NETEC

NETEC COVID-19 Webinar Series:

COVID-19: Current State of the Pandemic

EMORY MEDICINE | UNMC Nebraska Medicine | NYC HEALTH+ HOSPITALS | Bellevue

Welcome

Trish Tennill, RN, BSN

Overview

NETEC

- **Welcome**: Trish Tennill, RN, BSN
- **COVID-19 Current State of the Pandemic** : Amanda Klinger, MD
- **NETEC Resources**: Trish Tennill, RN, BSN
- **Questions and Answers with NETEC**: Vikram Mukherjee, MD

Welcome

NETEC

National Emerging Special Pathogens Training and Education Center

Mission Statement

To increase the capability of the United States public health and health care systems to safely and effectively manage individuals with suspected and confirmed special pathogens

For more information

Please visit us at www.netec.org
or email us at info@netec.org

NETEC Overview

NETEC

Assessment

Empower hospitals to gauge their readiness using
Self-Assessment

Measure facility and healthcare worker readiness using
Metrics

Provide direct feedback to hospitals via
On-Site Assessment

Education

Provide self-paced education through
Online Trainings

Deliver didactic and hands-on simulation training via
In-Person Courses

COVID-19 focused
Webinars

Technical Assistance

Onsite & Remote Guidance

Compile
Online Repository
of tools and resources

Develop customizable
Exercise Templates
based on the HSEEP model

Provide
Emergency On-Call Mobilization

Research Network

Online Repository
Built for rapid implementation of clinical research protocols

Develop Policies, Procedures and Data Capture Tools
to facilitate research

Create infrastructure for a
Specimen Biorepository

Cross-Cutting, Supportive Activities

COVID-19: Current State of the Pandemic

Amanda Klinger, MD

Objectives

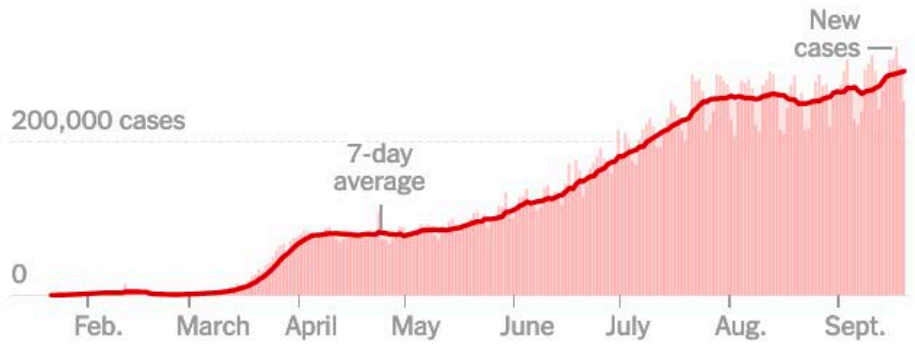
NETEC

- Describe the current pandemic hotspots, in the US and globally including the epidemiology of the current wave of infections
- Discuss the country-wide testing needs to mitigate and suppress COVID-19 infections
- Review the evidence regarding possible re-infections of COVID-19
- Interpret the data behind the newest therapeutic guidelines for COVID-19 (remdesivir, convalescent plasma, and steroids)

Where Are We Now?

World COVID-19 Case Counts

By The New York Times Updated September 21, 2020, 8:48 P.M. E.T.



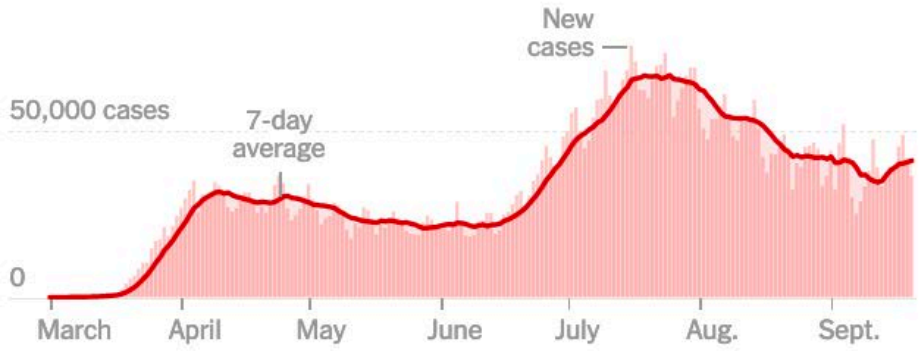
	TOTAL REPORTED	ON SEPT. 20	14-DAY CHANGE
Cases	31.1 million+	253,013	+8%
Deaths	961,858	3,687	Flat

Includes confirmed and probable cases where available. 14-day change trends use 7-day averages.

https://www.nytimes.com/interactive/2020/world/coronavirus-maps.html

United States COVID-19 Case Counts

By The New York Times Updated September 21, 2020, 8:48 P.M. E.T.

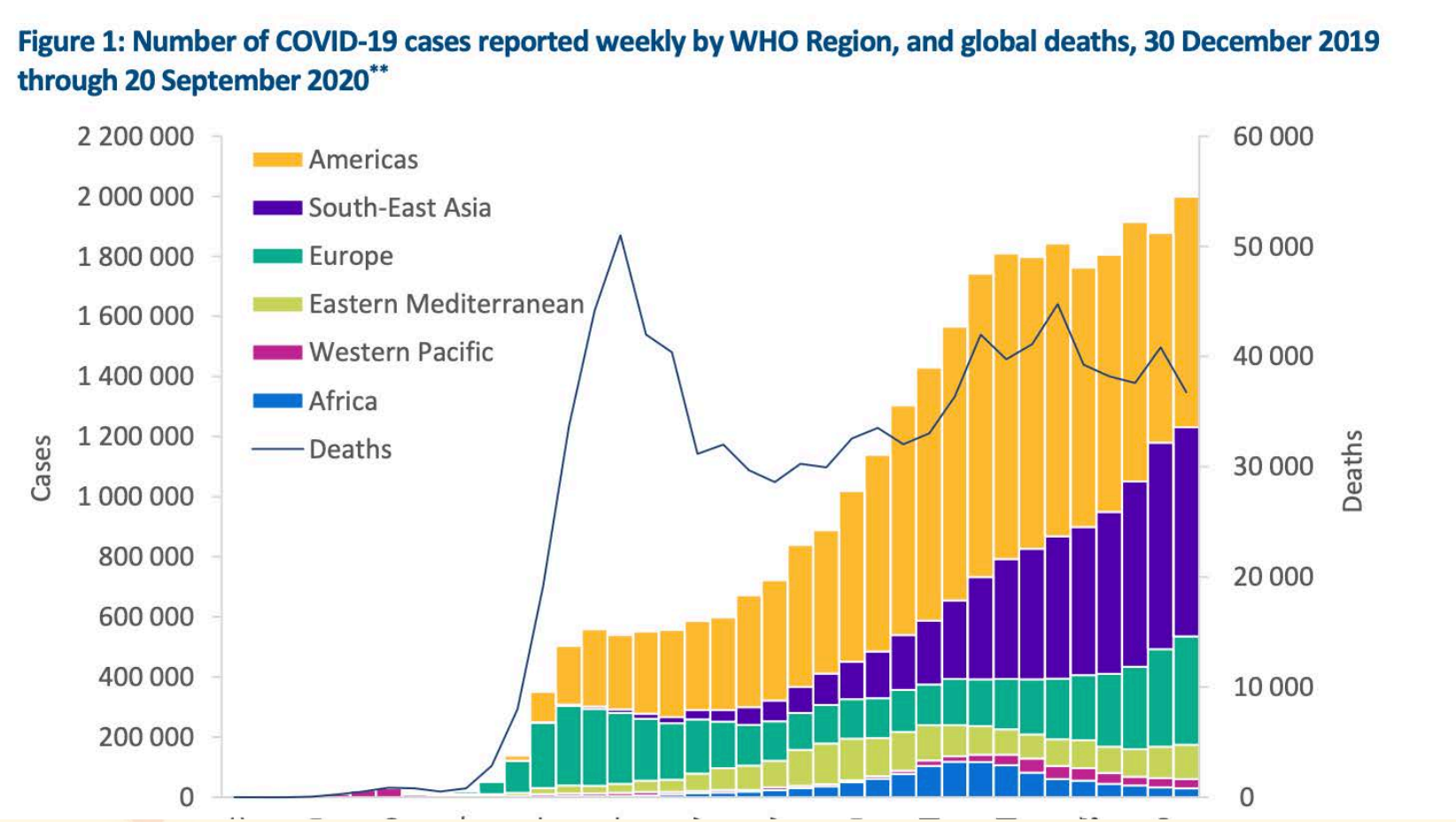


	TOTAL REPORTED	ON SEPT. 20	14-DAY CHANGE
Cases	6.8 million+	36,401	+1%
Deaths	199,740	213	–7%

Includes confirmed and probable cases where available. 14-day change trends use 7-day averages.

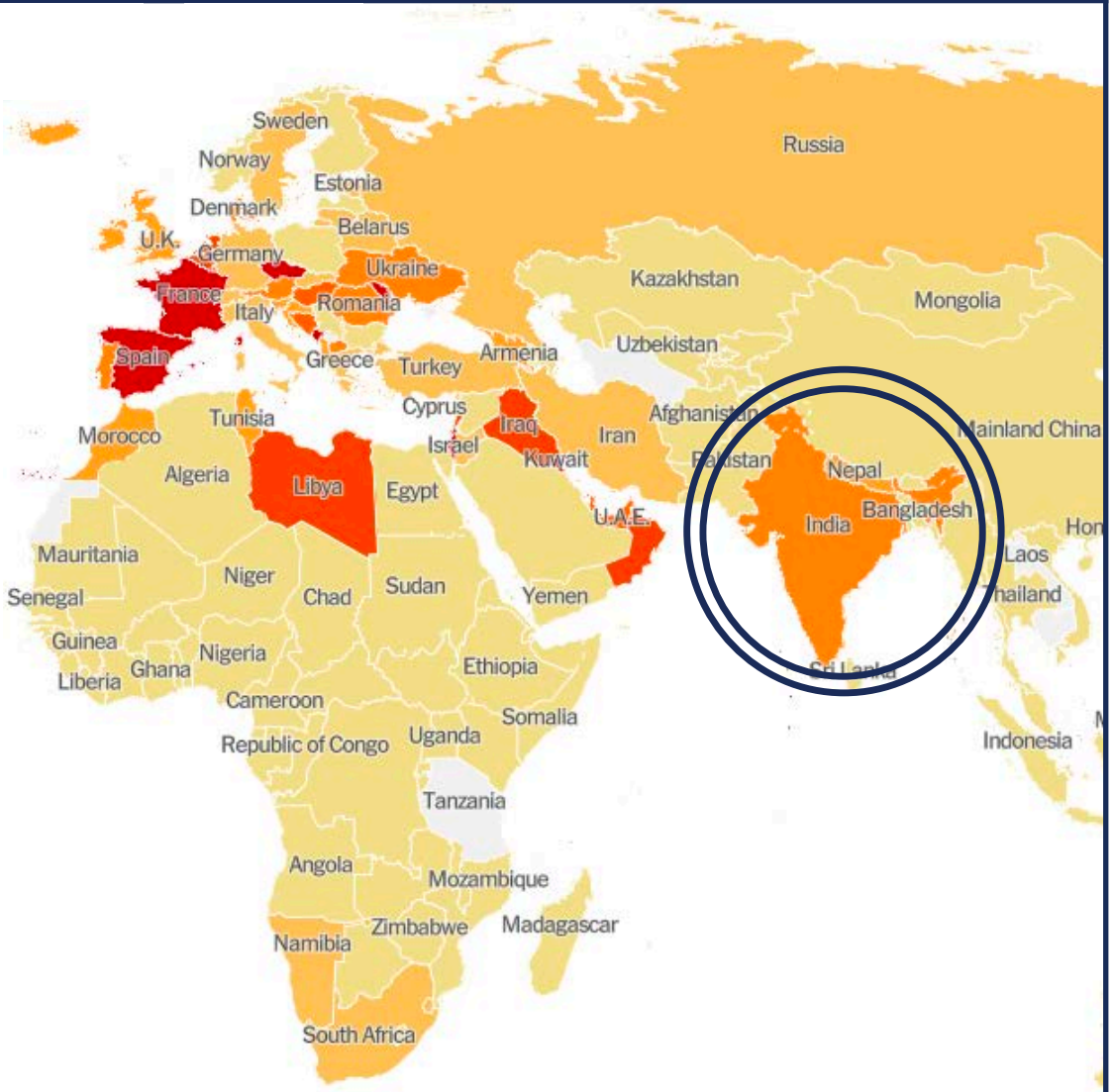
https://www.nytimes.com/interactive/2020/us/coronavirus-us-cases.html

Where Are We Now?



Worldwide Hotspots: South East Asia

- **Highest number of new cases:**
  - **India**
  - **Indonesia**
  - **Bangladesh**
- **India**
  - **Strict lockdown late March to late May**
  - **Movement from urban cases to rural cases (people traveling)**
  - **Second highest in total cases and third highest in death toll**
  - **>90,000 new infections per day**
    - **Fastest increase of all countries**
  - **Hotspot region = state of Maharashtra, home to Mumbai**
  - **Lowest per capita death rate**

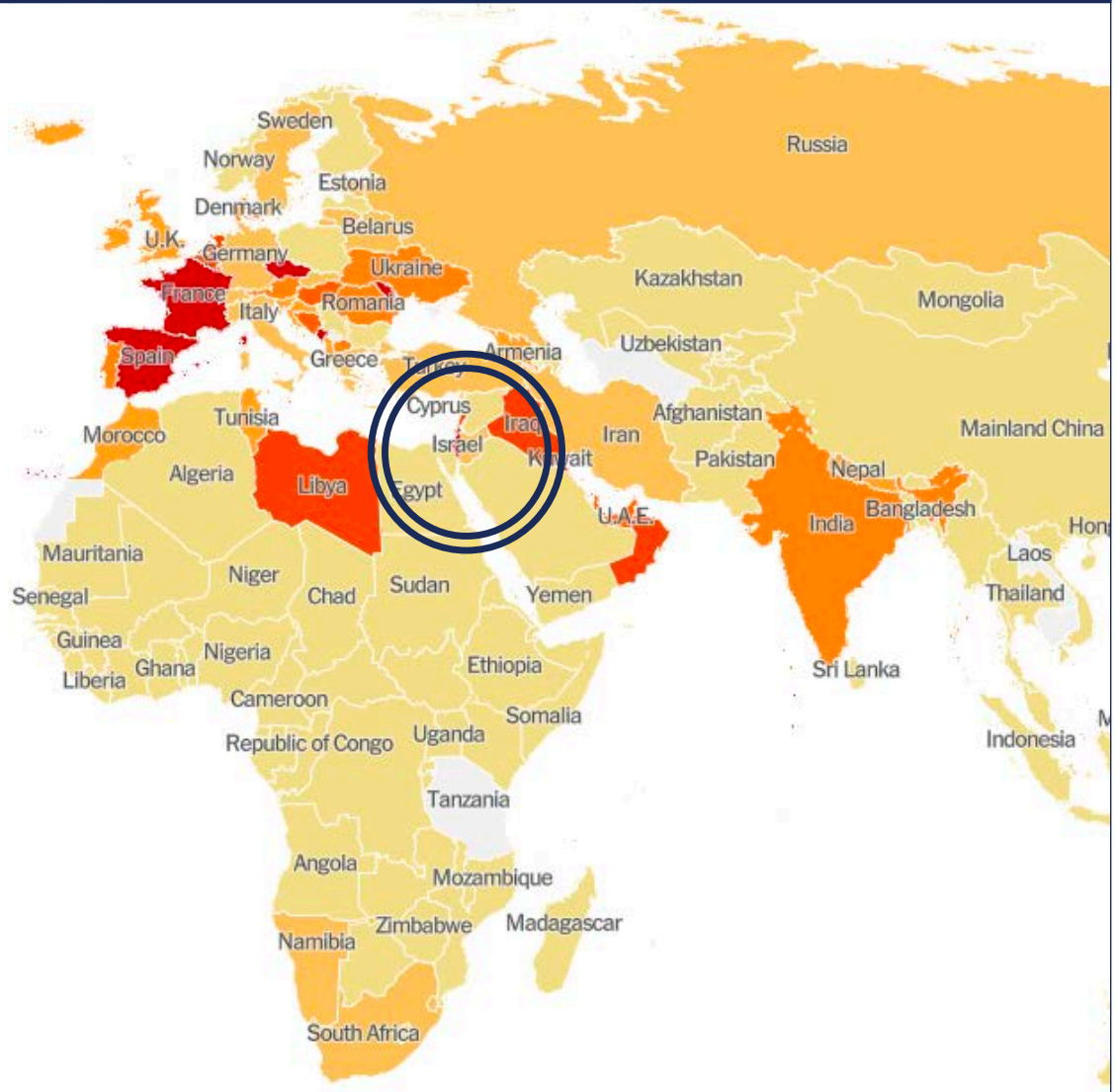


Worldwide Hotspots: Europe

- Second waves of infection developing
- Spain
  - Attributed to faster opening of nightclubs and bars
  - Mortality rate = 50% of May (12%→6.6%)
  - Median age of sufferers = 37 compared to 60
  - Asymptomatic cases are approximately 50%
- France
  - Mostly affecting young people
  - Schools have had to reclose
  - Cause thought to be waning social distancing efforts
- United Kingdom
  - Boris Johnson to pass restrictions on bars and restaurants
  - Projecting 50,000 new cases per day in the next month

Worldwide Hotspots: Israel

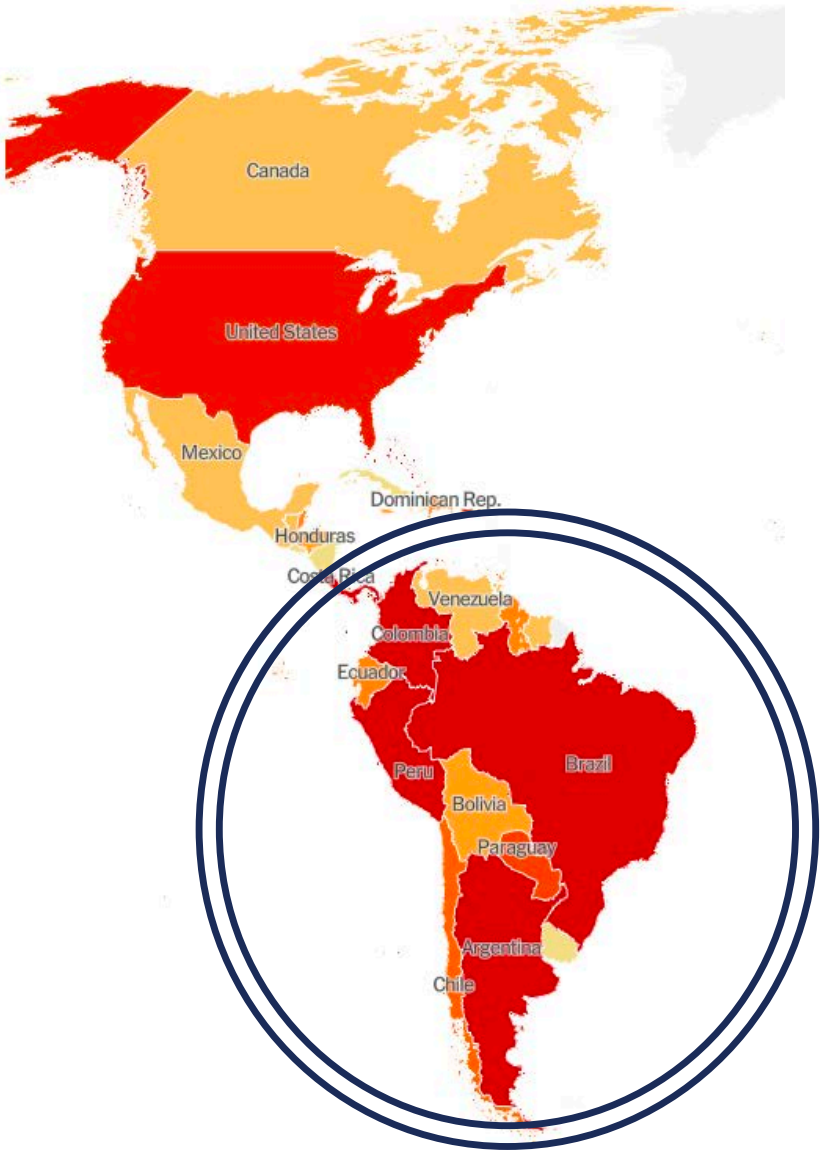
- **Israel**
  - **Current increase began in July**
  - **Significant infighting in government about how to manage outbreaks**
  - **Daily cases surpassing 3,000**
  - **Highest per capita 7-day average in new cases**
  - **New lockdown started**
  - **Highest prevalence areas:**
    - **Arab communities**
    - **Ultra-Orthodox communities**



The Americas

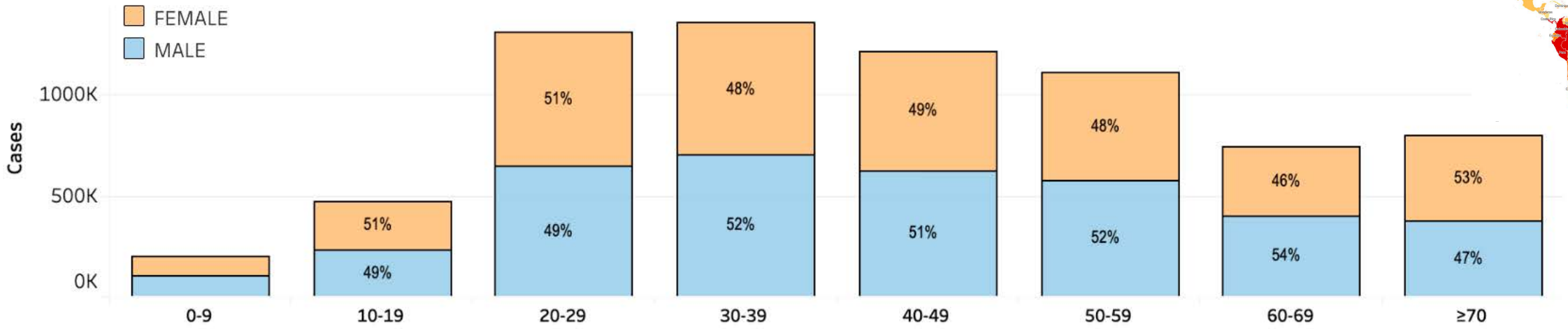
- **Highest number of cases:**
  - **United States of America**
  - **Brazil**
  - **Argentina**
  - **Colombia**

Argentina's test positivity rates = 40%!

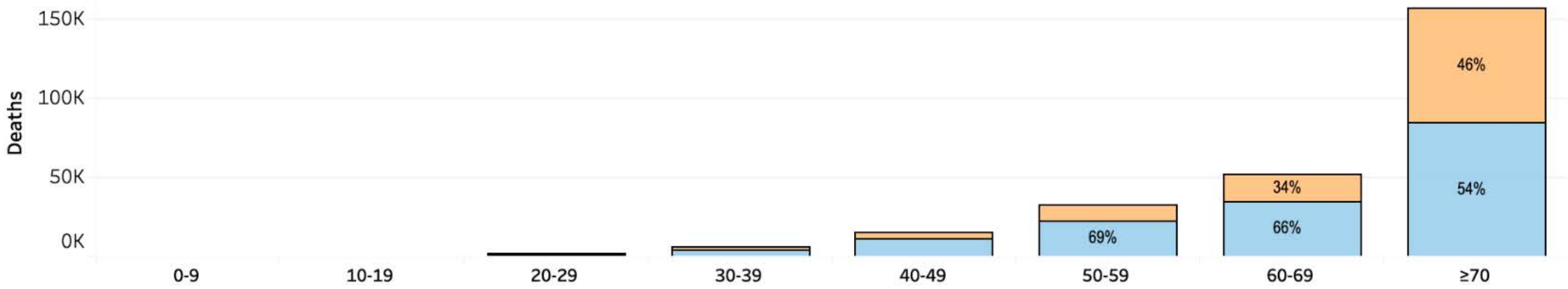


The Americas

Total confirmed cases by age group



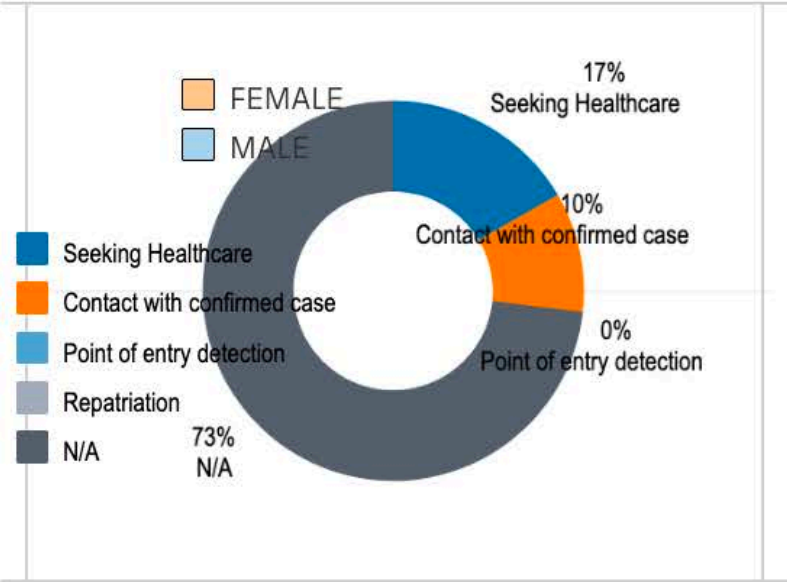
Total confirmed deaths by age group



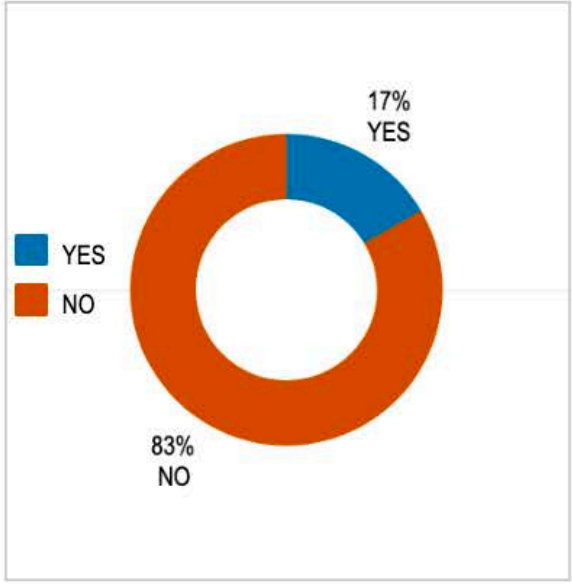
https://ais.paho.org/phip/viz/COVID-19EpiDashboard.asp

The Americas

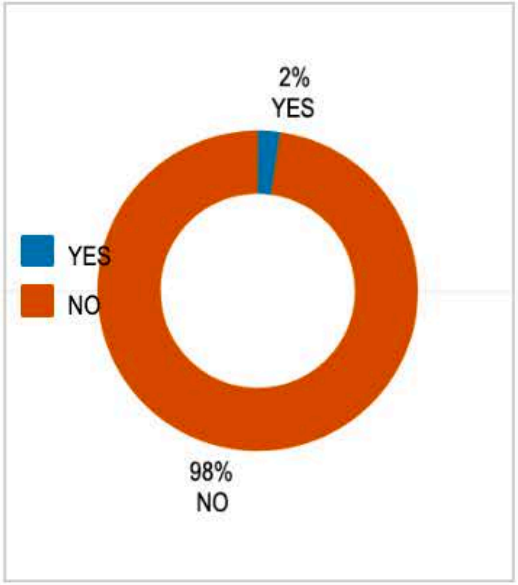
Reason for samples taken



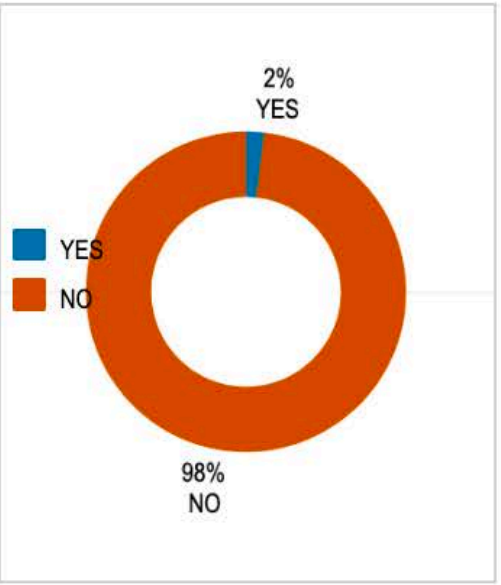
Patient admitted to hospital



Patient received care in ICU



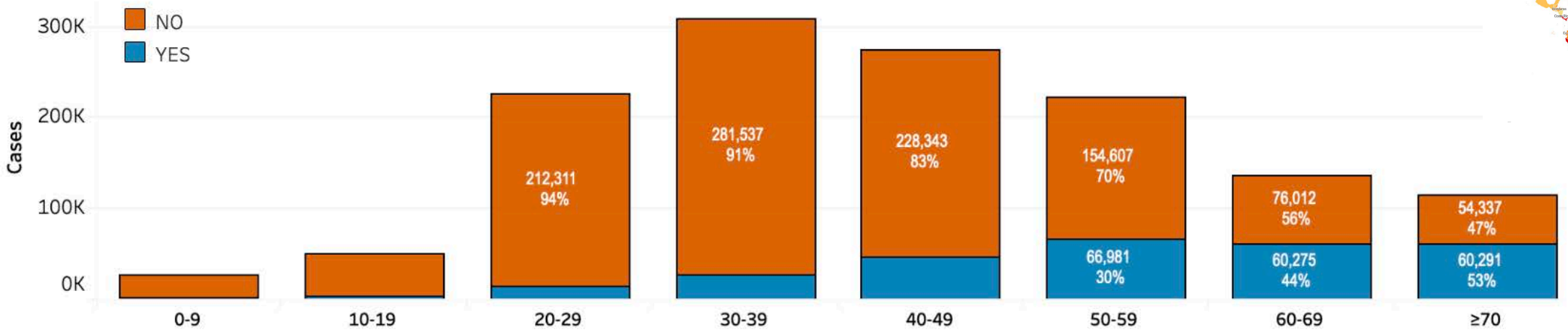
Patient ventilated



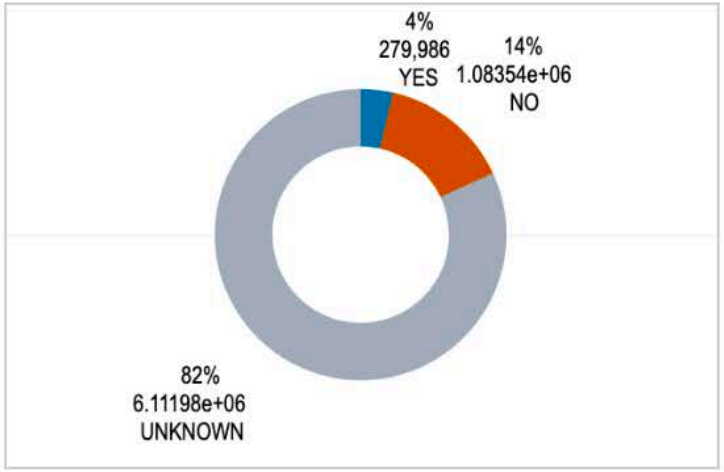
https://ais.paho.org/phip/viz/COVID-19EpiDashboard.asp

The Americas

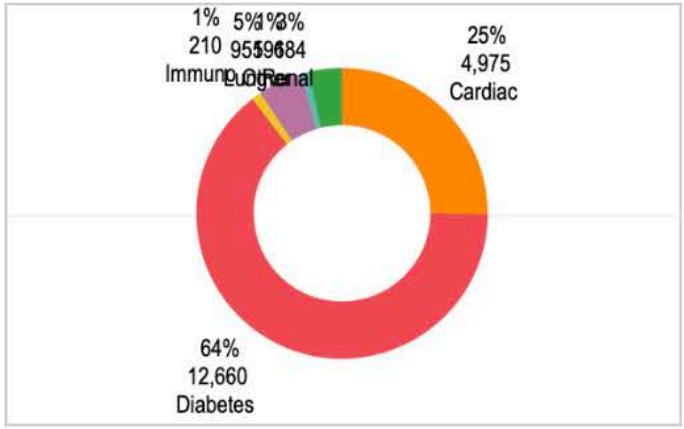
Total confirmed cases with comorbidities by age group



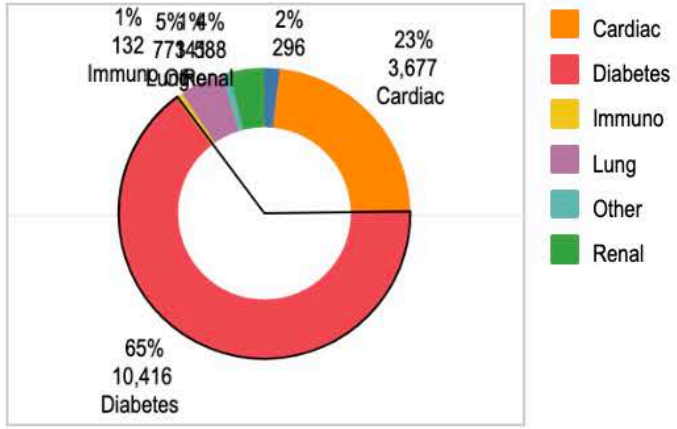
At least one comorbidity



Comorbidities among ICU patients n = 20,792



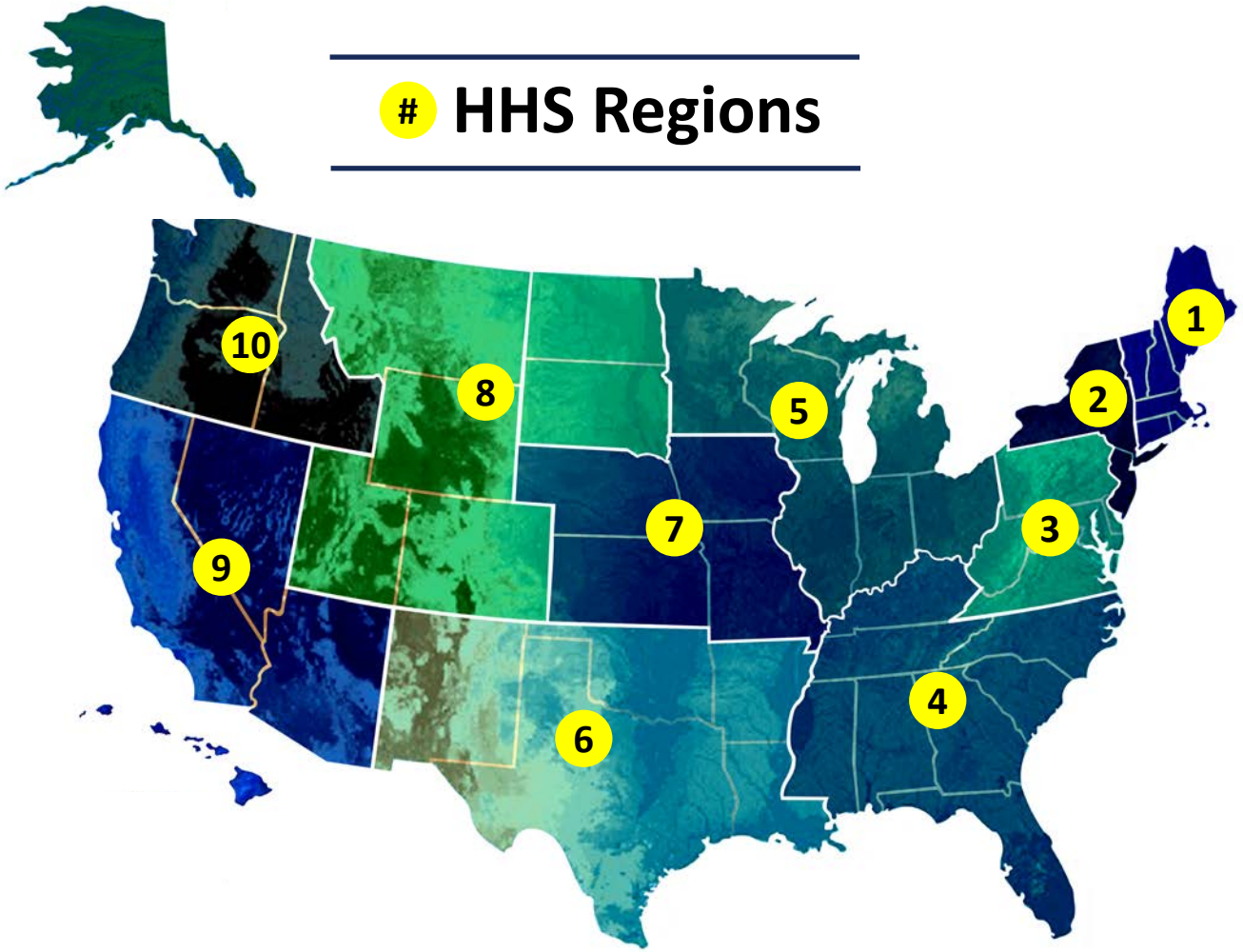
Comorbidities among ventilated patients n = 16,023



https://ais.paho.org/phip/viz/COVID-19EpiDashboard.asp

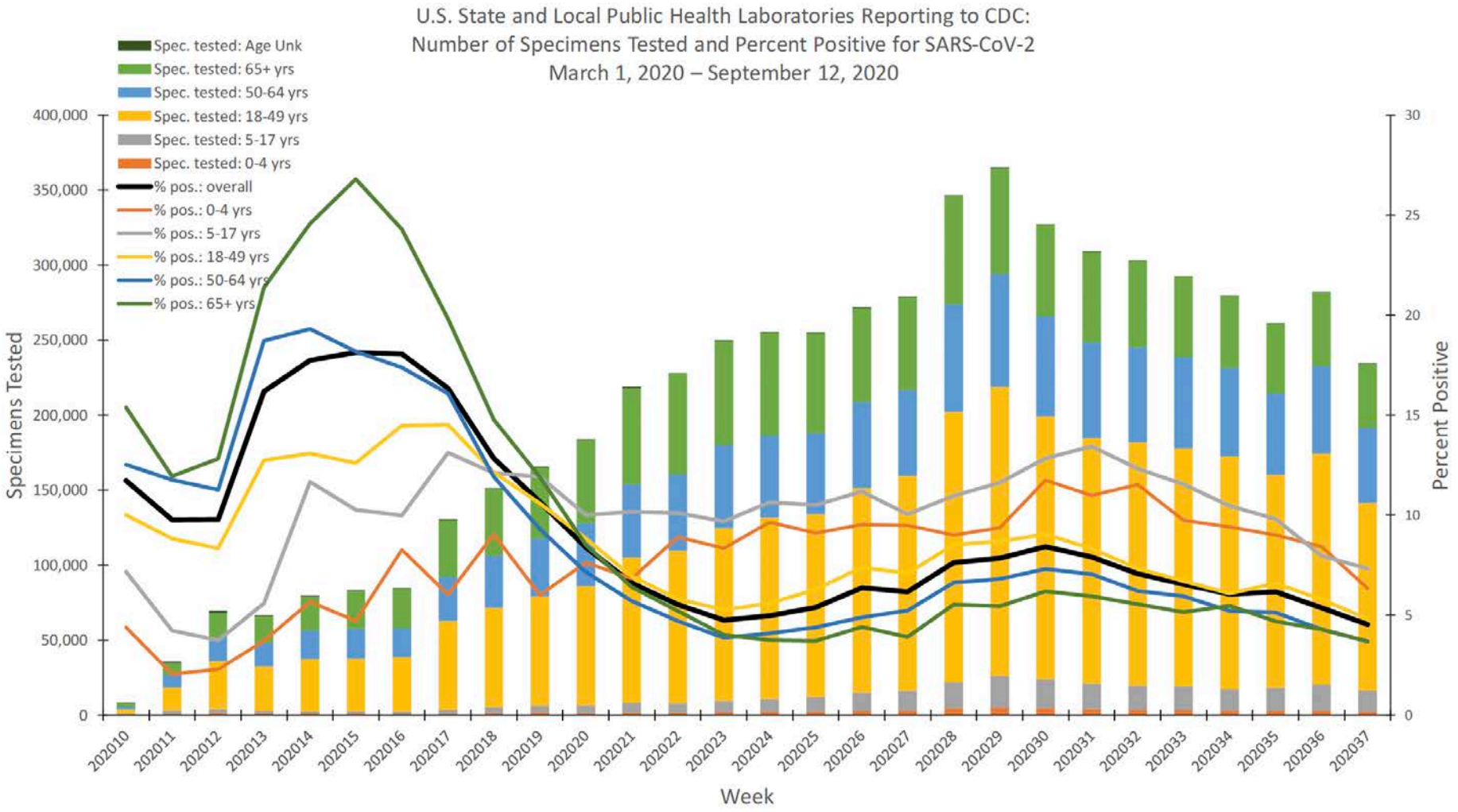
US Hotspots

- **Highest percentages:**
  - Region 4 (South East) = 7.5%
  - Region 6 (South Central) = 8.3%
  - Region 7 (Central) = 8.9%
- **Slight increase in positive tests:**
  - Regions 2 and 8



Who is Getting Infected?

Public Health Laboratories



CENTERS FOR DISEASE CONTROL AND PREVENTION

https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html

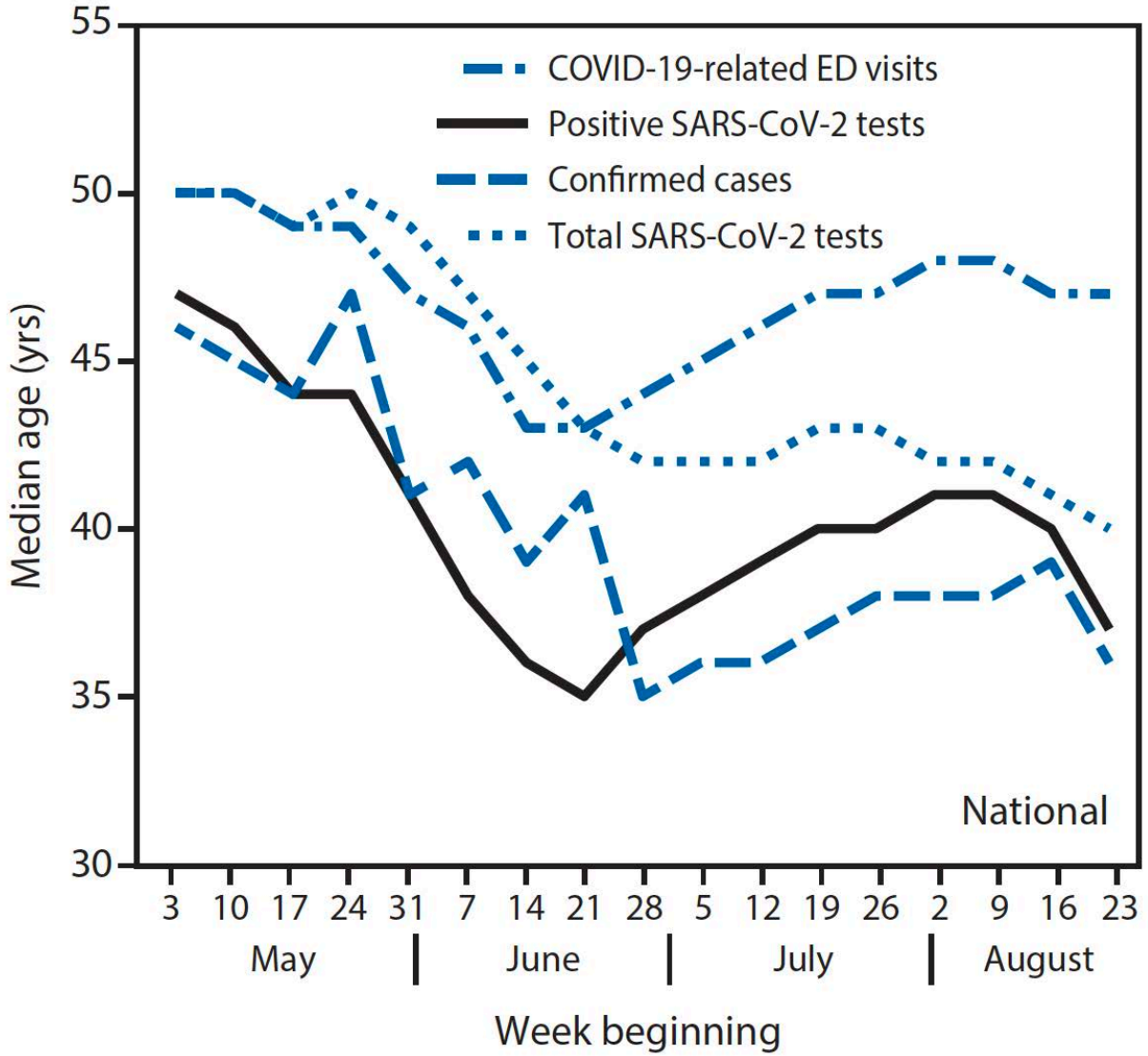
Changing Age Distribution

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Early Release / Vol. 69
September 23, 2020

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

Tegan K. Boehmer, PhD[1]; Jourdan DeVies, MS[1]; Elise Caruso, MPH[1]; Katharina L. van Santen, MSPH[2]; Shichao Tang, PhD[1]; Carla L. Black, PhD[1]; Kathleen P. Hartnett, PhD[1]; Aaron Kite-Powell, MS[1]; Stephanie Dietz, PhD[1]; Matthew Lozier, PhD[1]; Adi V. Gundlapalli, MD, PhD[1]

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

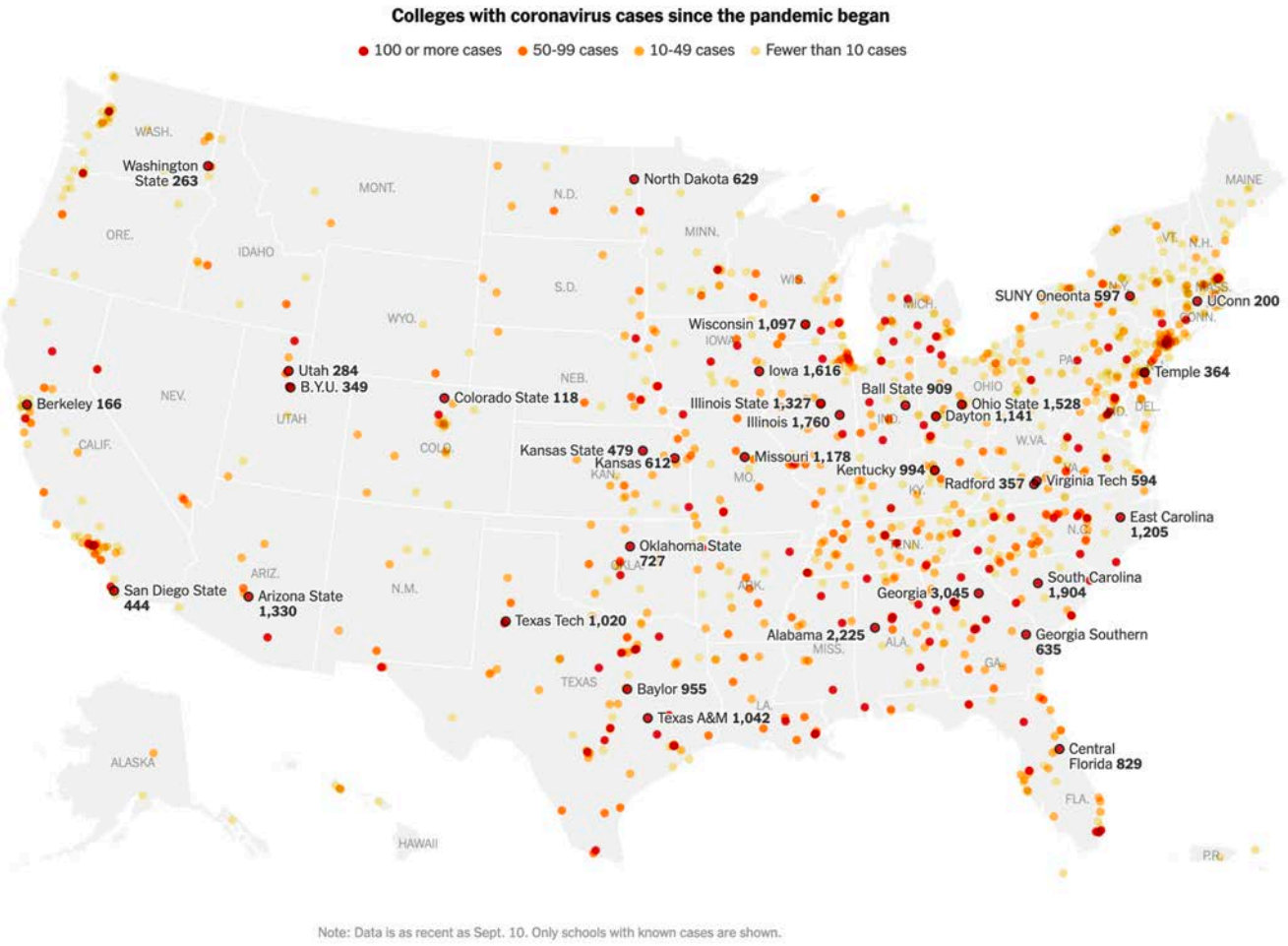


College Openings

Tracking Covid at U.S. Colleges and Universities

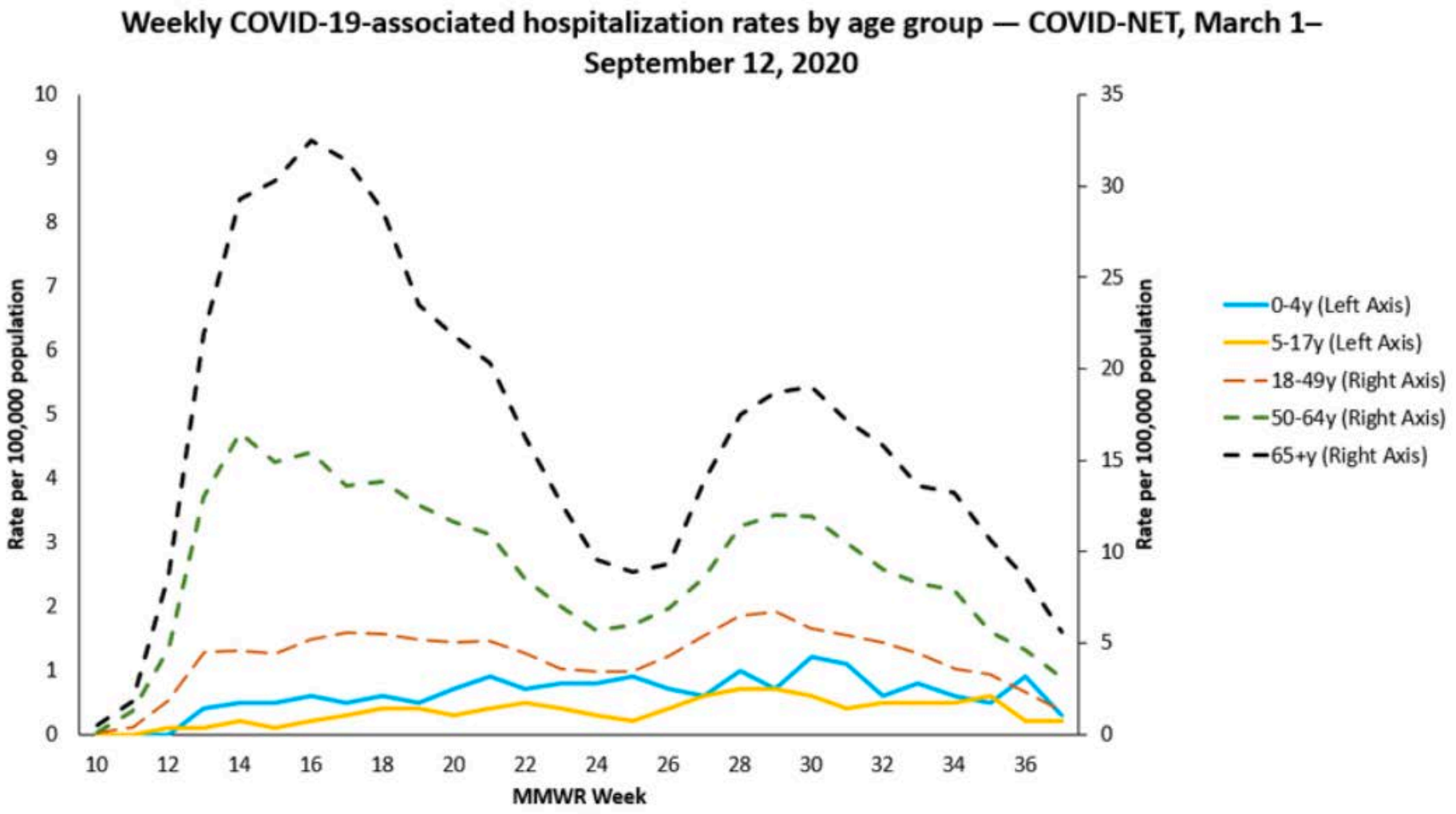
By The New York Times Updated Sept. 10, 2020

88,000+ Cases | **1,190+** Colleges



https://www.nytimes.com/interactive/2020/us/covid-college-cases-tracker.html

COVID-19-Associated Hospitalization Rates by Age Group



CDC
Centers for Disease Control and Prevention

https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html

Characteristics and Outcomes of COVID-19

JAMA Network

From: **Characteristics and Outcomes of COVID-19 Patients During Initial Peak and Resurgence in the Houston Metropolitan Area**

JAMA. 2020;324(10):998-1000. doi:10.1001/jama.2020.15301

Table Title: Sociodemographic, Comorbidity, Clinical, and Outcome Differences Between Surge 1 and Surge 2 of COVID-19 Hospitalizations at Houston Methodist, Texas

Table. Sociodemographic, Comorbidity, Clinical, and Outcome Differences Between Surge 1 and Surge 2 of COVID-19 Hospitalizations at Houston Methodist, Texas

	Surge 1: March 13 to May 15 (64 d)[a]	Surge 2: May 16 to July 7 (53 d)[a]	Difference (95% CI)[b]	*P* value
No.	774	2130		
Demographic and social characteristics				
Age, mean (SD), y	59.9 (16.9)	57.3 (17.4)	−2.62 (−4.04 to −1.20)	<.001
Age ≤50 y, No. (%)	208 (26.9)	736 (34.6)	7.68 (3.96 to 11.40)	<.001
Non-Hispanic race, No. (%)[c]				
White	257 (45.2)	543 (46.1)	0.97 (−4.02 to 5.95)	.70
Black	256 (45.0)	534 (45.4)	0.38 (−4.60 to 5.36)	.88
Asian	46 (8.1)	83 (7.1)	−1.03 (−3.71 to 1.64)	.44
Other	10 (1.8)	17 (1.4)	−0.31 (−1.59 to 0.96)	.62
Hispanic or Latino, No. (%)[c]	196 (25.7)	910 (43.3)	17.64 (13.89 to 28.79)	<.001
Insurance, No. (%)				
Commercial	305 (39.4)	769 (36.1)	−3.30 (−7.30 to 0.70)	.10
Medicare	333 (43.0)	774 (36.3)	−6.69 (−10.73 to −2.64)	.001
Self-pay	88 (11.4)	423 (19.9)	8.49 (5.68 to 11.30)	<.001
Medicaid	32 (4.1)	141 (6.6)	2.49 (0.73 to 4.24)	.01
Other	16 (2.1)	23 (1.1)	−0.99 (−0.21 to −0.11)	.04
Zip code income, median (IQR), $	65 805 (48 790 to 86 034)	60 765 (46 300 to 76 163)	−5040 (−7641 to −2439)	<.001
Comorbidity profile[d]				
Charlson Comorbidity Index, median (IQR) score	3 (1 to 6)	2 (1 to 4)	−1 (−1.30 to −0.71)	<.001
Diabetes (with or without complications), No. (%)	312 (40.3)	475 (32.0)	−8.34 (−12.54 to −4.15)	<.001
Hypertension, No. (%)	427 (55.3)	583 (38.8)	−16.52 (−20.81 to −12.24)	<.001
Obesity (BMI ≥30), No. (%)	261 (33.9)	383 (25.7)	−8.19 (−12.20 to −4.18)	<.001

Table. Sociodemographic, Comorbidity, Clinical, and Outcome Differences Between Surge 1 and Surge 2 of COVID-19 Hospitalizations at Houston Methodist, Texas

	Surge 1: March 13 to May 15 (64 d)[a]	Surge 2: May 16 to July 7 (53 d)[a]	Difference (95% CI)[b]	*P* value
Therapies, No. (%)				
Remdesivir	87 (11.2)	472 (22.2)	10.92 (8.08 to 13.76)	<.001
Convalescent plasma therapy	89 (11.5)	235 (11.0)	−0.47 (−3.08 to 2.15)	.72
Enoxaparin	494 (63.8)	1546 (72.6)	8.76 (4.88 to 12.64)	<.001
Hydroxychloroquine	436 (56.3)	11 (0.5)	−55.81 (−59.32 to −52.31)	<.001
Other anticoagulants	333 (43.0)	635 (29.8)	−13.21 (−17.20 to −9.22)	<.001
Pulmonary diagnoses, severity of care indicators, and outcomes, No. (%)[d]				
Pneumonia	658 (85.3)	1435 (87.8)	2.53 (−0.43 to 5.50)	.09
Acute respiratory distress syndrome	146 (18.9)	76 (5.1)	−13.81 (−16.79 to −10.84)	<.001
Lower respiratory tract infection	23 (3.0)	13 (0.9)	−2.11 (−3.41 to −0.82)	<.001
Acute bronchitis	20 (2.6)	24 (1.6)	−0.98 (−2.27 to 0.32)	.11
ICU admission	295 (38.1)	427 (20.1)	−18.07 (−21.89 to −14.25)	<.001
Invasive mechanical ventilator use	186 (24.0)	230 (10.8)	−13.23 (−16.52 to −9.95)	<.001
Ventilation days, median (IQR)[e]	13 (5 to 26)	5.7 (3 to 10.3)	−7.31 (−9.58 to −5.05)	<.001
Extracorporeal membrane oxygenation	15 (1.9)	6 (0.3)	−1.65 (−2.65 to −0.66)	<.001
Currently hospitalized	0	652 (30.6)	30.61 (28.65 to 32.57)	<.001
Died	94 (12.1)	75 (3.5)	−8.62 (−11.05 to −6.19)	<.001
Died (excluding currently hospitalized)[d]		75 (5.1)	−7.07 (−9.63 to −4.51)	<.001
Died (ICU admissions excluding currently hospitalized)[d,f]	81 (27.5)	49 (22.9)	−4.56 (−12.15 to 3.03)	.24
Length of hospital stay, median (IQR), d[d]	7.1 (3.9 to 14.4)	4.8 (2.8 to 7.8)	−2.31 (−2.78 to −1.84)	<.001

Date of download: 9/11/2020
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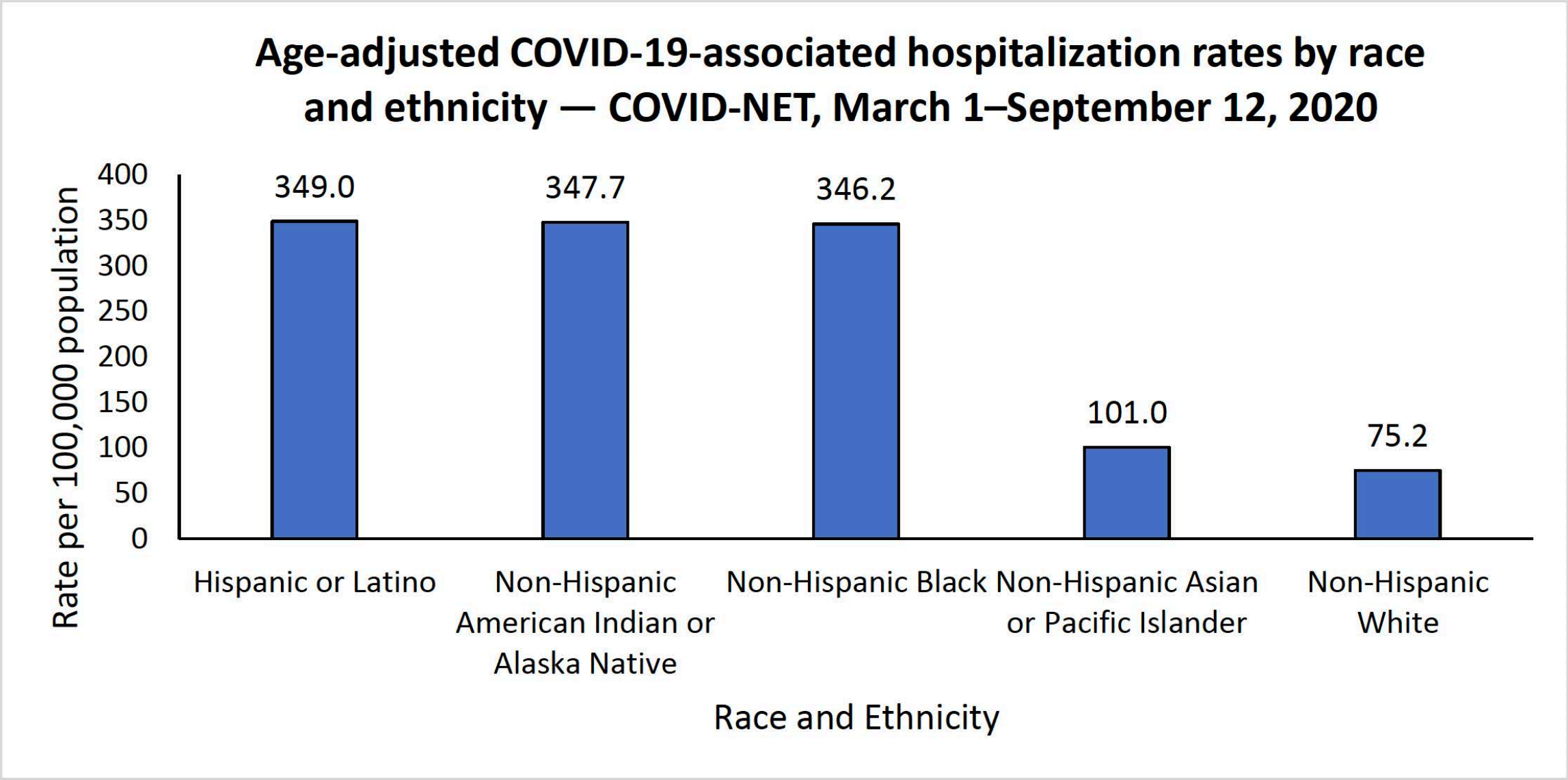
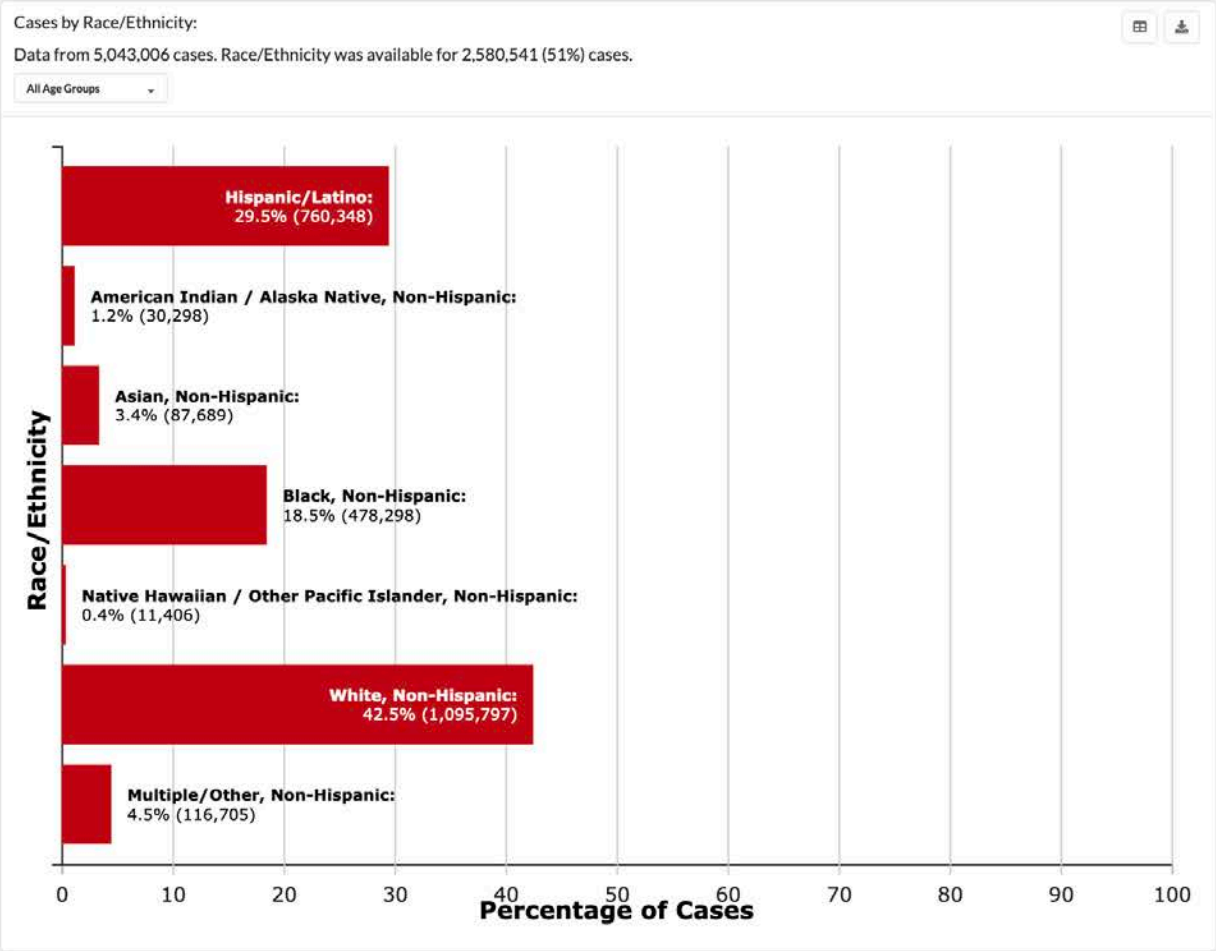
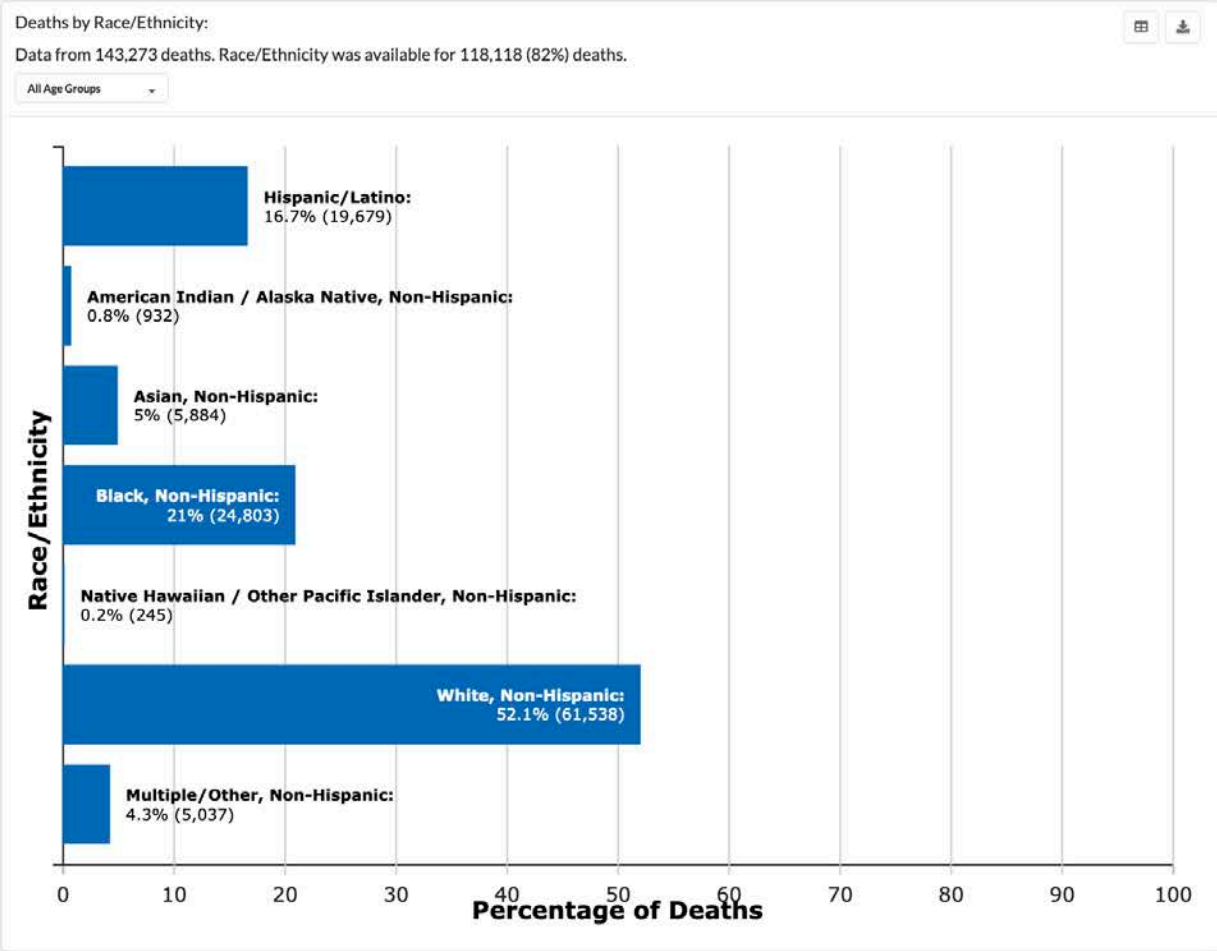
Racial Disparities



https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html

Racial Disparities





https://covid.cdc.gov/covid-data-tracker/?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fcases-updates%2Fcases-in-us.html#demographics

Seroprevalence in the US

New York City Data from Round 2

Seroprevalence Detail for New York City Metro Area

About the study

Site: New York City Metro Area Round: 2

23.2% (95% confidence interval: 20.0 - 26.3%)
Age and sex standardized seroprevalence estimate

April 25 - May 6 2020
When samples were collected

281,670
Cases reported by 5/6/2020

2,832,000
Estimated infections based on seroprevalence

At Least 10x higher
Difference between estimated number of infections based on seroprevalence and reported case counts

Catchment area: Suffolk, Kings, Queens, Nassau, New York, Westchester, Richmond, Bronx

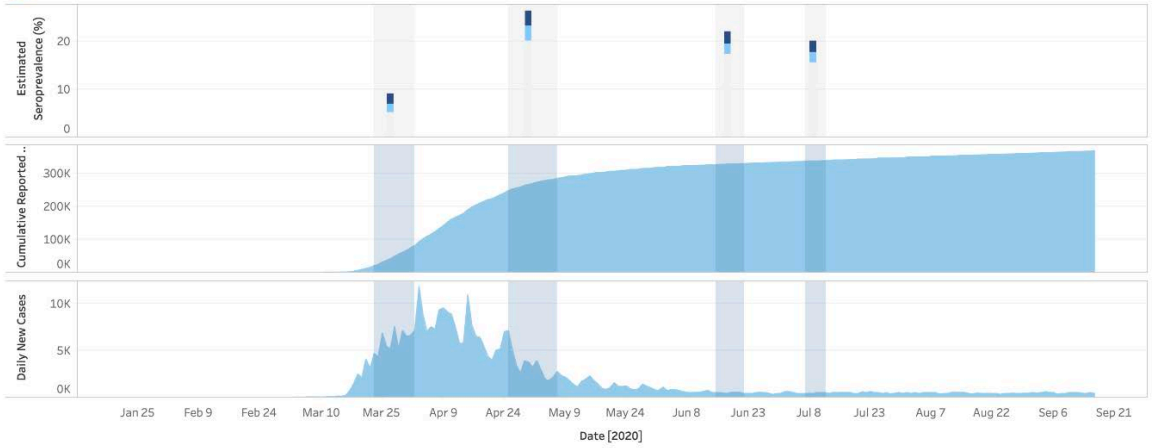
Number of samples collected: 1,116

Age-Specific Seroprevalence Estimate

		Samples
0-18	21.5%	238
19-49	23.6%	268
50-64	29.1%	170
65+	15.8%	440

Sex-Specific Seroprevalence Estimate

		Samples
Male	22.6%	584
Female	19.4%	532



Limitations: A full list of limitations interpreting this data can be found at https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/commercial-lab-surveys.html#interpreting-serology-results

Utah Data from Round 4

Seroprevalence Detail for Utah

About the study

Site: Utah Round: 4

2.7% (95% confidence interval: 1.8 - 3.9%)
Age and sex standardized seroprevalence estimate

July 6 - July 15 2020
When samples were collected

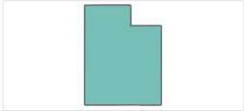
28,303
Cases reported by 7/15/2020

58,000
Estimated infections based on seroprevalence

At Least 2x higher
Difference between estimated number of infections based on seroprevalence and reported case counts

Catchment area: Adults 19+ (State-wide)

Number of samples collected: 1,824

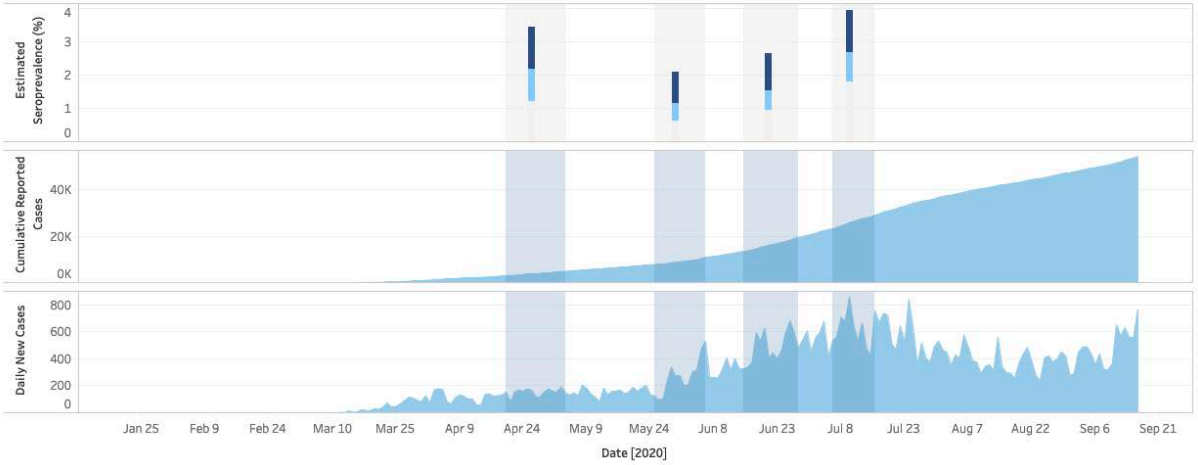


Age-Specific Seroprevalence Estimate

		Samples
0-18	0.0%	39
19-49	3.3%	744
50-64	2.2%	525
65+	0.8%	516

Sex-Specific Seroprevalence Estimate

		Samples
Male	2.2%	1,047
Female	2.3%	777



Limitations: A full list of limitations interpreting this data can be found at https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/commercial-lab-surveys.html#interpreting-serology-results

https://covid.cdc.gov/covid-data-tracker/?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fcases-updates%2Fcommercial-labs-interactive-serology-dashboard.html#serology-surveillance

COVID-19 Current State of the Pandemic

NETEC

Testing Needs

- **Minimum level of testing needed to mitigate the disease:**
  - **Daily capacity to test anyone who has flu-like symptoms**
  - **AND an additional 10 people per positive virus test**

- **Goals for suppression of the virus are much higher**

Image credit: https://covid19.sanantonio.gov/News-Events/Featured-News/Getting-Tested

Two Approaches to Combating COVID-19

2 Approaches To Combating COVID-19

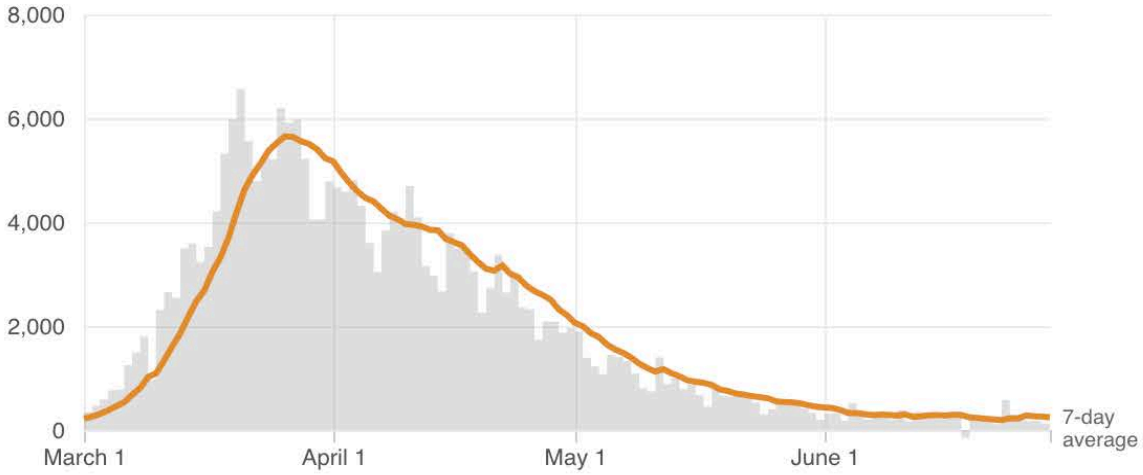
Mitigation

WHAT A CASE CURVE LOOKS LIKE (TENNESSEE)

- **Methods:** Testing of symptomatic people, contact tracing and isolation help slow the transmission rate. Mask wearing, social distancing and stay-home orders used as needed.
- **Effect:** Cases go down temporarily, but many infections remain undetected and outbreaks can spike as social distancing is loosened.
- **Target:** 10% or fewer tests come back positive.

Suppression

WHAT A CASE CURVE LOOKS LIKE (ITALY)

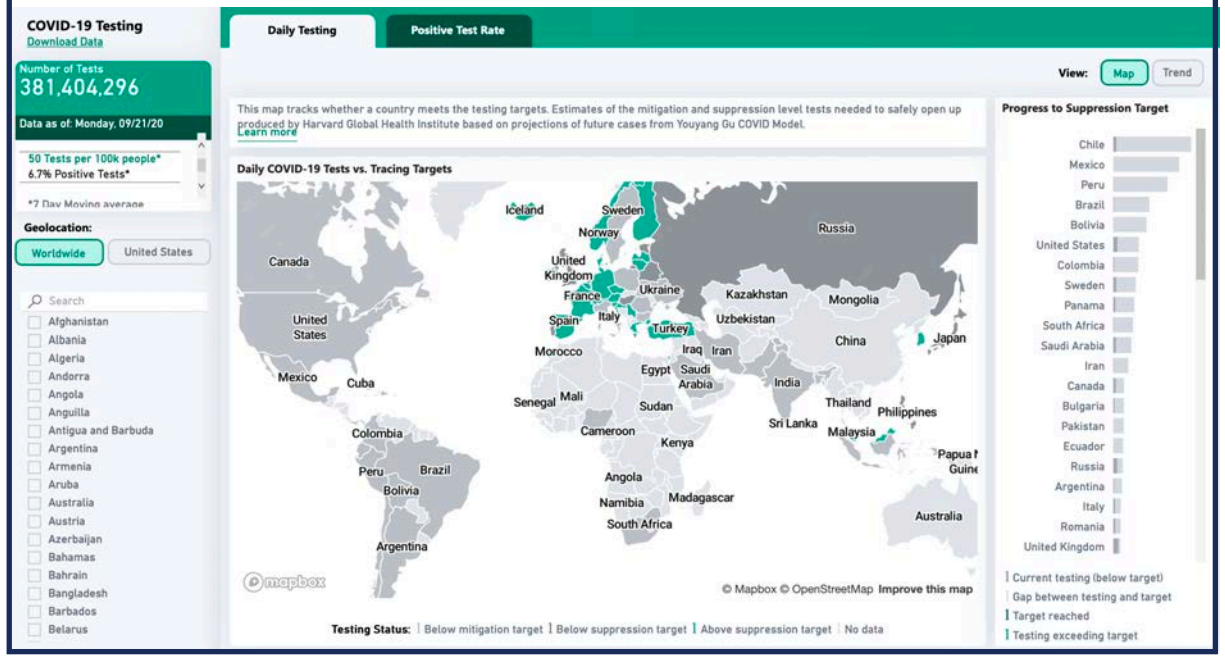


- **Methods:** Regular proactive testing of asymptomatic people in high-risk situations, paired with contact tracing and isolation. Mask-wearing, social distancing and hand-washing are still practiced.
- **Effect:** Cases are detected and isolated before outbreaks can grow. New cases dwindle and remain at or near zero.
- **Target:** 3% or fewer tests come back positive.

Source: Harvard Global Health Institute, TTSI Collaborative, Center for Systems Science and Engineering at Johns Hopkins University (as of June 29)

Current Testing Levels Worldwide

Daily Testing Levels for the World

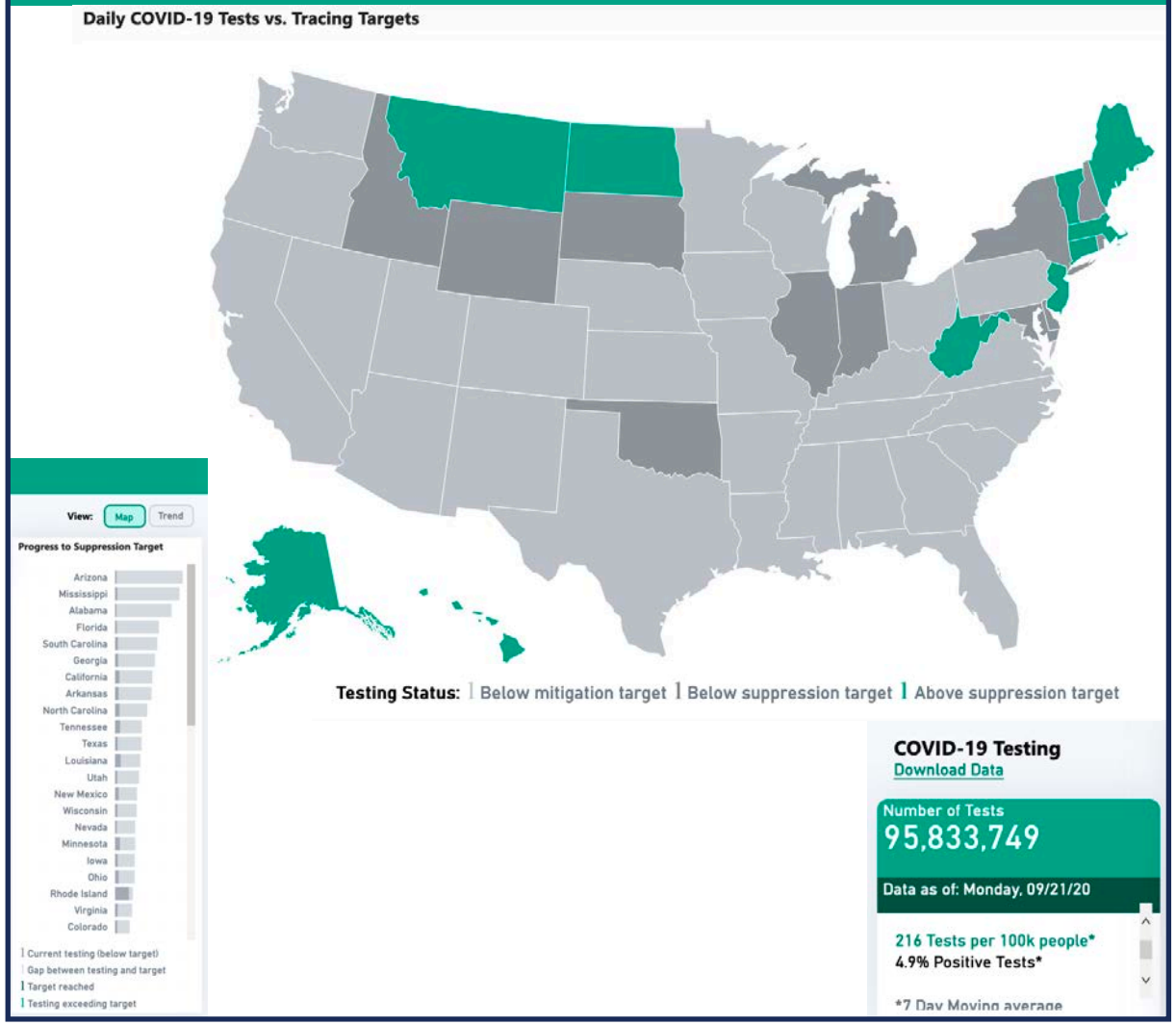


Positive Testing Levels for the World

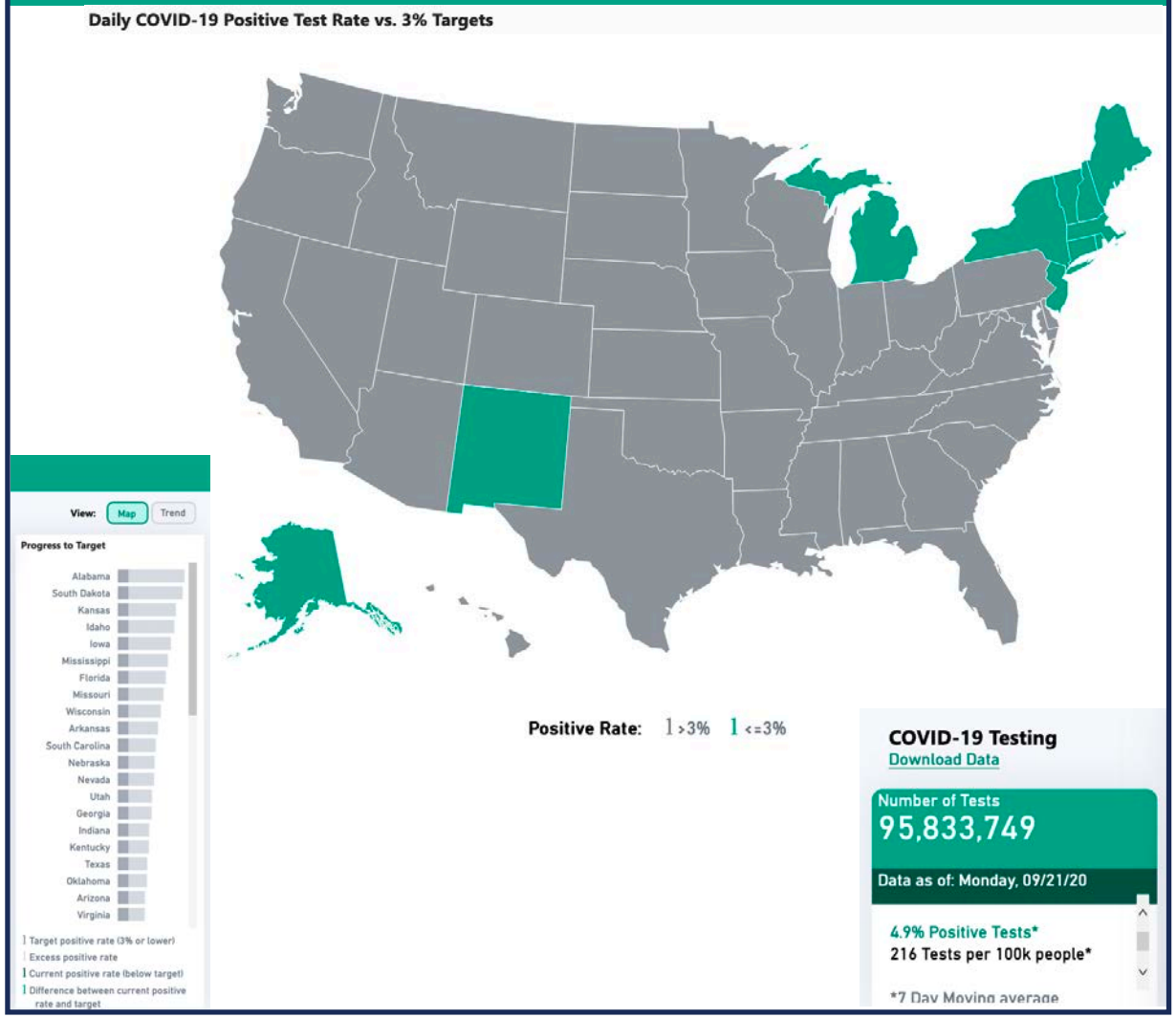
https://globalepidemics.org/july-6-2020-state-testing-targets/

Current Testing Levels in the US

Daily Testing Levels in the United States



Positive Testing Levels in the United States



https://globalepidemics.org/july-6-2020-state-testing-targets/

EXAMPLE:

Meets Mitigation and Does not Meet Suppression

SELECT A LOCATION: New York

Outbreak: Moderate relative to the state's population size. New cases are lower than 2 weeks ago.

Testing: Currently **meets mitigation** and **does not meet suppression** testing targets.

New daily COVID-19 cases (7-day average) *June 23-29*	688 cases/day *4 per 100K*
Current daily testing (7-day average) *June 23-29*	58,688 tests *302 per 100K*
Daily testing needed for **mitigation**	29,591 tests *152 per 100K*
Daily testing needed for **suppression**	105,633 tests *543 per 100K*

Notes: These testing targets, from the Harvard Global Health Institute and the TTSI Collaborative, are based on estimates of how many new COVID-19 cases might exist on July 6 based on outbreak data as of June 29. Daily new cases and daily testing are averages of data reported June 23-29. Data quality varies by state.

Source: Harvard Global Health Institute, TTSI Collaborative, Center for Systems Science and Engineering at Johns Hopkins University, The COVID Tracking Project, Census Bureau 2019 population estimates

EXAMPLE:

Does not Meet Mitigation And Does not Meet Suppression

SELECT A LOCATION: Georgia

Outbreak: Significant relative to the state's population size. New cases are higher than 2 weeks ago.

Testing: Currently **does not meet mitigation** and **suppression** testing targets.

New daily COVID-19 cases (7-day average) *June 23-29*	1,927 cases/day *18 per 100K*
Current daily testing (7-day average) *June 23-29*	16,442 tests *155 per 100K*
Daily testing needed for **mitigation**	64,048 tests *603 per 100K*
Daily testing needed for **suppression**	237,270 tests *2,235 per 100K*

Notes: These testing targets, from the Harvard Global Health Institute and the TTSI Collaborative, are based on estimates of how many new COVID-19 cases might exist on July 6 based on outbreak data as of June 29. Daily new cases and daily testing are averages of data reported June 23-29. Data quality varies by state.

Source: Harvard Global Health Institute, TTSI Collaborative, Center for Systems Science and Engineering at Johns Hopkins University, The COVID Tracking Project, Census Bureau 2019 population estimates

COVID-19 Current State of the Pandemic

NETEC

Barriers	Next Steps
Testing capacity and speed in each state is variable Supply chain is overstressed	Move to rapid antigen tests?

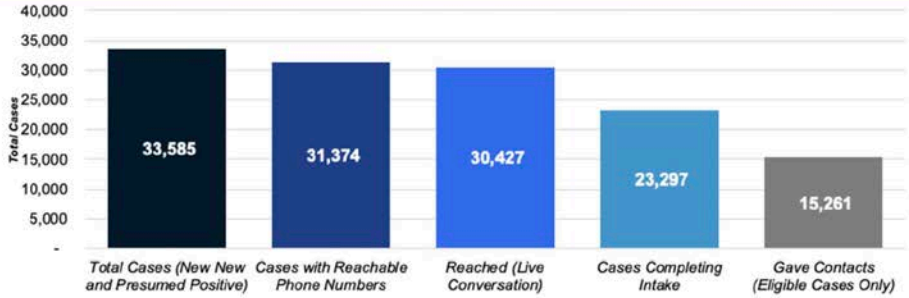
Test and Tracing Corps – New York City

Contact Tracing Program Performance Over Time

Program Goals	Cumulative Results	Last 2 Week Period (8/23 – 9/5)
90% of all cases reached	**91%** of all cases reached	**93.3%** of all cases reached
75% of all cases complete intake	**69%** of all cases complete intake	**76.5%** of all cases complete intake
75% of all contacts complete intake	**56%** of all contacts complete intake	**59.8%** of all contacts complete intake

1

Cumulative Progress through New COVID-19 Cases



Among cumulative cases as of this week...

33,585	93%	91%	69%	70%
Total Cases	of all cases had a reachable phone number.	of all cases were reached for a live conversation.	of all cases complete intake.	of eligible cases completing intake gave contacts.

Among cumulative cases as of last week...

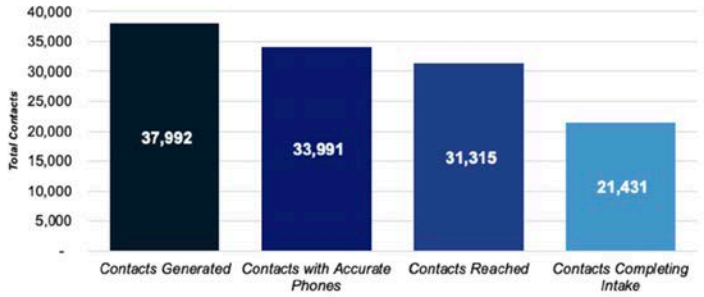
31,305	93%	90%	69%	71%
Total Cases	of all cases had a reachable phone number. (29,174)	of all cases were reached for a live conversation. (28,288)	of all cases complete intake. (21,552)	of eligible cases completing intake gave contacts. (14,177)

NYC HEALTH+ HOSPITALS

https://hhinternet.blob.core.windows.net/uploads/2020/09/test-and-trace-data-metrics-20200909.pdf

Test and Tracing Corps – New York City

Cumulative Progress through New COVID-19 Contacts



Among cumulative contacts as of this week...

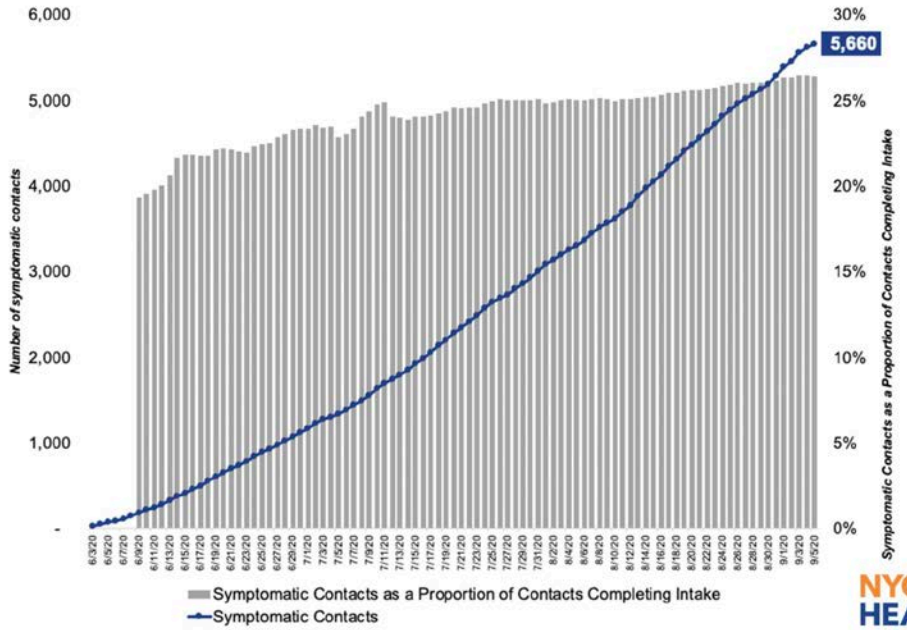
37,992	89%	82%	56%
Total Contacts	of all contacts had a reachable phone number.	of all contacts were reached for a live conversation.	of all contacts complete intake.

Among cumulative contacts as of last week...

35,100	89%	82%	56%
Total Contacts	of all contacts had a reachable phone number. (31,287)	of all contacts were reached for a live conversation. (28,878)	of all contacts complete intake. (19,695)

NYC HEALTH+ HOSPITALS

Cumulative Symptomatic Contacts



**Symptomatic cases are identified through the process of following up on contacts, as opposed to regular testing.*

NYC HEALTH+ HOSPITALS

https://hhinternet.blob.core.windows.net/uploads/2020/09/test-and-trace-data-metrics-20200909.pdf

COVID-19 Current State of the Pandemic

NETEC

Massachusetts Test and Tracing Through PIH

MA Contact Tracing: Total Cases and Contacts and Percentage Outreach Completed

Cases Identified for Outreach: 99,286 (Apr. 10, 2020 – Sept. 5, 2020)	
Local Health Departments: 66,112 Cases Identified for Outreach	Community Tracing Collaborative: 33,174 Cases Identified for Outreach

Contacts Identified for Outreach: 66,123 (Apr. 10, 2020 – Sept. 5, 2020)	
Local Health Departments: 39,282 Contacts Identified for Outreach	Community Tracing Collaborative: 26,841 Contacts Identified for Outreach

Case Outreach Completed: 91.5% (Apr. 10, 2020 – Sept. 5, 2020)	
Local Health Departments: 94.8% Cases with Outreach Completed	Community Tracing Collaborative: 84.9% Cases with Outreach Completed

Contact Outreach Completed: 78.4% (Apr. 10, 2020 – Sept. 5, 2020)	
Local Health Departments: 70.6% Contacts with Outreach Completed	Community Tracing Collaborative: 89.8% Contacts with Outreach Completed

Total Workforce (Sept. 8, 2020)	**1,887**
Local Health + MDPH	1,200
CTC	687

Combined case investigation, contact tracing, and monitoring workforce

Note: The COVID-19 Community Tracing Collaborative (CTC) began operation on April 10, 2020. Data in this dashboard reflects the combined contact tracing of Local Health Departments, Massachusetts Department of Public Health (MDPH) and the CTC since that date. Prior to April 10, 2020, all COVID-19 contact tracing in Massachusetts was conducted by Local Health Departments.

https://www.mass.gov/doc/weekly-covid-19-public-health-report-september-9-2020/download

COVID-19 Current State of the Pandemic

NETEC

Are Re-infections Possible?

- Several reports have been published of possible re-infection cases
- Until end of August, all were found to have other explanations for their repeat positive PCR test
- 2 new published cases in Hong Kong and Nevada were announced at the end of August

COVID-19 Current State of the Pandemic

NETEC

Re-infections

RESEARCH

CORONAVIRUS

SARS-CoV-2 infection protects against rechallenge rhesus macaques

Abishek Chandrashekar[1]*, Jinyan Liu[1]*, Amanda J. Martinot[1,2]*, Katherine McMahan[1]*, Noe B. Mercado[1]*, Lauren Peter[1]*, Lisa H. Tostanoski[1]*, Jingyou Yu[1]*, Zoltan Maliga[3], Michael Nekorchuk[4], Kathleen Busman-Sahay[4], Margaret Terry[4], Linda M. Wrijil[2], Sarah Ducat[2], David R. Martinez[5], Caroline Atyeo[3,6], Stephanie Fischinger[6], John S. Burke[6], Matthew D. Slein[6], Laurent Pessaint[7], Alex Van Ry[7], Jack Greenhouse[7], Tammy Taylor[7], Kelvin Blade[7], Anthony Cook[7], Brad Finneyfrock[7], Renita Brown[7], Elyse Teow[7], Jason Velasco[7], Roland Zahn[8], Frank Wegmann[8], Peter Abbink[1], Esther A. Bondzie[1], Gabriel Dagotto[1,3], Makda S. Gebre[1,3], Xuan He[1], Catherine Jacob-Dolan[1,3], Nicole Kordana[1], Zhenfeng Li[1], Michelle A. Lifton[1], Shant H. Mahrokhian Lori F. Maxfield[1], Ramya Nityanandam[1], Joseph P. Nkolola[1], Aaron G. Schmidt[6,9], Andrew D. Miller[10], Ralph S. Baric[5], Galit Alter[6,9], Peter K. Sorger[3], Jacob D. Estes[4], Hanne Andersen[7], Mark G. Lewis[7], Dan H. Barouch[1,6,9]†

- Rhesus Macaques exposed to SARS-CoV-2 were re-challenged with the same strain of virus on day 35 after initial infection
- Peak viral load was lower in the nasal swab and bronchoalveolar lavage specimens
- Limitations:
  - Rhesus macaques, not human infection
  - Re-infected very soon after initial infection

Case #1

- 33-year-old man living in Hong Kong
- In March 2020 had cough, sore throat, fever, headache
- 3/26/20: positive for SARS-CoV-2
- 3/29/20: hospitalized
- 4/14/20: discharged from hospital
  - 2 negative PCR tests done prior to discharge
- Traveled to Spain, with stop in the United Kingdom
- 8/15/20: Tested positive for SARS-CoV-2 on return at the Hong Kong airport
- Remained asymptomatic
  - No changes on CXR
  - No significant lab abnormalities
- Serial PCR tests showed reduction in cycle threshold

Case #1

- Specimens from first episode and second episode = negative for IgG
- Test done on day 5 post-second episode = positive for IgG
- Genomic analysis done
  - Cases were from a different clade/lineage
  - First genome = closely related to USA and England strains from March + April 2020
  - Second genome = closely related to Switzerland and England strains from July + August 2020
- 4.5 months between the two infection episodes

Case #2

- 25-year-old from Reno, Nevada
  - No history of immunosuppressing conditions
  - Not on any immunosuppressive medications
- 3/25/20: Onset of sore throat, cough, headache, nausea, diarrhea
- 4/18/20: Tested positive for SARS-CoV-2
- 4/27/20: Symptoms resolved
- 5/9/20: Negative PCR test
- 5/26/20: Negative PCR test
- 5/28/20: started to develop fevers, headache, dizziness, cough, nausea, diarrhea
- 5/31/20: presented to care, CXR performed with normal appearance, sent home
- 6/5/20: presented again, was found to be hypoxemic, transferred to nearest ED
  - CXR showed new patchy bilateral interstitial opacities
  - RT-PCR positive for SARS-CoV-2
- 6/6/20: IgM/IgG for SARS-CoV-2 positive

Case #2

- Second infection occurred at the same time as their parent was diagnosed positive for SARS-CoV-2
- Sequencing is ongoing of the parent's viral genome to see if it is similar to the second infection in the index patient
- Number of mutations from Case A to Case B = rate of 83.64 substitutions per year compared to 23.12 per year
- Virus A and B were in the same clade --> exposure to the virus may not result in 100% immunity for all individuals

Cases #3 and #4

- One case in the Netherlands and one in Belgium have been reported, but not published
- Most details unknown so far
- Netherlands
  - Elderly person with weakened immune system
- Belgium
  - 50-year-old woman had coronavirus in March and diagnosed again in June
  - First and second case were mild
  - Developed very few antibodies after her first infection

COVID-19 Current State of the Pandemic

NETEC

Ongoing Questions

? How often does re-infection happen and why?

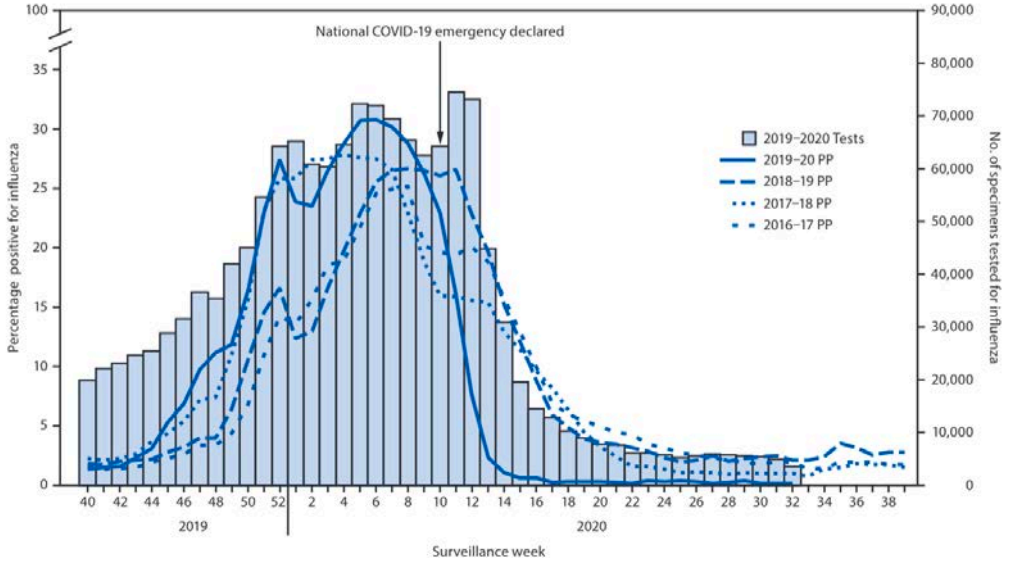
? Will cases be as severe as the first infection?

? When re-infection happens, will these new cases carry the same risk of transmission as the first infection?

Influenza + COVID-19

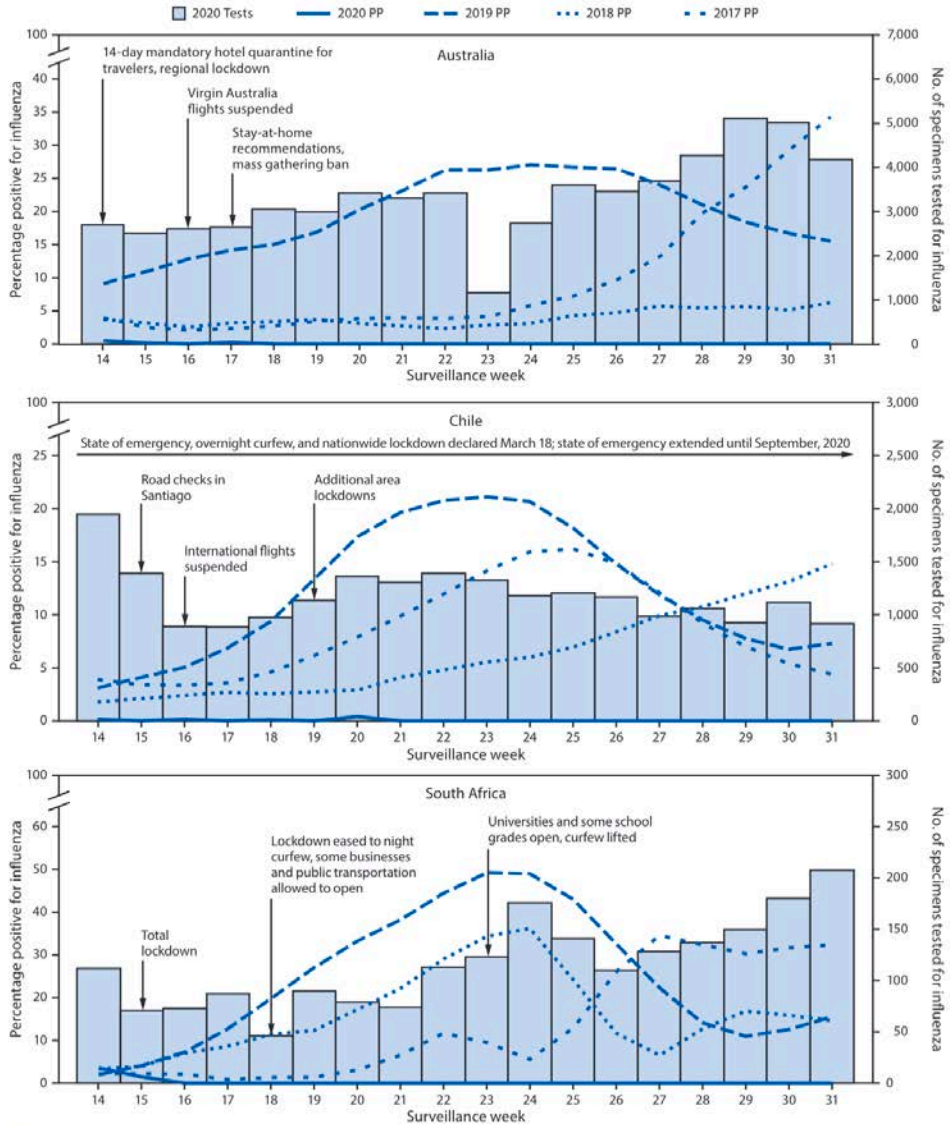
- **Summer circulation of influenza in the US is currently at historical lows**
  - **0.20% in 2020 versus 2.35% in 2019**
- **Data from Australia, Chile, South Africa show very low influenza activity during June-August 2020**
  - **0.06% compared to 13.7%**

FIGURE 1. Number of respiratory specimens tested and percentage testing positive for influenza, by year — United States, 2016–17 through 2019–20 seasons



Source: FluView Interactive. https://www.cdc.gov/flu/weekly/fluviewinteractive.htm.
Abbreviation: PP = percentage positive.

FIGURE 2. Number of specimens tested and percentage testing positive for influenza, by year — Australia, Chile, and South Africa, April–August (weeks 14–31), 2017–20



Source: FluNet. https://www.who.int/influenza/gisrs_laboratory/flunet/en/.
Abbreviation: PP = percentage positive.

COVID-19 Current State of the Pandemic

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Latest Treatment Updates

Remdesivir

Corticosteroids

Convalescent Plasma

Image credit: NIAID - Colorized scanning electron micrograph of an apoptotic cell (tan) infected with SARS-COV-2 virus particles (orange), isolated from a patient sample

COVID-19 Current State of the Pandemic

NETEC

Latest Treatment Updates: Remdesivir

- Nucleotide analogue, inhibitor of the viral RNA-dependent, RNA polymerase
- Shows inhibitory activity against MERS-CoV and SARS-CoV-1
- Originally trialed in Ebola epidemic

NETEC

Latest Treatment Updates: Remdesivir

ORIGINAL ARTICLE

Remdesivir for the Treatment of Covid-19 — Preliminary Report

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*

Latest Treatment Updates: Remdesivir

Table 1. Demographic and Clinical Characteristics at Baseline.*

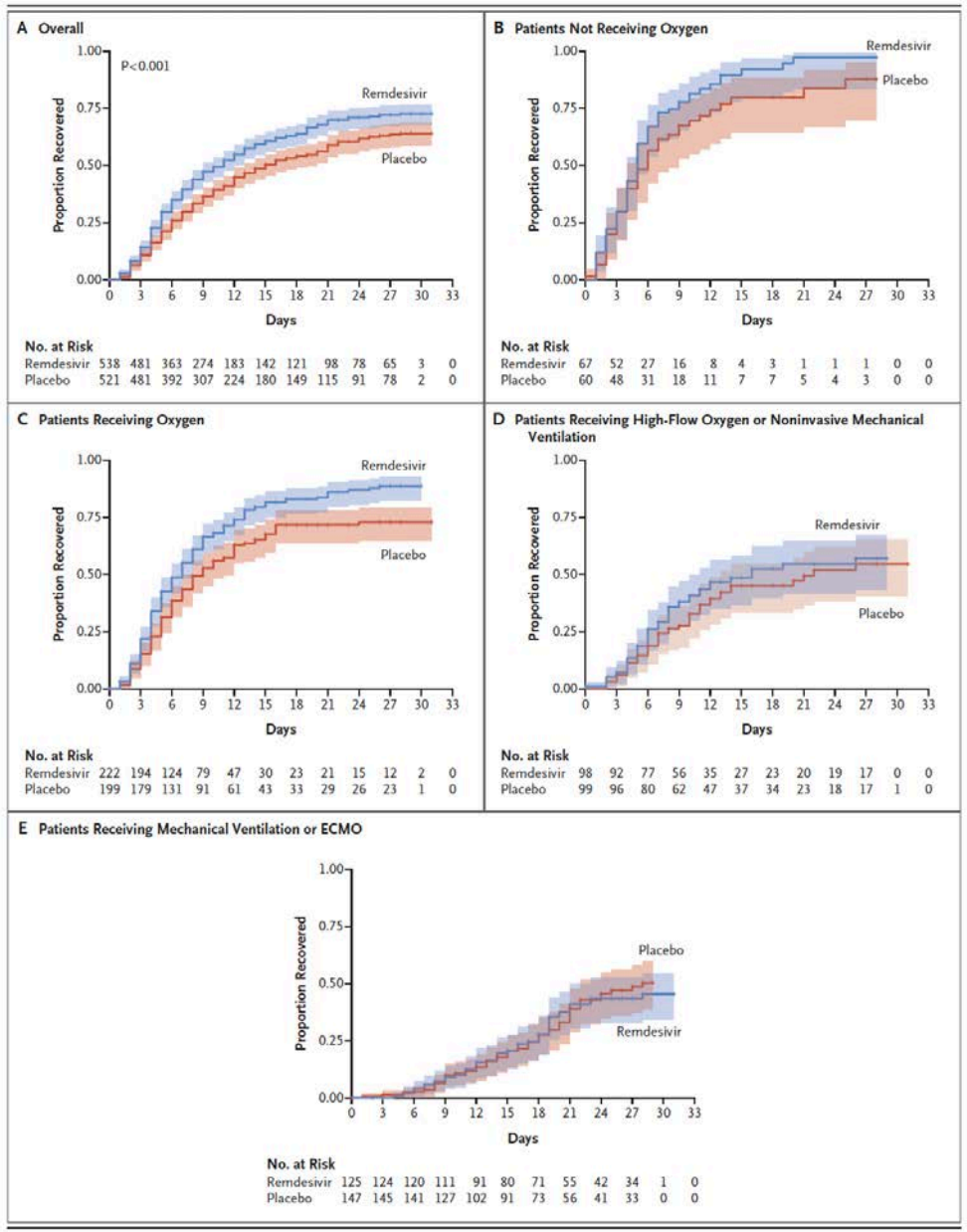
Characteristic	All (N=1063)	Remdesivir (N=541)	Placebo (N=522)
Age — yr	58.9±15.0	58.6±14.6	59.2±15.4
Male sex — no. (%)	684 (64.3)	352 (65.1)	332 (63.6)
Race or ethnic group — no. (%)†			
American Indian or Alaska Native	7 (0.7)	4 (0.7)	3 (0.6)
Asian	134 (12.6)	77 (14.2)	57 (10.9)
Black or African American	219 (20.6)	108 (20.0)	111 (21.3)
White	565 (53.2)	279 (51.6)	286 (54.8)
Hispanic or Latino — no. (%)	249 (23.4)	132 (24.4)	117 (22.4)
Median time (IQR) from symptom onset to randomization — days‡	9 (6–12)	9 (6–12)	9 (7–13)
No. of coexisting conditions — no. /total no. (%)‡			
None	193/920 (21.0)	91/467 (19.5)	102/453 (22.5)
One	248/920 (27.0)	131/467 (28.1)	117/453 (25.8)
Two or more	479/920 (52.1)	245/467 (52.5)	234/453 (51.7)
Coexisting conditions — no./total no. (%)			
Hypertension	460/928 (49.6)	231/469 (49.3)	229/459 (49.9)
Obesity	342/925 (37.0)	177/469 (37.7)	165/456 (36.2)
Type 2 diabetes	275/927 (29.7)	144/470 (30.6)	131/457 (28.7)
Score on ordinal scale — no. (%)			
4. Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care (Covid-19–related or otherwise)	127 (11.9)	67 (12.4)	60 (11.5)
5. Hospitalized, requiring supplemental oxygen	421 (39.6)	222 (41.0)	199 (38.1)
6. Hospitalized, receiving noninvasive ventilation or high-flow oxygen devices	197 (18.5)	98 (18.1)	99 (19.0)
7. Hospitalized, receiving invasive mechanical ventilation or ECMO	272 (25.6)	125 (23.1)	147 (28.2)
Baseline score missing	46 (4.3)	29 (5.4)	17 (3.3)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. IQR denotes interquartile range. The full table of baseline characteristics is available in the Supplementary Appendix.

† Race and ethnic group were reported by the patients. The number of patients in other races and ethnic groups are listed in Table S1 in the Supplementary Appendix.

‡ As of April 28, 2020, data on symptom onset were missing for 15 patients; data on coexisting conditions were missing for 133 patients and were incomplete for 10 patients.

Latest Treatment Updates: Remdesivir



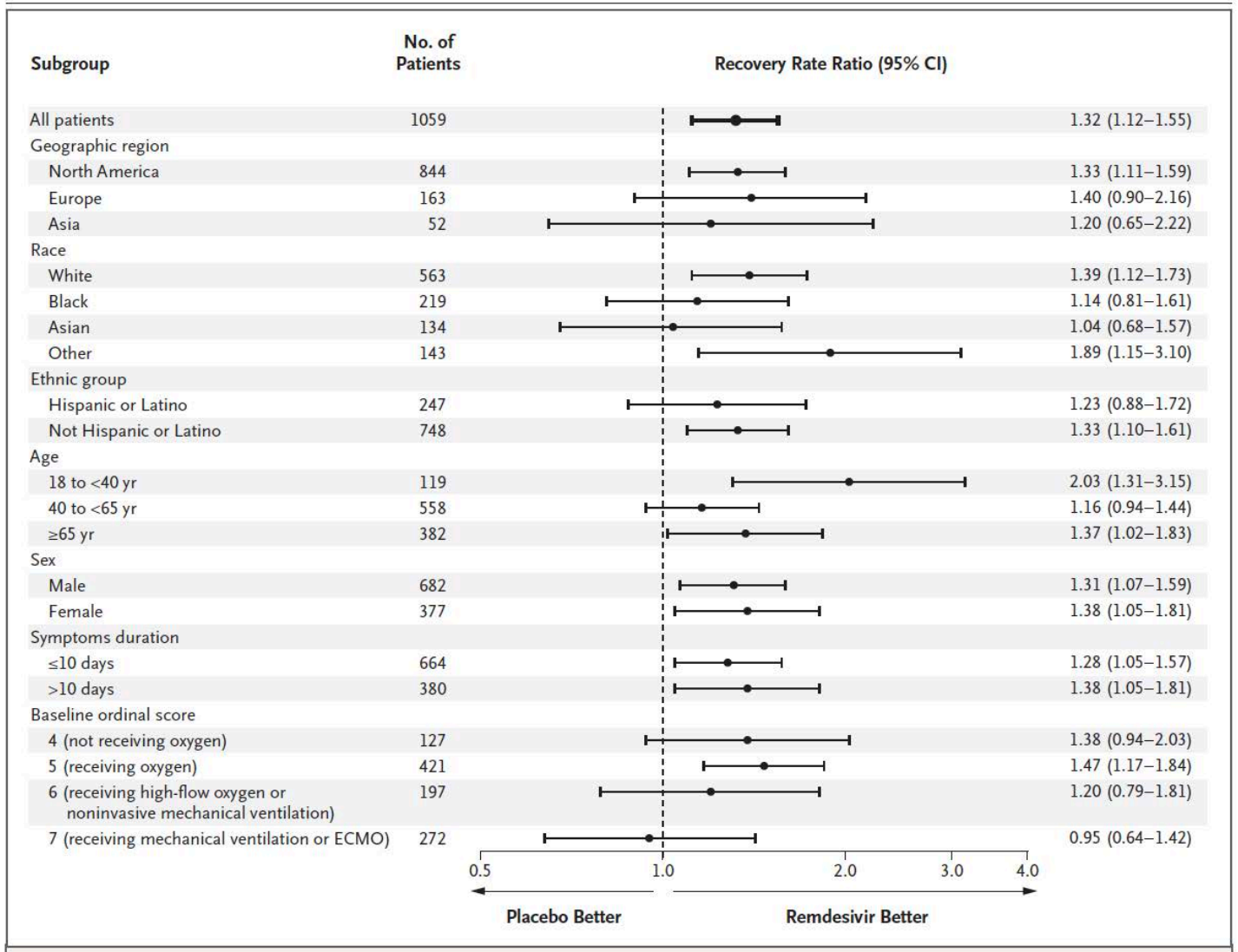


Figure 3. Time to Recovery According to Subgroup.

The widths of the confidence intervals have not been adjusted for multiplicity and therefore cannot be used to infer treatment effects. Race and ethnic group were reported by the patients.

COVID-19 Current State of the Pandemic

NETEC

Latest Treatment Updates: Remdesivir

JAMA Network

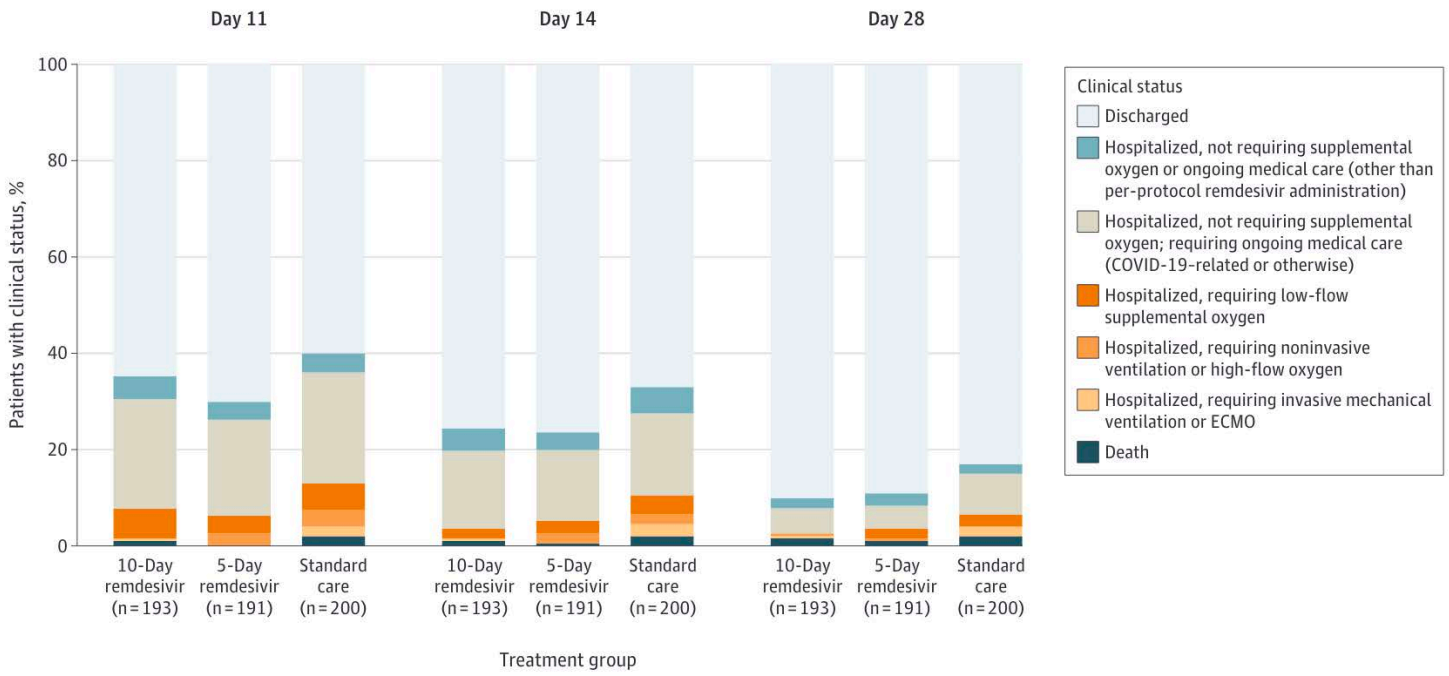
Research

JAMA | Original Investigation

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

Christoph D. Spinner, MD; Robert L. Gottlieb, MD, PhD; Gerard J. Criner, MD; José Ramón Arribas López, MD; Anna Maria Cattelan, MD; Alex Soriano Viladomiu, MD; Onyema Ogbuagu, MD; Prashant Malhotra, MD; Kathleen M. Mullane, DO; Antonella Castagna, MD; Louis Yi Ann Chai, MD; Meta Roestenberg, MD; Owen Tak Yin Tsang, MD; Enos Bernasconi, MD; Paul Le Turnier, MD; Shan-Chwen Chang, MD; Devi SenGupta, MD; Robert H. Hyland, DPhil; Anu O. Osinusi, MD; Huyen Cao, MD; Christiana Blair, MS; Hongyuan Wang, PhD; Anuj Gaggar, MD, PhD; Diana M. Brainard, MD; Mark J. McPhail, MD; Sanjay Bhagani, MD; Mi Young Ahn, MD; Arun J. Sanyal, MD; Gregory Huhn, MD; Francisco M. Marty, MD; for the GS-US-540-5774 Investigators

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

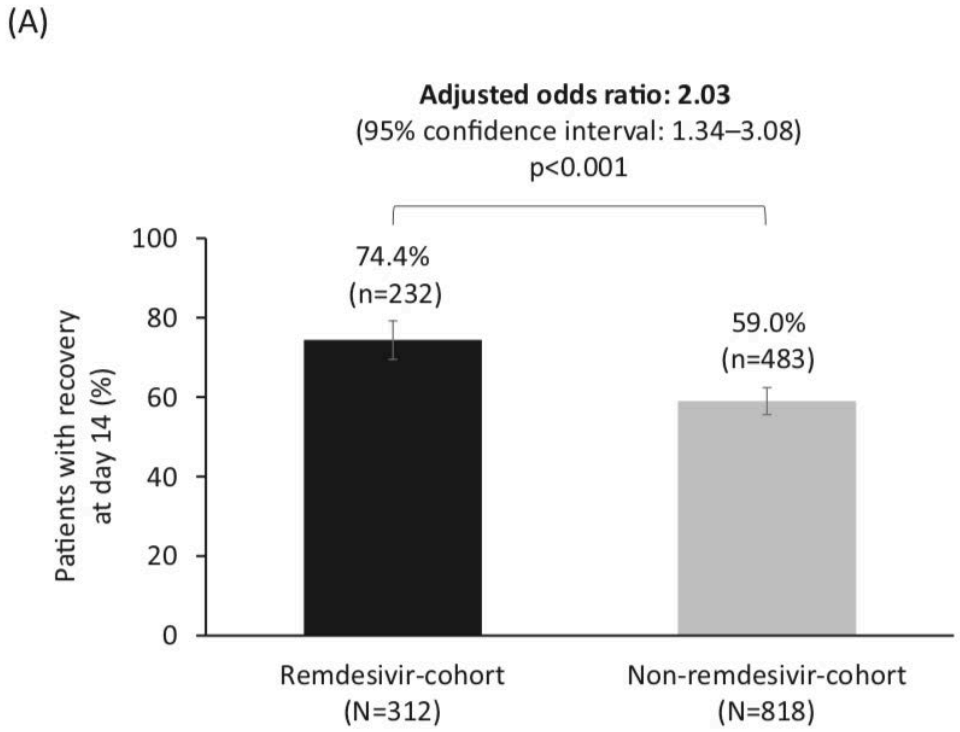


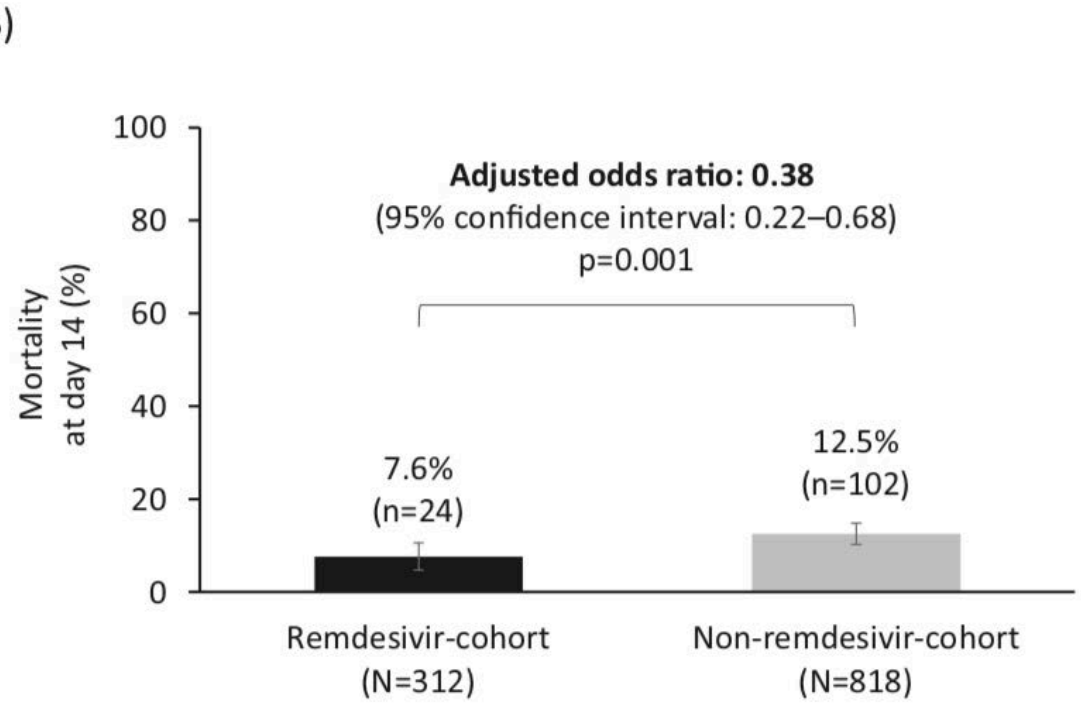
COVID-19 indicates coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation. All percentage values in each point category are provided in eTables 5 and 6 in Supplement 3. At day 11, $P = .18$ for comparison of the distribution of the 10-day remdesivir group vs standard care and $P = .02$ for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

NETEC

Latest Treatment Updates: Remdesivir

- **Remdesivir for severe COVID-19 versus a cohort receiving standard of care**





COVID-19 Current State of the Pandemic

NETEC

Latest Treatment Updates: Remdesivir

- **Lingering Questions:**

? Optimal patient population?

? Optimal duration of therapy?

? Effect on meaningful clinical outcomes?

? Any interaction with corticosteroids?

NETEC

Latest Treatment Updates: Corticosteroids

Background:

- **Steroid use in ARDS has been studied and recently shown improvement in mortality**
- **There have been studies in SARS-CoV-1, MERS, and influenza which showed slower clearance of viral RNA**

SARS: Systematic Review of Treatment Effects

Lauren J. Stockman[1,2*], Richard Bellamy[3], Paul Garner[4]

1 Centers for Disease Control and Prevention, Respiratory and Enteric Viruses Branch, Atlanta, Georgia, United States of America, **2** Department of Veterans' Affairs, Atlanta Research and Education Foundation, Decatur, Georgia, United States of America, **3** James Cook University Hospital, Middlesbrough, United Kingdom, **4** Liverpool School of Tropical Medicine, Liverpool, United Kingdom

Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial

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Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome

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Effects of early corticosteroid treatment on plasma SARS-associated *Coronavirus* RNA concentrations in adult patients

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Latest Treatment Updates: Corticosteroids

The Recovery Trial

Table 1. Characteristics of the Patients at Baseline, According to Treatment Assignment and Level of Respiratory Support.*

Characteristic	Treatment Assignment		Respiratory Support Received at Randomization		
	Dexamethasone (N=2104)	Usual Care (N=4321)	No Receipt of Oxygen (N=1535)	Oxygen Only (N=3883)	Invasive Mechanical Ventilation (N=1007)
Age†					
Mean — yr	66.9±15.4	65.8±15.8	69.4±17.5	66.7±15.3	59.1±11.4
Distribution — no. (%)					
<70 yr	1141 (54)	2504 (58)	659 (43)	2148 (55)	838 (83)
70 to 79 yr	469 (22)	859 (20)	338 (22)	837 (22)	153 (15)
≥80 yr	494 (23)	958 (22)	538 (35)	898 (23)	16 (2)
Sex — no. (%)					
Male	1338 (64)	2749 (64)	891 (58)	2462 (63)	734 (73)
Female‡	766 (36)	1572 (36)	644 (42)	1421 (37)	273 (27)
Median no. of days since symptom onset (IQR)§	8 (5–13)	9 (5–13)	6 (3–10)	9 (5–12)	13 (8–18)
Median no. of days since hospitalization (IQR)	2 (1–5)	2 (1–5)	2 (1–6)	2 (1–4)	5 (3–9)
Respiratory support received — no. (%)					
No oxygen	501 (24)	1034 (24)	1535 (100)	NA	NA
Oxygen only	1279 (61)	2604 (60)	NA	3883 (100)	NA
Invasive mechanical ventilation	324 (15)	683 (16)	NA	NA	1007 (100)
Previous coexisting disease					
Any	1174 (56)	2417 (56)	911 (59)	2175 (56)	505 (50)
Diabetes	521 (25)	1025 (24)	342 (22)	950 (24)	254 (25)
Heart disease	586 (28)	1171 (27)	519 (34)	1074 (28)	164 (16)
Chronic lung disease	415 (20)	931 (22)	351 (23)	883 (23)	112 (11)
Tuberculosis	6 (<1)	19 (<1)	8 (1)	11 (<1)	6 (1)
HIV infection	12 (1)	20 (<1)	5 (<1)	21 (1)	6 (1)
Severe liver disease¶	37 (2)	82 (2)	32 (2)	72 (2)	15 (1)
Severe kidney impairment‖	166 (8)	358 (8)	119 (8)	253 (7)	152 (15)
SARS-CoV-2 test result					
Positive	1850 (88)	3848 (89)	1333 (87)	3416 (88)	949 (94)
Negative	247 (12)	453 (10)	193 (13)	452 (12)	55 (5)
Test result not yet known	7 (<1)	20 (<1)	9 (1)	15 (<1)	3 (<1)

* Plus–minus values are means ±SD. HIV denotes human immunodeficiency virus, IQR interquartile range, NA not applicable, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.

† There was a significant (P=0.01) difference in the mean age between patients in the dexamethasone group and those in the usual care group, but there were no significant differences between the groups in any other baseline characteristic.

‡ Included in this category were 6 pregnant women.

§ Data regarding the number of days since symptom onset were missing for 4 patients in the dexamethasone group and 13 patients in the usual care group; these patients were excluded from estimates of the median number of days since onset.

¶ Severe liver disease was defined as requiring ongoing specialist care.

‖ Severe kidney impairment was defined as an estimated glomerular filtration rate of less than 30 ml per minute per 1.73 m^2.

Latest Treatment Updates: Corticosteroids

The Recovery Trial

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

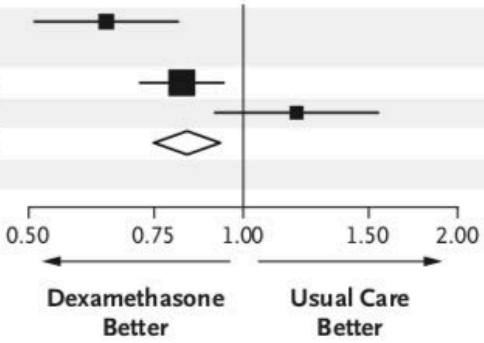

Figure 3. Effect of Dexamethasone on 28-Day Mortality, According to Respiratory Support at Randomization.
Shown are subgroup-specific rate ratios for all the patients and for those who were receiving no oxygen, receiving oxygen only, or undergoing invasive mechanical ventilation at the time of randomization. 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.

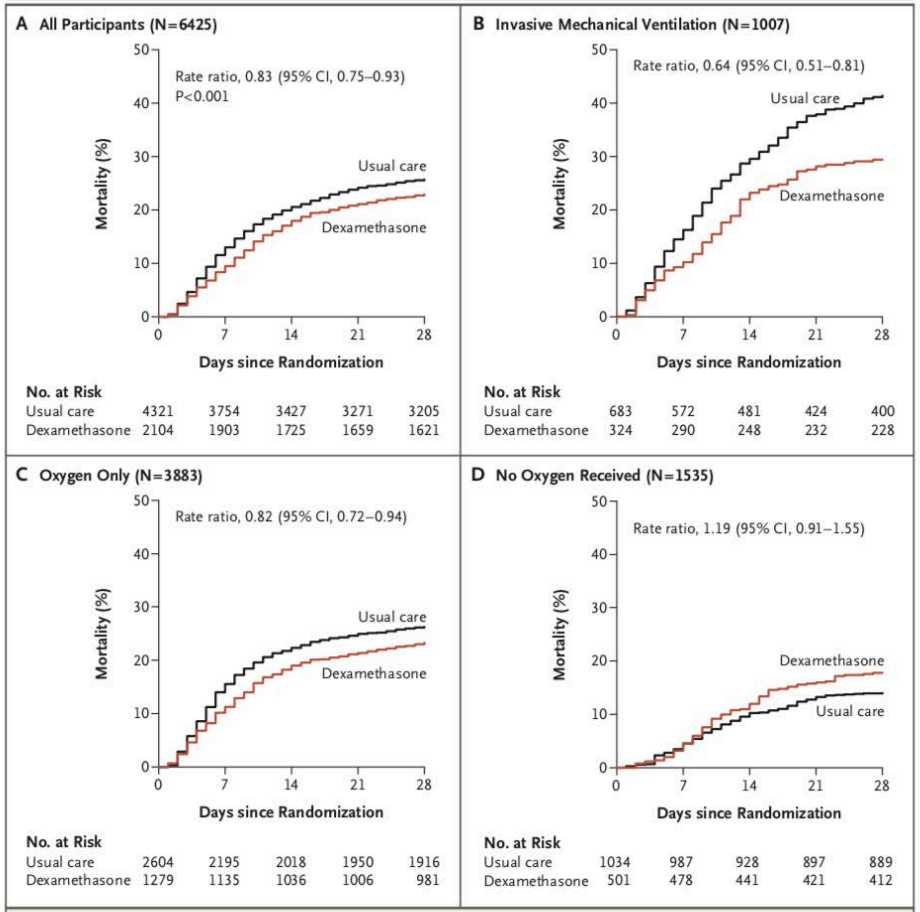

Figure 2. Mortality at 28 Days in All Patients and According to Respiratory Support at Randomization.
Shown are Kaplan–Meier survival curves for 28-day mortality among all the patients in the trial (primary outcome) (Panel A) and in three respiratory-support subgroups according to whether the patients were undergoing invasive mechanical ventilation (Panel B), receiving oxygen only without mechanical ventilation (Panel C), or receiving no supplemental oxygen (Panel D) at the time of randomization. The Kaplan–Meier curves have not been adjusted for age. The rate ratios have been adjusted for the age of the patients in three categories (<70 years, 70 to 79 years, and ≥80 years). Estimates of the rate ratios and 95% confidence intervals in Panels B, C, and D were derived from a single age-adjusted regression model involving an interaction term between treatment assignment and level of respiratory support at randomization.

Latest Treatment Updates: Corticosteroids

The Recovery Trial

Table 2. Primary and Secondary Outcomes.

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

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Latest Treatment Updates: Corticosteroids

Steroid WHO Meta-Analysis

- After the RECOVERY trial was published, most studies stopped enrollment early
- WHO REACT working group spoke to all the trial investigators for the steroid trials registered; agreed to participate and share data
- Risk of bias in trials was assessed as “low” for 6/7 trials
- Summary odds ratio = 0.66 (95% CI, 0.53-0.82, $p<0.001$) for all-cause mortality
  - Excluding RECOVERY trial, OR = 0.77 (95% CI, 0.56-1.07)
- No increase in adverse events
- Strength = 1703 patients included
- Limitation = RECOVERY trial provided 57% of the data

Latest Treatment Updates: Corticosteroids

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

JAMA. Published online September 02, 2020. doi:10.1001/jama.2020.17023

Table 1. Characteristics of Included Trials

	DEXA-COVID 19	CoDEX	RECOVERY	CAPE COVID	COVID STEROID	REMAP-CAP	Steroids-SARI[a]
ClinicalTrials.gov identifier	NCT04325061	NCT04327401	NCT04381936	NCT02517489	NCT04348305	NCT02735707	NCT04244591
Planned sample size	200	350	NA	290	1000	NA[b]	80
Eligibility criteria	• Intubation • Mechanical ventilation • Moderate to severe ARDS per Berlin criteria[9] • Confirmed COVID-19	• Intubation • Mechanical ventilation • Moderate to severe ARDS per Berlin criteria[9] • Onset of ARDS <48 h before randomization • Probable or confirmed COVID-19	Criteria[c] used for this meta-analysis: Intubation Suspected or confirmed COVID-19	• Minimal severity • Admitted to ICU or intermediate care unit • Oxygen (≥6 L/min) • Probable or confirmed COVID-19	• Oxygen (≥10 L/min) • Confirmed COVID-19	• Admitted to ICU receiving high-flow nasal oxygen with FIO_2 ≥0.4 at ≥30 L/min, noninvasive or invasive ventilatory support, or receiving vasopressors • Probable or confirmed COVID-19	• Admitted to ICU with PaO_2:FIO_2 <200 mm Hg on positive pressure ventilation (invasive or noninvasive) or high-flow nasal canulae >45 L/min • Confirmed COVID-19
Corticosteroid							
Drug name	Dexamethasone	Dexamethasone	Dexamethasone	Hydrocortisone	Hydrocortisone	Hydrocortisone	Methylprednisolone
Dosage and administration	20 mg/d intravenously × 5 d and then 10 mg/d intravenously × 5 d	20 mg/d intravenously × 5 d and then 10 mg/d intravenously × 5 d	6 mg/d orally or intravenously	Continuous intravenous infusion × 8 d or 14 d (200 mg/d × 4 d or 7 d; 100 mg/d × 2 d or 4 d; 50 mg/d × 2 d or 3 d)	200 mg/d intravenously × 7 d (continuous or bolus dosing every 6 h)	50 mg intravenously every 6 h × 7 d[d]	40 mg intravenously every 12 h × 5 d
Dose classification	High	High	Low	Low	Low	Low	High
Control intervention	Usual care	Usual care	Usual care	Placebo	Placebo	Usual care	Usual care
Primary outcome	60-d mortality	Ventilator-free days	28-d mortality	21-d treatment failure (death or persistent requirement for mechanical ventilation or high-flow oxygen therapy)	Days alive without life support at 28 d	Composite of hospital mortality and ICU organ support-free days to 21 d	Lower lung injury score at 7 d and 14 d
Mortality outcome, d	28	28	28	21	28	28	30
Serious adverse event definitions	• Secondary infections of pneumonia, sepsis, or other similar • Pulmonary embolism	• Mortality • Infections • Insulin use	• Cause-specific mortality • Ventilation • Dialysis • Cardiac arrhythmia (in a subset) • Other that were believed to be related to study treatment	• Any • Excluded some listed in protocol • Excluded expected adverse events related to the patient's disease or comorbidity	• New episodes of septic shock (Sepsis-3 criteria) • Invasive fungal infection • Clinically important gastrointestinal bleeding • Anaphylaxis	• Per ICH good clinical practice guidelines (events not already captured as a trial end point; eg, mortality) • When the event may reasonably have occurred because of study participation	• Secondary bacterial infections • Barotrauma • Severe hyperglycemia • Gastrointestinal bleeding requiring transfusion • Acquired weakness
Location	Spain	Brazil	UK	France	Denmark	Australia, Canada, European Union, New Zealand, UK, US	China

Abbreviations: ARDS, acute respiratory distress syndrome; CAPE COVID, Community-Acquired Pneumonia: Evaluation of Corticosteroids in Coronavirus Disease; CoDEX, COVID-19 Dexamethasone; COVID-19, coronavirus disease 2019; COVID STEROID, Hydrocortisone for COVID-19 and Severe Hypoxia; DEXA-COVID 19, Efficacy of Dexamethasone Treatment for Patients With ARDS Caused by COVID-19; FIO_2, fraction of inspired oxygen; ICU, intensive care unit; NA, not applicable; RECOVERY, Randomized Evaluation of COVID-19 Therapy; REMAP-CAP, Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia; Sepsis-3, Third International Consensus Definitions for Sepsis and Septic Shock; Steroids-SARI, Glucocorticoid Therapy for COVID-19 Critically Ill Patients With Severe Acute Respiratory Failure.

[a] Trial did not specify whether adverse events were serious or nonserious.

[b] No sample size was specified at the start of the trial.

[c] The RECOVERY trial also recruited hospitalized patients with suspected or confirmed COVID-19 who were not receiving invasive mechanical ventilation at randomization.

[d] Too few patients were randomized to the high-dose group to permit separate analyses.

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COVID-19 Current State of the Pandemic

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Latest Treatment Updates: Corticosteroids

Steroids in COVID-19

CoDEX trial	• Studied in LMIC, mortality rate was much higher than in RECOVERY trial • Patients not on many other treatments due to lack of availability • 35% of standard care group received steroids • Trial was underpowered for mortality
REMAP-CAP trial	• Adaptive, point-of-care trial • Fixed dose versus shock dependent steroid treatment • 15% of standard care received steroids
CAPE COVID trial	• Double-blinded trial • Excluded septic shock patients • Trial underpowered - only 50% of target were enrolled

Latest Treatment Updates: Corticosteroids

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

JAMA. Published online September 02, 2020. doi:10.1001/jama.2020.17023

Drug and trial	ClinicalTrials.gov identifier	Initial dose and administration	No. of deaths/total No. of patients: Steroids	No. of deaths/total No. of patients: No steroids	Odds ratio (95% CI)	Weight, %
Dexamethasone						
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	2/7	2/12	2.00 (0.21-18.69)	0.92
CoDEX	NCT04327401	High: 20 mg/d intravenously	69/128	76/128	0.80 (0.49-1.31)	18.69
RECOVERY	NCT04381936	Low: 6 mg/d orally or intravenously	95/324	283/683	0.59 (0.44-0.78)	57.00
Subgroup fixed effect			166/459	361/823	0.64 (0.50-0.82)	76.60
Hydrocortisone						
CAPE COVID	NCT02517489	Low: 200 mg/d intravenously	11/75	20/73	0.46 (0.20-1.04)	6.80
COVID STEROID	NCT04348305	Low: 200 mg/d intravenously	6/15	2/14	4.00 (0.65-24.66)	1.39
REMAP-CAP	NCT02735707	Low: 50 mg every 6 h intravenously	26/105	29/92	0.71 (0.38-1.33)	11.75
Subgroup fixed effect			43/195	51/179	0.69 (0.43-1.12)	19.94
Methylprednisolone						
Steroids-SARI	NCT04244591	High: 40 mg every 12 h intravenously	13/24	13/23	0.91 (0.29-2.87)	3.46
Overall (fixed effect) $P = .31$ for heterogeneity; $I^2 = 15.6\%$			222/678	425/1025	0.66 (0.53-0.82)	100.0
Overall (random effects[a])			222/678	425/1025	0.70 (0.48-1.01)	

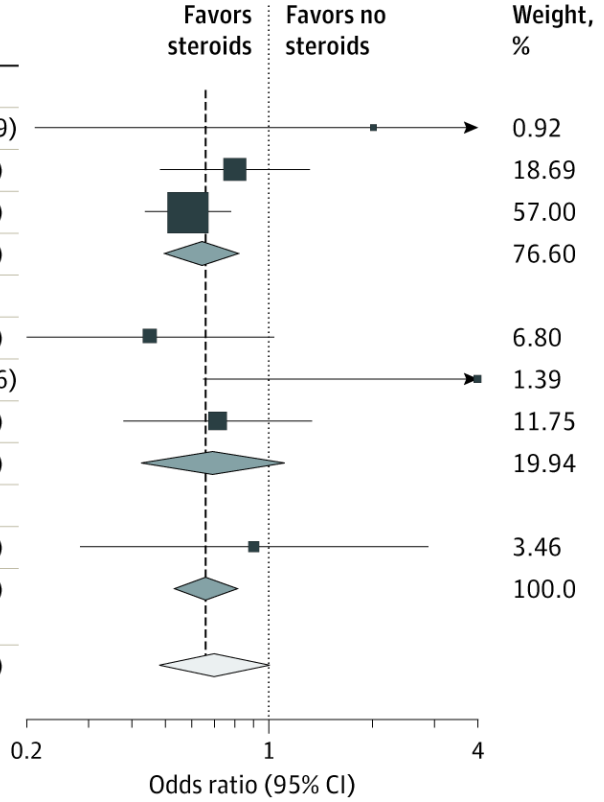

Figure Legend:

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

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Latest Treatment Updates: Corticosteroids

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JAMA. Published online September 02, 2020. doi:10.1001/jama.2020.17023

Subgroup	No. of deaths/total No. of patients: Steroids	No. of deaths/total No. of patients: No steroids	Odds ratio (95% CI)	Weight, %
Invasive mechanical ventilation (IMV)				
No (I^2 = 0%)	14/70	28/74	0.41 (0.19-0.88)	2.7
Yes (I^2 = 44.1%)	208/608	397/951	0.69 (0.55-0.86)	31.7
Oxygen treatment without IMV (RECOVERY)	298/1279	682/2604	0.86 (0.73-1.00)	65.6
Taking vasoactive medication				
No (I^2 = 0%)	51/184	68/184	0.55 (0.34-0.88)	50.2
Yes (I^2 = 0%)	76/169	74/158	1.05 (0.65-1.69)	49.8
Age, y				
≤60 (I^2 = 0%)	72/338	141/483	0.67 (0.48-0.94)	42.7
>60 (I^2 = 49.7%)	150/339	284/541	0.69 (0.51-0.93)	57.3
Sex				
Female (I^2 = 0%)	60/202	106/286	0.66 (0.43-0.99)	27.4
Male (I^2 = 14.7%)	162/476	319/739	0.66 (0.51-0.84)	72.6
Symptomatic, d				
≤7 (I^2 = 69.1%)	51/130	99/211	0.63 (0.39-1.04)	22.4
>7 (I^2 = 0%)	139/418	293/693	0.64 (0.49-0.83)	77.6

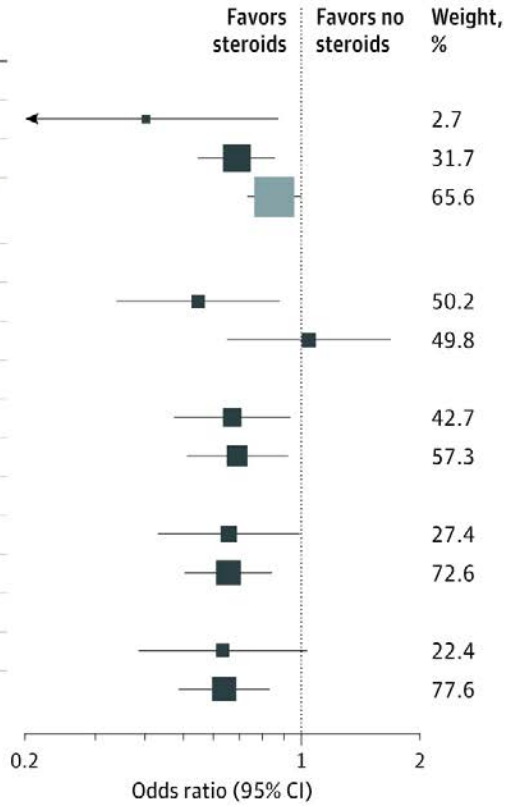

Figure Legend:

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.

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Latest Treatment Updates: Corticosteroids

WHO Recommendations

Recommendation #1

- **We recommend systemic corticosteroids rather than no systemic corticosteroids for the treatment of patients with severe and critical COVID-19 (strong recommendation, based on moderate certainty evidence).**

Recommendation #2

- **We suggest not to use corticosteroids in the treatment of patients with non-severe COVID-19 (conditional recommendation, based on low certainty evidence).**

Table 1. Mutually exclusive categories of illness severity

Critical COVID-19	Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock or other conditions that would normally require the provision of life-sustaining therapies, such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.
Severe COVID-19	Defined by any of: • oxygen saturation < 90% on room air. • respiratory rate > 30 breaths per minute in adults and children > 5 years old; ≥ 60 in children less than 2 months; ≥ 50 in children 2–11 months; and ≥ 40 in children 1–5 years old. • signs of severe respiratory distress (i.e. accessory muscle use, inability to complete full sentences; and in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs).
Non-severe COVID-19	Defined as absence of any signs of severe or critical COVID-19.

Caution: The panel noted that the oxygen saturation threshold of 90% to define severe COVID-19 was arbitrary and should be interpreted cautiously when used for determining which patients should be offered systemic corticosteroids. For example, clinicians must use their judgement to determine whether a low oxygen saturation is a sign of severity or is normal for a given patient suffering from chronic lung disease. Similarly, a saturation above 90–94% on room air may be abnormal if the clinician suspects that this number is on a downward trend. Generally, if there is any doubt, the panel suggested erring on the side of considering the illness as severe.

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Latest Treatment Updates: Corticosteroids

Lingering Questions

- ? Optimal dose of corticosteroid?
- ? Optimal durations of corticosteroid?
- ? When to start treatment with corticosteroid?
  - What are the effects of corticosteroids on non-severe disease?
- ? What is the long-term effect of corticosteroids on mortality and functional outcomes?
- ? Can corticosteroids be used in under-represented populations?
- ? How do corticosteroids interact with other COVID-19 treatments?

COVID-19 Current State of the Pandemic

NETEC

Latest Treatment Updates: Convalescent Plasma

- FDA Emergency Use Authorization enacted August 23rd, 2020
  - Decision made based on historical evidence, in addition to new publications by Mayo Clinic
  - Reiterated that RCTs need to be done to truly evaluate its benefit
  - Should not amend current ongoing RCTs due to the EUA announcement
  - Units must be tested for antibody titer levels
    - Use of high titer is recommended
    - Low titer is at discretion of physician in specific patients

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Latest Treatment Updates: Convalescent Plasma

Historical evidence:

- **Systematic review of convalescent plasma in SARS-CoV-1 and severe influenza showed a trend towards reduction in mortality**
  - **Studies were of low quality, lacked control groups, were at risk of bias**
- **In MERS, some small studies were done, but very few plasma samples had high enough levels of neutralizing antibodies**

COVID-19 Current State of the Pandemic

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Latest Treatment Updates: Convalescent Plasma

- The COVID-19 Evidence:
- 2 RCTs
  - Liu et al. in Wuhan, China
  - Gharbharan et al. in the Netherlands
- 3 Controlled trials
  - 2 in the Middle East
  - 1 in China
- 4 Retrospective matched cohort studies
- Several small case series

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Mayo Clinic EAP

- Primary goal = provide access to convalescent plasma
- Secondary goal = demonstrate safety of convalescent plasma
- Population: 35,322 patients
  - 52.3% in ICU, 27.5% receiving mechanical ventilation
- Findings
  - Low overall rate of adverse events
  - Efficacy assessment was based on dose-response relationship between antibody titers and clinical outcomes
    - 21% reduction in 7-day mortality (14% to 11%) in non-intubated patients treated with high titer plasma versus low titer plasma
    - In patients <80 years old, not intubated, given plasma within 72 hours of diagnosis, there was a reduction in 7-day mortality from 11.3% to 6.3% with high titer plasma versus low titer plasma
    - For adjusted 7-day and 30-day mortality, transfusion within 3 days and high antibody levels was associated with reduced mortality

COVID-19 Current State of the Pandemic

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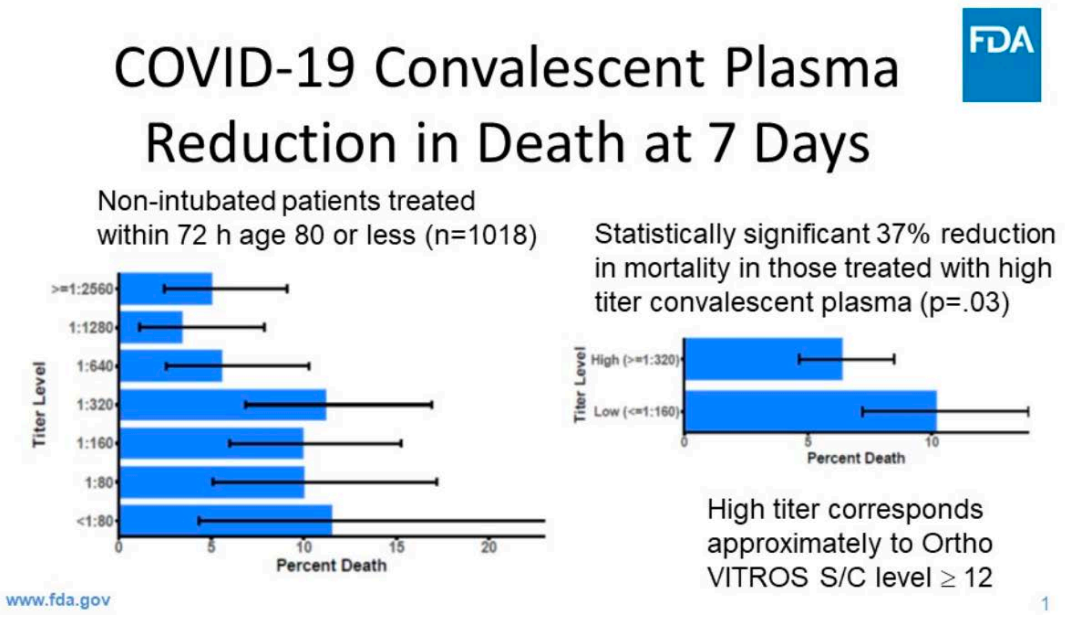
Mayo Clinic EAP



https://www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-convalescent-plasma-potential-promising-covid-19-treatment

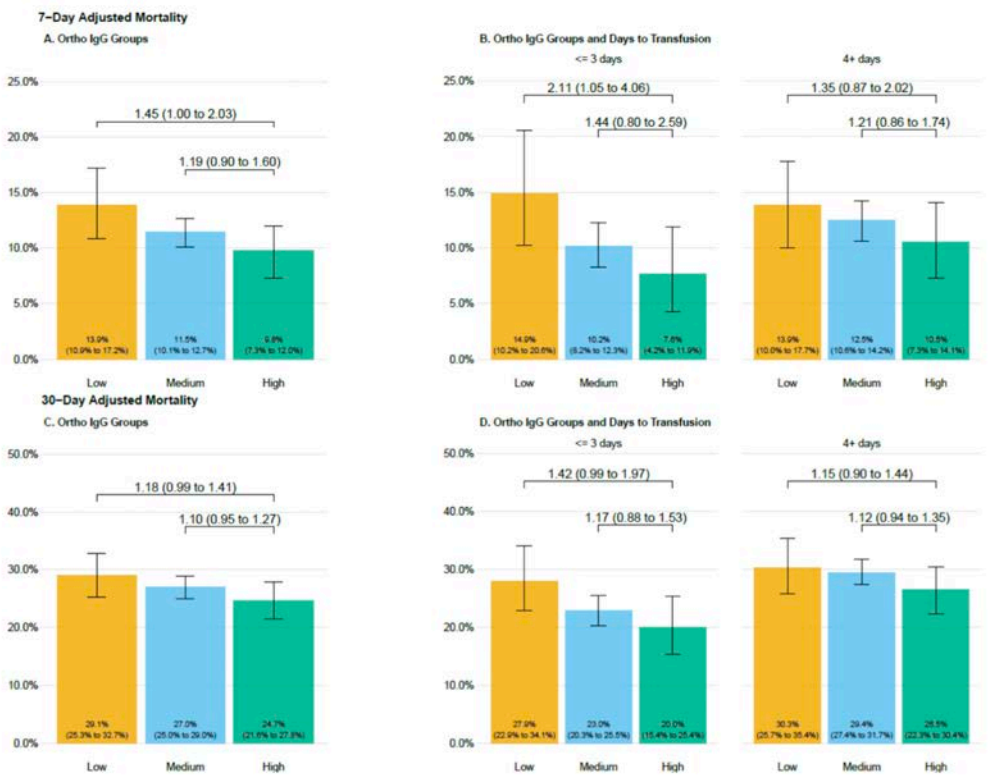


Figure 2. Seven day (A, B) and 30-day (C, D) adjusted mortality stratified by antibody 520 groupings in patients transfused with COVID-19 convalescent plasma

Latest Treatment Updates: Convalescent Plasma

Table 2.

Patients' Clinical Status at Randomization and Medications Received

[a]The values shown were based on total number of patients who contributed values. Details of medications used were provided in eTable 7 in Supplement 3.

All patients	Convalescent plasma group (n = 52)	Control group (n = 51)
Time between symptom onset and randomization, median (IQR), d	27 (22-39) [n = 49]	30 (19-38) [n = 48]
≤14 d, No. (%)	3/49 (6.1)	5/48 (10.4)
>14 d, No. (%)	46/49 (93.9)	43/48 (89.6)
Interval between symptom onset and admission, median (IQR), d	12 (5-20) [n = 49]	10 (6-16) [n = 48]
6-Point scale at study day 1, No. (%)		
2- Hospitalization, no supplemental oxygen	1/51 (2.0)	1/50 (2.0)
3- Hospitalization, requiring supplemental oxygen (not high-flow or noninvasive ventilation)	15/51 (29.4)	15/50 (30.0)
4- Hospitalization, requiring noninvasive ventilation and/or high-flow supplemental oxygen	21/51 (41.2)	23/50 (46.0)
5- Hospitalization, requiring extracorporeal membrane oxygenation and/or invasive mechanical ventilation	14/51 (27.5)	11/50 (22.0)
Medications used after randomization		
Antiviral	41/46 (89.1)	44/49 (89.8)
Antibacterial	38/46 (82.6)	39/49 (79.6)
Chinese herbal medicine	26/46 (56.5)	30/49 (61.2)
Steroids	21/46 (45.7)	16/49 (32.7)
Antifungal	15/46 (32.6)	13/49 (26.5)
Human immunoglobulin	13/46 (28.3)	11/49 (22.5)
Interferon	12/46 (26.1)	7/49 (14.3)

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Table 3. **Primary and Secondary Clinical Outcomes at Day 28[a]**

	Convalescent plasma group (n = 52)	Control group (n = 51)	Absolute difference (95% CI)[b]	Effect estimate (95% CI)	*P* value[c]
All patients					
Primary clinical outcome					
Time to clinical improvement, median (IQR),d[d]	28.00 (13.00-Indeterminate)	Indeterminate (18.00-Indeterminate)	−2.15 (−5.28 to 0.99)	HR, 1.40 (0.79-2.49)	.26
Clinical improvement rate, No./total (%)[e]					
At day 7	5/52 (9.6)	5/51 (9.8)	−0.2% (−11.6% to 11.2%)	OR, 0.98 (0.27-3.61)	.97
At day 14	17/52 (32.7)	9/51 (17.6)	15.0% (−1.4% to 31.5%)	OR, 2.27 (0.90-5.71)	.08
At day 28	27/52 (51.9)	22/51 (43.1)	8.8% (−10.4% to 28.0%)	OR, 1.42 (0.65-3.09)	.37
Secondary clinical outcomes					
Discharge rate at 28 d, No./total (%)	26/51 (51.0)	18/50 (36.0)	15.0% (−4.1% to 34.1%)	OR, 1.85 (0.83-4.10)	.13
Time from randomization to discharge, median (IQR), d[d]	28.00 (13.00-Indeterminate)	Indeterminate (19.00-Indeterminate)	−2.43 (−5.56 to 0.69)	HR, 1.61 (0.88-2.95)	.12
Time from hospitalization to discharge, median (IQR),d[d]	41.00 (31.00-Indeterminate)	53.00 (35.00-Indeterminate)	−11.95 (−26.33 to 2.43)	HR, 1.68 (0.92-3.08)	.09
Mortality at 28 d, No./total (%)	8/51 (15.7)	12/50 (24.0)	−8.3% (−23.8% to 7.2%)	OR, 0.59 (0.22-1.59)	.30
Time from randomization to death, median (IQR), d[d]	Indeterminate	Indeterminate (26.00-Indeterminate)	0.52 (−2.10 to 3.14)	HR, 0.74 (0.30-1.82)	.52
Viral nucleic acid negative rate, No./total (%)					
At 24 h	21/47 (44.7)	6/40 (15.0)	29.7% (11.7% to 47.7%)	OR, 4.58 (1.62-12.96)	.003
At 48 h	32/47 (68.1)	13/40 (32.5)	35.6% (15.9% to 55.3%)	OR, 4.43 (1.80-10.92)	<.001
At 72 h	41/47 (87.2)	15/40 (37.5)	49.7% (32.0% to 67.5%)	OR, 11.39 (3.91-33.18)	<.001

Critical and severe disease outcomes can be found here:

URL will go here

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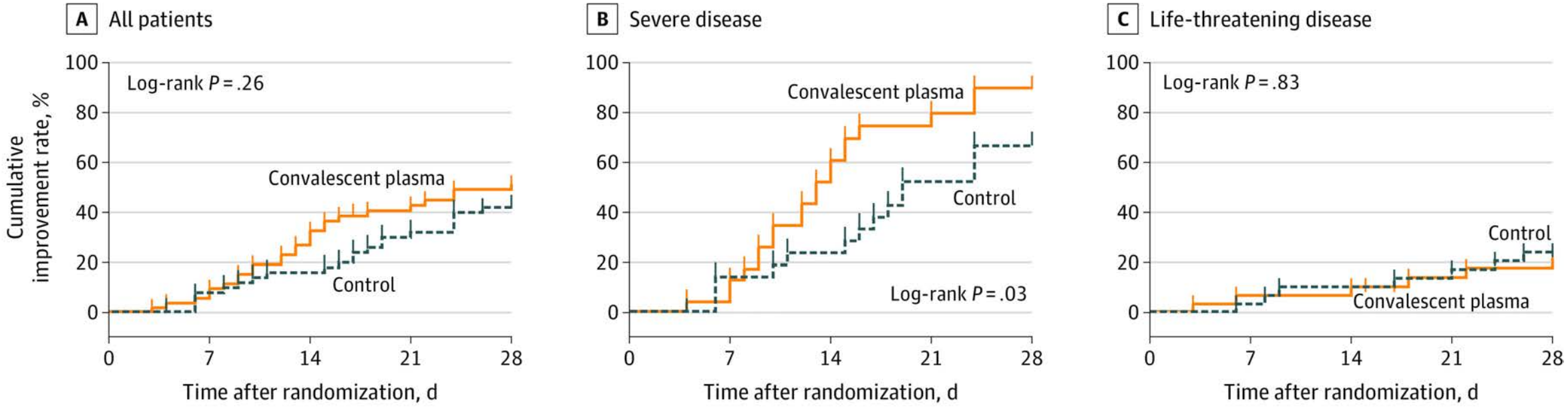
Figure 2.

Time to Clinical Improvement in Patients With COVID-19

The cumulative improvement rate is the percentage of patients who experienced a 2-point improvement or were discharged alive from the hospital. Ticks on the curves indicate censored events. All patients who did not reach clinical improvement were observed for the full 28-day period or until death. COVID-19 indicates coronavirus disease 2019.

The median (IQR) follow-up times for the convalescent plasma group and control group, respectively, were 15 (10-28) days and 24 (13-28) days overall; 13 (10-16) and 18.5 (11-26) days among those with severe COVID-19; and 28 (12-28) and 26 (15-28) days among those with life-threatening COVID-19.



No. at risk															
Control	51	46	42	35	29	22	18	16	10	7	29	28	26	25	22
Convalescent plasma	52	49	38	28	24	23	22	11	5	2	29	27	27	23	22

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7270883/

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Figure 1a. PRNT50 in - donors of whom ConvP was used in the study (grey) and in - study patients at baseline (black).

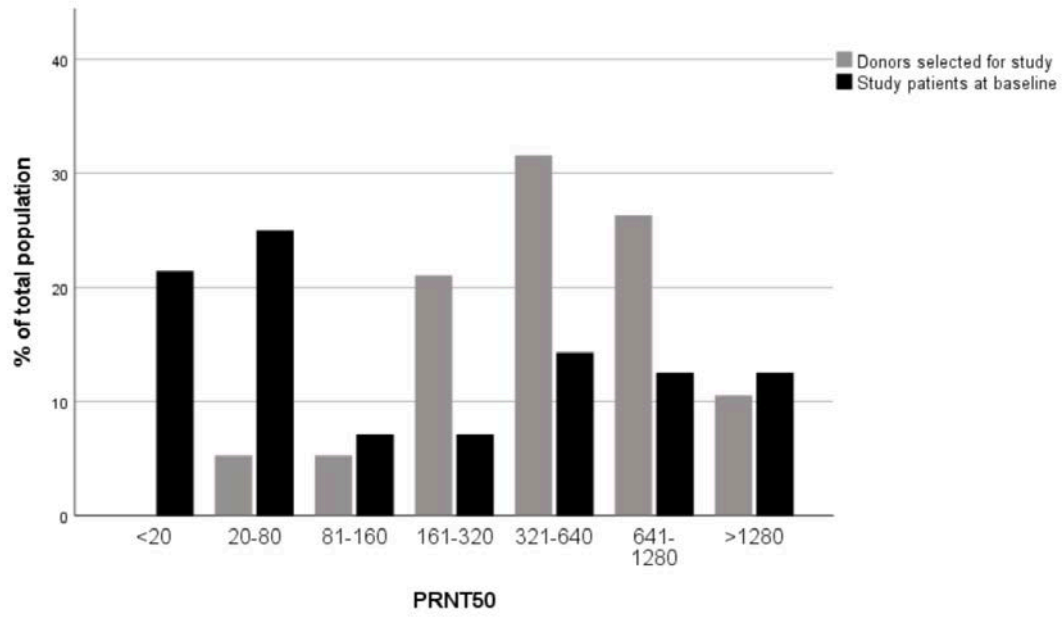
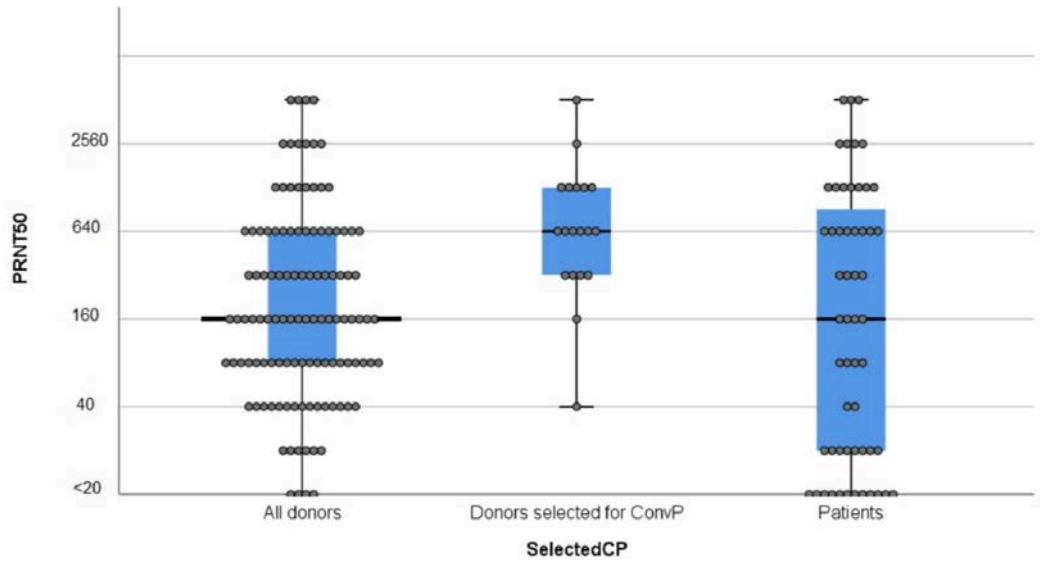


Figure 1b. PRNT50 titers in overall donor population (n=115), donors of whom ConvP was used (n=19) and patients at baseline (n=56). P=0.398 for the difference between all donors and patients and p=0.011 for difference between Donors selected for ConvP and patients.



Questions and Answers

NETEC Resources

Trish Tennill, RN, BSN

Resources: NETEC

NETEC is Here to Help

NETEC will continue to build resources, develop online education, and deliver technical training to meet the needs of our partners

Ask for help!

- Send questions to **info@netec.org** - they will be answered by NETEC SMEs
- Submit a Technical Assistance request at **NETEC.org**

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