in 36%
- Diverse population: Hispanic 35%, Black 5%
- Also reduced time to symptom resolution (10 days vs 14 days, both doses)
- Jun 4: EUA at lower dose; this lower dose may be administered SC when IV is not feasible or would delay treatment



Weinreich DM et al NEJM 2021; Press release

Sotrovimab

- EUA May 2021
- Interim results phase 3 trial
- N = 583 high-risk patients; obesity in 63%
- Diverse population: Hispanic 63%, Black 7%
- Preclinical data suggest two mechanisms: blocking viral entry and clearing infected cells
- March 2021: IDMC recommended stopping enrollment in placebo group because of efficacy
- Being studied with bamlanivimab and other mAbs

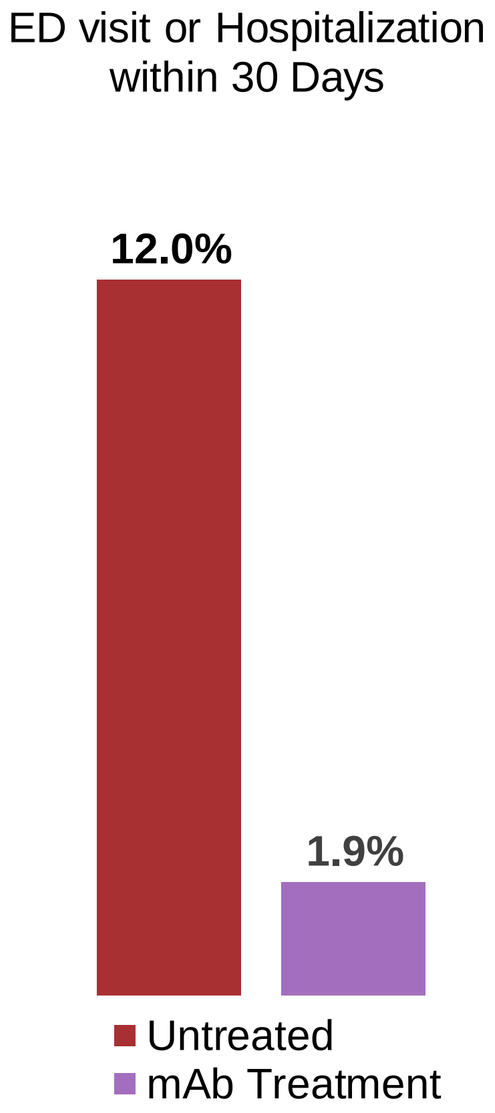


Gupta et al NEJM 2021; Press release

Real-World Study of Monoclonal Antibodies

Single-center retrospective cohort study (Feb 2021)

- Urban city, population ~ 500,000
  - 56.4% Non-White, poverty rate 23.4%
- People with COVID-19 who visited outpatient clinic or medical center
  - 598 patients, 39% Hispanic
  - 45% eligible for/received mAbs
  - No significant difference in sex, race, ethnicity between treated and untreated groups
  - Compared with historical control (before availability of mAbs)
- After adjusting for age, gender, comorbidities, risk of ED visit or hospitalization 82% lower in patients who received mAbs
  - Higher risk of need for medical visit in untreated group than in clinical trial of bamlanivimab



EUAs for Outpatients Only:

Casirivimab + Imdevimab, Bamlanivimab + Etesevimab, Sotrovimab

Mild-Moderate COVID-19 Outpatients

- High risk for COVID-19 complications
- Ages ≥ 12 years
- Within 10 days of symptom onset (earlier is better)
- Monitor patients during administration and 1 hour after
- Administer in settings where providers have immediate access to medications to treat severe reactions and ability to activate emergency medical system

Information sheets for providers available, with criteria for eligibility:

https://www.fda.gov/media/143892/download (casirivimab + imdevimab)
https://www.fda.gov/media/145802/download (bamlanivimab + etesevimab)
https://www.fda.gov/media/149534/download (sotrovimab)

Criteria for Monoclonal Antibodies

The following conditions/factors may place adults and pediatric patients (ages 12-17 and ≥40 kg) at high risk for progression to severe COVID-19:

- Older age (eg ≥65 years)
- Overweight or obesity (BMI > 25 kg/m^2)
- Pregnancy
- Diabetes
- Chronic kidney disease
- Immunosuppressive disease or use of immunosuppressive treatment
- Cardiovascular disease
- Chronic lung disease
- Sickle cell disease
- Neurodevelopment disorders
- Medical-related technological dependence, (eg, tracheostomy)
- Other conditions associated with risk of progression (eg, race or ethnicity. see CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people- with-medical-conditions.html)
- Health care providers should consider the benefit-risk for an individual patient

June 2021: The FDA EUAs revised to expand list of conditions that place patients with mild-moderate COVID-19 at increased risk of progression

Recommendations for Monoclonal Antibodies

NIH (9/15/21)

Recommends use of bamlanivimab/ etesevimab OR casirivimab/imdevimab OR sotrovimab in outpatients at high risk

IDSA (8/17/21)

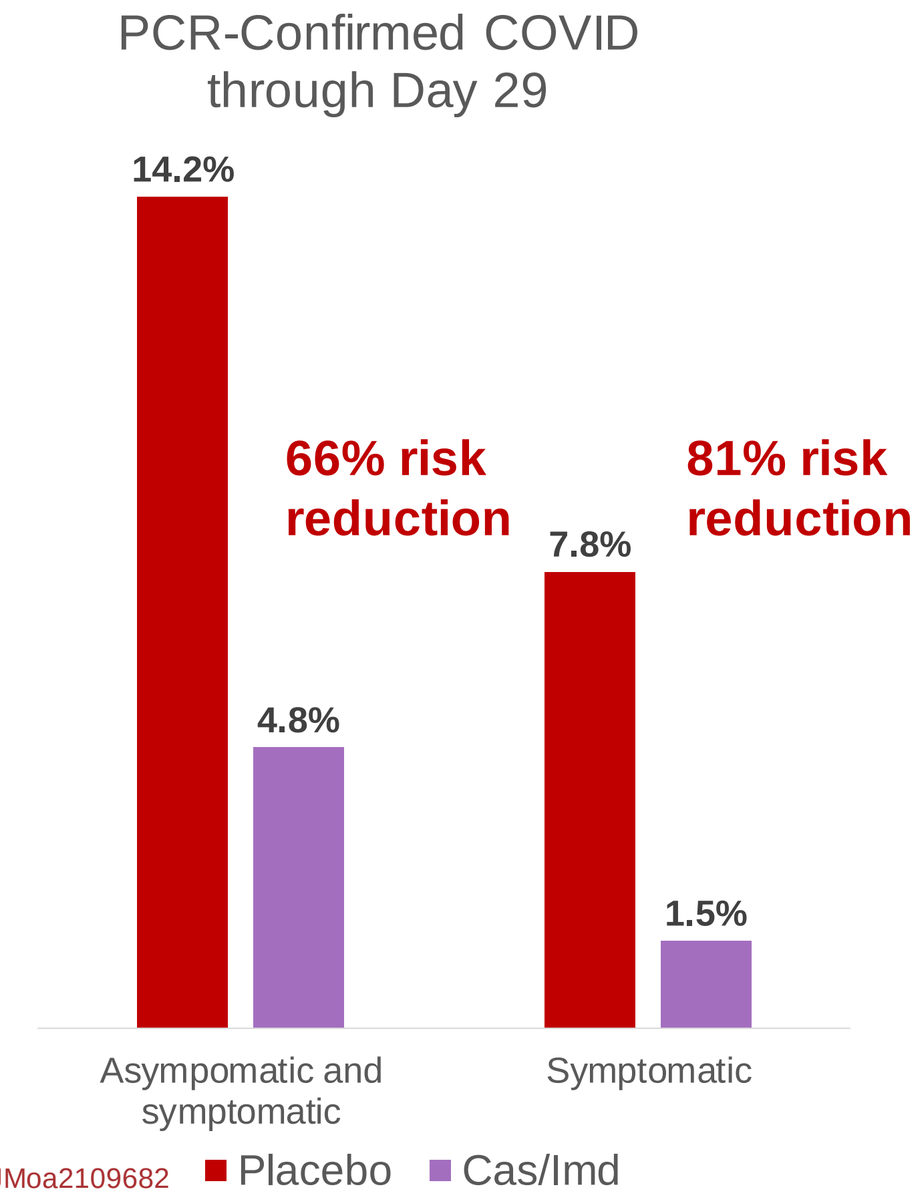
Suggests use of bamlanivimab/ etesevimab OR casirivimab/imdevimab OR sotrovimab in outpatients with mild to moderate illness at high risk for severe disease

Local variant susceptibility may be considered in choice of most appropriate antibody

https://www.covid19treatmentguidelines.nih.gov/; https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management

Casirivimab + Imdevimab as Post-Exposure Prophylaxis

- N = 1505, all seronegative and asymptomatic at baseline
  - Lived in household with SARS-CoV-2-postive contact
  - 41% Hispanic, 9% Black
- Randomized to 600 mg/600 mg casirivimab/imdevimab subcutaneously within 96 hours of index case confirmation
- 76% risk reduction in people who had high risk for progression to severe disease
- Resolution of symptoms: 3.2 weeks for placebo, 1.2 for casirivimab/imdevimab
- **EUA expanded July 30**
  - People at high risk who are unvaccinated or expected to have inadequate response to vaccine
  - Ages ≥ 12 yrs within 6 ft x 15 minutes cumulatively over 24 h with confirmed COVID-19 individual



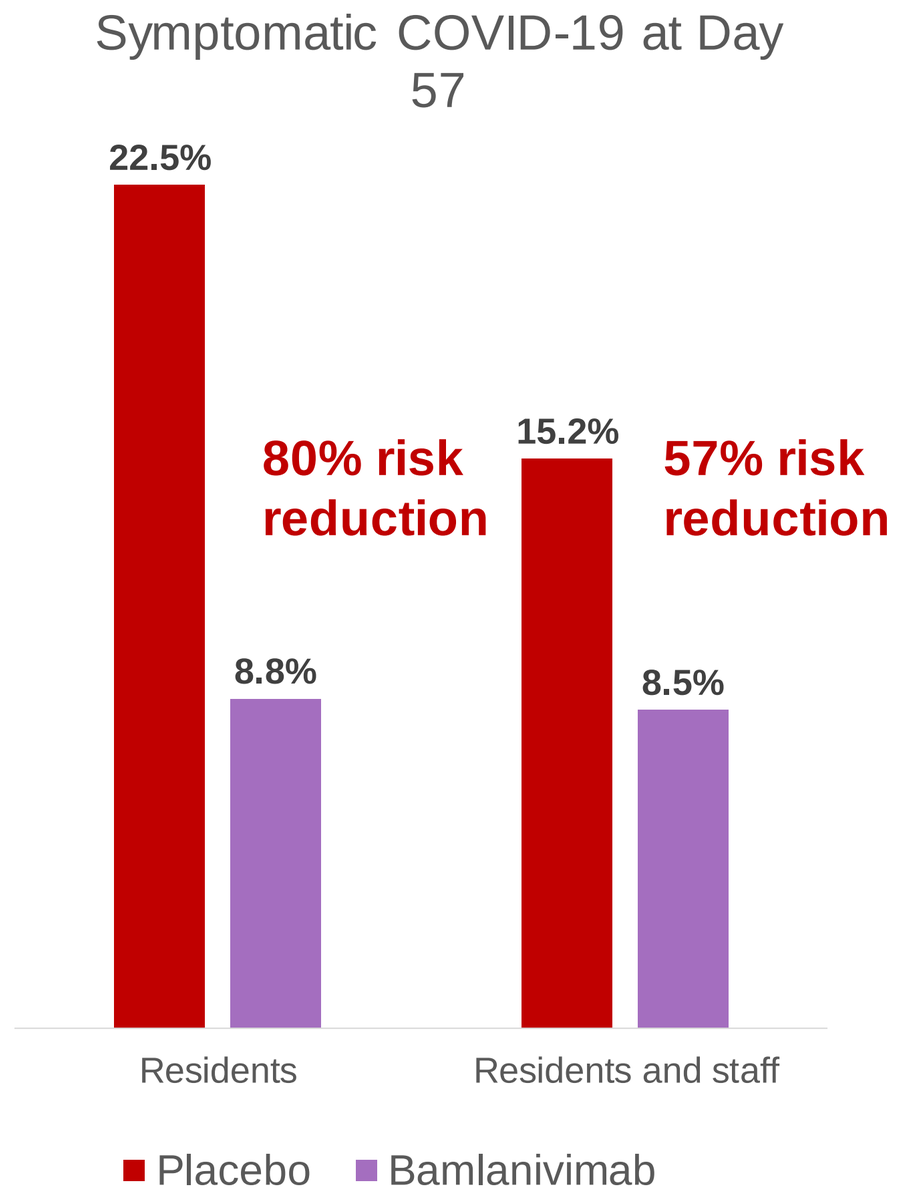
https://www.fda.gov/media/145611/download

O'Brien et al. Subcutaneous REGEN-COV antibody combination to prevent Covid-19 *NEJM* DOI: August 202110.1056/NEJMoa2109682

Bamlanivimab + Etesevimab as Post-Exposure Prophylaxis

- BLAZE-2 (N = 966), all seronegative and asymptomatic at baseline
  - Residents and staff of skilled nursing facilities after confirmed infection at facility
  - 5% Hispanic, 8% Black
- Randomized to 4,200 bamlanivimab alone
- Four deaths in placebo arm; none in bamlanivimab group

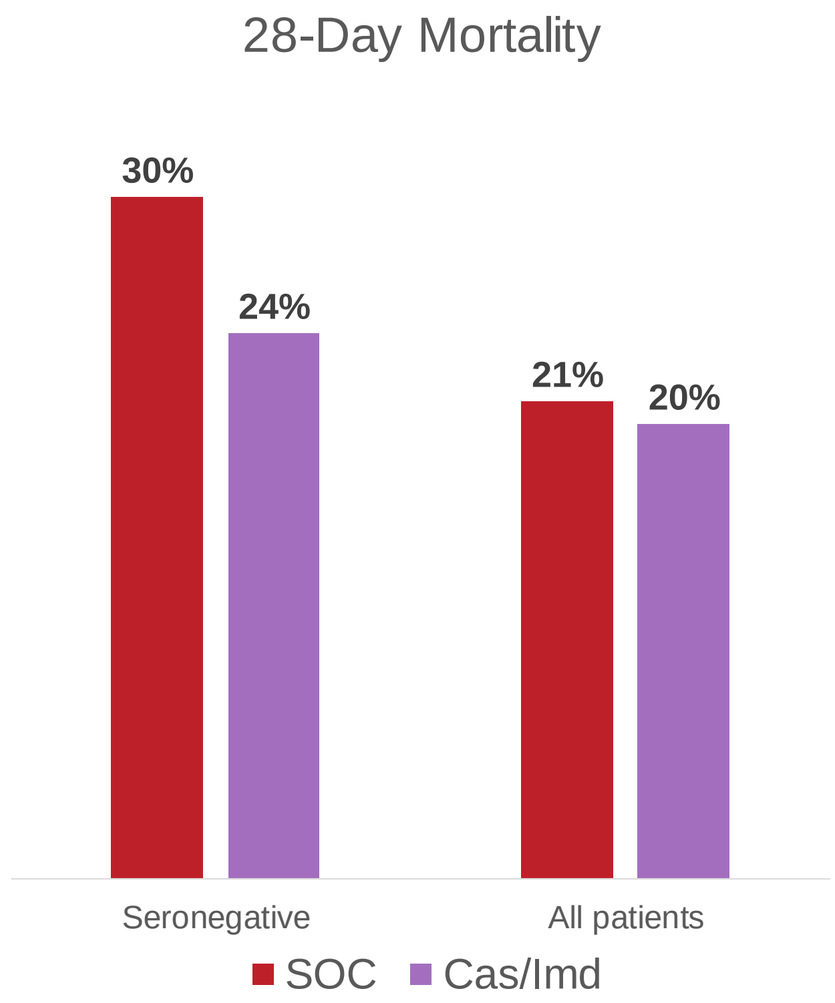
- **EUA expanded September 2021**
  - People at high risk who are unvaccinated or expected to have inadequate response to vaccine
  - Ages ≥ 12 yrs within 6 ft x 15 minutes cumulatively over 24 h with confirmed COVID-19 individual



Cohen MS JAMA 2021;326 https://www.fda.gov/media/145802/download

Casirivimab + Imdevimab in Hospitalized Patients: RECOVERY – not yet authorized

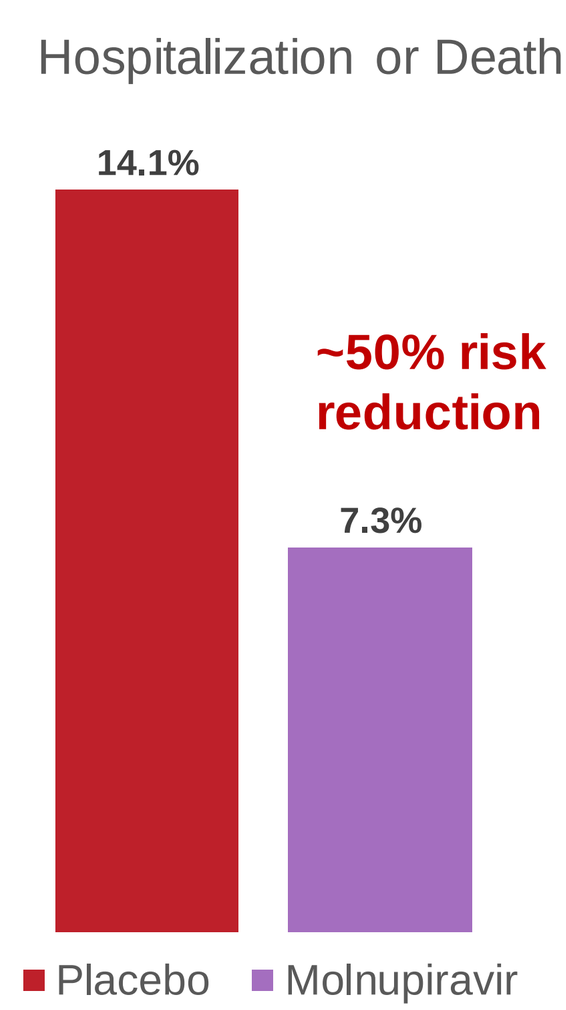
- N = 9785 hospitalized patients; mean age 61.9
- Design: open-label; standard of care or SOC plus single dose casirivimab + imdevimab
- 94% receiving corticosteroids; median time since symptom onset 9 days
- Seronegative patients:
  - 28-day mortality: 24% vs 30% (RR, .80; 95% CI, .70-.91); no benefit for overall population
  - Progression to invasive ventilation/death: 30% vs 37% (RR, .83; 95% CI, .75-.92); no benefit overall population



Recovery Group. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. medRxiv preprint https://doi.org/10.1101/2021.06.15.21258542

Molnupiravir (Under FDA Review for EUA)

- N = 775 outpatients (not vaccinated) with at least one risk factor for severe disease
- Interim analysis RCT: five-day course; within 5 days of symptom onset, trial halted early by independent data monitoring committee
- No deaths in treatment group (8 in placebo)
- Effective against Gamma, Delta, Mu variants
- Applied for EUA October 2021
- Previously shown to reduce viral load



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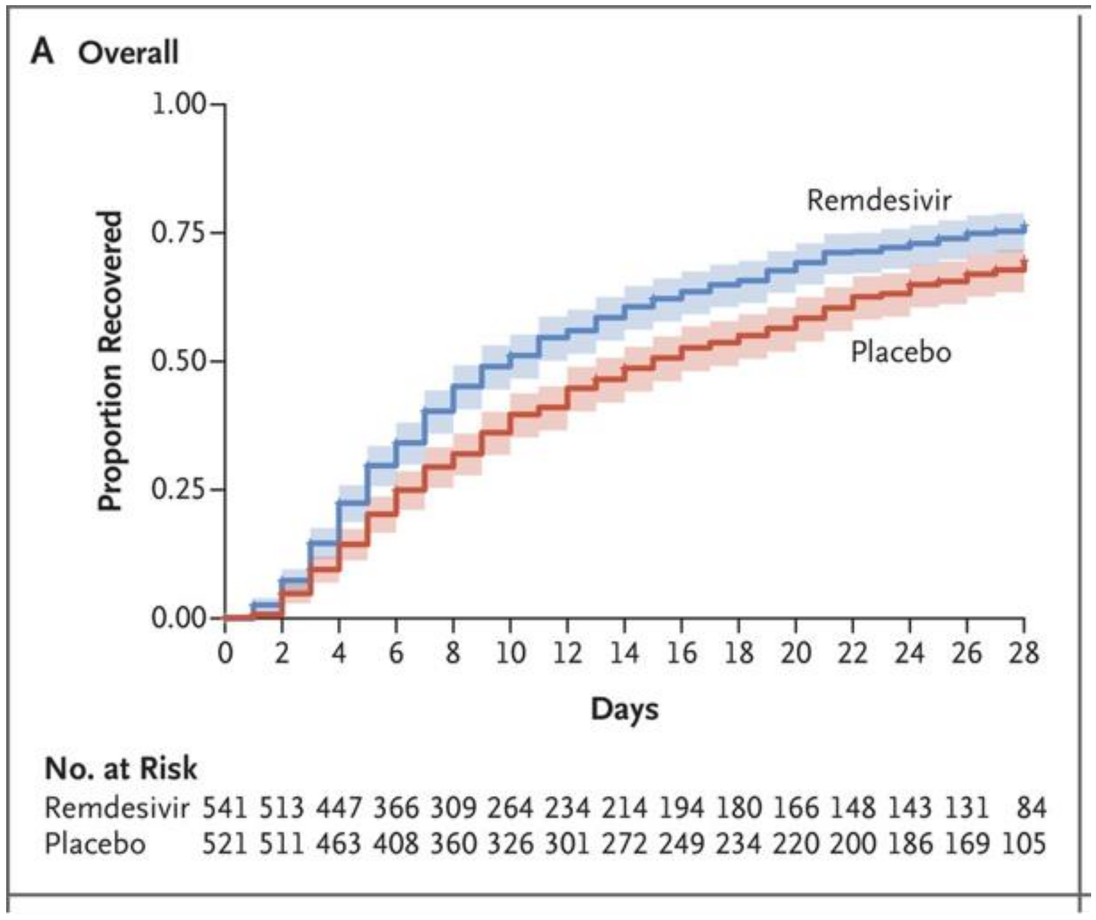
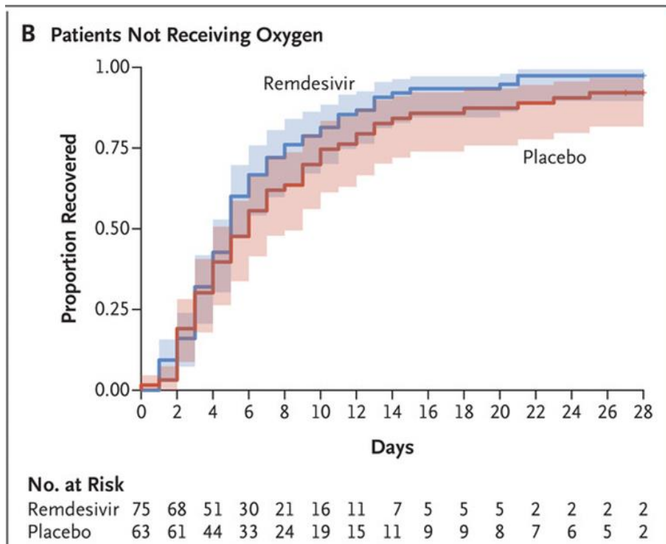
HOSPITALIZED PATIENTS

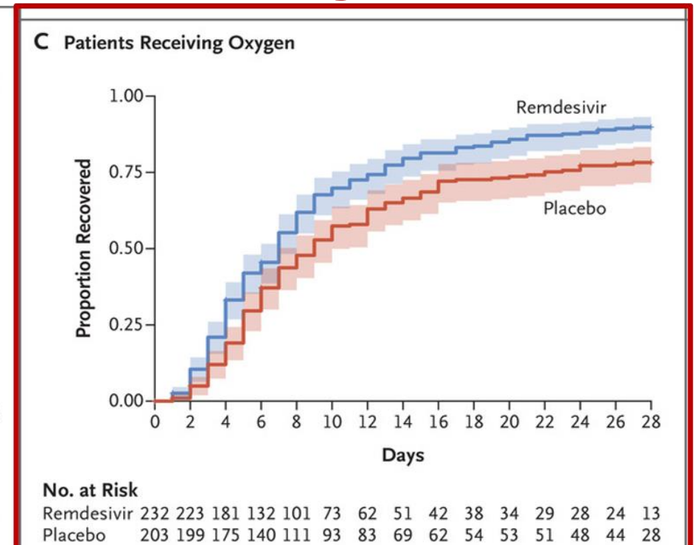
NIH Recommendations

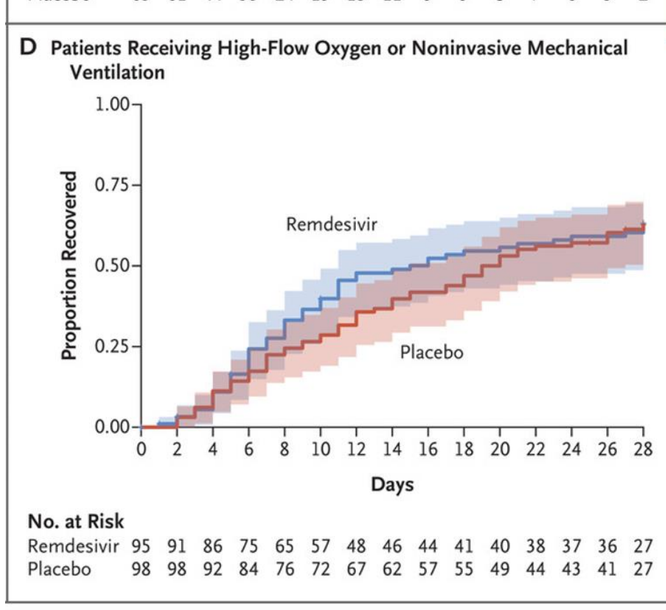
Disease Severity	Panel's Recommendations
Hospitalized but does not require supplemental oxygen	Recommend against dexamethasone or other corticosteroid Insufficient data for/against the routine use of remdesivir (may be appropriate for patients at high risk of disease progression)
Hospitalized and requires supplemental oxygen	One of the following: • Remdesivir (eg, for patients requiring minimal supplemental oxygen) • Dexamethasone + remdesivir (eg, increasing amounts of supplemental oxygen) • Dexamethasone (eg, when combination with remdesivir cannot be used)
Hospitalized and requires oxygen delivery through a high-flow device or noninvasive ventilation	One of the following: • Dexamethasone • Dexamethasone + remdesivir Recently hospitalized, rapidly increasing oxygen needs + systemic inflammation: • Baricitinib OR tocilizumab plus one of the above • If neither baricitinib nor tocilizumab are available/feasible, tofacitinib may replace baricitinib or sarilumab may replace tocilizumab.
Hospitalized and requires invasive mechanical ventilation or ECMO	Dexamethasone Patients within 24 hours of ICU admission: • Dexamethasone + tocilizumab • If tocilizumab is not available/feasible, may substitute sarilumab

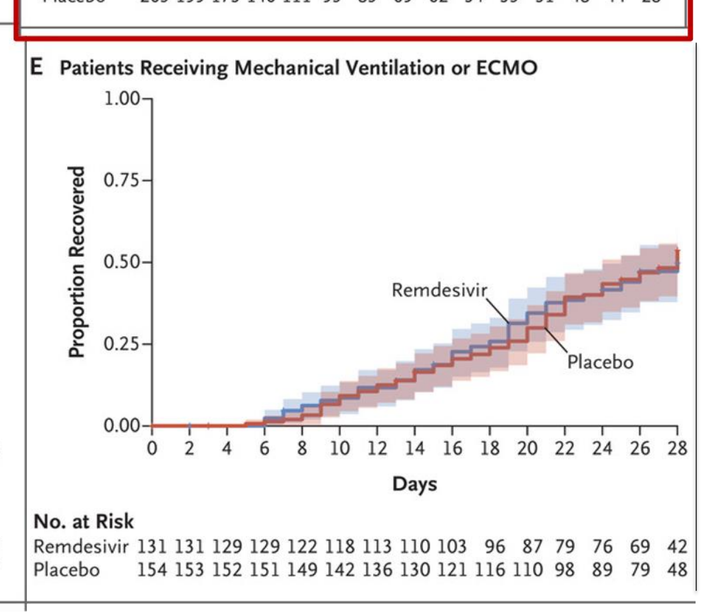
Remdesivir: ACTT-1 – Estimates of Recovery











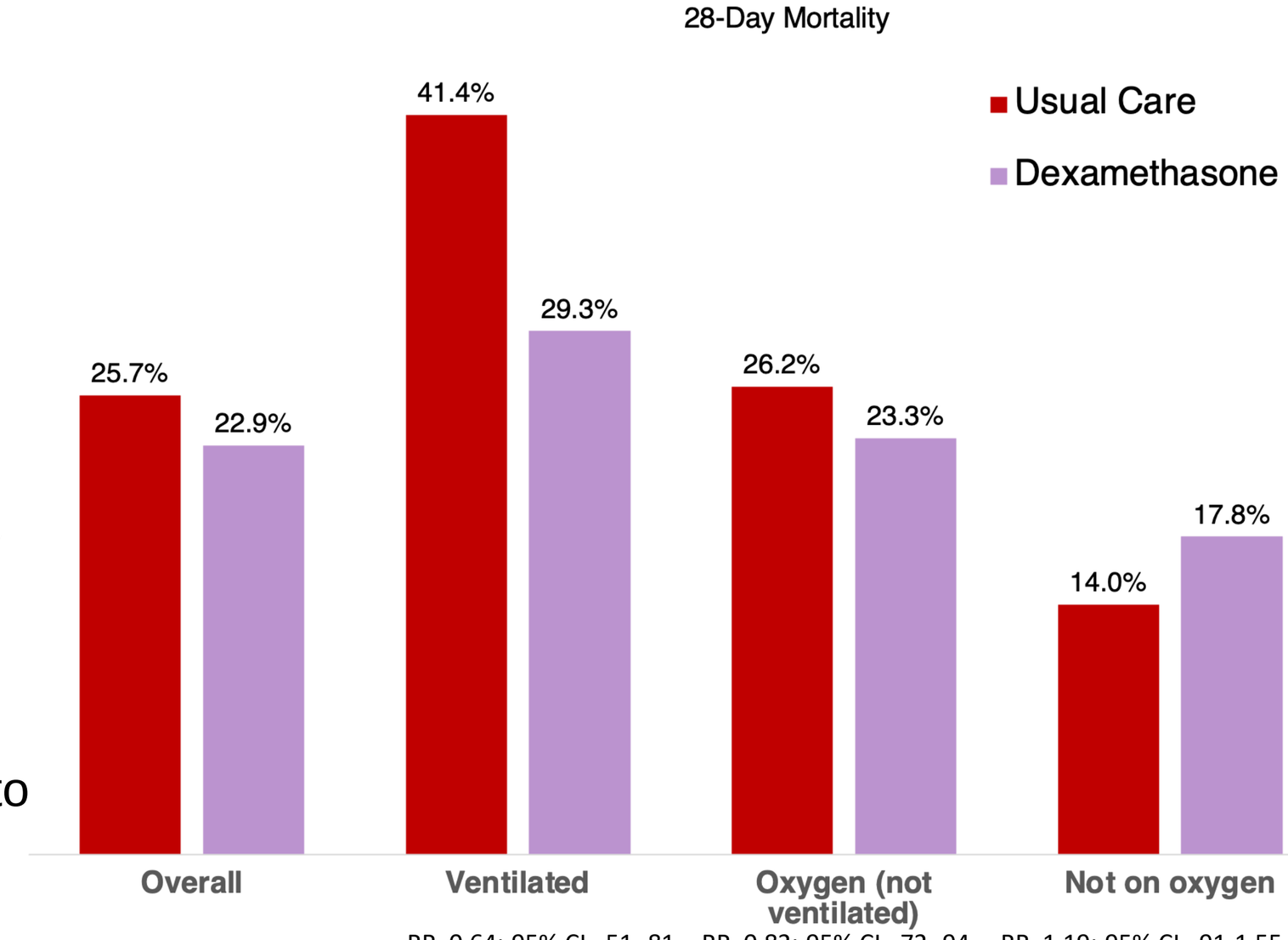
Patients receiving oxygen (not through high-flow or mechanical ventilation) had greatest benefit.

Beigel, NEJM 2020;383(19):1813-1826.

Dexamethasone Trial Arm (RECOVERY Trial)

- UK trial
  - 2:1 ratio
  - 4321 control vs 2104 dexamethasone
  - Trial halted

- First drug to show mortality benefit
  - On mechanical ventilation or on oxygen
  - Those not on oxygen, trend to worse outcomes

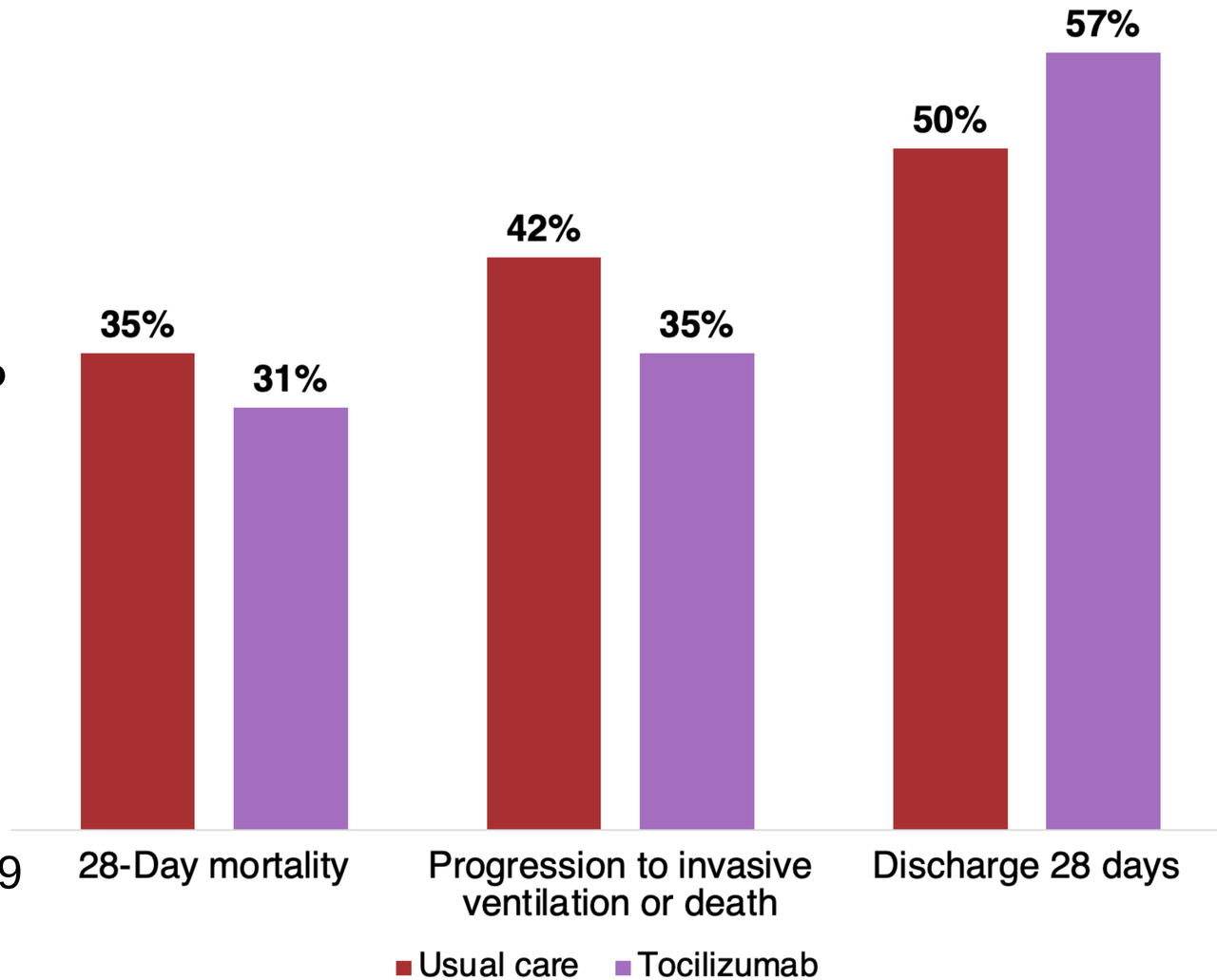


Recovery Group et al. NEJM 2020.

Tocilizumab Trial Arm (RECOVERY Trial)

- UK trial
  - 2022 Tocilizumab vs 2094 Usual care
    - 82% on steroid
    - 41% requiring NIV; 45% no respiratory support
    - Enrolled 9-10 days (avg) after symptom onset
  - SpO2 < 92% or requiring oxygen and CRP ≥ 75 mg/L)
  - Single IV dose (2nd dose clinician discretion)

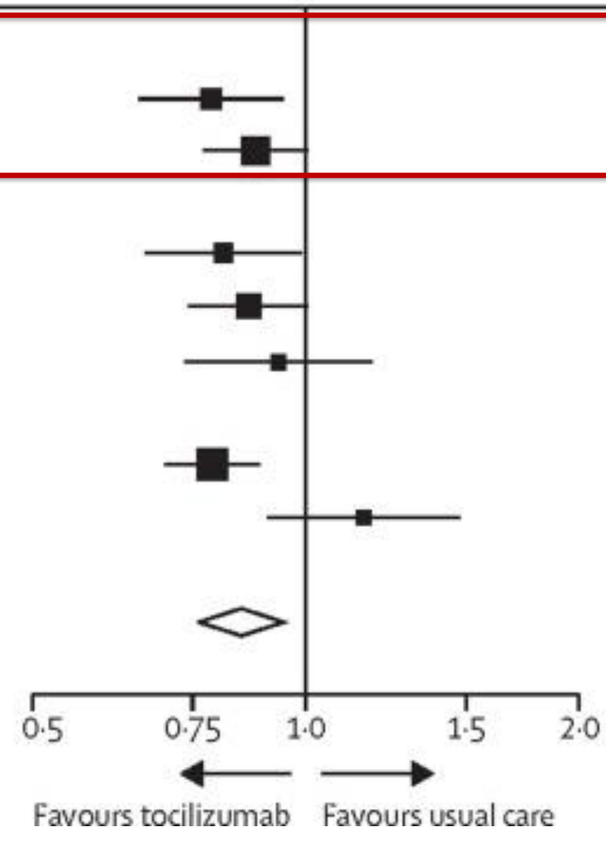
- Outcomes:
  - 28-day mortality: 15% decrease
  - 28-day discharge: 22% increase
  - Progression to inv ventilation: 21% decrease
  - Median days discharge: usual care >28 vs toci 19



RECOVERY Collaborative Group. Lancet 2021 DOI: https://doi.org/10.1016/S0140-6736(21)00676-0

RECOVERY - Tocilizumab

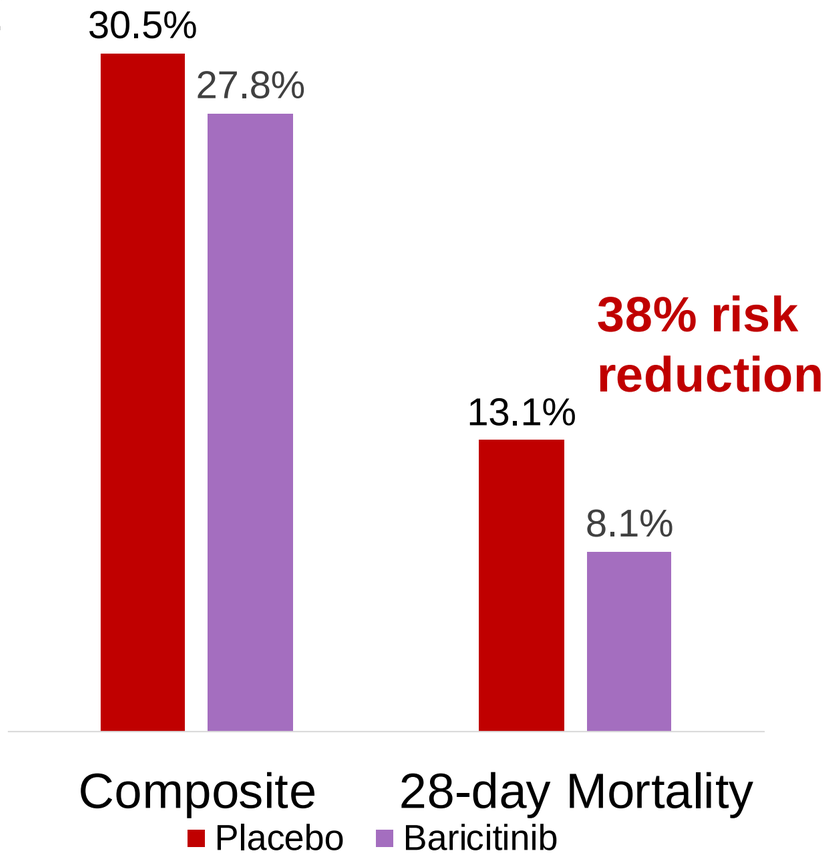
	Tocilizumab group	Usual care group	Risk ratio (95% CI)
Days since symptom onset (χ^2_1=1·1; p=0·30)			
≤7	214/668 (32%)	256/660 (39%)	0·78 (0·65–0·94)
>7	407/1354 (30%)	473/1433 (33%)	0·88 (0·77–1·01)
Respiratory support at randomisation (χ^2_1=0·8; p=0·38)			
No ventilator support*	180/935 (19%)	214/933 (23%)	0·81 (0·67–0·99)
Non-invasive ventilation†	310/819 (38%)	366/867 (42%)	0·86 (0·74–1·00)
Invasive mechanical ventilation‡	131/268 (49%)	149/294 (51%)	0·93 (0·74–1·18)
Use of corticosteroids§ (χ^2_1=7·7; p=0·01)			
Yes	482/1664 (29%)	600/1721 (35%)	0·79 (0·70–0·89)
No	139/357 (39%)	127/367 (35%)	1·16 (0·91–1·48)
Unknown	0/1 (0%)	2/6 (33%)	..
All participants	**621/2022 (31%)**	**729/2094 (35%)**	**0·85 (0·76–0·94)**
			p=0·0028



RECOVERY Collaborative Group. Lancet 2021 DOI: https://doi.org/10.1016/S0140-6736(21)00676-0

Baricitinib

- ACTT-2 trial: improved time to recovery when given with remdesivir in patients who require supplemental oxygen (exc MV), but this trial did not evaluate effect of baricitinib with corticosteroids.
- COV-Barrier trial: N = 1525 patients receiving standard of care (remdesivir in 19% and corticosteroids in 79.3%)
  - Primary endpoint: death or progression to HF oxygen, noninvasive ventilation, MV, or ECMO – not significant
  - Secondary endpoint: all-cause mortality – HR, .57 (95% CI, .41-.78)
    - Greatest improvement in mortality those on high-flow oxygen or noninvasive ventilation (17.5% for baricitinib vs. 29.4% for placebo; HR .52; 95% CI, .33-.80).



COVID19

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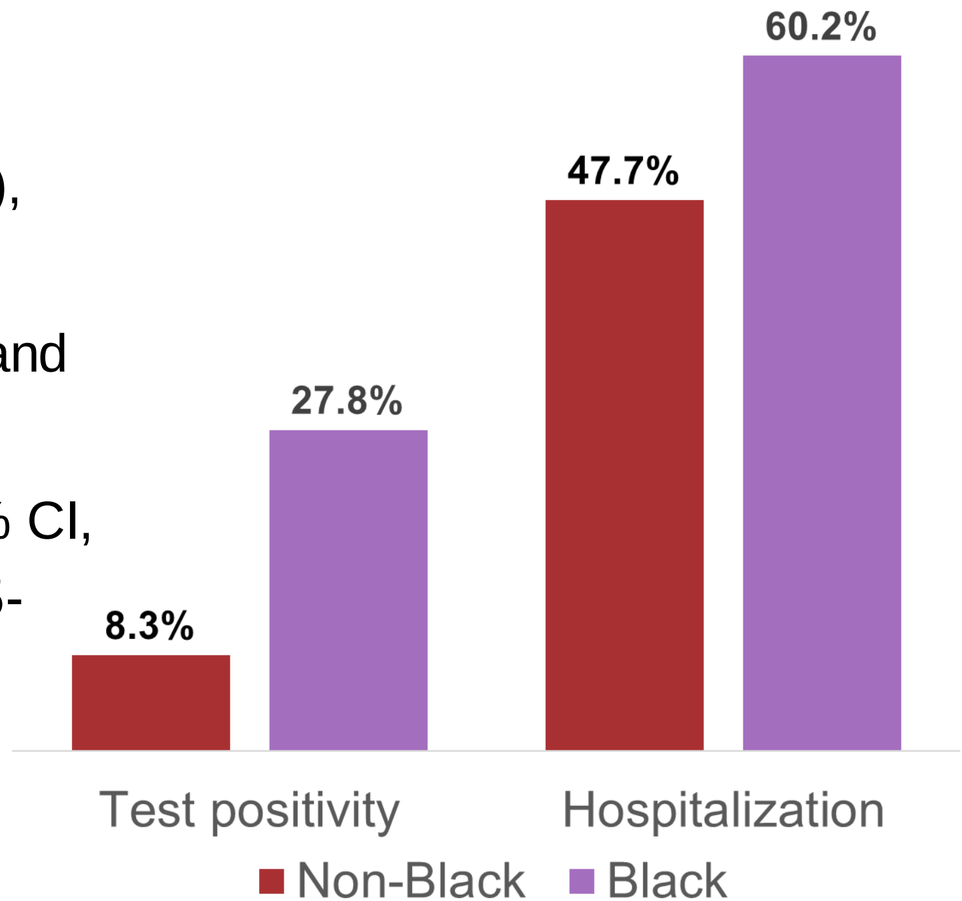
DISPARITIES PERSIST

COVID-19 – Devastating for Black and Latinx Communities

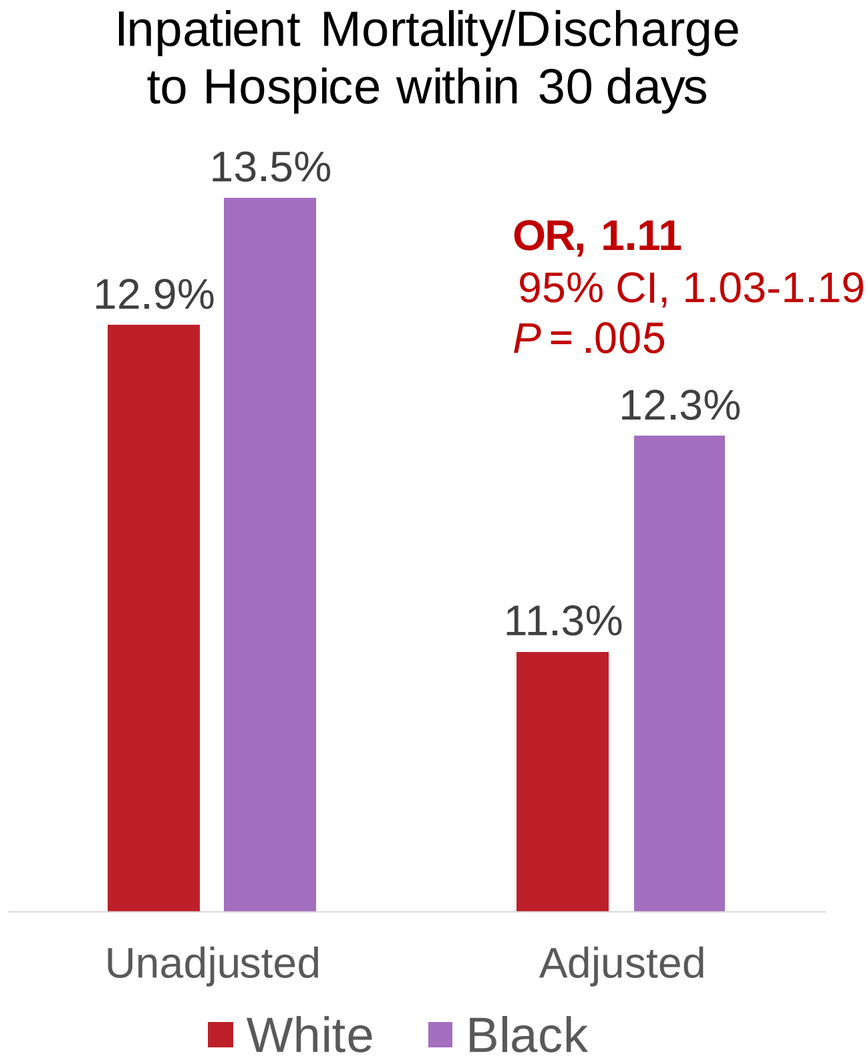
Milwaukee Academic Center, March 2020

- N = 2,595
  - ≥ 3 comorbidities: Black, 28.9%; non-Black, 22.4%
  - Poverty status: Black, 49.4%; non-Black, 18.1%
  - COVID positivity associated with Black race (OR, 5.37), male sex (OR, 1.55), age ≥ 60 yr (OR, 2.04;)
  - Hospitalization associated with Black race (OR, 1.85) and poverty (OR, 3.84)
  - ICU admission associated with poverty (OR, 3.58; 95% CI, 1.08-11.80) but not Black race (OR, 1.52; 95% CI, 0.75-3.07)
  - Neither race nor poverty associated with death or mechanical ventilation



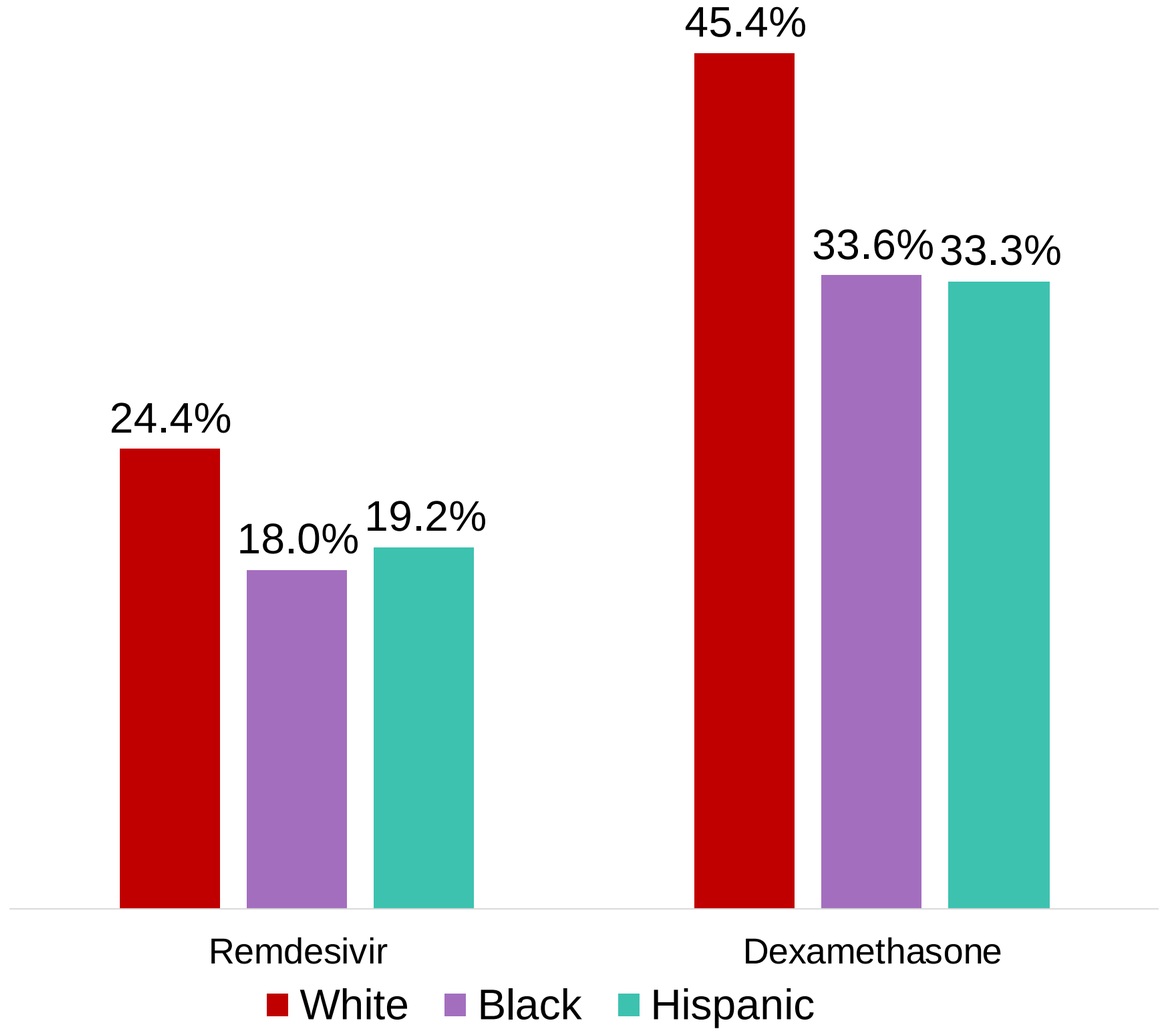
Patient & Hospital Factors Associated with Differences in Mortality Rate

- N >44,000 Medicare beneficiaries
  - 76% White, 24% Black; mean age 76.3
  - 1,188 hospitals in 41 states
- After adjusting for age, sex, comorbidities, income, and date of admission, Black patients had greater odds of death/hospice (OR, 1.11; 95% CI, 1.03-1.19; *P* = .005).
- Increased mortality for Black people associated with treating hospital
  - Racial segregation, worse finances/poorer resources in hospitals in disadvantaged areas, and varying referral patterns direct Black patients to one hospital over another
- *In simulation*, if Black patients went to same hospitals in same distribution as White patients, overall risk of mortality would have declined from 13.5% to 12.2%

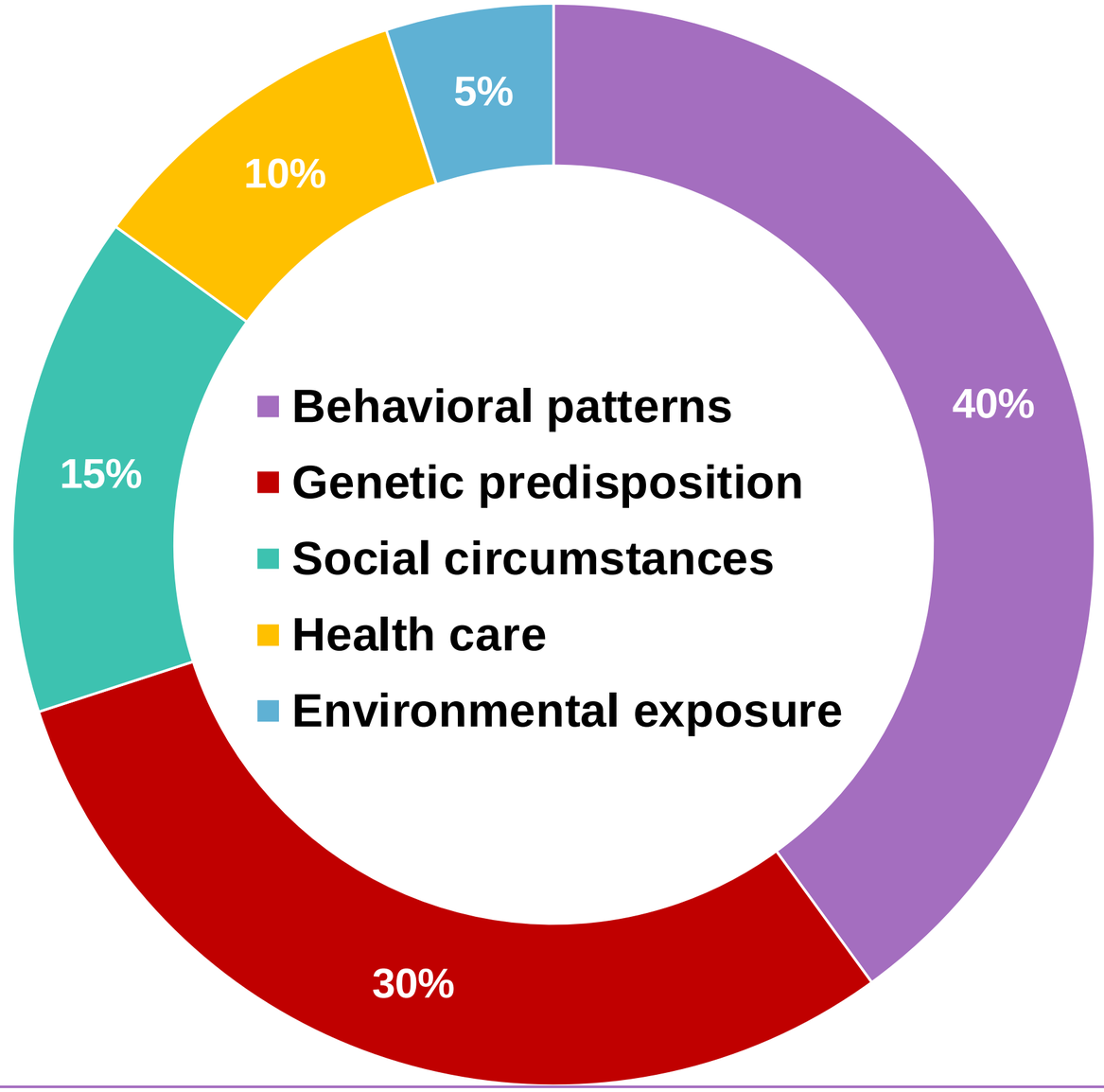


Varying “Standards of Care”

- Retrospective cohort study evaluating use of remdesivir and dexamethasone
  - 43 health systems in the US
  - ~139,000 adults with COVID-19
- Dexamethasone and remdesivir use varied across health centers
- Dexamethasone appears to be underused among people who are on mechanical ventilation
- Variation in patient case mix, drug access, treatment protocols, quality of care



Determinants of Health



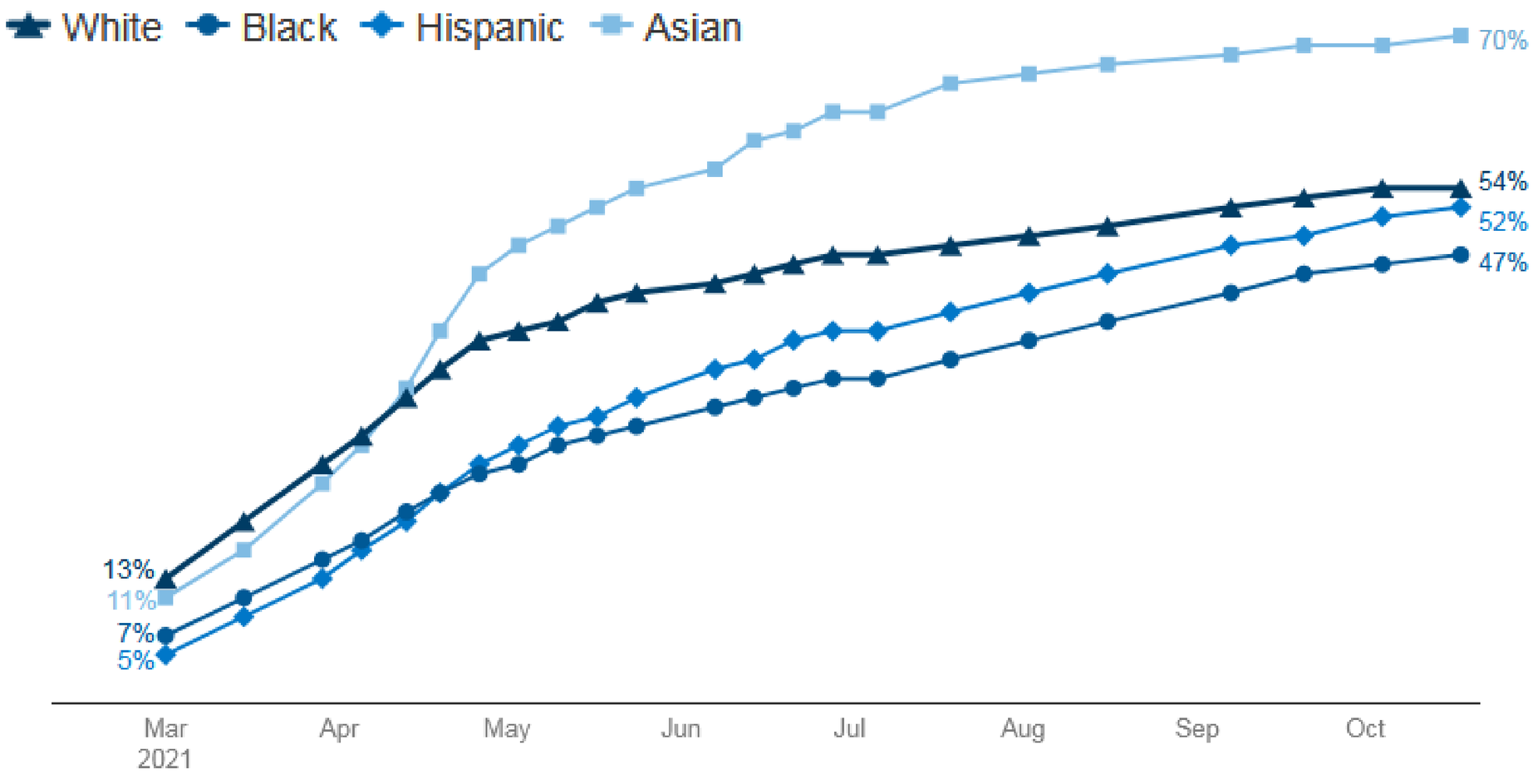
Social Determinants of Health

Economic Stability	Neighborhood & Physical Environment	Education	Food	Community & Social Context	Health Care System
Employment Income Expenses Debt Medical bills Support	Housing Transportation Safety Parks Playgrounds Walkability Zip code	Literacy Language Early childhood education Vocational training Higher education	Hunger Access to healthy options	Social integration Support systems Community engagement Discrimination Stress	Health coverage Provider availability Provider linguistic and cultural competency Quality of care

Health Outcomes

Mortality, Morbidity, Life expectancy, Health care expenditures, Health status, Functional limitations

Receipt of ≥1 Vaccine Dose by Race through 10/18/21



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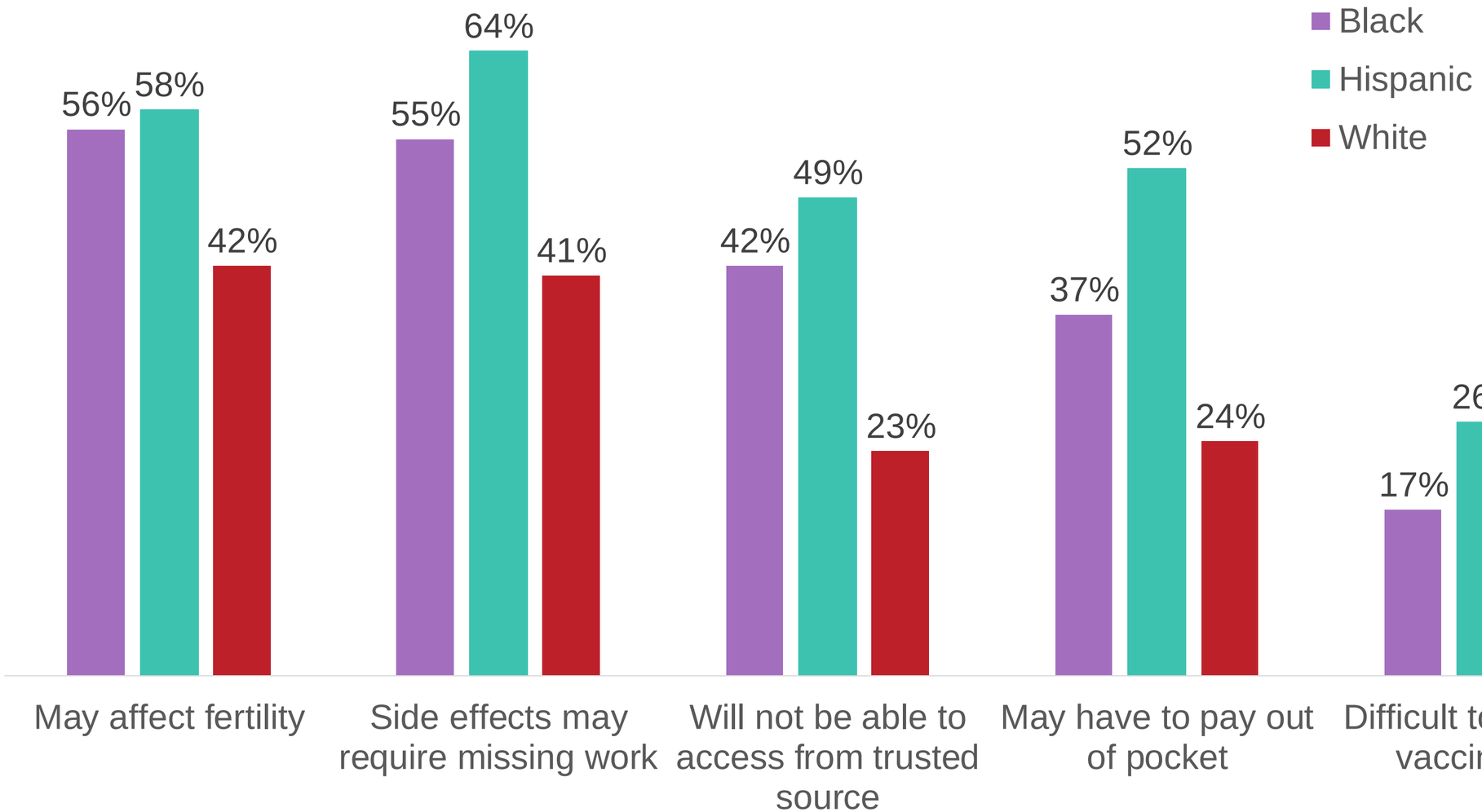
Concerns with COVID-19 Vaccine



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Vaccine Acceptance and Access Among Black and Latinx Communities

Focus groups with 72 Black and Latinx participants in New Haven, CT revealed three major themes

1. Pervasive mistreatment of Black and Latinx communities and associated distrust
   - *Historical and present-day mistreatment contribute to distrust* and acceptance of vaccine
2. Informing trust via trusted messengers and messages, choice, social support, and diversity
   - Want information from *trusted messengers* who are reliable sources to them
3. Addressing structural barriers to vaccination access
   - Many barriers impacted vaccine access, including *concerns of vaccine supply in Black/Brown communities* being impacted by White communities; sign-up process causing fatigue; insurance concerns

Balasuriya L et al JAMA Netw Open; 2021

Summary

- Being Black, American Indian/Alaska Native, or Latinx is associated with a higher risk of COVID-19 infection, hospitalization, and death
  - Unequal health risks are the result of different conditions where people live, work, learn, gather, and age (social determinants of health)
  - Structural barriers, beliefs, and other factors contribute to variations in vaccination
- Monoclonal antibodies are available for outpatients at high risk of severe disease or hospitalization. Molnupiravir, an oral antiviral that reduced hospitalization and death by ~ 50%, is currently under review
- NIH guidelines for hospitalized patients include remdesivir (antiviral) and immunosuppressants (dexamethasone, tocilizumab). Recommendations vary by level of disease severity and other factors