Disclosure

Opinions, interpretations and viewpoints presented here today are my own, are not endorsed by, and do not represent, those of my employers
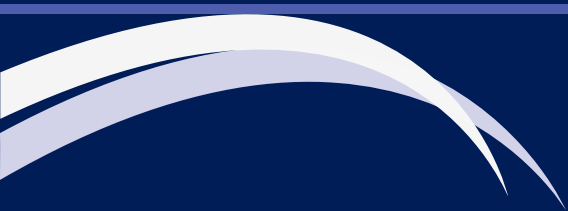
Outline

- Background: definitions, history and microbiology
- Epidemiology: US and worldwide
- Symptoms, comorbidities and treatments
- Antibody response and vaccine development
- Prevention
- Impact on other physical and mental health conditions
- Future directions

Background

- Definitions
  - SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
  - COVID-19: coronavirus disease 2019 - the illness caused by SARS-CoV-2
    - initially called "2019 novel coronavirus" and "2019-nCoV"

- History
  - First cases of unexplained severe pneumonia reported in late 2019
  - Likely originated in an animal host and then infected humans

- Microbiology
  - SARS-CoV-2 belongs to a family of viruses called Coronaviruses
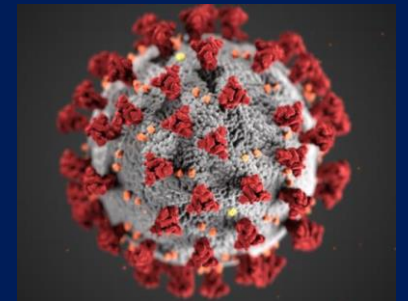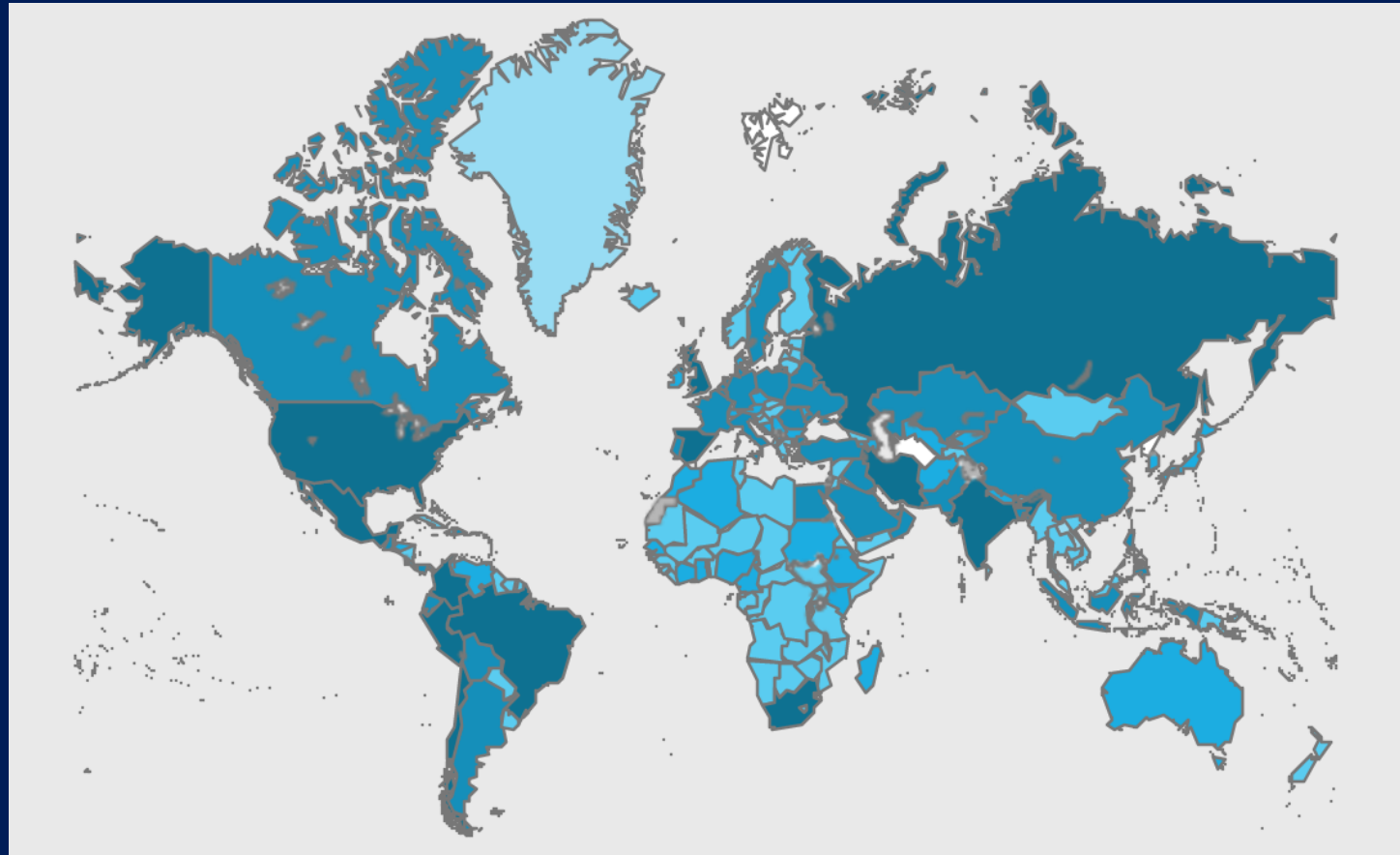 - Related to SARS-CoV and MERS-CoV

Image source: CDC Image Library, www.cdc.gov

Infectivity and Transmission

- SARS-CoV-2 is very contagious
  - R_0: current estimate by the CDC is 2.5
  - Doubling time estimates: 2.3 - 7 days
  - Goal $R_0 < 1$ for the pandemic to stop
- Asymptomatic and pre-symptomatic transmission
  - Period of greatest risk of transmission/infectivity now believed to be at least 2 and up to 5 days prior to the infected person showing any symptoms
  - Up to 50% of cases of COVID-19 are believed to stem from pre-symptomatic and asymptomatic transmission

https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html

Epidemiology

WHO Coronavirus Disease (Covid-19) Dashboard, https://covid19.who.int

Epidemiology

- The US has 4.23% of the world population, a quarter of all the COVID-19 cases and nearly a quarter of the deaths
- Cases as of 8/16/20:

	Infected	Deaths
Globally	21,260,750	761,018
USA	5,258,565 (25%)	167,201 (22%)

WHO Coronavirus Disease (Covid-19) Dashboard, https://covid19.who.int

Epidemiology

Top 10 causes of death in the US in 2017 (in thousands):

1. Heart disease: 647

2. Cancer: 599

3. Accidents: 170

4. Chronic lower respiratory diseases: 160

5. Stroke: 146

6. Alzheimer's disease: 121

7. Diabetes: 84

8. Influenza and pneumonia: 56

9. Kidney disease: 50

10. Suicide: 47

https://www.cdc.gov/nchs/fastats/deaths.htm

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Epidemiology

COVID-19 death rates by race and age

https://www.brookings.edu, June 16, 2020
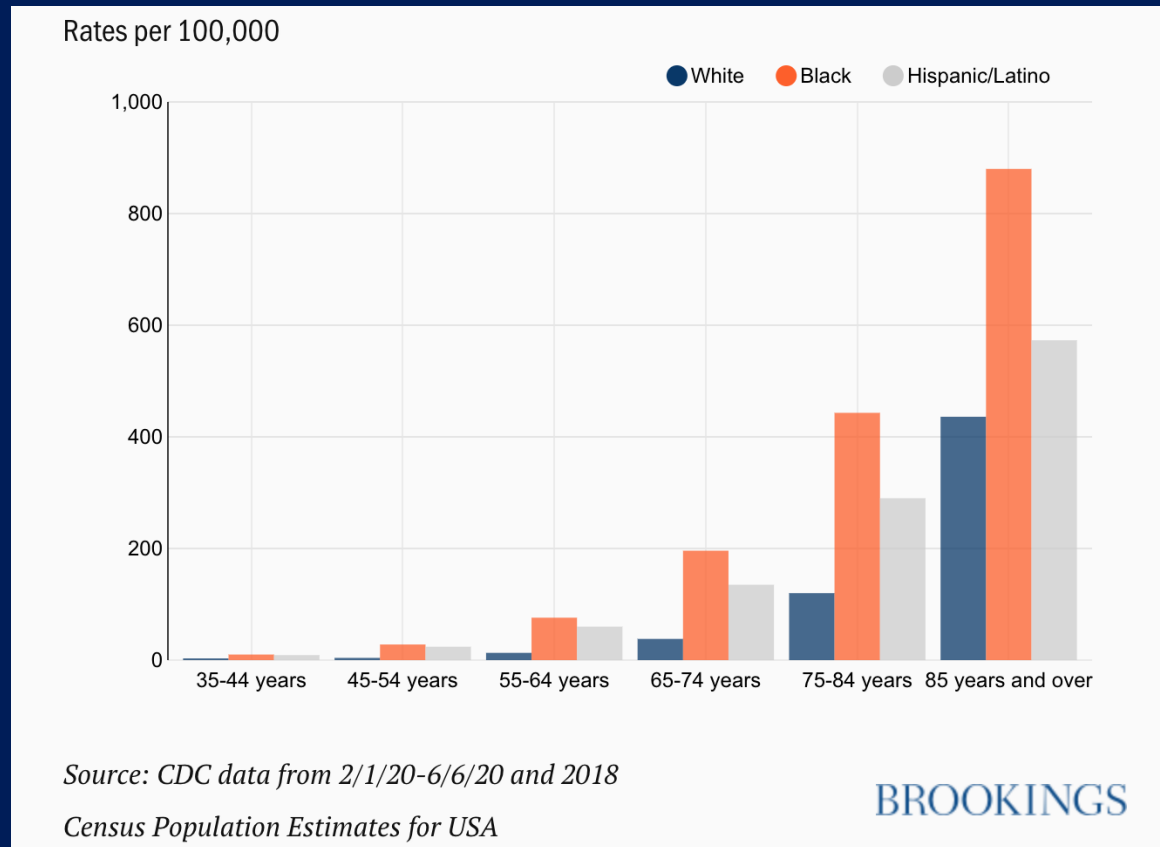
Symptoms and Signs of COVID-19

- Systemic:
  - Fever, chills, fatigue, loss of appetite, diffuse body aches and muscle aches
  - In severe cases: intense dysregulated inflammation (cytokine storm)

- Respiratory: cough, shortness of breath, difficulty breathing, low oxygen levels

- Gastrointestinal: nausea, vomiting, diarrhea, abdominal pain

- Cardiac: syncope (passing out), high blood pressure, myocarditis, heart failure

- Nervous system: headache, loss of sense of taste or smell, confusion, stroke

- Blood disorders: hypercoagulability (increased clotting)

Clinical Course

- Overall, majority of patients recover
  - Significant symptoms may linger for several weeks
- Older age and comorbidities increase the risk of severe disease and death
  - Heart disease
  - Chronic obstructive pulmonary disease (COPD)
  - Immunosuppression from organ transplant
  - Chronic kidney disease
  - Obesity
  - Cancer
  - Type 2 diabetes
  - Sickle cell disease
  - Many other conditions are potential risk factors: smoking, ?e-cigarettes/vaping

https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html

Clinical Course

- Children, on average, develop milder symptoms, but are not immune from COVID-19 or its complications
  - COVID-19 rates in kids are steadily increasing
  - Some have developed severe illness and required ICU admission
  - Post-COVID Multisystem Inflammatory Syndrome (MIS-C)
    - Can occur several weeks after acute infection
    - Symptoms can progress rapidly
  - Potentially harbor higher viral load vs adults while exhibiting fewer symptoms
    - Concerns over children playing a role in transmission
    - Ongoing discussions regarding safety of reopening schools

Clinical Course

- Unique challenges of COVID-19
  - Variable clinical course
  - Challenges in predicting who will develop severe disease even when accounting for risk factors and comorbidities
  - Question of insufficient vs over-exuberant immune response
    - Similar questions emerged during the 2009 H1N1 influenza pandemic, especially for younger and healthier patients with severe disease

Clinical Course

- Unique challenges of COVID-19
  - Rapid deterioration frequently > 1 week after onset of symptoms, including after a period of stability
  - Cardiac events frequently observed following improvement in respiratory failure
  - Prolonged critical illness with long-lasting morbidity in survivors
    - Sequelae of severe critical illness
    - Prolonged time on the ventilator
    - Long and unpredictable recovery

Treatment Overview

- Multiple clinical trials around the world working on finding effective therapies

- Specific therapies recently shown to confer benefit
  - Remdesivir
  - Dexamethasone
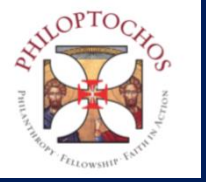
Treatment: Remdesivir

- Developed in 2009 for hepatitis C, then repurposed for other indications (including Ebola)

- Studied in Covid-19 started in early 2020 based on activity against SARS and MERS in animal models

- Earlier trial in China (Feb-March 2020) did not show benefit

Treatment: Remdesivir

- Most recent efficacy data comes from a randomized double-blind placebo-controlled trial
  - 1063 patients with Covid-19 and lower respiratory tract infection
  - Remdesivir shortened time to recovery (primary outcome)
  - Trend towards improved mortality but didn't reach statistical significance
  - Contraindicated in renal failure
    - commonly seen with Covid-19 precluding use
  - Major side effect is liver toxicity
    - some degree of liver injury commonly develops during the course of critical illness, including in patients with Covid-19

Beigel JH, Tomashek KM, Dodd LE et al., NEJM [published online ahead of print May 22, 2020]
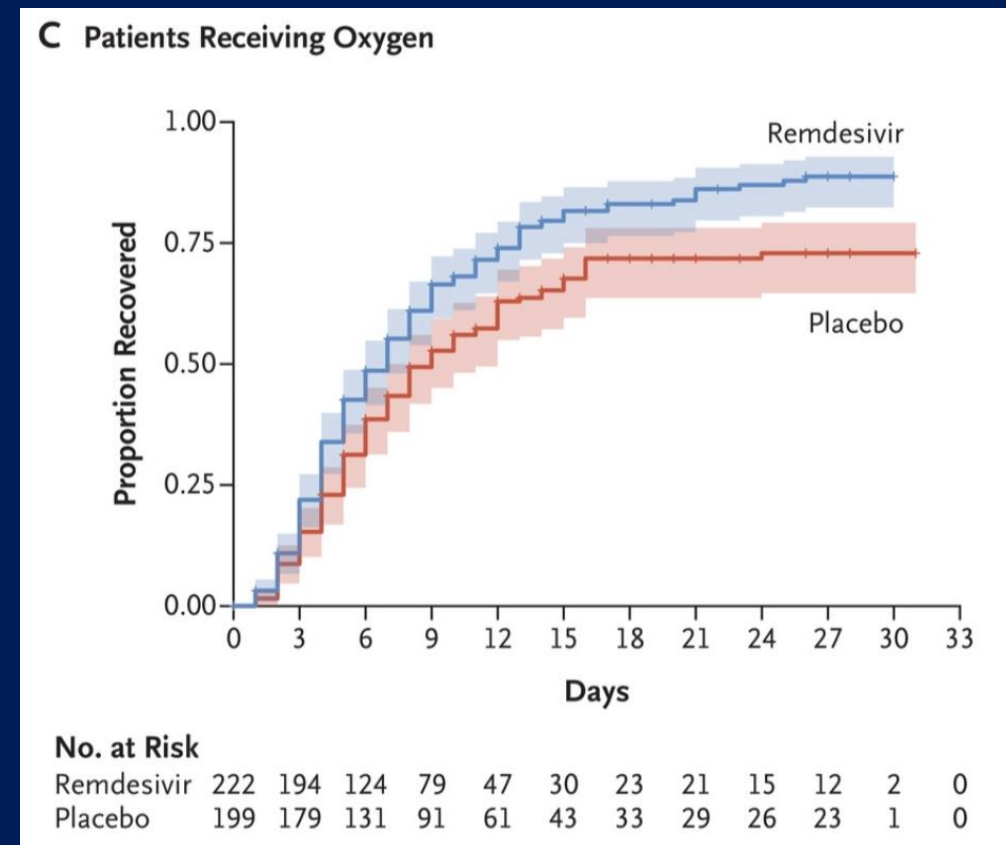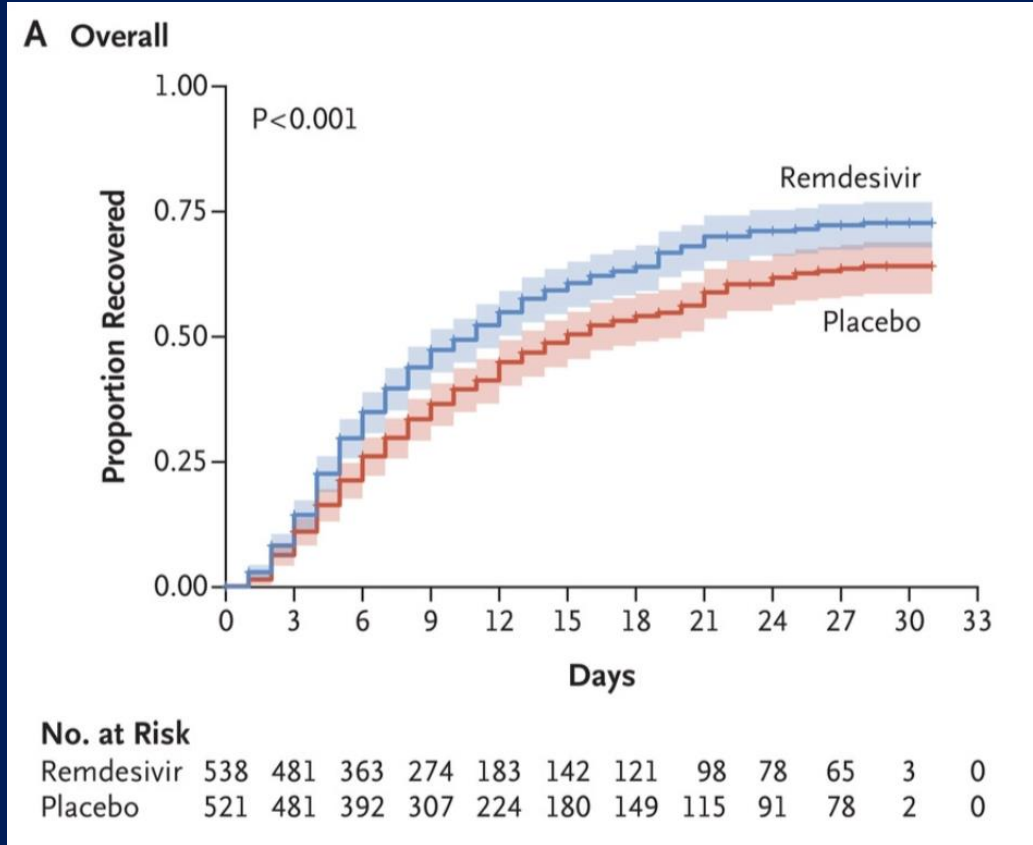
Treatment: Remdesivir

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

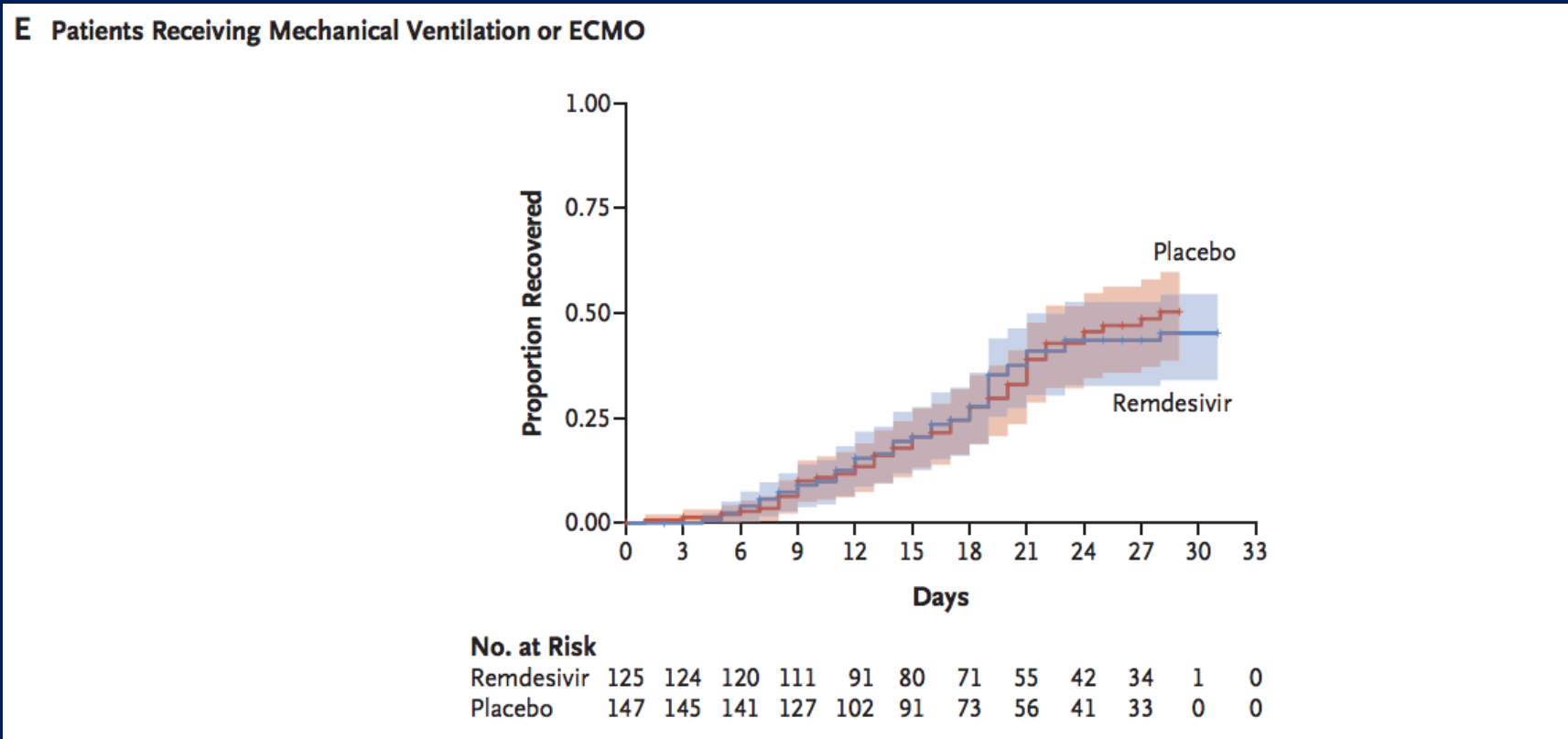Remdesivir for the Treatment of Covid-19
— Preliminary Report

Beigel JH, Tomashek KM, Dodd LE et al., NEJM [published online ahead of print May 22, 2020]

Treatment: Remdesivir

Beigel JH, Tomashek KM, Dodd LE et al., NEJM [published online ahead of print May 22, 2020]

Treatment: Remdesivir

E Patients Receiving Mechanical Ventilation or ECMO

Placebo

Remdesivir

No. at Risk
Remdesivir 125 124 120 111 91 80 71 55 42 34 1 0
Placebo   147 145 141 127 102 91 73 56 41 33 0 0

Beigel JH, Tomashek KM, Dodd LE et al., NEJM [published online ahead of print May 22, 2020]

Treatment: Dexamethasone

- Synthetic corticosteroid used in clinical practice for over 60 years
- Recent preliminary evidence of benefit from a randomized open-label trial
  - 2104 patients who were hospitalized with COVID-19 randomized to dexamethasone or usual care
  - Dexamethasone reduced mortality in patients requiring supplemental oxygen

Treatment: Dexamethasone

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

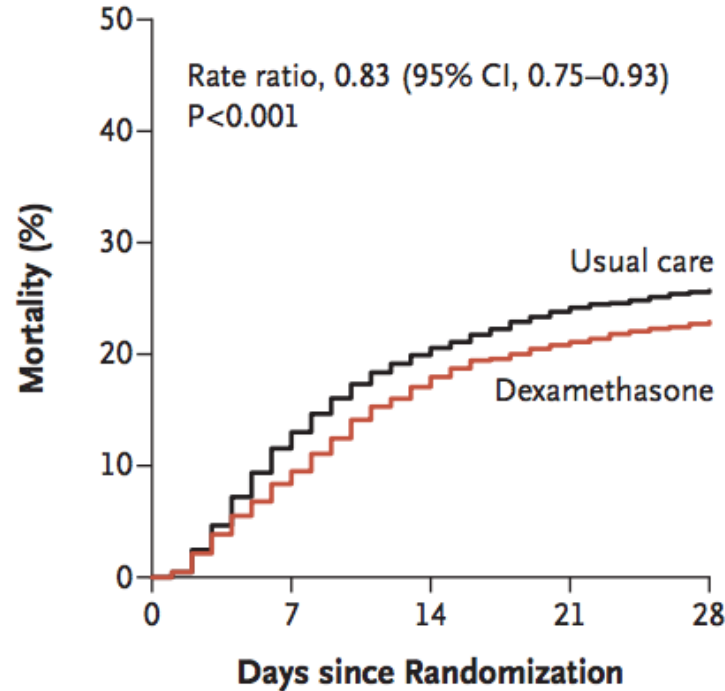Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

Treatment: Dexamethasone

Treatment: Dexamethasone

B Invasive Mechanical Ventilation (N=1007)

Rate ratio, 0.64 (95% CI, 0.51–0.81)

Usual care

Dexamethasone

Mortality (%) vs Days since Randomization
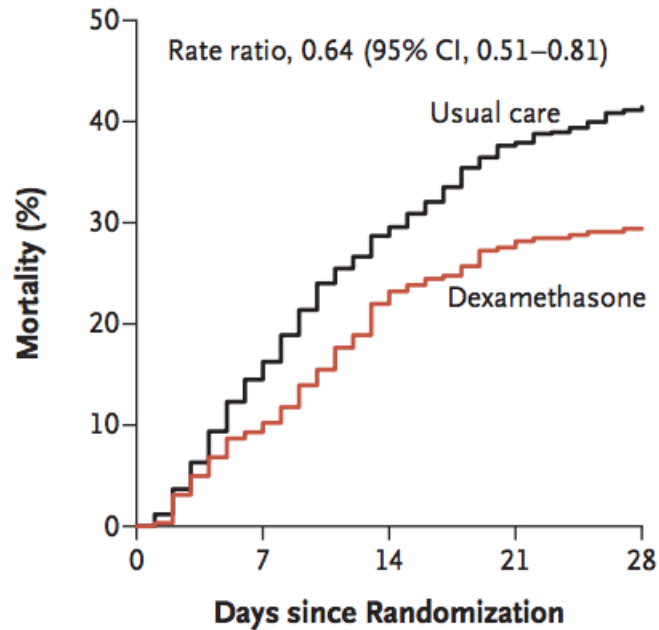
No. at Risk

Usual care	683	572	481	424	400
Dexamethasone	324	290	248	232	228

C Oxygen Only (N=3883)

Rate ratio, 0.82 (95% CI, 0.72–0.94)

Usual care

Dexamethasone

Mortality (%) vs Days since Randomization
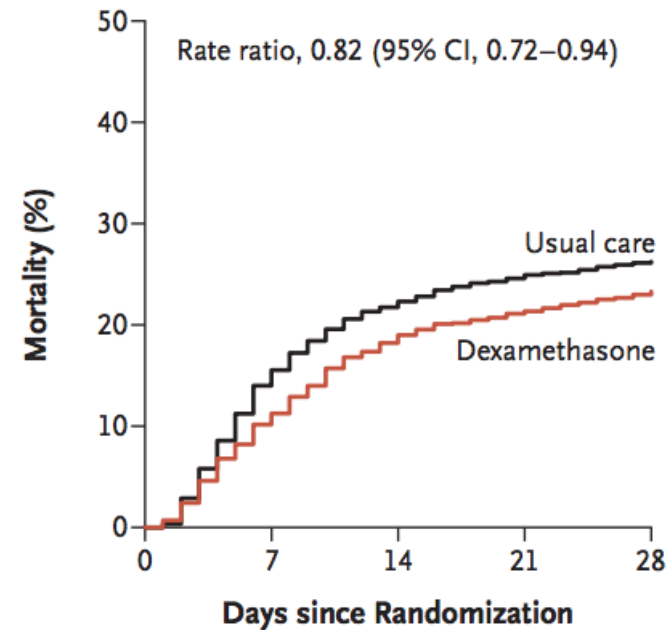
No. at Risk

Usual care	2604	2195	2018	1950	1916
Dexamethasone	1279	1135	1036	1006	981

Treatment: Dexamethasone

Treatment: Dexamethasone

Respiratory Support at Randomization	Dexamethasone	Usual Care	Rate Ratio (95% CI)	
	no. of events/total no. (%)			
Invasive mechanical ventilation	95/324 (29.3)	283/683 (41.4)		0.64 (0.51–0.81)
Oxygen only	298/1279 (23.3)	682/2604 (26.2)		0.82 (0.72–0.94)
No oxygen received	89/501 (17.8)	145/1034 (14.0)		1.19 (0.91–1.55)
All Patients	**482/2104 (22.9)**	**1110/4321 (25.7)**		**0.83 (0.75–0.93)**
				P<0.001

Chi-square trend across three categories: 11.5

0.50   0.75   1.00   1.50   2.00

Dexamethasone Better   Usual Care Better
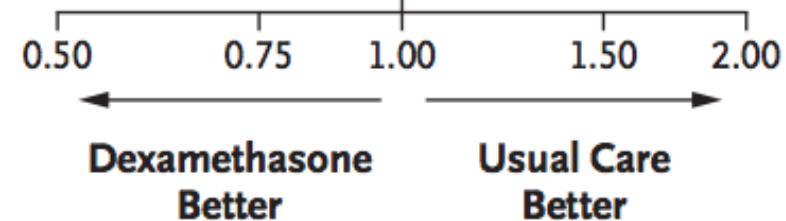
Immune Response

- Are antibodies protective against future infection?
    - Can someone who has had COVID-19 get it again?
    - How long does the potential protective effect of antibodies last?
    - What about herd immunity?
- Emerging role of memory T cells

Vaccine Development

- Vaccine development process usually takes several years
- Final stage of testing in humans (Phase 2/3 or Phase 3 clinical trials) started for 8 vaccines globally (3 developed in the US and Europe)
  - Most optimistic prognoses estimated end of 2020 or early 2021 for completion of testing and beginning of production
  - Vaccine doses will most likely be distributed sequentially and based on risk of exposure and developing severe disease

Prevention

- In the absence of curative treatments and an effective vaccine, preventative measures are key in slowing down viral spread and stopping the pandemic

- Effective prevention strategies:
  - Physical distance of at least 6 feet
  - Masks: correct and consistent use
 - Hand hygiene: hand washing, hand sanitizer use
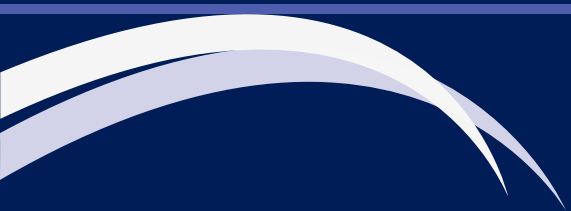
Prevention

Evidence supporting universal mask use

- Study evaluating transmissibility of influenza and seasonal coronavirus
  - Surgical face masks significantly reduced detection of influenza virus in respiratory droplets and coronavirus in aerosols[1]
- Case series from Beijing
  - Consistent mask wearing by household contacts of patients with Covid-19 decreased the odds of transmission by 79%, most effective when worn all the time vs after the patient developed symptoms[2]

[1] Leung N et al. Nature Medicine; 26 (May 2020)
[2] Wang Y et al. BMJ Global Health 2020;5:e002794

Prevention
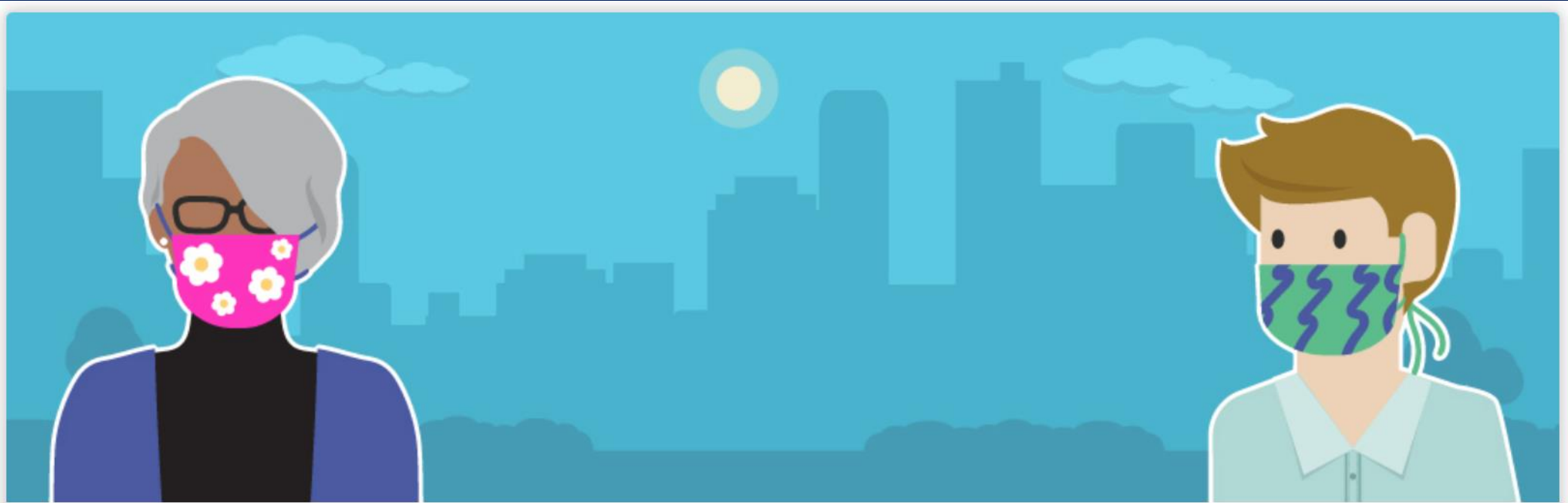
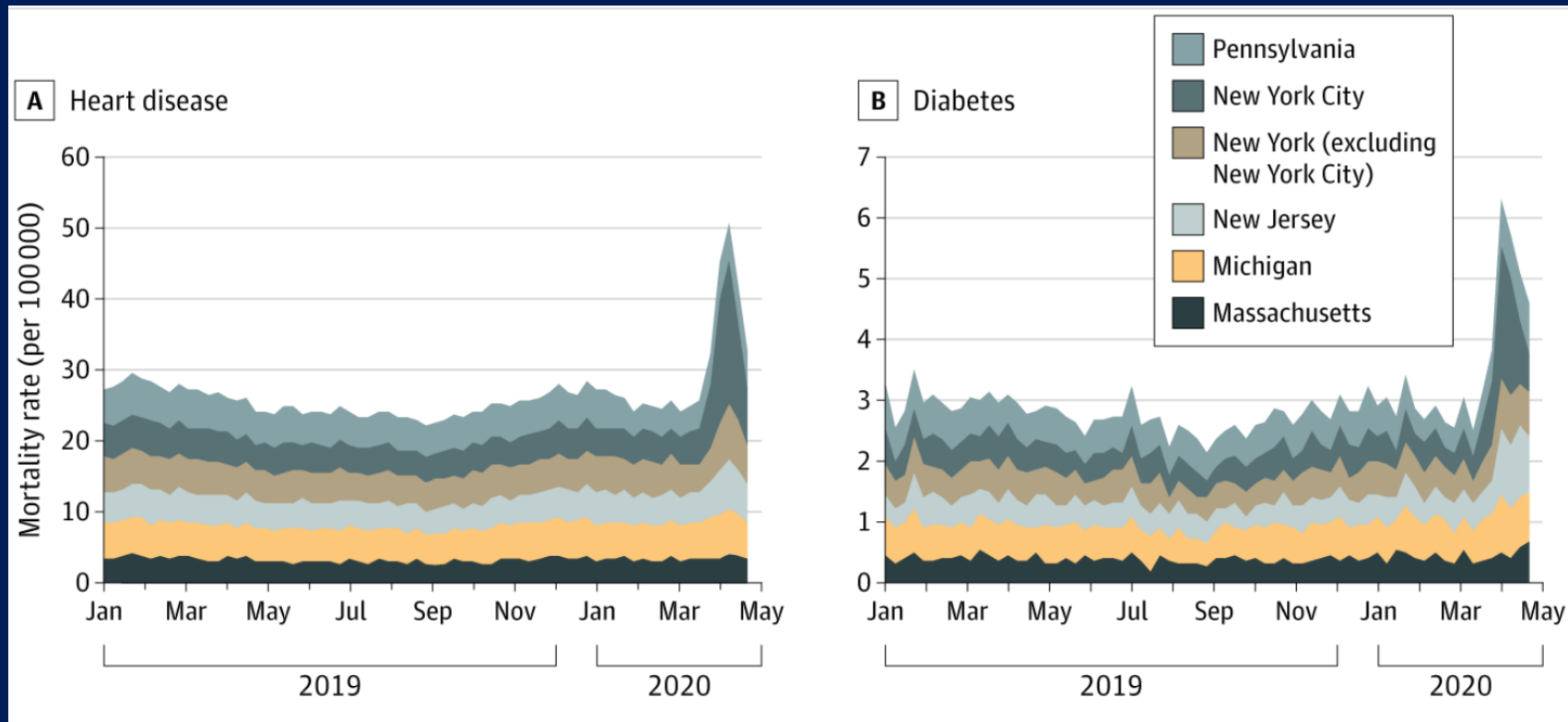Your mask may protect them. Their mask may protect you.

Prevention

Impact on Other Health Conditions

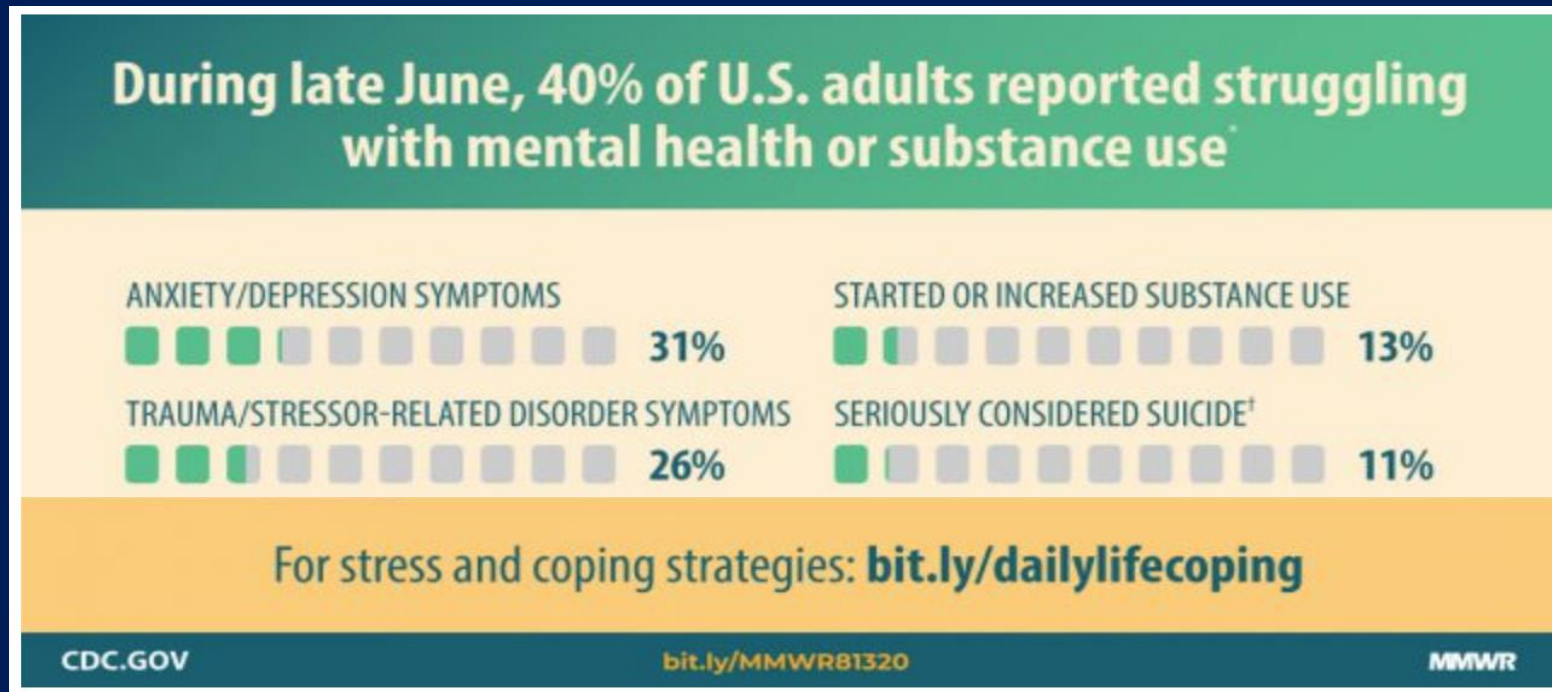Over 30,000 excess non-COVID deaths reported in March and April

Woolfe S et al., Excess Deaths from COVID-19 and Other Causes, March-April 2020, JAMA. 2020;324(5):510-513

Impact on Mental Health

Survey of US adults age 18 and over during last week of June regarding symptoms in the preceding 30 days

Czeisler MÉ et al. MMWR Morb Mortal Wkly Rep 2020;69:1049–1057
https://www.cdc.gov/mmwr/volumes/69/wr/mm6932a1.htm

Impact on Mental Health

- Difficulties in accessing mental health and addiction treatment services

- Stressors induced or exacerbated by the pandemic
  - Social isolation
  - Job and housing loss or insecurity
  - Anxiety and fear of contagion

- Rise in opioid-related overdoses during the COVID-19 pandemic
  - More than 40 states have reported increases in opioid-related mortality*

*https://www.ama-assn.org/system/files/2020-08/issue-brief-increases-in-opioid-related-overdose.pdf

Conclusions

- We know more today than we did in 2019
  - Improved infection control measures
  - Promising treatment options
  - Accelerated vaccine development

- Many questions remain
  - Evolving clinical presentations and lingering effects on survivors
  - Enormous physical and mental health toll of the disease and the pandemic
  - Challenges with epidemiological modeling and separating the "waves"
  - Concerns for the fall and winter season

- **Everyone can play an active role in helping to control the pandemic**

Questions