

Today's Agenda

Time (MT)	Presentation	Presenter(s)
Noon – 12:05 pm	Welcome, Announcements, Introductions	Lachelle Smith, Director, ECHO Idaho
12:05 – 12:10 pm	Idaho Epidemiology Curves and Public Health Updates	Carolyn Buxton Bridges, MD, FACP
12:10 – 12:30 pm	Treatment Updates and Case Management	Cathy Oliphant, PharmD
12:30 – 1 pm	COVID-19 Patient Case Discussion	ECHO Community of Practice

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University of Idaho
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Idaho Epidemiology Curves and Public Health Updates

Carolyn Buxton Bridges, MD, FACP

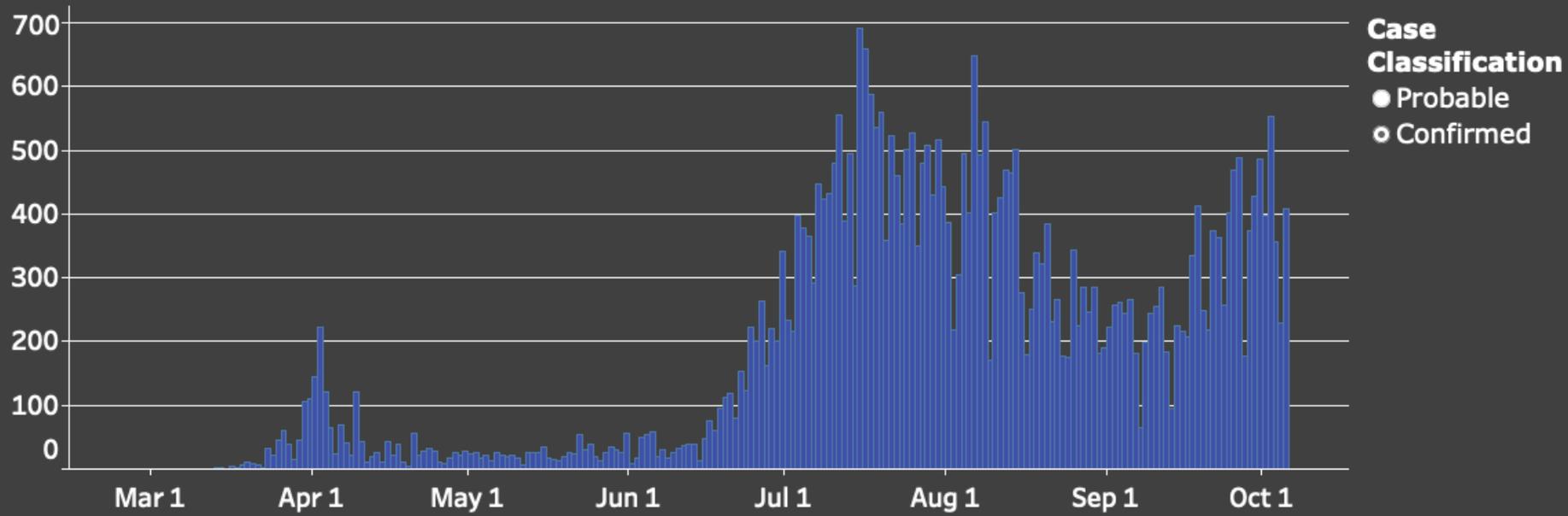
Governor's Coronavirus Working Group, Former CDC Public Health Physician and Researcher

Case Counts and SARS-CoV-2 PCR Testing in Idaho

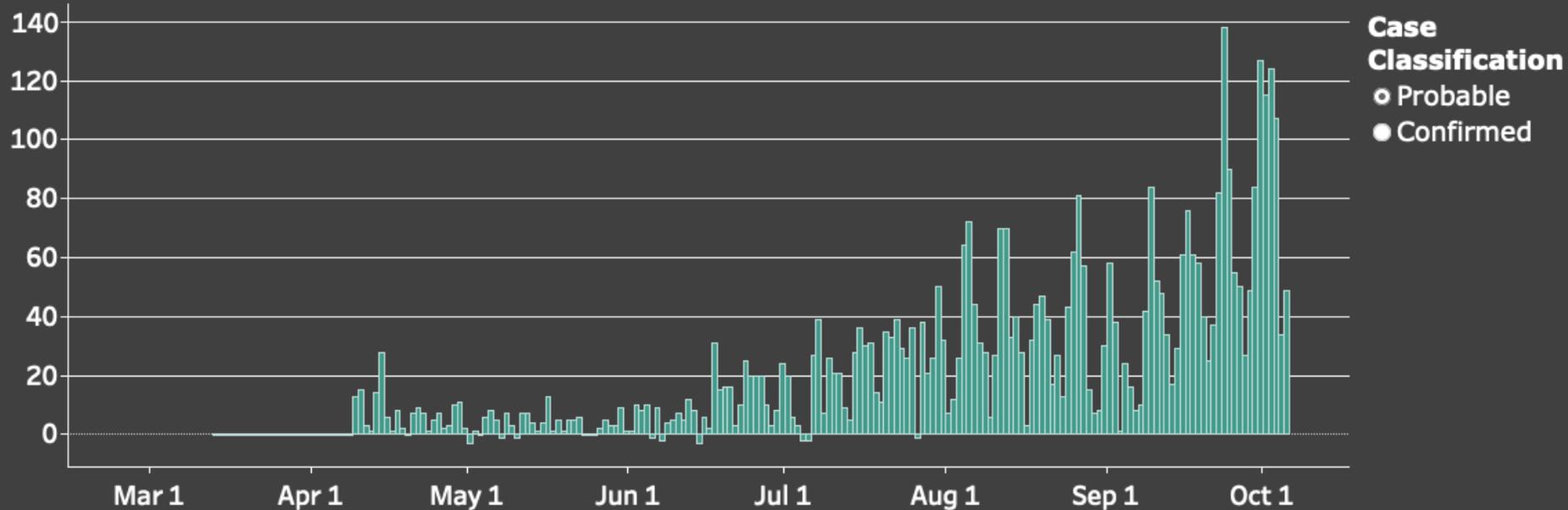
	5/19/2020	6/15/2020	7/13/2020	8/17/2020	9/13/2020	10/5/2020
Total lab-confirmed and probable	2,455	3,462 ($\Delta 556$)	11,402 ($\Delta 7,940$)	27,942 ($\Delta 16,540$)	35,532 ($\Delta 7,590$)	44,422 ($\Delta 8,890$)
Deaths	74 CFR =3.0	88 CFR =2.5	102 ($\Delta 14$) CFR =0.18	273 ($\Delta 171$) CFR=1.0	419 ($\Delta 146$) CFR=1.9	487 ($\Delta 68$) CFR=0.8
Hospitalizations	213	270	500 ($\Delta 230$)	1,129 ($\Delta 629$)	1,612 ($\Delta 483$)	1,911 ($\Delta 299$)
ICU admissions	89	100	144 ($\Delta 44$)	316 ($\Delta 172$)	424 ($\Delta 108$)	466 ($\Delta 42$)
Healthcare personnel	295	366 ($\Delta 57$)	760 ($\Delta 394$)	1,660 ($\Delta 900$)	2,404 ($\Delta 744$)	2,945 ($\Delta 541$)
Total tests	37,847	65,306 ($\Delta 17,436$)	129,540 ($\Delta 64,234$)	225,018 ($\Delta 95,478$)	277,368 ($\Delta 52,350$)	319,945 ($\Delta 42,577$)

<https://coronavirus.idaho.gov>

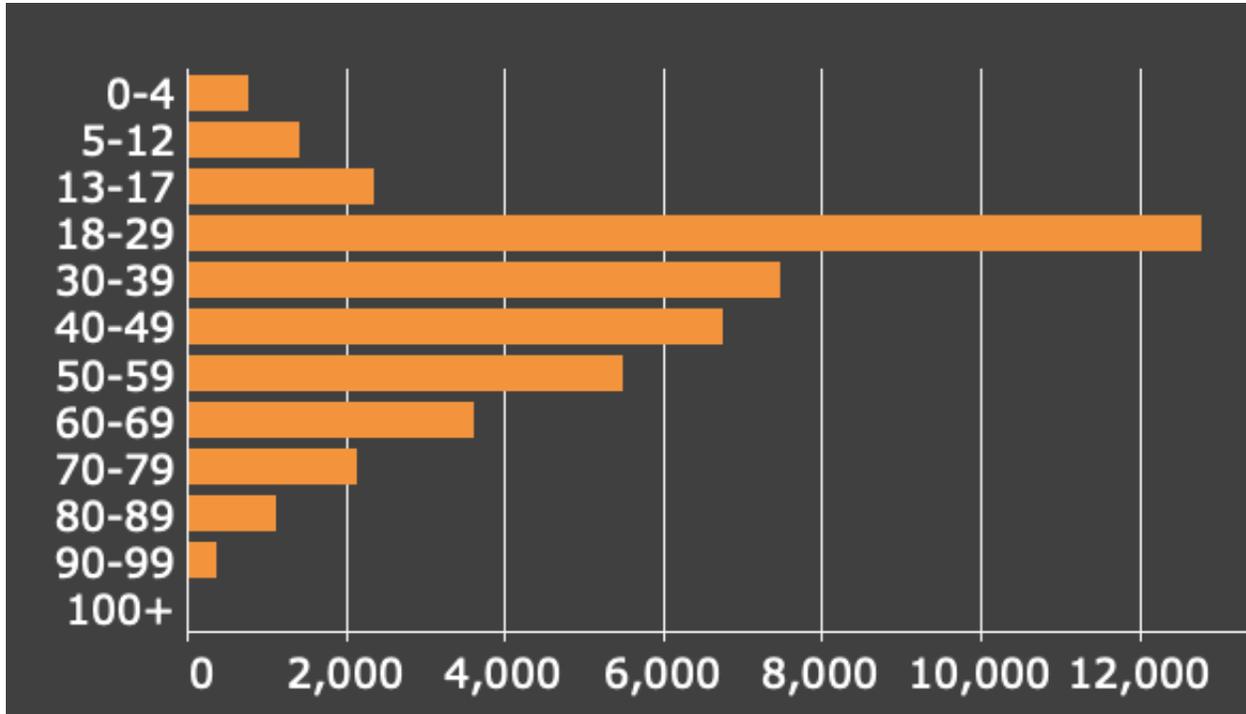
Daily Cases (by Date of Official State Notification)



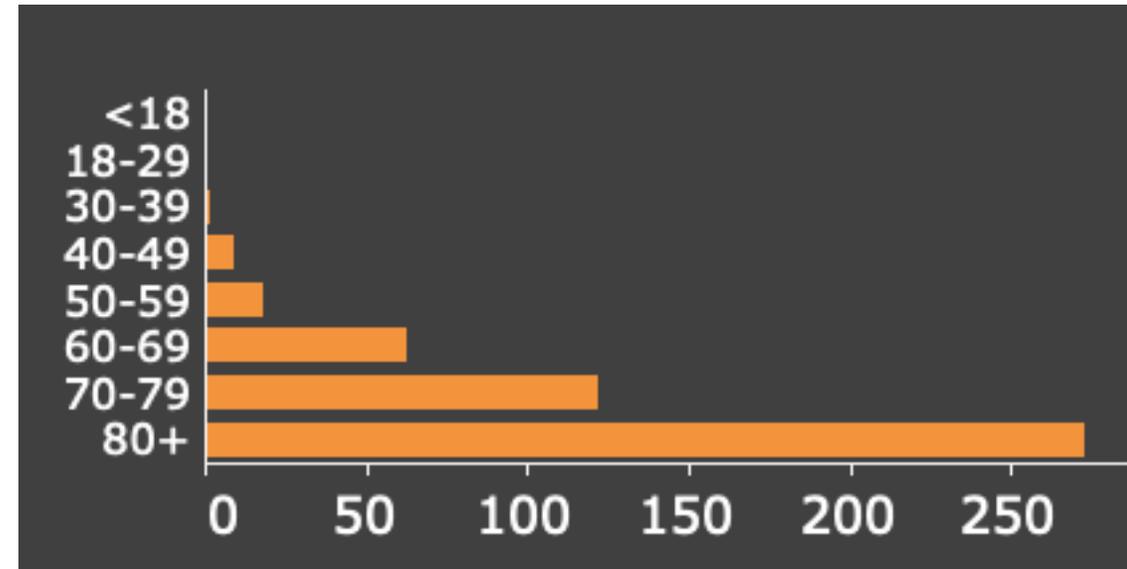
Daily Cases (by Date of Official State Notification)



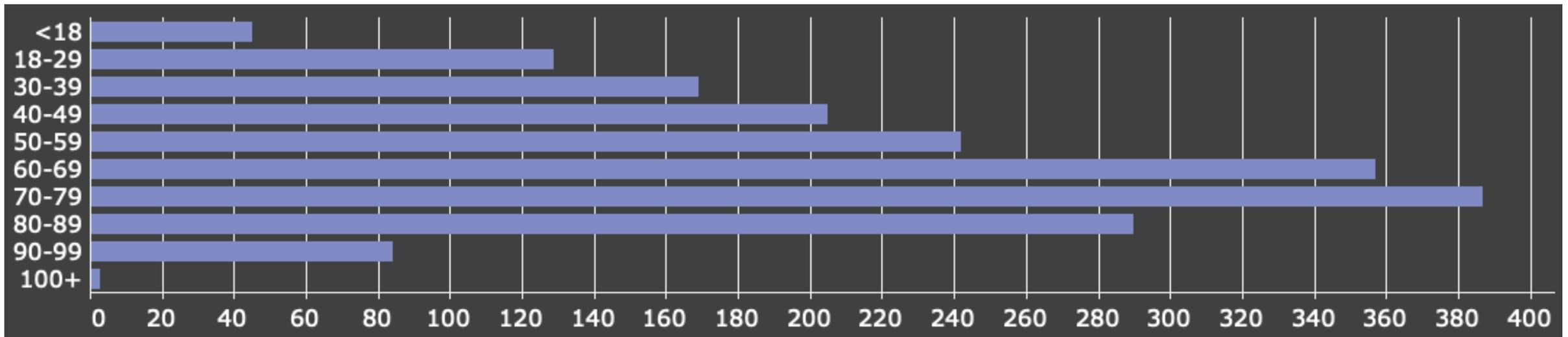
Cases



Deaths

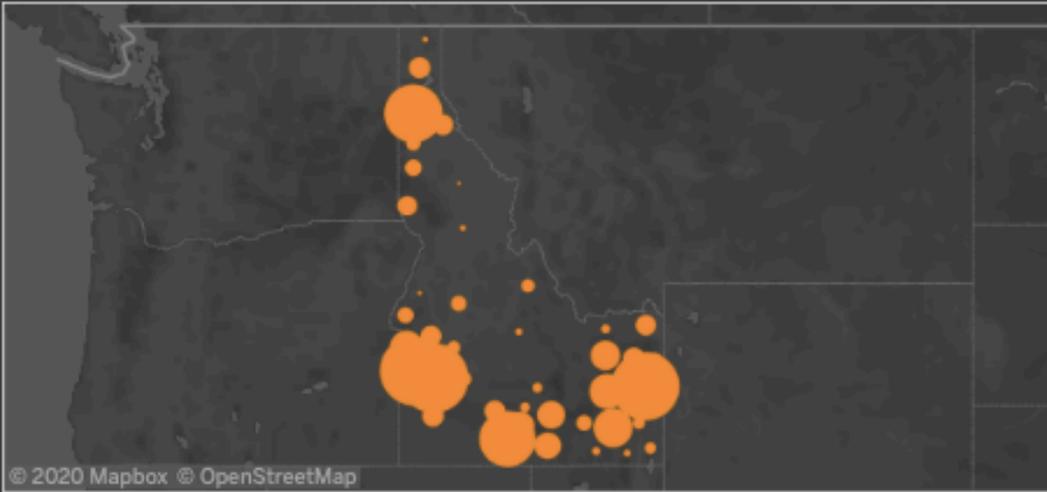


Hospitalizations

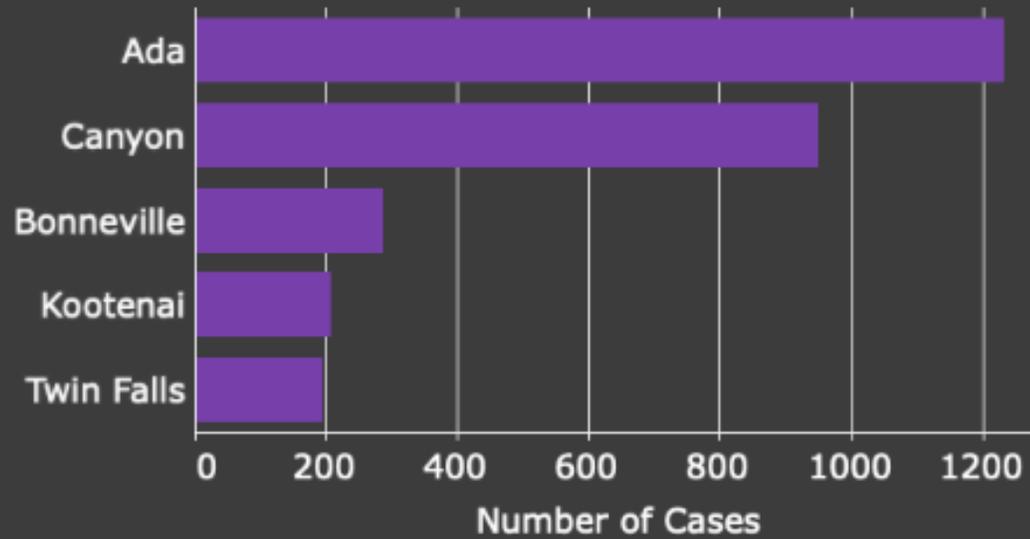


Use the slider to select week

8/8/2020

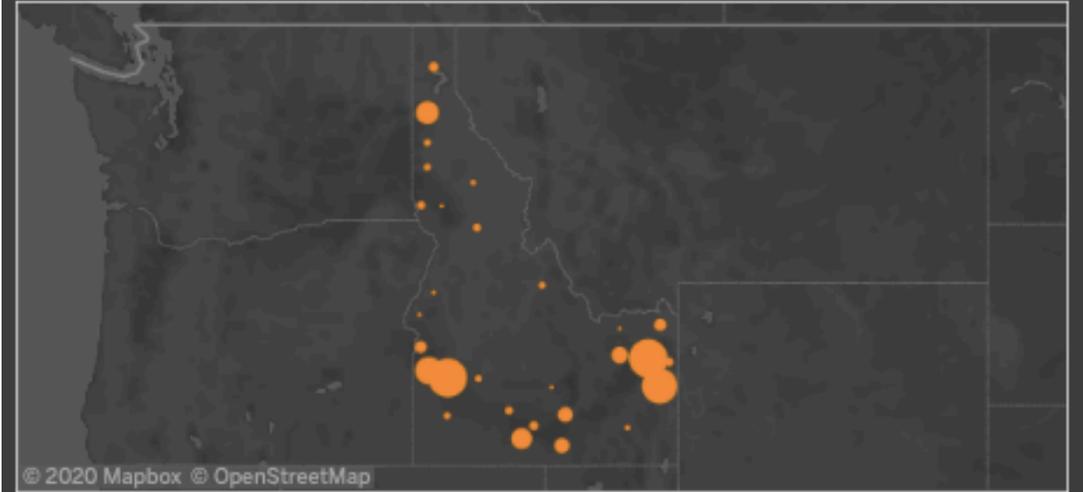


Counties With the Highest Number of Cases for Week Selected

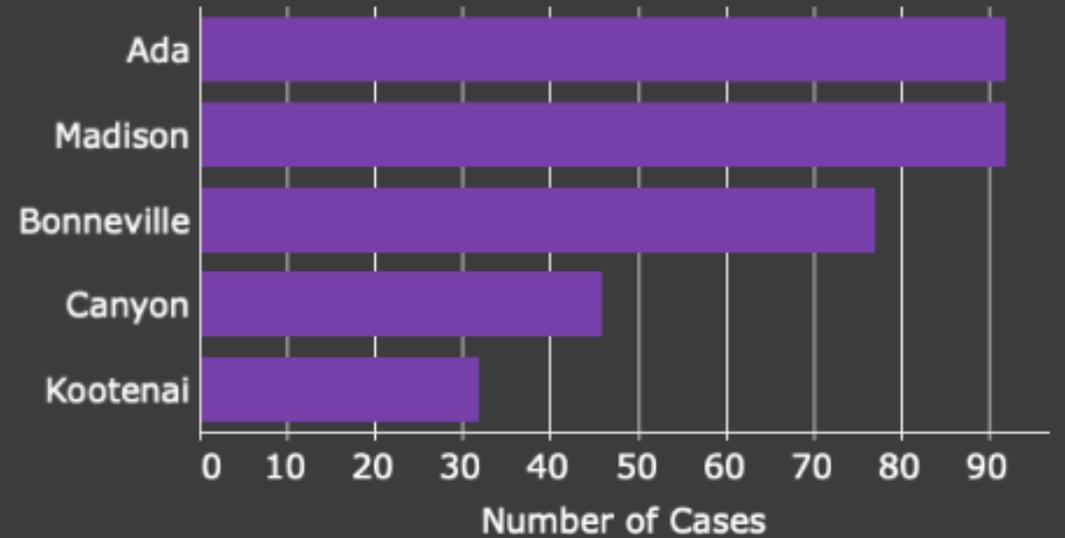


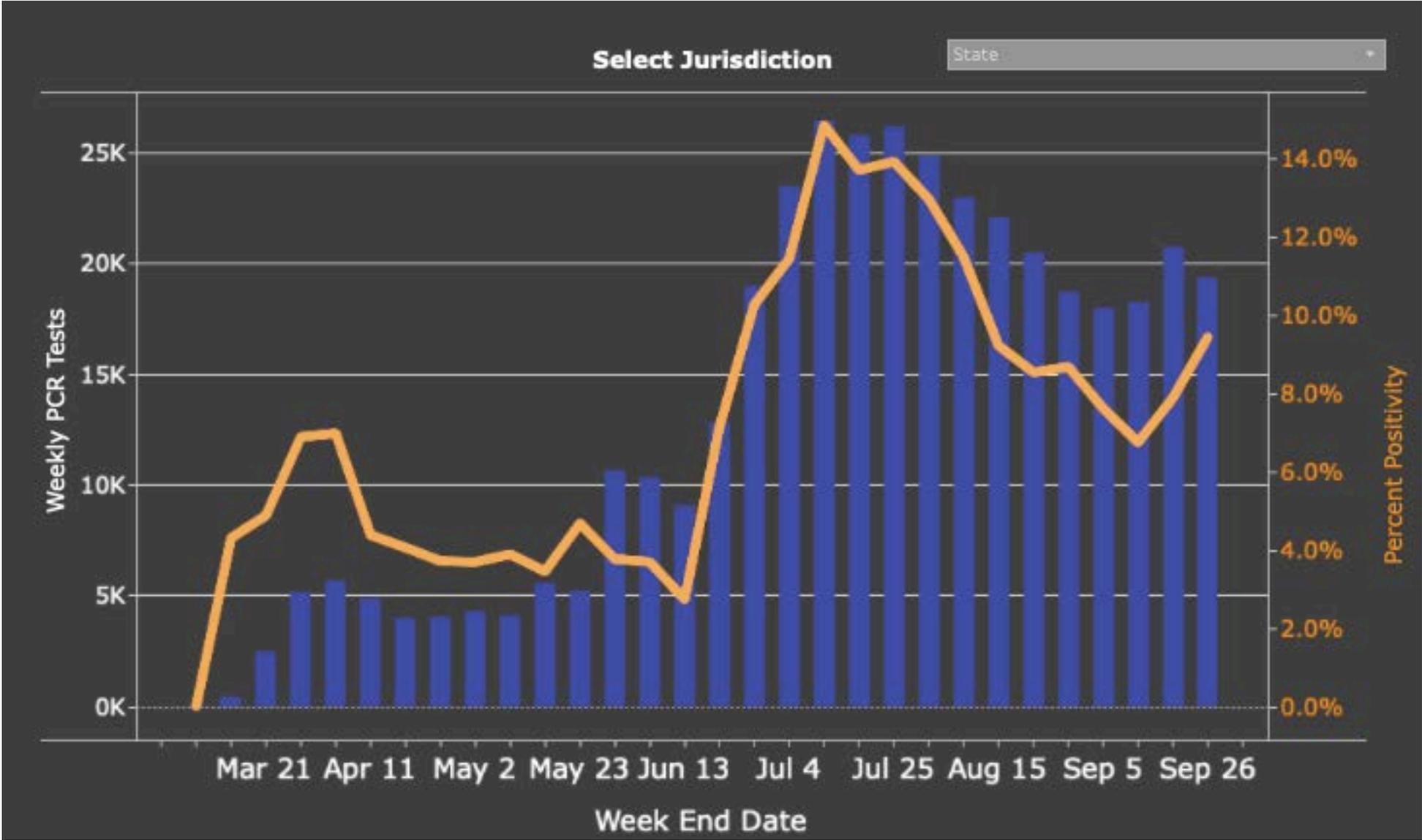
Use the slider to select week

10/10/2020



Counties With the Highest Number of Cases for Week Selected





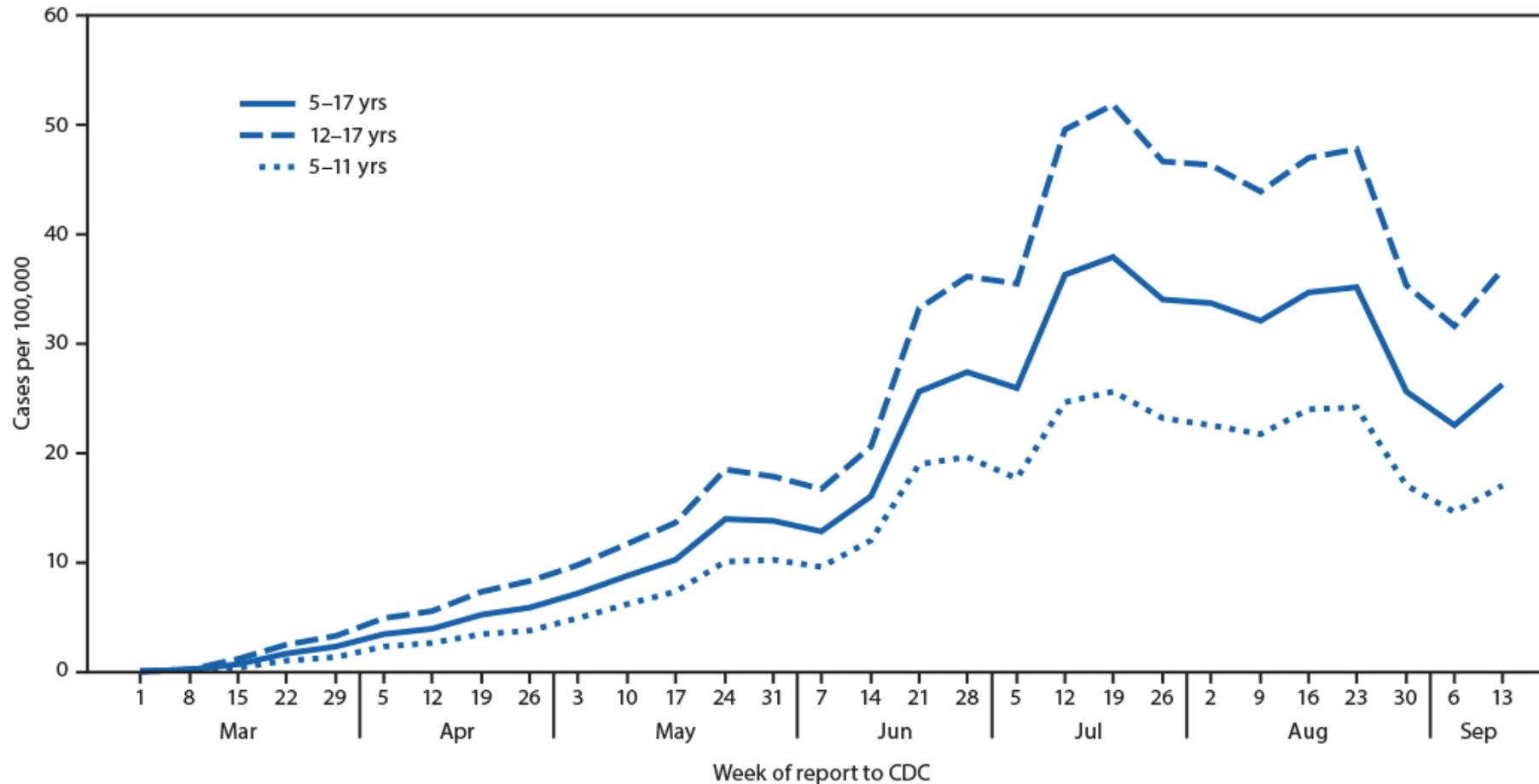
Relative impact in 0-17 year olds thus far

Date:	8/10/20 & before	8/17/20 & after
Cases:	2,263/25,100=9.0%	4,566/19,322=23.6%
Hosp:	29/1006=2.9%	16/905=1.8%
Deaths:	0	0

Total 3 children hospitalized with multisystem inflammatory syndrome

COVID-19 Trends Among School-Aged Children — United States, March 1–September 19, 2020, MMWR 2020

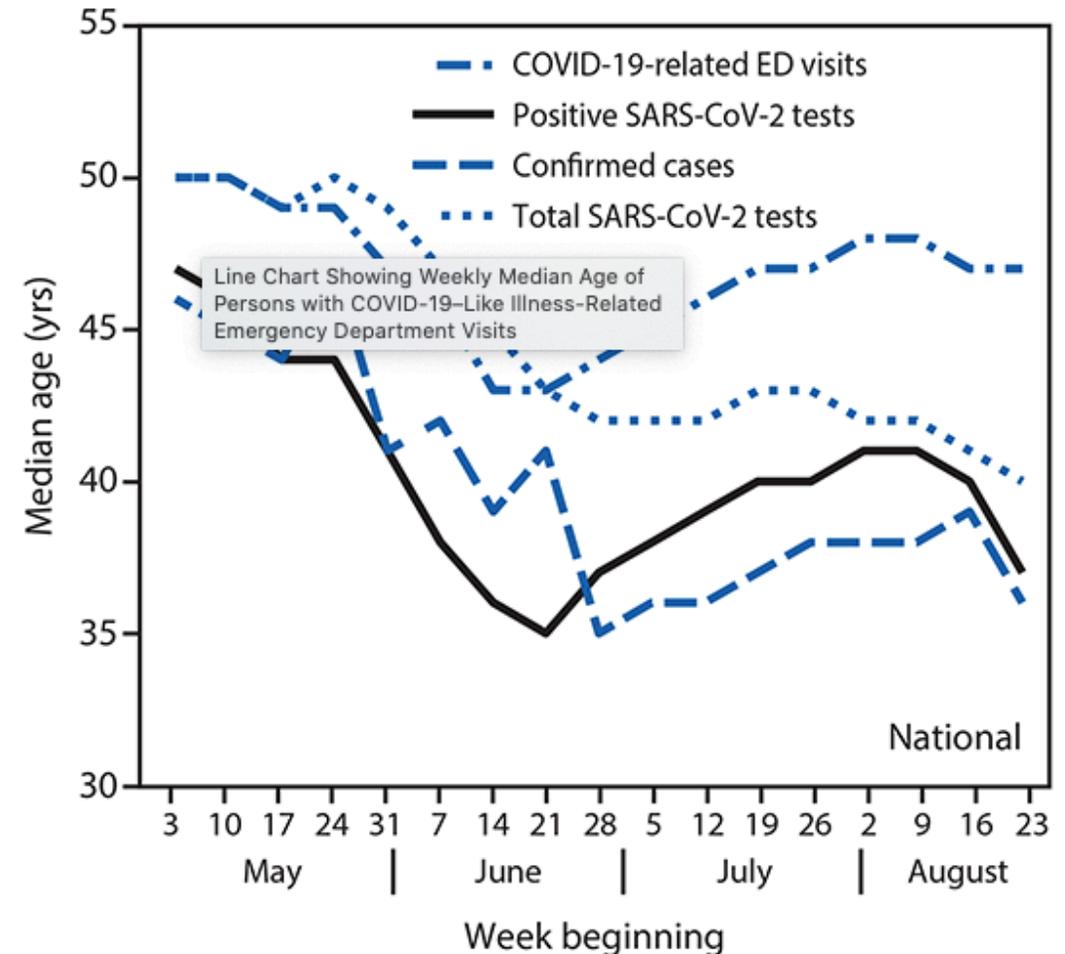
FIGURE 1. COVID-19 incidence* among school-aged children aged 5–11 years (N = 101,503) and 12–17 years (N = 175,782), by week — United States, March 1–September 19, 2020†



Changing Age Distribution of the COVID-19 Pandemic — United States, May–August 2020

Weekly / October 2, 2020 / 69(39);1404–1409

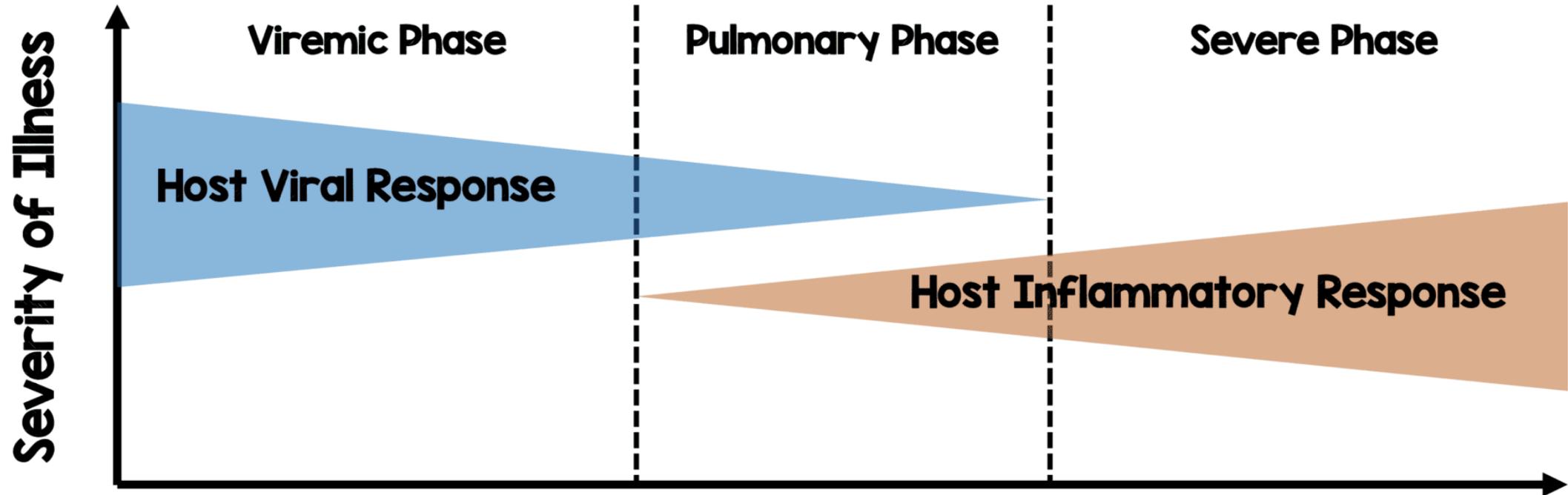
FIGURE 1. Weekly median age of persons with COVID-19–like illness-related emergency department (ED) visits,* positive SARS-CoV-2 reverse transcription–polymerase chain reaction (RT-PCR) test results,[†] and confirmed COVID-19 cases,[§] and of persons for whom all SARS-CoV-2 RT-PCR tests were conducted[¶] — United States, May 3–August 29, 2020



Treatment Updates and case Management

Cathy Oliphant, PharmD

Infectious Disease, Professor and Interim Chair, ISU College of Pharmacy



Time Course

Antivirals

Antivirals, Corticosteroids, Anticoagulation, Convalescent Plasma

Corticosteroids, Anticoagulation, IL-6 Inhibitors, JAK Inhibitors

Reduce duration of symptoms, minimize contagiousness, & potentially reduce progression of disease

Anti-inflammatory therapy

Anti-inflammatory and immunomodulatory therapy

Infection Phases

Viral Response

- Remdesivir
- Convalescent plasma
- Monoclonal antibodies

Host Inflammatory Response

- Corticosteroids
- IL-6 Inhibitors

Remdesivir – Emergency Use Authorization

- **FDA issued emergency use authorization (EUA) on May 1, 2020 for patients with severe disease**

“It is reasonable to believe that remdesivir may be effective in treating COVID-19, and that, given there are no adequate, approved, or available alternative treatments, the known and potential benefits to treat this virus currently outweigh the known and potential risks of the drug’s use”
- **FDA broadens EUA on August 28, 2020 for all hospitalized patients with COVID**
- Per the NIH guidelines, there is uncertainty in the clinical benefit of remdesivir in patients on high-flow, noninvasive or mechanical ventilation
- Emergency use authorization is for the treatment of suspected or laboratory confirmed COVID-19 in hospitalized adults and children with COVID disease
- Based on limited data
- This allows for distribution and emergency use of remdesivir only for the treatment of COVID-19; it remains an investigational drug and is not FDA approved
- Concerns about patient enrollment into randomized, controlled clinical trials

Remdesivir

- Best benefit if used with duration of symptoms < 10 days
 - Corresponds to viral phase
- EUA expanded to ALL hospitalized patients
 - Limited evidence of benefit in nonsevere patients
 - Best evidence in severe COVID patients requiring supplemental oxygen but not on high-flow oxygen, mechanical ventilation or ECMO
- In a randomized study, remdesivir seemed to shorten time to recovery (11 days vs 15 days; $p < 0.001$) in patients with a median time from onset s/s to remdesivir initiation < 10 d , but mortality was not statistically different (8% vs 11.6%; $p = 0.059$)

Remdesivir: Summary

- Hospitalized, severe patients
 - SpO₂ ≤ 94% on room air or
 - Requiring supplemental oxygen, mechanical ventilation, ECMO
- Data have demonstrated:
 - Shorter time to recovery (11d vs 15 d p<0.001) in patients with a median time from onset s/s to remdesivir initiation < 10 days
 - Improved discharge rates in patients with s/s < 10 days
 - Data more robust for those requiring supplemental oxygen but not on mechanical ventilation or ECMO
 - Treatment with remdesivir for > 5 days did not improve outcomes in patients receiving noninvasive positive-pressure ventilation or high-flow oxygen, receiving low-flow oxygen or breathing ambient air did not appear to improve outcomes

Remdesivir for the Treatment of COVID-19 – Adaptive COVID-19 Treatment Trial (ACTT)

- Randomized, controlled trial
 - Preliminary results of Adaptive Covid-19 Treatment Trial (ACTT)
- Enrollment 2/21-4/19/20
- 68 sites in the US, 21 countries in Europe and Asia
- 1063 patients (1059 evaluated)
 - 538 remdesivir
 - 521 placebo
- Median days w/ s/s = 9 days
- 85% on oxygen
- Results:
 - Remdesivir treated pts had a faster recovery time – 11 d vs 15 days ($p < 0.001$)
 - **31% faster recovery time**
 - **Most prominent in low-flow O2 group**
 - ***Earlier initiation of remdesivir was associated improved recovery***
 - 14 day mortality rate of 7.1% for remdesivir vs 11.9% for placebo ($p = 0.059$)
- Conclusions:
 - Remdesivir most beneficial for severe COVID pts however mortality rate of 7.1% indicates that additional studies with concomitant therapies should be conducted to further improve clinical outcomes

SIMPLE-1: Remdesivir for 5 or 10 Days in Patients with Severe Covid-19 (NEJM)

- Randomized, open-label, phase 3 trial
- Primary endpoint
 - Clinical status on day 14
- 397 patients
 - Not on mechanical vent at entry
 - 200 received 5 day regimen
 - Median duration of tx – 5 days
 - 197 received 10 day regimen
 - Median duration of tx – 9 days
- Findings:
 - *By day 14, 65% of pts in 5 day group showed clinical improvement compared with 54% of those in 10 day group*
 - Median LOS among pts D/C \leq 14 days for the 5 day group was 7 days and 8 days for 10 day group
 - At 14 days, 60% of patients in 5 day group vs 52% in the 10 day group were discharged
 - Discharge rates were higher in those who had earlier initiation of remdesivir (1st dose < 10 days s/s)
 - Mortality for 5 and 10 day was 8% vs 11%

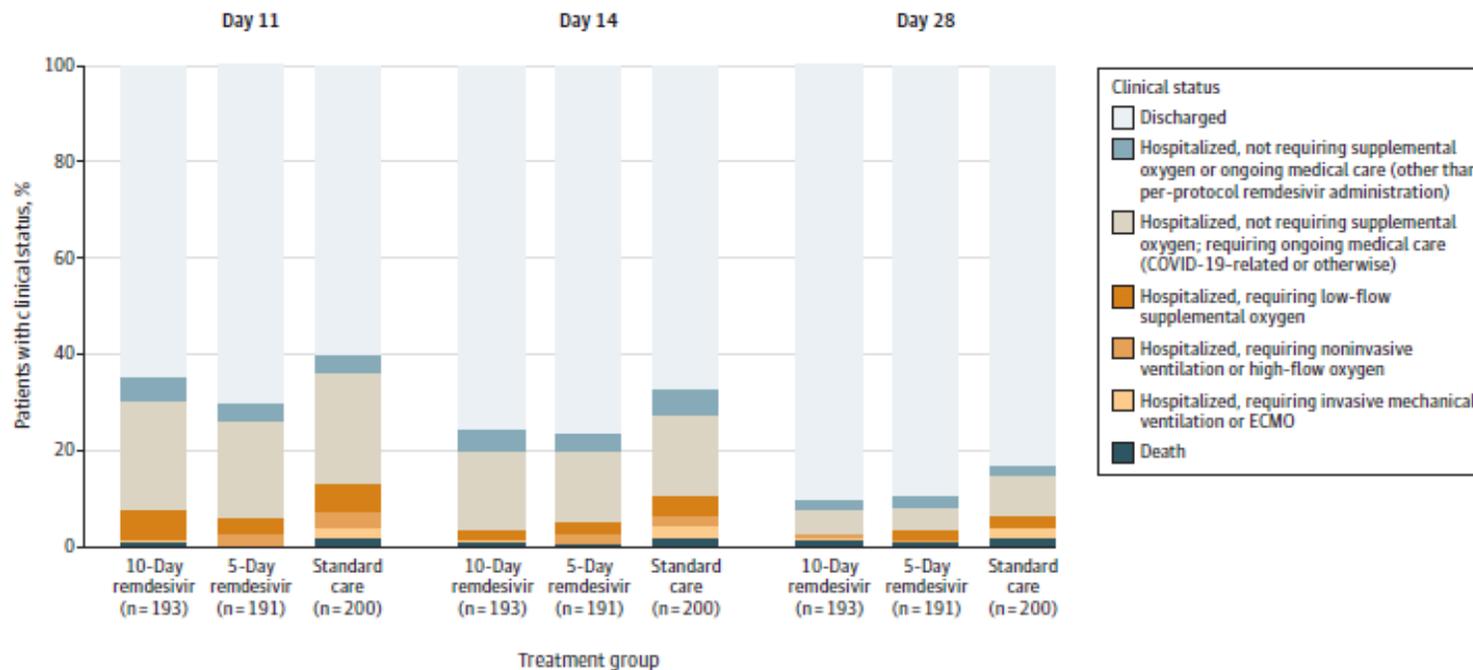
SIMPLE-2 Moderate COVID

- Randomized, open-label, phase 3 trial
- Primary endpoint
 - Clinical status on day 11
- 596 patients
 - Room air O₂ sat > 94%
 - 197 received 10 day regimen
 - Median duration of tx = 6
 - 199 received 5 day regimen
 - Median duration of tx = 5
- 5 day group were more likely to have clinical improvement at day 11 as compared to standard of care group (p=0.02)
- The 10 day treatment group did not have a statistically significant clinical status distribution as compared to the standard of care group (p=0.18)
- They concluded that 5 days of remdesivir was better than standard of care but 'the difference was of uncertain clinical significance

Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19

A Randomized Clinical Trial

Figure 2. Clinical Status on a 7-Point Ordinal Scale on Study Days 11, 14, and 28 by Treatment Group



COVID-19 indicates coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation. All percentage values in each point category are provided in eTables 5 and 6 in Supplement 3. At day 11, $P = .18$ for comparison of the distribution of the 10-day remdesivir group vs standard care and $P = .02$ for 5-day remdesivir vs standard care (Table 2). At day 14, $P = .03$ for comparisons

of both the 5-day and 10-day remdesivir groups vs standard care (eTable 5 in Supplement 3). At day 28, $P = .03$ for comparison of the 10-day remdesivir group vs standard care and $P = .08$ for 5-day remdesivir vs standard care (eTable 6 in Supplement 3). P values were calculated with the Wilcoxon rank sum test comparing the distribution of the groups.

Key Points

Question Does remdesivir provide a benefit on clinical status for patients hospitalized with moderate coronavirus disease 2019 (COVID-19) pneumonia?

Findings In this randomized, open-label, phase 3 trial that included 584 patients with moderate COVID-19, the day 11 clinical status distribution measured on a 7-point ordinal scale was significantly better for those randomized to a 5-day course of remdesivir (median length of treatment, 5 days) compared with those randomized to standard care. The difference for those randomized to a 10-day course (median length of treatment, 6 days) compared with standard care was not significantly different.

Meaning Hospitalized patients with moderate COVID-19 randomized to a 5-day course of remdesivir had a statistically significantly better clinical status compared with those randomized to standard care at 11 days after initiation of treatment, but the difference was of uncertain clinical importance.

ACTT-2: Remdesivir +/- Baricitinib

- Phase 3, randomized double-blind, placebo-controlled study
- Primary endpoint
 - Reduction in recovery time compared with remdesivir alone
- 1000 patients
 - Remdesivir
 - Remdesivir + baricitinib
 - Baricitinib is a JAK inhibitor
 - 4 mg baricitinib
- Patients treated with both agents had a 1 day reduction in median recovery time compared to remdesivir alone
- A secondary endpoint comparing outcomes at day 15 using an 8-point scale (fully recovered to death) was also met

<https://clinicaltrials.gov/ct2/show/NCT04401579>; <https://investor.lilly.com/news-releases/news-release-details/baricitinib-combination-remdesivir-reduces-time-recovery>

COVID-19 Convalescent Plasma

- Convalescent plasma is plasma obtained from COVID recovered donors which is used to transfer antibodies against COVID to others
 - Antibodies may bind to virus, neutralizing its infectivity
 - The antibodies may provide short term passive immunity
- May confer immediate immunity short-term
- May provide benefit
 - May prevent clinical infection
 - May reduce disease severity in those already exhibiting symptoms

Convalescent Plasma

- On 8/23/2020, the FDA authorized the emergency use authorization of convalescent plasma for hospitalized patients
- The FDA states that “it is reasonable to believe that COVID-19 convalescent plasma may be effective in lessening the severity or shortening the length of COVID-19 illness in some hospitalized patients. The agency also determined that the known and potential benefits of the product, when used to treat COVID-19, outweigh the known and potential risks of the product and that there are no adequate, approved, and available alternative treatments.”
- Data supporting the EUA is based on the use of convalescent plasma in > 70,000 individuals with COVID
- Data from randomized controlled trials is not available as all of these trials are ongoing

Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three-Month Experience

- The 35,322 transfused patients in the Expanded Access Program (EAP) received convalescent plasma
 - Critically-ill patients 52.3%
 - 27.5% receiving mechanical ventilation at the time of plasma transfusion
- Day 7 mortality rate was 8.7% if transfused ≤ 3 days of COVID-19 diagnosis but 11.9% if transfused ≥ 4 days after diagnosis ($p < 0.001$)
- 30-day mortality comparing those transfused ≤ 3 days vs ≥ 4 days (21.6% vs. 26.7%, $p < 0.0001$)
- High vs low antibody titers (unadjusted analysis)
 - 7 day mortality of high IgG plasma was 8.9% vs 13.7% for low IgG plasma
 - This reduction in mortality was also observed at 30 days

Convalescent Plasma: EAP Post hoc subgroup analyses

Mayo Clinic EAP Adjusted Analysis

- 3,082 patients who received single unit of plasma
- 30-day mortality for high-titer group was 24.7% vs 29.1% in low-titer group (not significant)
- Benefit in high-titer group who received plasma w/in 3 days of dx

FDA EAP Analysis

- 4,330 patients and donor neutralizing Ab titers
- Overall, no difference in mortality among high vs low-titer recipients
- In non-intubated group, mortality in high-titer was 11% vs 14% in low-titer (p=0.03)
 - <80 yrs & received high-titer plasma w/in 3 days of dx, 7-day mortality 6.3% vs 11.3% for low-titer (p=0.0008)

Convalescent Plasma: Unknowns

- True efficacy
- Who should receive it
- Optimal dose
 - Amount
 - # doses
- Optimal time to transfuse
- When to collect plasma from a COVID-recovered individual
 - Titer best associated with efficacy
- Safety unknown
 - Exacerbation of disease severity
 - Allergic reaction
 - Infectious complications
 - Transfusion related complications

Convalescent Plasma: NIH COVID-19 Treatment Guidelines

- Current data are insufficient to recommend for or against convalescent plasma for treating COVID
- The data from the Expanded Access Program are not sufficient to establish the efficacy or safety of convalescent plasma due to a lack of an untreated control group

Corticosteroids

- Anti-inflammatory
- May prevent cytokine storm, a hyperinflammatory response that contributes to COVID mortality
- Data is limited in COVID-19
- Do not use in non-critical patients or early in disease course
 - The RECOVERY Trial did not demonstrate a benefit with dexamethasone in patients not requiring supplemental oxygen
 - The RECOVERY Trial subgroup analysis showed no benefit in patients initiated on steroids prior to 7 days from first symptom onset

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

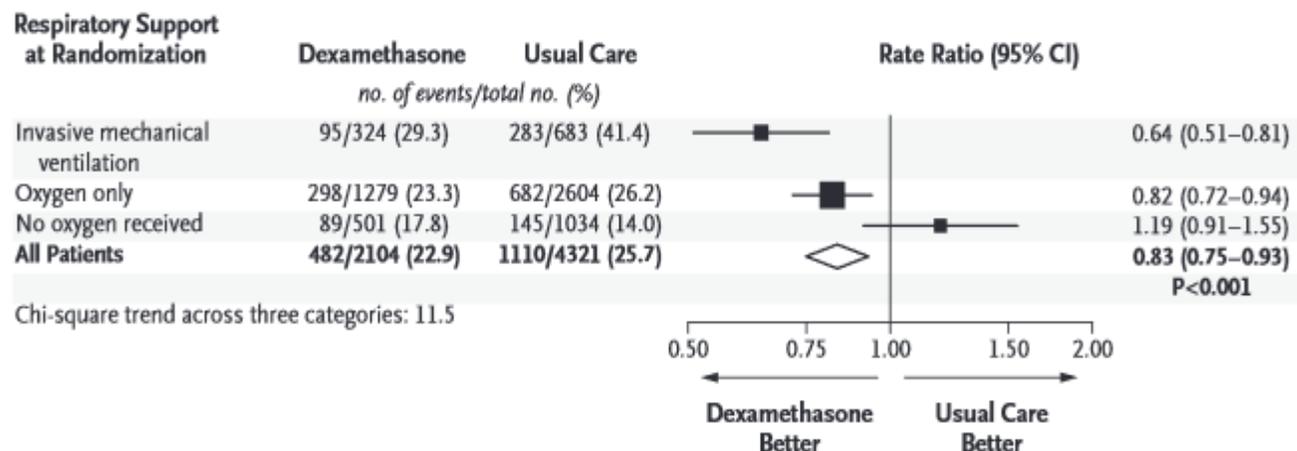


Figure 3. Effect of Dexamethasone on 28-Day Mortality, According to Respiratory Support at Randomization.

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.

Table 2. Primary and Secondary Outcomes.

Outcome	Dexamethasone (N=2104)	Usual Care (N=4321)	Rate or Risk Ratio (95% CI)*
	<i>no./total no. of patients (%)</i>		
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.

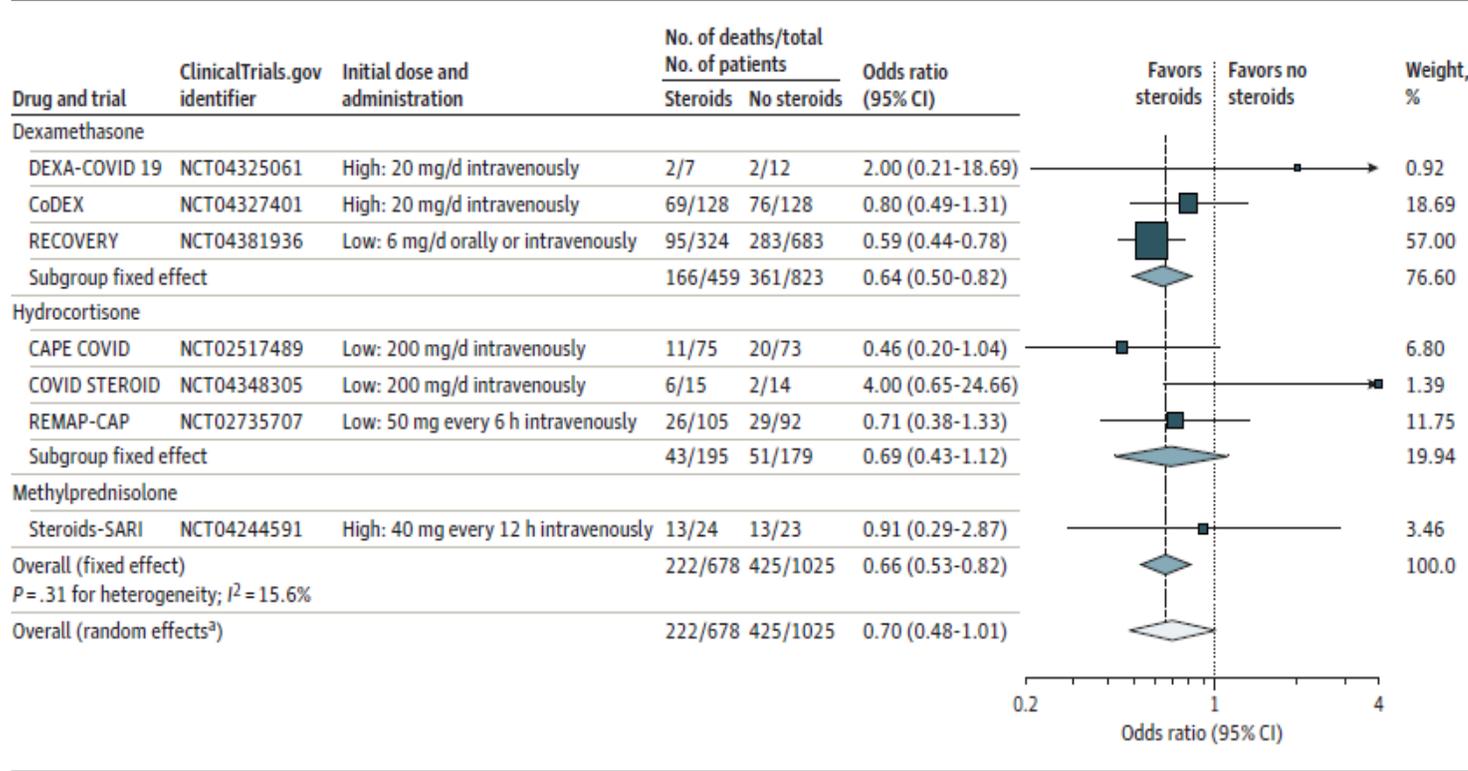
† Excluded from this category are patients who were receiving invasive mechanical ventilation at randomization.

<https://www.nejm.org/doi/pdf/10.1056/NEJMoa2021436?articleTools=true>

Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group

Figure 2. Association Between Corticosteroids and 28-Day All-Cause Mortality in Each Trial, Overall, and According to Corticosteroid Drug



The area of the data marker for each trial is proportional to its weight in the fixed-effect meta-analysis. The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial result is for patients who were receiving invasive mechanical ventilation at randomization. CAPE COVID indicates Community-Acquired Pneumonia: Evaluation of Corticosteroids in Coronavirus Disease; CoDEX, COVID-19 Dexamethasone; COVID STEROID, Hydrocortisone for COVID-19 and Severe Hypoxia; DEXA-COVID 19, Efficacy of Dexamethasone Treatment for Patients With ARDS Caused by COVID-19; REMAP-CAP, Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired

Pneumonia; Steroids-SARI, Glucocorticoid Therapy for COVID-19 Critically Ill Patients With Severe Acute Respiratory Failure.

^a The random-effects analysis estimates both the average and variability of effects across studies. The 95% CI for the average effect (shown here) is wide because there is a small number of studies, some of which have very small sample size. The prespecified primary analysis was the fixed-effect analysis, which should be used to guide clinical interpretation of the results.

Key Points

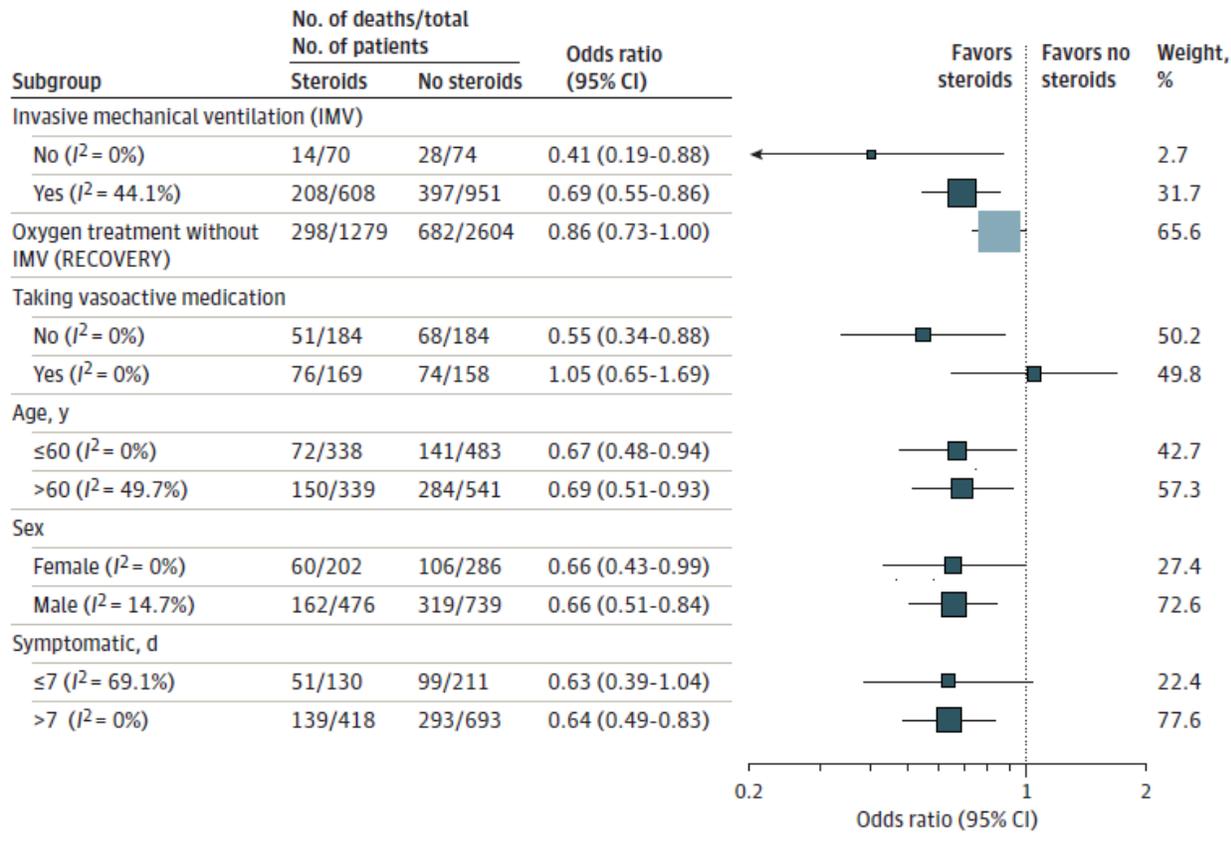
Question Is administration of systemic corticosteroids associated with reduced 28-day mortality in critically ill patients with coronavirus disease 2019 (COVID-19)?

Findings In this prospective meta-analysis of 7 randomized trials that included 1703 patients of whom 647 died, 28-day all-cause mortality was lower among patients who received corticosteroids compared with those who received usual care or placebo (summary odds ratio, 0.66).

Meaning Administration of systemic corticosteroids, compared with usual care or placebo, was associated with lower 28-day all-cause mortality in critically ill patients with COVID-19.

<https://jamanetwork.com/journals/jama/fullarticle/2770279>

Figure 3. Association Between Corticosteroids and 28-Day All-Cause Mortality Within Subgroups Defined by Patient Characteristics at the Time of Randomization



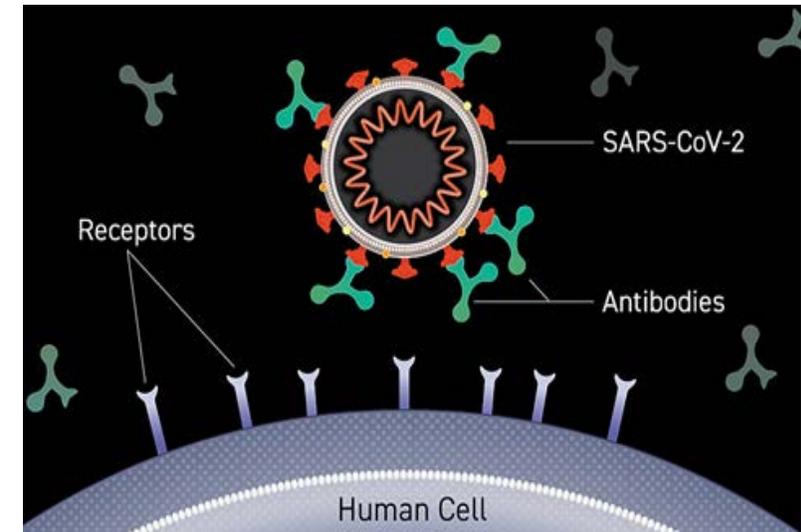
The area of the data markers is proportional to their weight in the meta-analysis. The estimated odds ratios were derived using fixed-effect meta-analyses across all trials for which data on the specified subgroup were available. The results for patients in the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial who required oxygen with or without noninvasive ventilation but were not receiving invasive mechanical ventilation at randomization is shown in a light blue box because these data were not otherwise included in this prospective meta-analysis.

Dexamethasone

- IDSA and NIH Guidelines recommend:
 - Dexamethasone 6 mg daily (IV or PO) for patients receiving mechanical ventilation or supplemental oxygen
 - Duration: 10 days or until hospital discharge (which occurs first)
- Do not use in patients not requiring supplemental oxygen
- IDSA Guidelines say that another corticosteroid (at an equivalent dose) may be substituted if dexamethasone not available
 - 32 mg methylprednisolone
 - 40 mg prednisone

Monoclonal Antibodies

- Monoclonal antibodies protect against COVID by blocking the virus from binding to host cells
- Monoclonal antibodies for COVID derived from blood samples of patients who have recovered from COVID
- Several antibodies being studied
 - LY-CoV555 (Eli Lilly) – early data show benefits
 - AZD7442 (AstraZeneca)
 - REGN-COV2 (Regeneron/Roche)
- Studied for prevention and treatment



Monoclonal Antibody: LY-CoV555

- BLAZE-1 – randomized, double-blind, placebo controlled PH 2 study for the treatment of mild-moderate symptomatic outpatient COVID
 - Treatment initiated w/in 3 days of diagnosis
- Expected to enroll 800 participants
- LY-CoV555 dosing:
 - 700 mg, 2800 mg, 7000 mg
 - Single infusion
- Interim analysis:
 - Viral load reduction with 2800 mg dose only
 - COVID related hospitalization or ED visit was 1.7% for LY-CoV555 recipients as compared to 6% for placebo
 - Those that were hospitalized had a more rapid improvement in s/s
 - LY-CoV555 was well tolerated
 - Viral RNA sequencing revealed LY-CoV555 resistance variants
 - Trial is ongoing combining LY-CoV555 with LY-CoV016, a 2nd monoclonal Ab

https://www.infectioncontroltoday.com/view/eli-lilly-neutralizing-antibodies-breakthrough-for-covid-19-treatment?utm_source

=sfmc&utm_medium=email&utm_campaign=09292020_AMB-20-ICD0155 ICT_eNL_US_Only&eKey=b2xpcGNhdGhAaXN1LmVkdQ==; <https://investor.lilly.com/news-releases/news-release-details/lilly-announces-proof-concept-data-neutralizing-antibody-ly>

Monoclonal Antibody: REGN-COV-2 (Regeneron)

- Double monoclonal antibody
- Initial preliminary data in non-hospitalized patients:
 - 275 patients
 - Randomized to single infusion
 - 8 gm vs 2.4 gm vs placebo
 - High-dose reduced viral load thru day 7
 - Both doses elicited a greater effect in patients who had not generated own Ab
 - 0.60 log₁₀ copies/ml reduction in viral load with high dose vs 0.51 log₁₀ copies/ml reduction with low dose
- Promising safety data to date
- Clinical trials
 - PH 2/3 Outpatient COVID (~1500 patients)
 - PH 3 Hospitalized patients
 - PH 3 Prevention of COVID in household contacts of infected individuals

[https://www.statnews.com/2020/09/29/regenerons-covid-19-antibody-may-help-non-hospitalized-patients-recover-faster-early-data-show/;](https://www.statnews.com/2020/09/29/regenerons-covid-19-antibody-may-help-non-hospitalized-patients-recover-faster-early-data-show/)

https://www.contagionlive.com/news/investigational-therapy-reduces-viral-load-in-nonhospitalized-covid19-patients?utm_source=sfmc&utm_medium=email&utm_campaign=9-30-20_CTGNE_COVID%20Update&eKey=b2xpcGNhdGhAaXN1LmVkdQ==

COVID-19 Patient Case Discussion

- 77yo M with hx of obesity, DM II, HTN, HLD and BPH, develops fatigue and cough 5 days after attending a family wedding.
- Patient notified by daughter that she and her family (who attended the wedding) have tested positive for COVID.
- He tests positive in your "drive up" clinic.

- Three days after positive test, patient's lips turn "a little blue" at home.
- Wife calls EMS - SpO2 84%, HR 104, RR 22
- Admitted to hospital.
- Treated with famotidine, melatonin, remdesivir and dexamethasone.
- Discharged to rehab facility.

What data on this treatment is available thus far?

What is the evidence for other treatments given in this case?

What is a superspreader?

JOIN US FOR OUR NEXT SESSION!

For information, please visit uidaho.edu/echo

Ongoing Resource List

RESOURCES FROM TODAY'S SESSION AND PAST SESSIONS CAN BE FOUND IN OUR ONGOING RESOURCE LIST.

<https://iecho.unm.edu/sites/uidaho/download.hns?i=440>