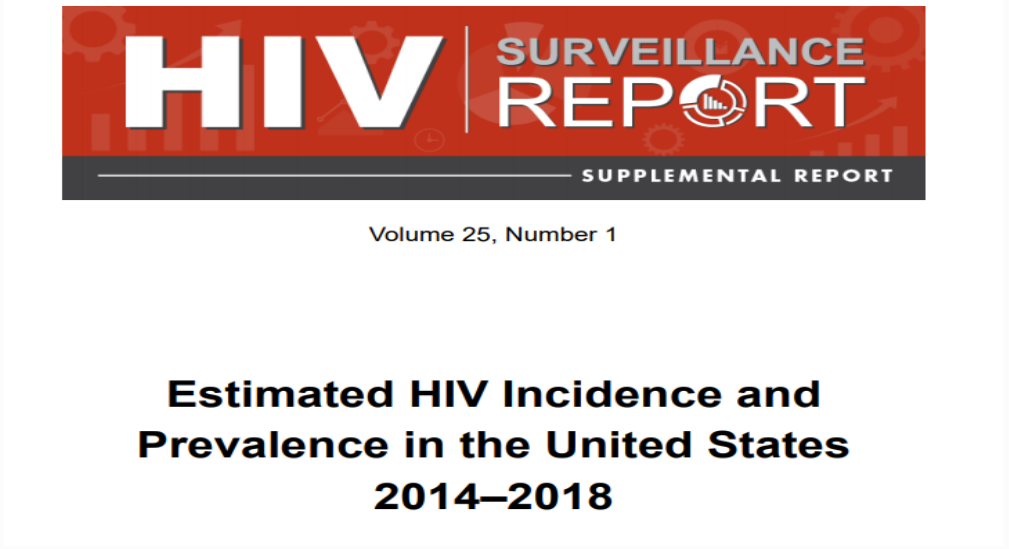
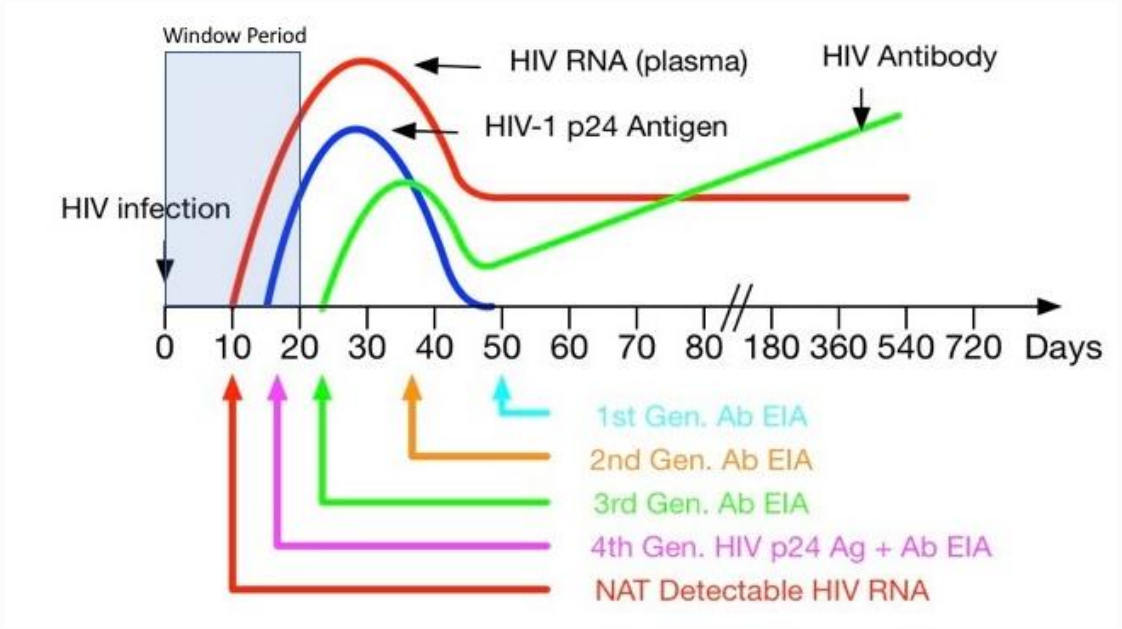
Divya Ahuja, MD, MRCP (London)
Prisma-University of South Carolina School of Medicine

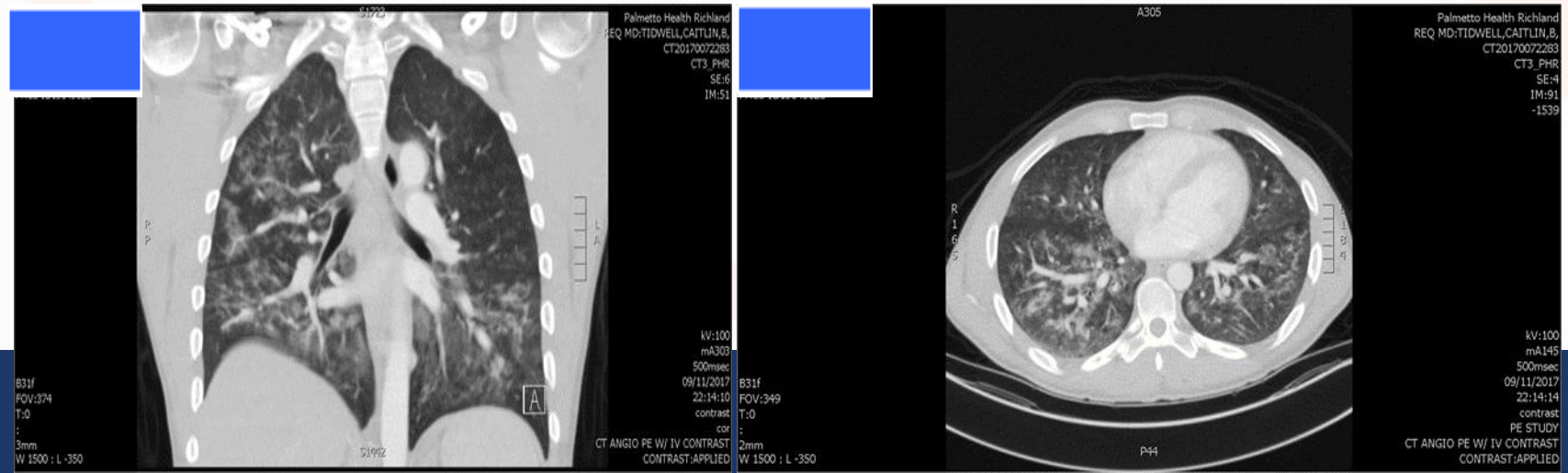


- US population- 330 million
- Patients with HIV -estimated 1.2 million
- **Simple Math:**
- **HIV prevalence >1/330 Americans**
  - Males- 0.7% (1/150 male Americans)
  - Females-0.2%

HIV testing > 99% sensitive and specific

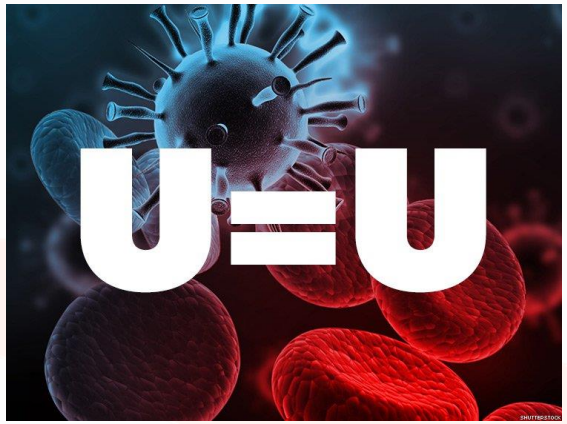
- We miss thousands of diagnosis every year
- Example :this patient seen in primary care providers office
- Treated for Chlamydia and gonorrhea but not checked for HIV.
- Admitted 7 months later with severe PCP pneumonia which could have been prevented





Antiretroviral therapy

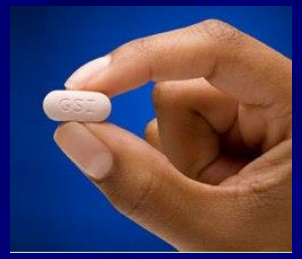
- ART (Antiretroviral therapy)
  - recommended for ALL HIV-infected individuals
- HIV is easier to treat than Diabetes, COPD, CHF
- For unfunded patients
  - Labs, medications, vaccines, doctors visits are all FREE and paid for by Ryan White Grants
  - Even given gas vouchers, cab vouchers
- Effective ART reduces transmission to almost **“0”**
  - Undetectable= Untransmissible
- In our clinic in Columbia, SC - out of 2500 HIV infected patients, > 90% are undetectable



ART- one tablet once a day!

Atripla

Genvoya



Complera

Juluca

Stribild

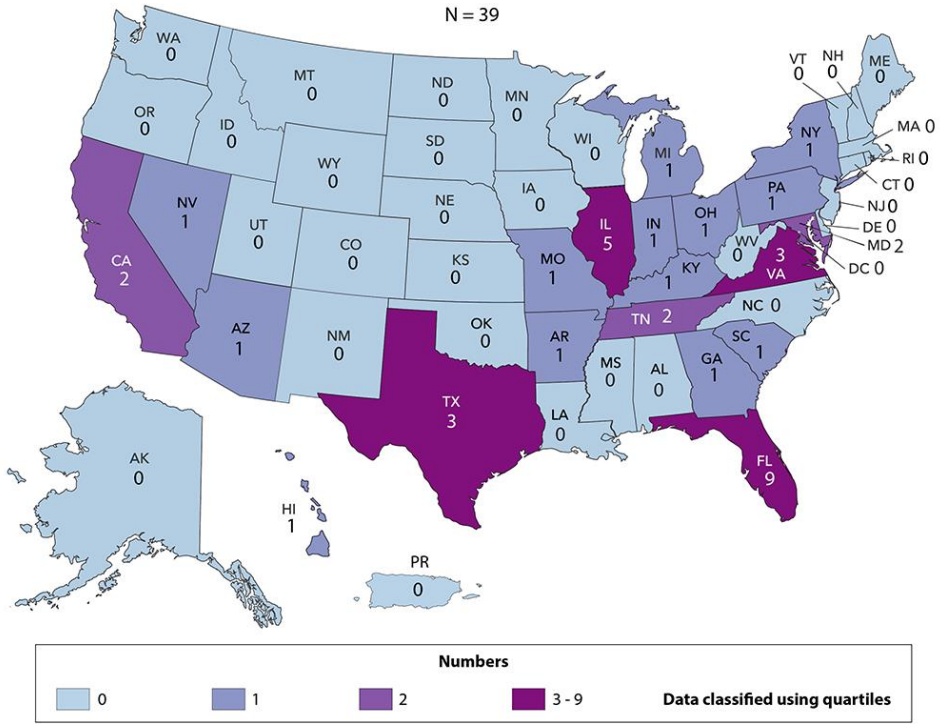
Triumeq

Odefsey

Biktarvy

HIV perinatal Transmission

- Test ALL pregnant women for HIV, HCV and Syphilis
- HIV Vertical transmission: usually peripartum
- Start ART after 1st trimester, or can continue medications if already on them
- Goal: To get the viral load < 20 ASAP
- Transmission Rate:
  - without intervention ~25%
  - With ART for the mother, the rate is <<1%
  - 1 infant with HIV in SC in 2017



HIV Pre-exposure prophylaxis (PrEP)

PrEP

A method of preventing an uninfected person from acquiring HIV

- Daily oral PrEP is highly effective

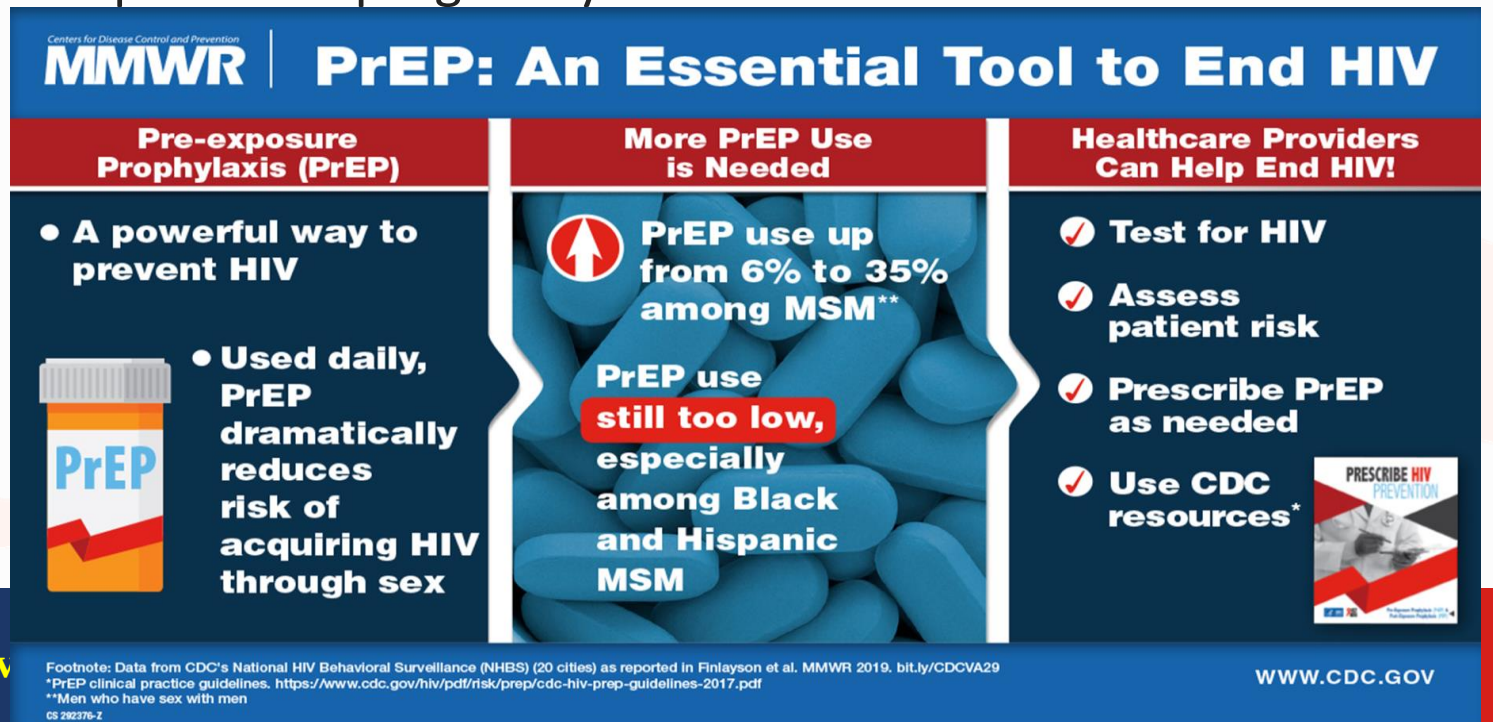
Fixed-dose combination

- F/TDF-Brand name **Truvada®**
  - for ALL persons at risk from sex or IVDU.
- F/TAF-Brand name **Descovy®**
  - for at risk from sex (but not receptive vaginal sex)

1. https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf

PrEP: The Guidelines

- Any licensed prescriber can prescribe PrEP
  - Specialization in infectious diseases is not required.
- PrEP is recommended as one prevention option for:
  - MSM (men who have sex with men)
  - Adult heterosexual men and women
  - Adult persons who inject drugs (PWID)
  - HIV-discordant couples during conception and pregnancy



- **South East Hepatitis C Telehealth Initiative**
- **And SC HIV PrEP Telehealth**
  - Free HCV/HIV PrEP tele-consultation program
  - CME accredited clinical training and case-based consultations via video conferencing for clinicians and other providers at FQHCs, Ryan White Clinics, AIDS Services Organizations, Substance Use centers
  - Participants from 8 Southeastern States

Hepatitis C

- The most important risk factor for HCV infection is past or current injection drug use
  - The estimated prevalence of chronic HCV infection is approximately **1.0%** (2013 to 2016)

    Hofmeister MG, Hepatology. 2019;69(3):1020-1031
- In the US, an estimated 4.1 million persons are
  - Positive for the anti-HCV antibody
- Of these approximately 2.4 million have current infection
  - i.e., are HCV RNA positive.

    Chou R, Dana Agency for Healthcare Research and Quality; 2020. AHRQ publication

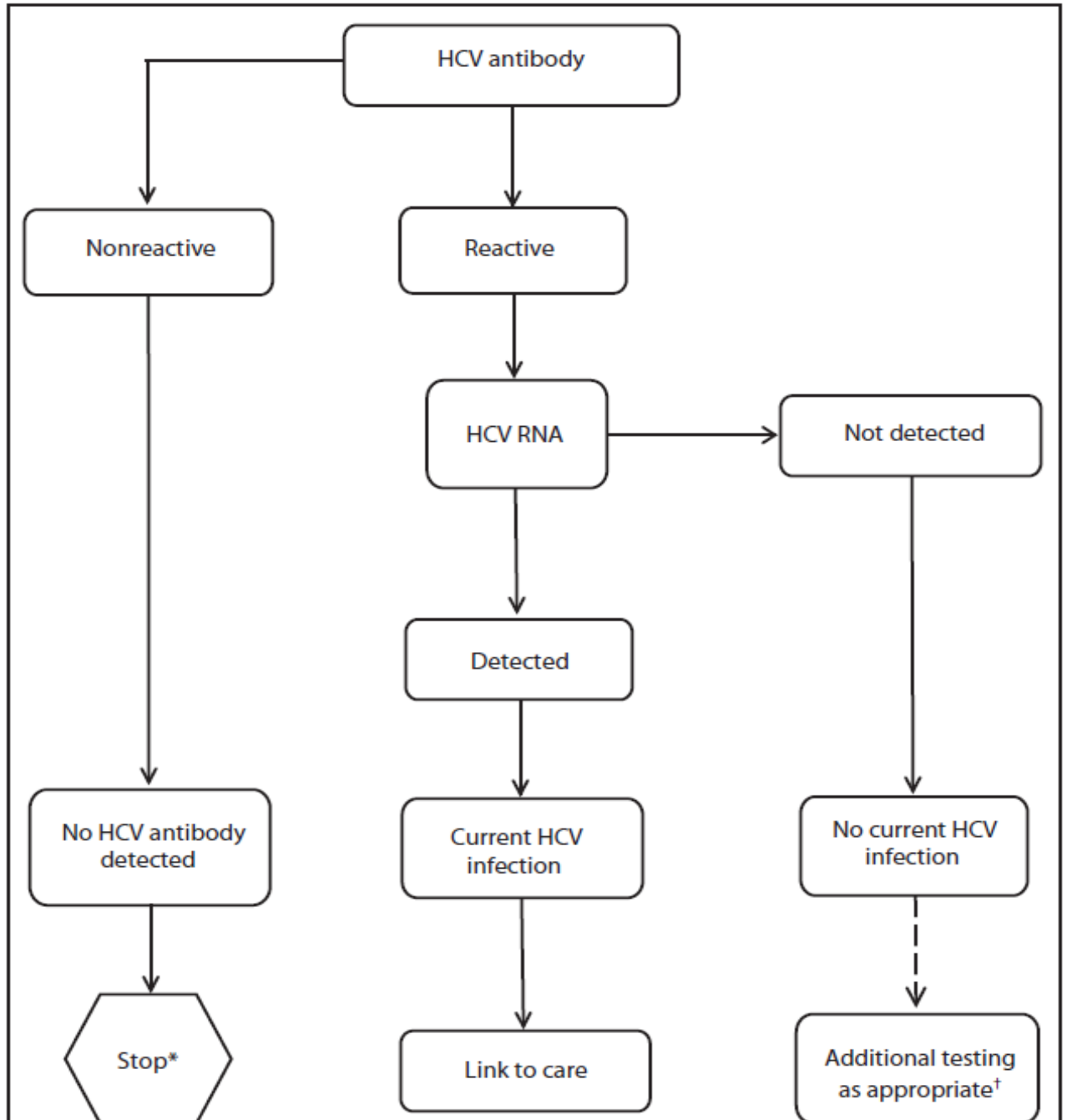
Hepatitis C Screening Recommendations

Population	Recommendation	Grade (What's This?)
Adults aged 18 to 79 years	The USPSTF recommends screening for hepatitis C virus (HCV) infection in adults aged 18 to 79 years.	B

One-Time Hepatitis C Testing

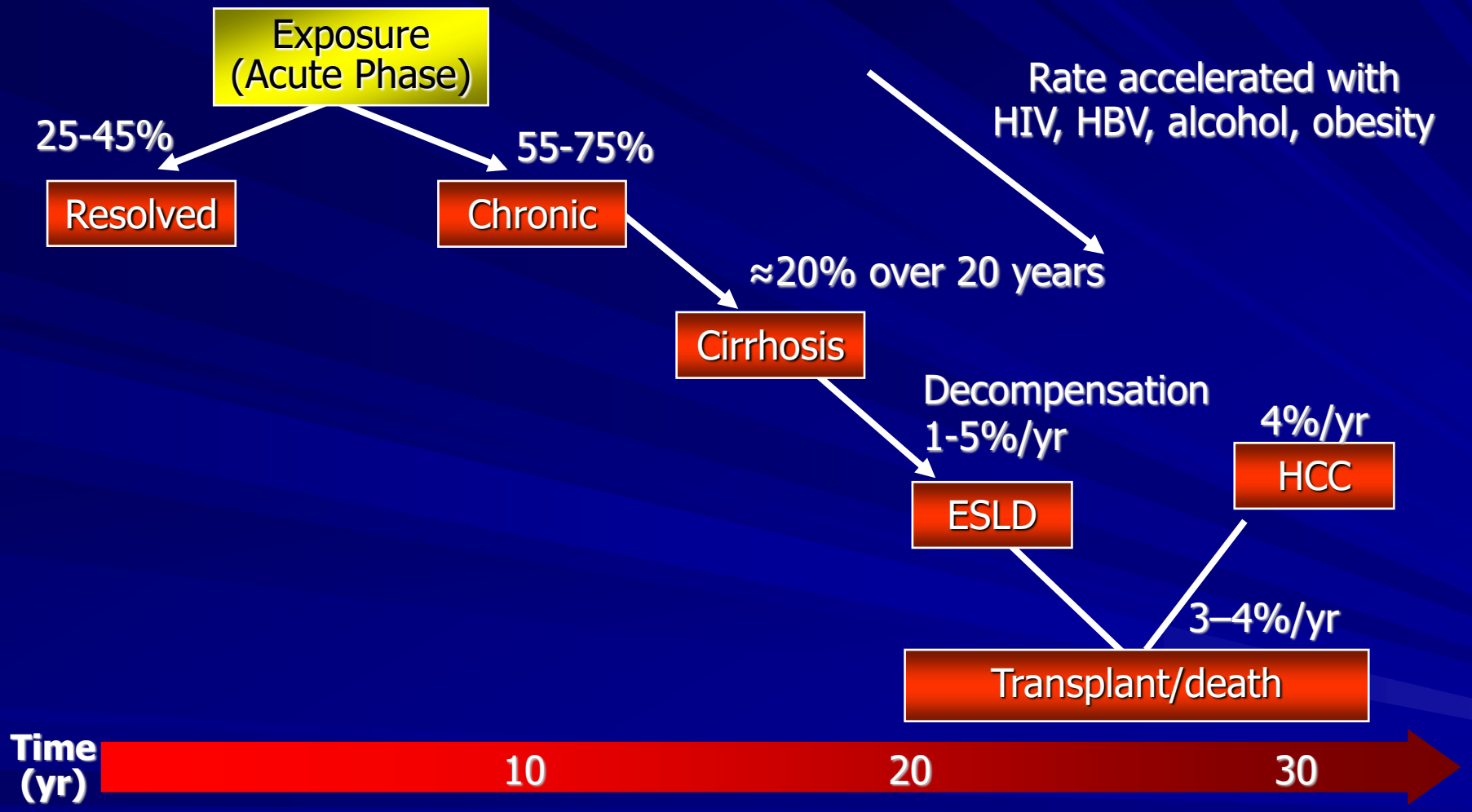
Recommendations for One-Time Hepatitis C Testing	
RECOMMENDED	RATING
One-time, routine, opt out HCV testing is recommended for all individuals aged 18 years and older.	I, B
One-time HCV testing should be performed for all persons less than 18 years old with behaviors, exposures, or conditions or circumstances associated with an increased risk of HCV infection (see below).	I, B
Periodic repeat HCV testing should be offered to all persons with behaviors, exposures, or conditions or circumstances associated with an increased risk of HCV exposure (see below).	IIa, C
Annual HCV testing is recommended for all persons who inject drugs and for HIV-infected men who have unprotected sex with men.	IIa, C

FIGURE. Recommended testing sequence for identifying current hepatitis C virus (HCV infection



MMWR / May 10, 2013

Natural History of HCV Infection



HCC = hepatocellular carcinoma

ESLD = end-stage liver disease

Modified from Di Bisceglie A, et al. *Hepatology*. 2000;31:1014-1018.

P-DS-D-041

Treatment of Chronic HCV

- Treatment is recommended for ALL pts with chronic HCV
  - Exception: life expectancy likely to be < 6 months
- Goal of Treatment is - **Sustained Virological Response**
  - **SVR-** equal to cure/eradication

  SVR is defined as
    - *Undetectable HCV viral Load ≥12 weeks after treatment completion*
- SVR is associated with
  - >70% reduction in the risk of Hepatocellular carcinoma
  - 90% decrease in liver-related mortality & liver transplantation

  Van der Meer AJ, et al. JAMA. 2012;308(24):2584-2593
- Current Directly acting antivirals have SVR > 98%
  - 1-3 tablets, once a day, for 8-12 weeks
  - Very well tolerated

HCV case

- 45 year male
  - H/O IVDU but none for > 15 years
- Creatinine normal, AST-43, ALT-45, Platelets- 222
- FIB-4--0.89; *(<1.45 suggests very low likelihood of fibrosis)*
- AST/Platelet ratio index(APRI)- 0.48; *(< 0.5 Low likelihood of fibrosis)*
- HIV- negative, HepBsAb- positive, HepBsAg- negative
- HCV Antibody –positive, HCV Viral load- 513,000, HCV- Genotype 1a
- Current Rx- amlodipine- 5mg PO daily
- Next steps?

AASLD: Simplified HCV Treatment Approach

Exclusions to Simplified Treatment

- Prior hepatitis C treatment
- End-stage renal disease
- HIV or HBsAg positive
- Current pregnancy
- Known or suspected hepatocellular carcinoma
- Prior liver transplantation
- Decompensated cirrhosis

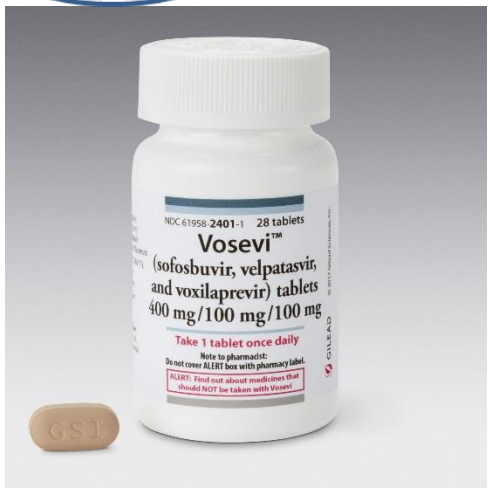
Eligible Patients:
Chronic hepatitis C without cirrhosis and no previous HCV therapy

- Assess cirrhosis (liver biopsy almost NEVER required)
  - Treat as non-cirrhotic if any of the following
  - FIB-4 < 3.25, platelet count > 150,000/mm^3, APRI < 2.0, *FibroScan* < 12.5 kPa
- Record medications and supplements, assess DDIs
- Conduct recommended baseline labs
- Provide patient education

Treatment Options:
GLE/PIB 3 pills/day for 8 wks (with food) or SOF/VEL 1 pill/day for 12 wks

AASLD Guidance. November 2019.

Available co-formulated DAAs



HCV diagnoses in Pregnancy

- The rate of vertical transmission from infected mothers to infants
  - 4-8% (11% if the mother is co-infected with HIV)
- DAA Rx in pregnancy not yet approved
- Massive increase in HCV diagnoses in pregnant women
  - Ohio, 2006 - 2015
    - Rate of pregnant women infected with HCV increased by 631%
  - Kentucky the rate increased > 200% between 2011 -2014
    - 1.6% of live births being to HCV+ women
  - Tennessee rate- increased 89%
  - West Virginia- 2.3% of births are to HCV+ women

AETC AIDS Education & Training Center Program Southeast

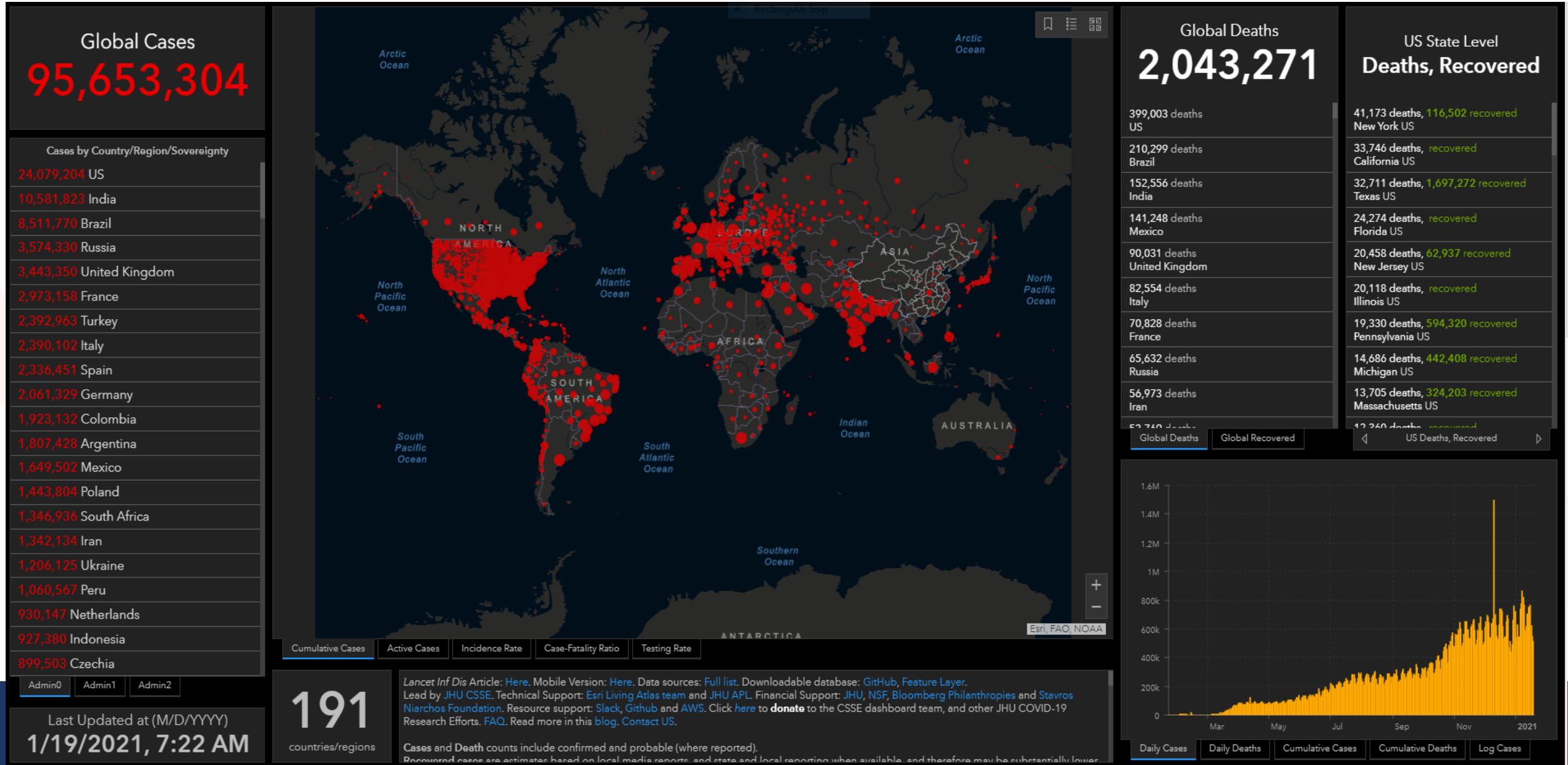
Monthy 1st and 3rd Wednesday and
12:00pm-1:00pm EST
11:00am-12:00pm CST
09:00am-10:00am PST

4th Wednesday
12:00pm-1:00pm CST
01:00pmpm-2:00pm EST
10:00am-11:00am PST

South East Viral Hepatitis Interactive Case Conference

Free, CME Accredited case discussion , three times a month
Present your cases!!!

COVID-19


Global Cases
95,653,304
Cases by Country/Region/Sovereignty
24,079,204 US
10,581,823 India
8,511,770 Brazil
3,574,330 Russia
3,443,350 United Kingdom
2,973,158 France
2,392,963 Turkey
2,390,102 Italy
2,336,451 Spain
2,061,329 Germany
1,923,132 Colombia
1,807,428 Argentina
1,649,502 Mexico
1,443,804 Poland
1,346,936 South Africa
1,342,134 Iran
1,206,125 Ukraine
1,060,567 Peru
930,147 Netherlands
927,380 Indonesia
899,503 Czechia
Admin0
Admin1
Admin2
Last Updated at (M/D/YYYY)
1/19/2021, 7:22 AM
Arctic Ocean
North Pacific Ocean
North Atlantic Ocean
South Pacific Ocean
South Atlantic Ocean
Indian Ocean
Southern Ocean
NORTH AMERICA
SOUTH AMERICA
EUROPE
ASIA
AFRICA
AUSTRALIA
ANTARCTICA
Esri, FAO, NOAA
Cumulative Cases
Active Cases
Incidence Rate
Case-Fatality Ratio
Testing Rate
191
countries/regions
Lancet Inf Dis Article: Here. Mobile Version: Here. Data sources: Full list. Downloadable database: GitHub, Feature Layer.
Lead by JHU CSSE. Technical Support: Esri Living Atlas team and JHU APL. Financial Support: JHU, NSF, Bloomberg Philanthropies and Stavros Niarchos Foundation. Resource support: Slack, Github and AWS. Click here to donate to the CSSE dashboard team, and other JHU COVID-19 Research Efforts. FAQ. Read more in this blog. Contact US.
Cases and Death counts include confirmed and probable (where reported).
Global Deaths
2,043,271
399,003 deaths US
210,299 deaths Brazil
152,556 deaths India
141,248 deaths Mexico
90,031 deaths United Kingdom
82,554 deaths Italy
70,828 deaths France
65,632 deaths Russia
56,973 deaths Iran
Global Deaths
Global Recovered
US State Level
Deaths, Recovered
41,173 deaths, 116,502 recovered New York US
33,746 deaths, recovered California US
32,711 deaths, 1,697,272 recovered Texas US
24,274 deaths, recovered Florida US
20,458 deaths, 62,937 recovered New Jersey US
20,118 deaths, recovered Illinois US
19,330 deaths, 594,320 recovered Pennsylvania US
14,686 deaths, 442,408 recovered Michigan US
13,705 deaths, 324,203 recovered Massachusetts US
US Deaths, Recovered
1.6M
1.4M
1.2M
1M
800k
600k
400k
200k
0
Mar
May
Jul
Sep
Nov
2021
Daily Cases
Daily Deaths
Cumulative Cases
Cumulative Deaths
Log Cases

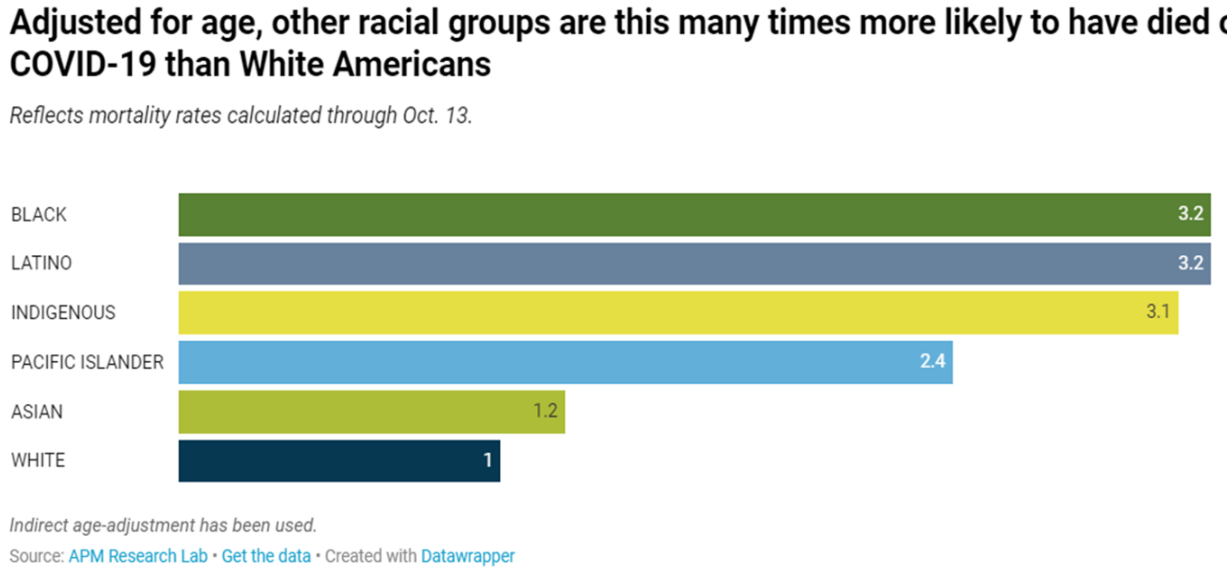
SC, 12.06.2020

Table 1. Ranking of COVID-19 among the leading causes of mortality this week, assuming uniform deaths of non-COVID causes throughout the year

Cause name	Weekly deaths	Ranking
COVID-19	173	1
Ischemic heart disease	172	2
Tracheal, bronchus, and lung cancer	75	3
Chronic obstructive pulmonary disease	73	4
Stroke	73	5
Chronic kidney disease	39	6
Alzheimer's disease and other dementias	36	7
Colon and rectum cancer	28	8
Diabetes mellitus	27	9
Lower respiratory infections	25	10

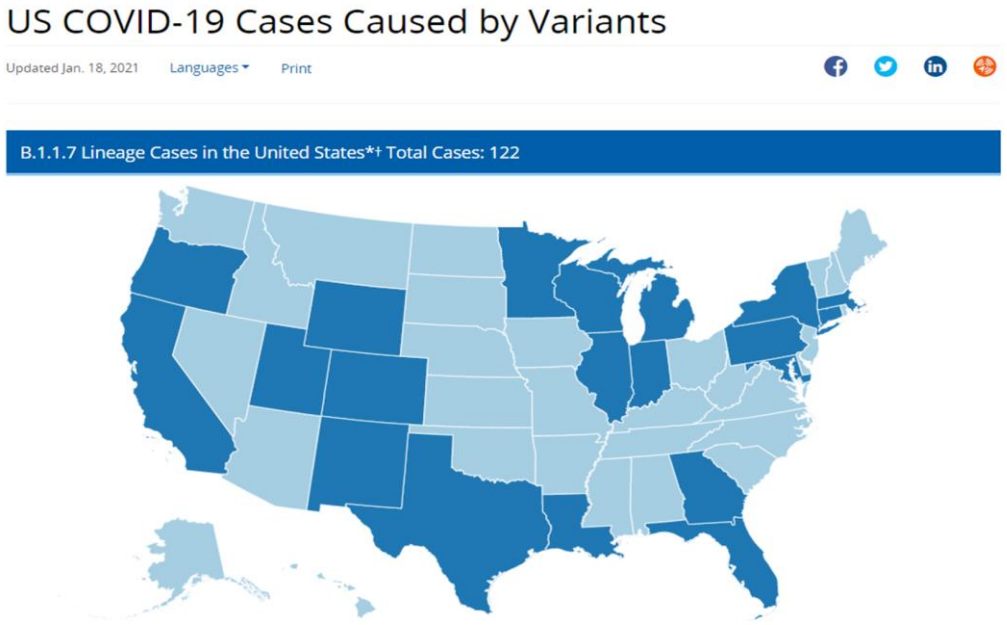
COVID-19 the leading cause of death now
Rapidly approaching 400,000 deaths in the US

Black and Latino groups
disproportionately affected



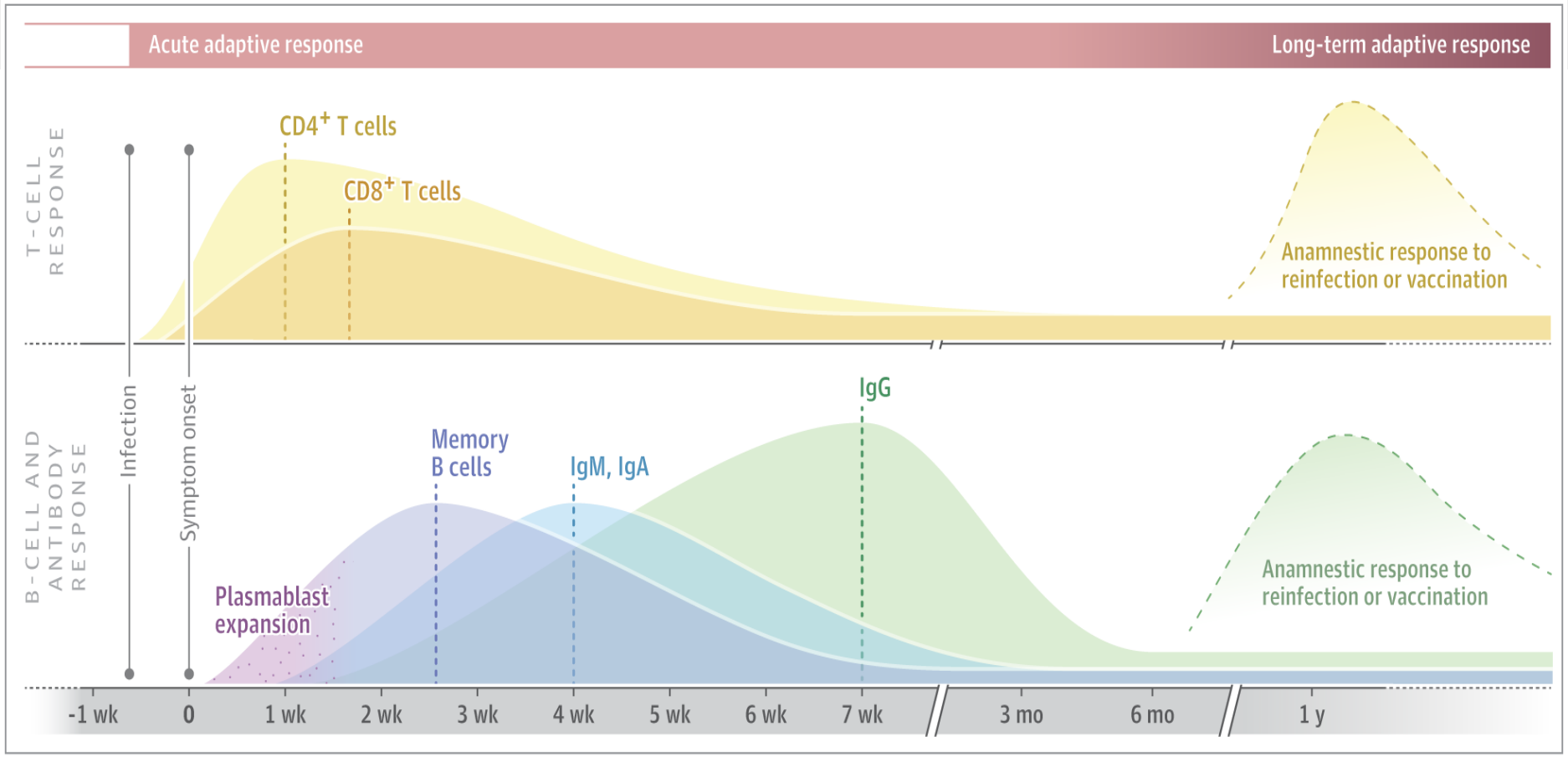
New COVID-19 variants

- RNA viruses frequently mutate; not all are important
- **UK** (September) variant ~60% recent infections
  - Estimates UK variant 56% more transmissible
  - No evidence of increased severity
- Mutation in receptor binding domain of spike protein
- South Africa (October) also S:N501Y but not related
- UK and SA variants associated w/ higher viral load
- Total cases in the US so far-122



JAMA Network™

From: **COVID-19 and the Path to Immunity** JAMA. 2020;324(13):1279-1281. doi:10.1001/jama.2020.16656



Adaptive Immunity to Coronavirus Disease 2019 infection.

Decline in SARS-CoV-2 Antibodies After Mild Infection Among Frontline Health Care Personnel in a Multistate Hospital Network — 12 States, April–August 2020

Weekly / November 27, 2020 / 69(47);1762–1766

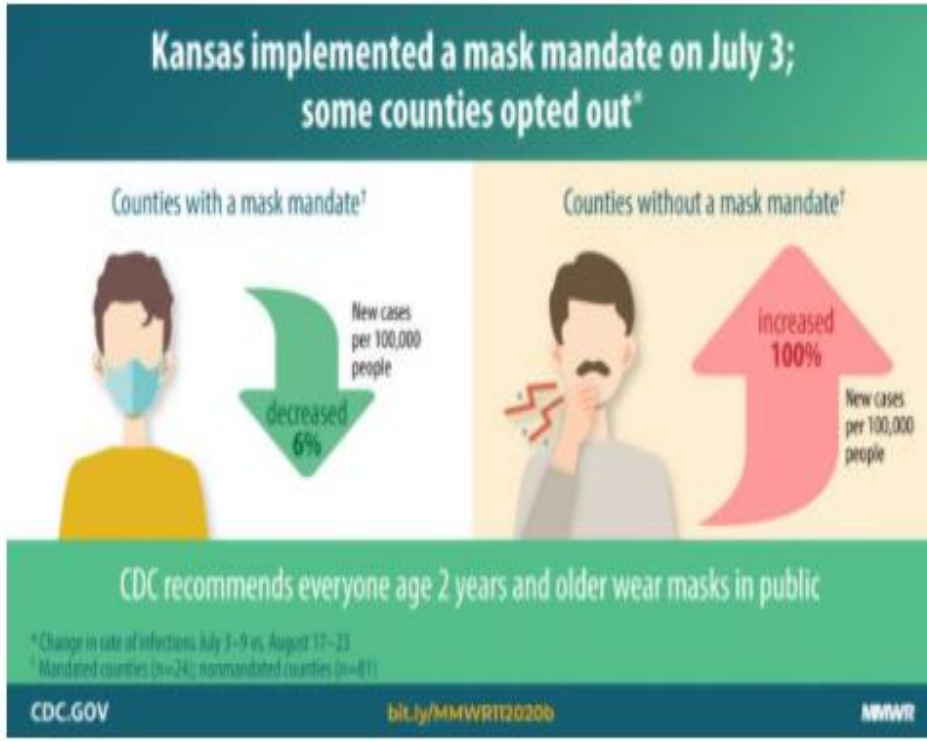
- Once infected most persons develop antibodies in 2–3 weeks
  - IgG titers rise during the weeks following infection
- This Study:
  - 3,248 health care personnel; 194 (6.0%) had antibodies at baseline
  - Upon follow up of 156 frontline health care personnel
    - 94% experienced a decline at repeat testing approximately 60 days later
    - **28% seroreverted to below the threshold of positivity**
  - Participants with higher initial antibodies had less decline

Prevention and Prophylaxis of SARS-CoV-2 Infection

Trends in County-Level COVID-19 Incidence in Counties With and Without a Mask Mandate — Kansas, June 1–August 23, 2020

Miriam E. Van Dyke, PhD[1]; Tia M. Rogers, PhD[1]; Eric Pevzner, PhD[2]; Catherine L. Satterwhite, PhD[3]; Hina B. Shah, MPH[4]; Wyatt J. Beckman, MPH[4]; Farah Ahmed, PhD[5]; D. Charles Hunt, MPH[4]; John Rule[6]

- **MASKS work**
- On July 2, 2020, the governor of Kansas issued an executive order requiring masks
  - CDC and the Kansas DHEC analyzed trends in county-level COVID-19 incidence
    - Decrease in counties with a mask mandate
    - Net increase - 100% in counties without a mandate
  - These findings are consistent with declines in COVID-19 cases observed in 15 states and the District of Columbia



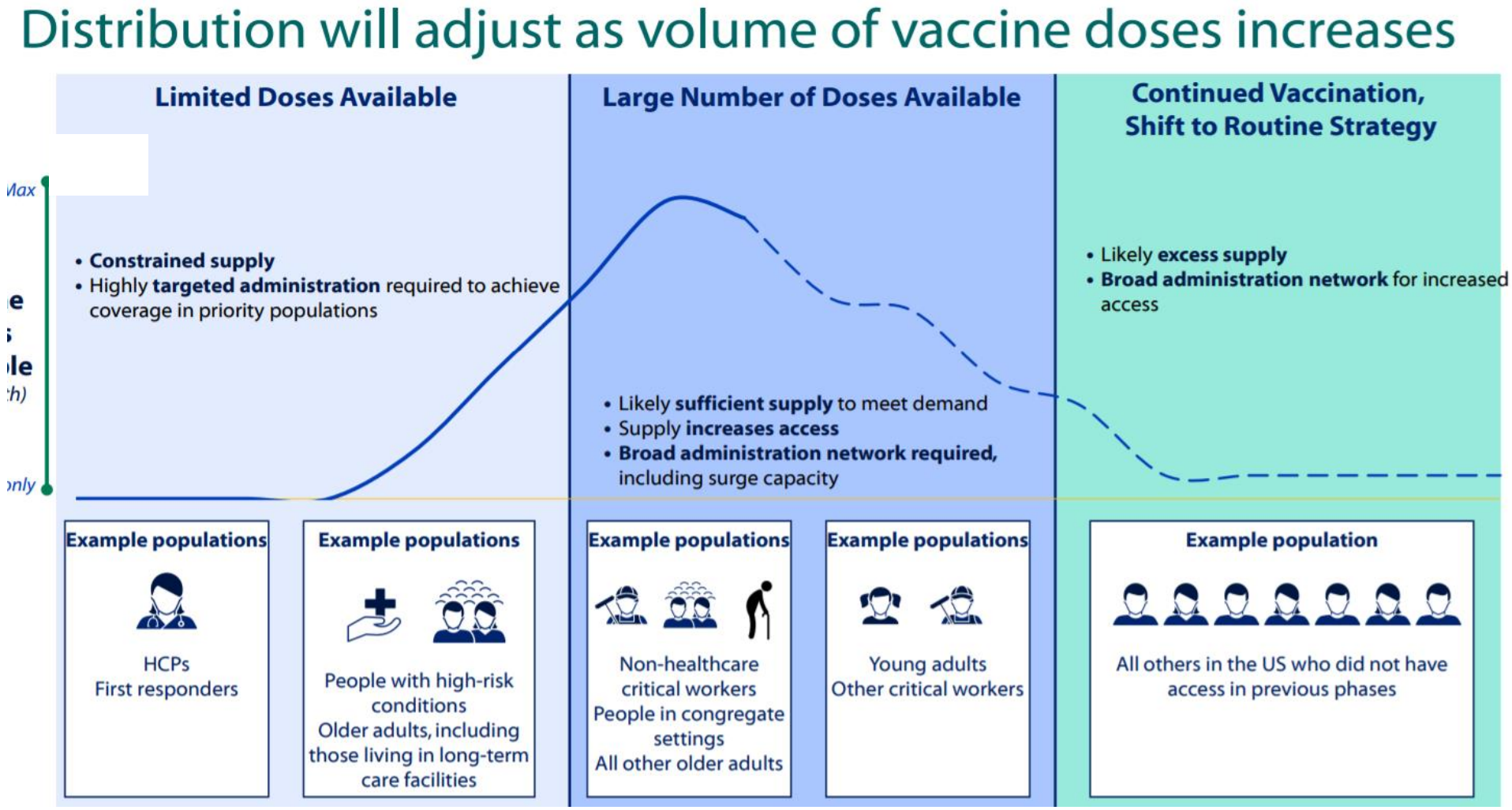
Hydroxychloroquine for Prevention of Covid-19 No benefit

- Nov 24, 2020 (Spain)
  - Randomized Trial of asymptomatic contacts of patients with confirmed Covid-19
    - Randomized to Hydroxychloroquine X 7 days or placebo
  - The primary outcome was PCR-confirmed, symptomatic Covid-19 within 14 days
    - Hydroxychloroquine – 5.7%
    - Usual-care group- 6.2%
- August 2020 (US and Canada)
  - Randomized, double-blind, placebo-controlled trial
  - Tested hydroxychloroquine as postexposure prophylaxis.
    - Hydroxychloroquine -11.8%
    - Placebo -14.3%

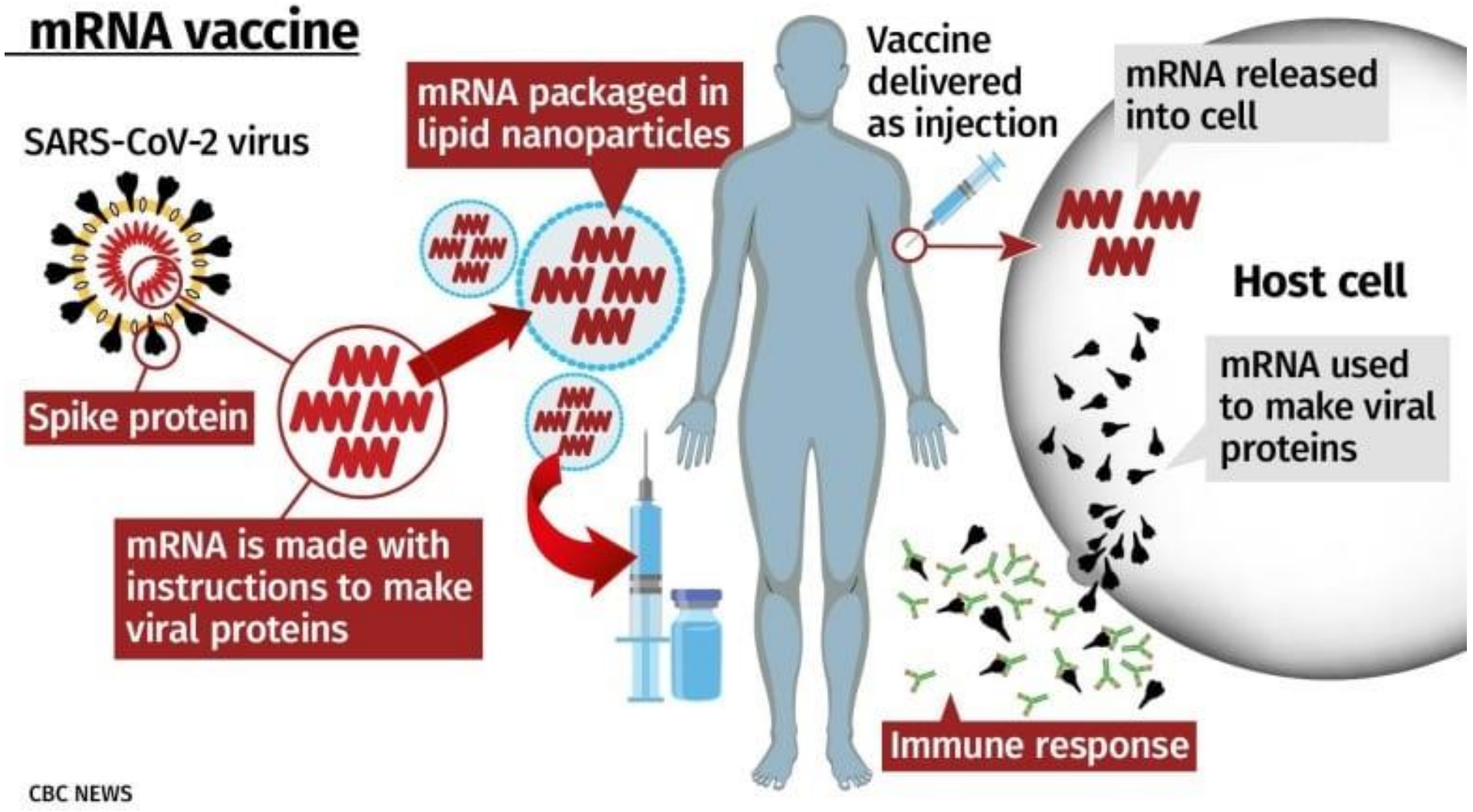
Vitamin C, Zinc and Vitamin D in COVID-19

- NIH Recommendations
- Vitamin D:
  - There are **insufficient data** to recommend either for or against the use of vitamin D for the prevention or treatment of COVID-19
- Vitamin C
  - There are **insufficient data** to recommend either for or against the use of vitamin C for the treatment of COVID-19 in non-critically ill patients.
- Zinc:
  - There are **insufficient da**ta to recommend either for or against the use of Zn

Phased COVID-19 vaccine allocation

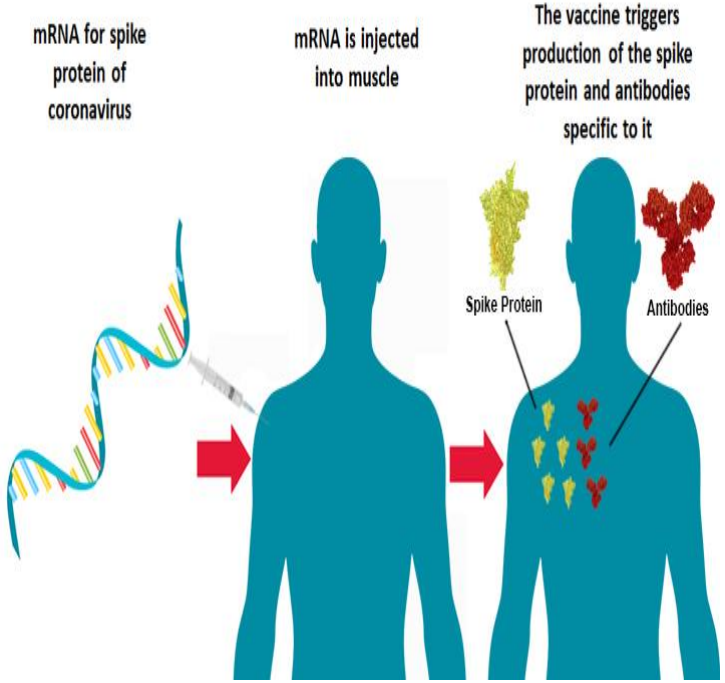


New vaccine technology

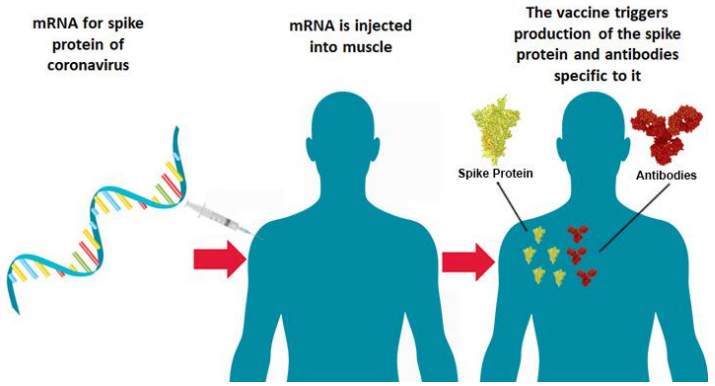


Pfizer

- Based on a SARS-CoV-2 spike glycoprotein (S) antigen m RNA formulated in lipid nanoparticles (LNPs).
  - store at -70℃
  - 2 injections 21 days apart
- Phase 3 study > 42,000 people
  - 95% efficacious: Immunity 7 days after 2nd dose
- Injection site reactions occurred in 84.1% of recipients
  - fatigue - 62.9%
  - headache - 55.1%
  - chills - 31.9%
  - fever - 14.2%.
- Severe reactions
  - 2.8% of volunteers > 55
  - 4.6% of those < 55;



Moderna



- Store at -20℃
  - Refrigerate up to 30 days
- 2 injections 28 days apart
- Phase 3 study, >30,000 people
  - 94% efficacious: Immunity 14 days after 2nd dose
- > 50% - fatigue, myalgias, chills, headache after second dose
- Mild-moderate pain at the injection site in almost all
- Cannot mix and match Pfizer and Moderna vaccines

https://www.nejm.org/doi/full/10.1056/NEJMoa2022483?query=recirc_mostViewed_railB_article

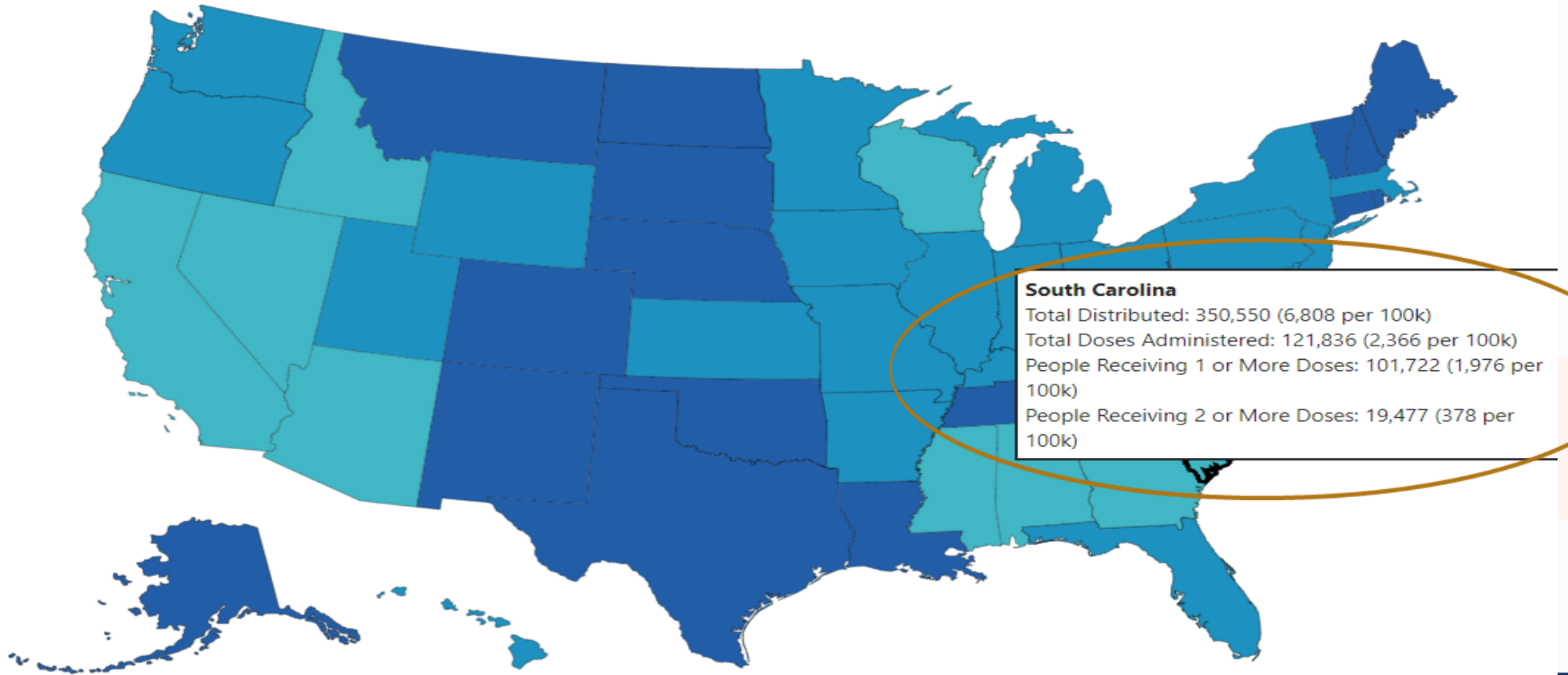
COVID-19 Vaccinations in the United States

Overall US COVID-19 Vaccine Distribution and Administration

Total Doses Distributed	Total Doses Administered	Number of People Receiving 1 or More Doses	Number of People Receiving 2 Doses
31,161,075	12,279,180	10,595,866	1,610,524

CDC | Updated: Jan 15 2021 As of 6:00am ET

Total Doses Administered Reported to the CDC by State/Territory and for Selected Federal Entities per 100,000



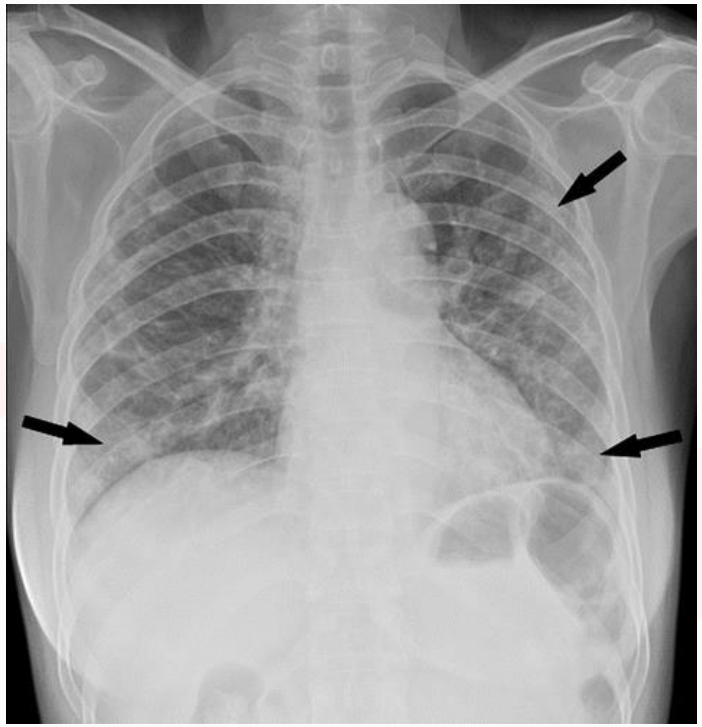
What about kids and pregnant women?

- **Pregnant women** excluded from vaccine trials
  - mRNA vaccine does not contain a live virus
  - Theoretical risk of fetal harm from mRNA vaccines is very low
  - The Society for Fetal and Maternal Medicine recommends that healthcare workers, who are considered prioritized for vaccination, be offered the vaccine if pregnant
- **Children:**
  - Pfizer vaccine approved for ages 16 and up
  - Moderna for ages 18 and up
  - When will there be COVID-19 vaccine for children?
    - —Not for months, but continue with other vaccines

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS *(Recommendations are listed in order of preference in each category below; however, all options are considered acceptable.)*
Not Hospitalized ***or*** **Hospitalized but Does Not Require Supplemental Oxygen**	No specific antiviral or immunomodulatory therapy recommended The Panel **recommends against** the use of **dexamethasone (AI)** See the Remdesivir section for a discussion of the data on using this drug in hospitalized patients with moderate COVID-19.[a]
Hospitalized and Requires Supplemental Oxygen **(but Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)**	**Remdesivir** 200 mg IV for one day, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge, whichever comes first **(AI)**[b,c,d] ***or*** **Remdesivir** (dose and duration as above) plus **dexamethasone**[e] 6 mg IV or PO for up to 10 days or until hospital discharge, whichever comes first **(BIII)**[f] If **remdesivir** cannot be used, **dexamethasone**[e] may be used instead **(BIII)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	**Dexamethasone**[d] plus **remdesivir** at the doses and durations discussed above **(AIII)**[f] ***or*** **Dexamethasone**[d,e] at the dose and duration discussed above **(AI)**
Hospitalized and Requires Invasive Mechanical Ventilation or ECMO	**Dexamethasone**[d,e] at the dose and duration discussed above **(AI)** ***or*** **Dexamethasone**[e] plus **remdesivir** for patients who have recently been intubated at the doses and durations discussed above **(CIII)**[f]

Mild to moderate COVID-19 infection

- 55 year male, well controlled hypertension, has loss of taste and smell
- Telehealth visit with PCP
  - Temp 100.5, RR- 22
  - **O2 sats – 95% on RA**
  - CXR- shown
- What treatment options does he have?



- Patients are considered to have **mild-moderate disease**
  - Clinical or radiographic evidence of lower respiratory infection
  - AND a **SpO_2 ≥94**% on RA

Mild to Moderate disease- NIH Guidelines

- Remdesivir
  - Insufficient data for the Panel to recommend either for or against remdesivir
    - In ACTT-1 there was no observed benefit for remdesivir
- Corticosteroids
  - The Panel recommends **against** the use of dexamethasone (AI) or other corticosteroids for the treatment of COVID-19 in mild to moderate disease (AIII)
  - RECOVERY Trial : worse outcomes if steroids given to patients not requiring O2
    - **28 day mortality higher in steroid arm in mild to moderate disease**
      - 17.8% - dexamethasone arm
      - 14% - control arm

Emergency Use Authorizations for

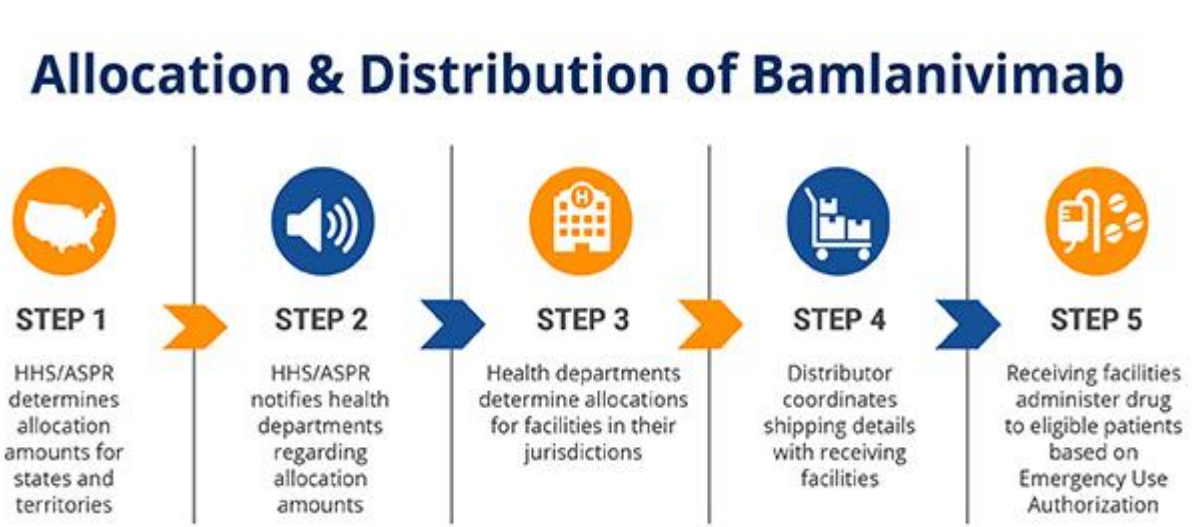
1.bamlanivimab

2.casirivimab/imdevimab

Both of these are recombinant human monoclonal antibodies which bind to spike protein receptor-binding domain (RBD)

If given early in mild COVID-19 infection, may reduce progression and hospitalization in patients with risk factors

Drug itself is free



Emergency Use Authorizations for monoclonal antibodies High-Risk Criteria

- <u>All Patients (who meet at least 1 of the following criteria):</u>
  - BMI ≥35
  - Chronic kidney disease
  - Diabetes
  - Immunosuppressive disease
  - Receiving immunosuppressive treatment
  - Age ≥ 65 years
  - Age ≥ 55 years AND have any of the following
    - Cardiovascular disease
    - Hypertension
    - COPD/other chronic respiratory disease
- <u>Adolescents (Age 12-17 years) who meet at least 1 of the following criteria:</u>
  - BMI ≥85th percentile for age/gender
  - Sickle cell disease
  - Congenital or acquired heart disease
  - Neurodevelopmental disorders
  - Chronic Medical-related technological dependence [e.g., tracheostomy,etc]
  - Asthma, reactive airway, or other chronic respiratory disease that requires daily medication for control

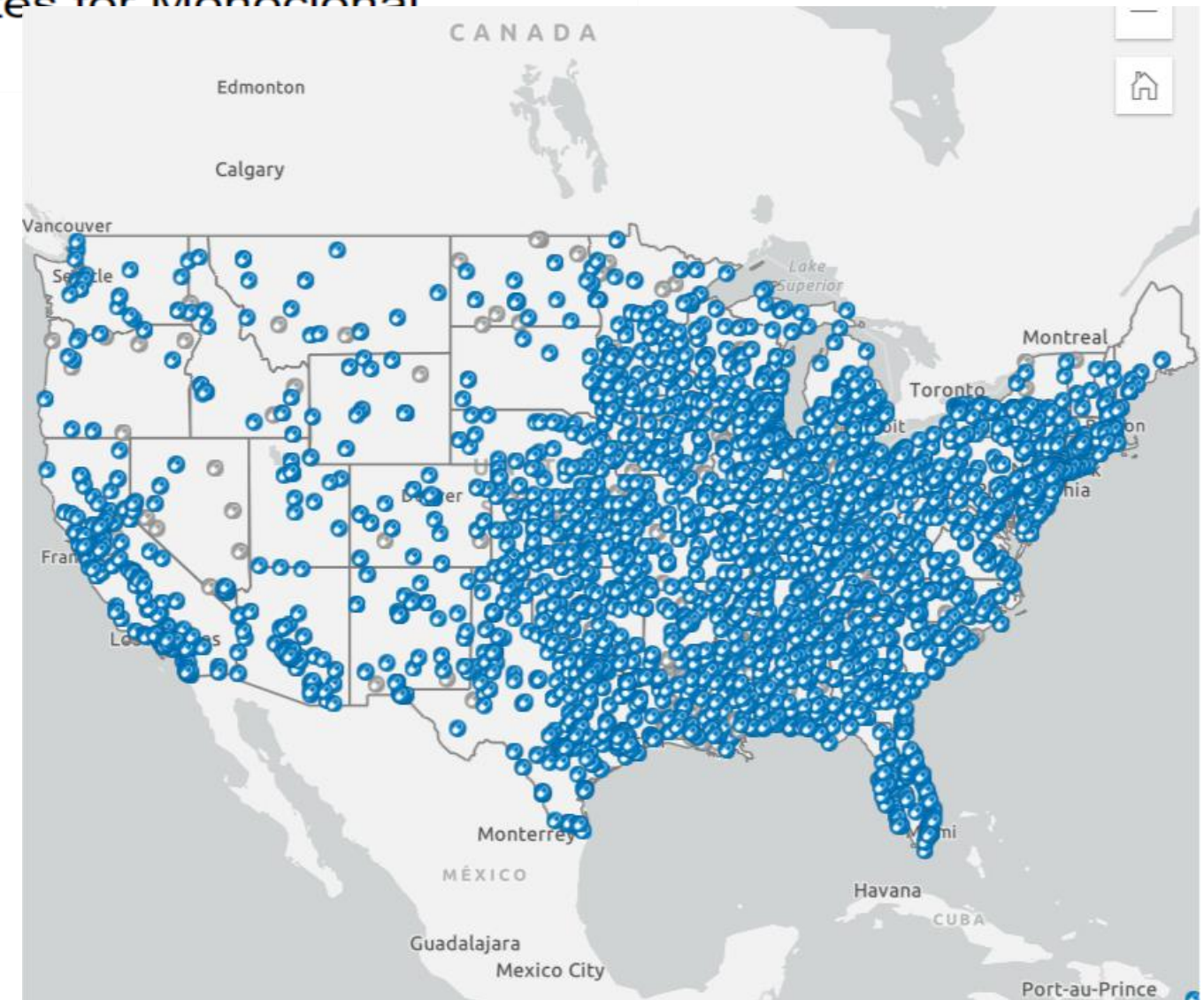
Locator Map for sites giving monoclonal antibody infusions

Total 4000 given so far in SC
150,000 given nationwide

FOR IMMEDIATE RELEASE
January 11, 2021

Contact: ASPR Media
202-205-8117
asprmedia@hhs.gov

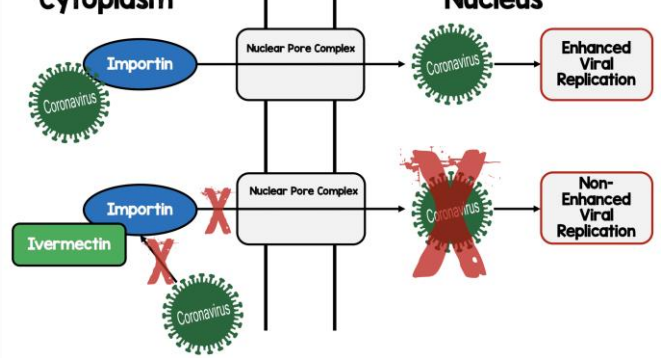
HHS Launches Web-Based Locator for COVID-19 Outpatient Treatment Sites for Monoclonal Antibodies



NIH Guidelines

- There are **insufficient data** to recommend either for or against the use of Bamlanivimab or for Casirivimab Plus Imdevimab for the treatment of outpatients with mild to moderate COVID-19.
- **Should not be considered** the standard of care for the treatment of patients with COVID-19.
- Patients who are hospitalized for COVID-19 should not receive bamlanivimab outside of a clinical trial.
  - *Can be given* to a hospitalized patient not requiring supplemental O2 and fulfilling other criteria
  - Patients at **highest risk for COVID-19 progression** should be prioritized for use of the drug through the EUA.

Ivermectin



- Ivermectin is an FDA approved antiparasitic drug - used to treat tropical diseases, including onchocerciasis, helminthiases, and scabies
- Mixed data from studies
  - Some clinical studies showed no benefits or worsening of disease after ivermectin use
  - Others reported shorter time to resolution of disease manifestations , greater reduction in inflammatory markers, shorter time to viral clearance, or lower mortality rates
- **NIH Recommendation**
  - The COVID-19 Treatment Guidelines Panel **recommends neither for nor against** the use of **ivermectin** for the treatment of COVID-19, except in a clinical trial **(AIII)**.
  -
  - This language changed on January 15 from against to neither for or against

Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults

Romina Libster, M.D., Gonzalo Pérez Marc, M.D., Diego Wappner, M.D., Silvina Coviello, M.S., Alejandra Bianchi, Virginia Braem, Ignacio Esteban, M.D., Mauricio T. Caballero, M.D., Cristian Wood, M.D., Mabel Berrueta, M.D., Aníbal Rondan, M.D., Gabriela Lescano, M.D., et al., for the Fundación INFANT–COVID-19 Group*

- Early convalescent plasma may reduce progression in high risk patients
- Study from Argentina published in NEJM 2 weeks ago
  - Trial of convalescent plasma involving 160 patients with COVID-19
    - **Mean overall age, 77**; 72% female
- Randomized to receive IV convalescent plasma or saline
  - **Infusion given within 72 hours** of symptom onset.
    - Plasma preparations had high anti–SARS-CoV-2 spike protein IgG titers
- Progression to severe respiratory disease
  - Plasma recipients (16%)
  - Placebo recipients (25%); *P*<0.03, relative risk reduction, 48%; NNT- 7

Fluvoxamine

Fluvoxamine vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19

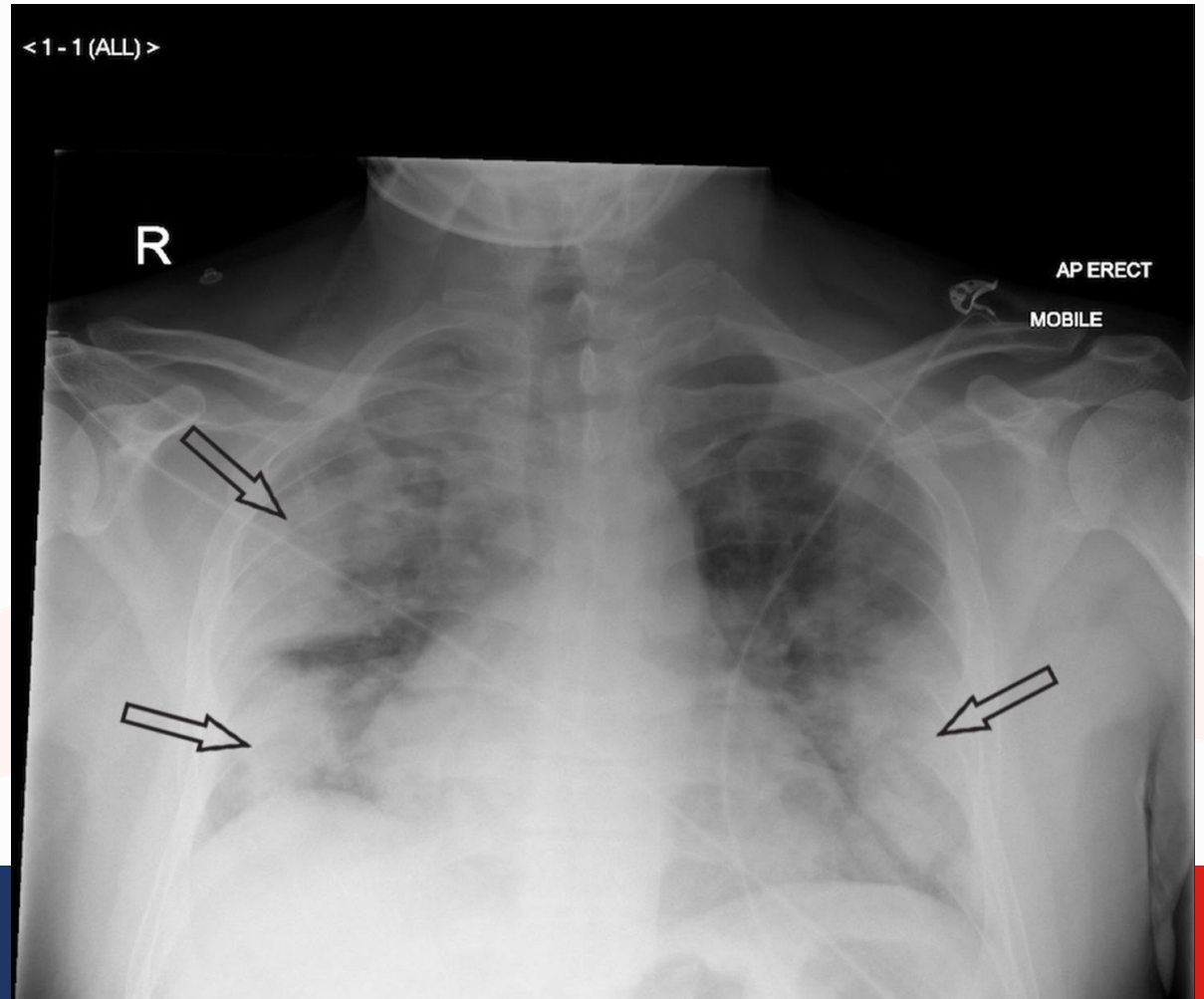
A Randomized Clinical Trial

Eric J. Lenze, MD[1]; Caline Mattar, MD[2]; Charles F. Zorumski, MD[1]; et al

- 152 trial participants > 18 years or older
- All lived in either Missouri or Illinois
  - Mild COVID-19
- Randomized 1:1 to receive either fluvoxamine or placebo
- Primary outcome- respiratory deterioration within 7 days of diagnosis
  - Fluvoxamine- 0/80
  - Placebo- 6/72 (8.3%)

Severe COVID-19

- 65 year male, CKD, BMI- 35, CAD, hospitalized with COVID-19
- RR-24, on 4l by Nasal cannula,



Recommendations for non ventilated patients

- Hospitalized Patients with COVID-19 Who Require Supplemental Oxygen
  - But not on Oxygen Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO

Remdesivir 200 mg intravenously X 5 days

OR

A combination of remdesivir plus dexamethasone 6 mg IV or orally for up to 10 days or until hospital discharge

OR

If remdesivir cannot be used, dexamethasone may be used instead

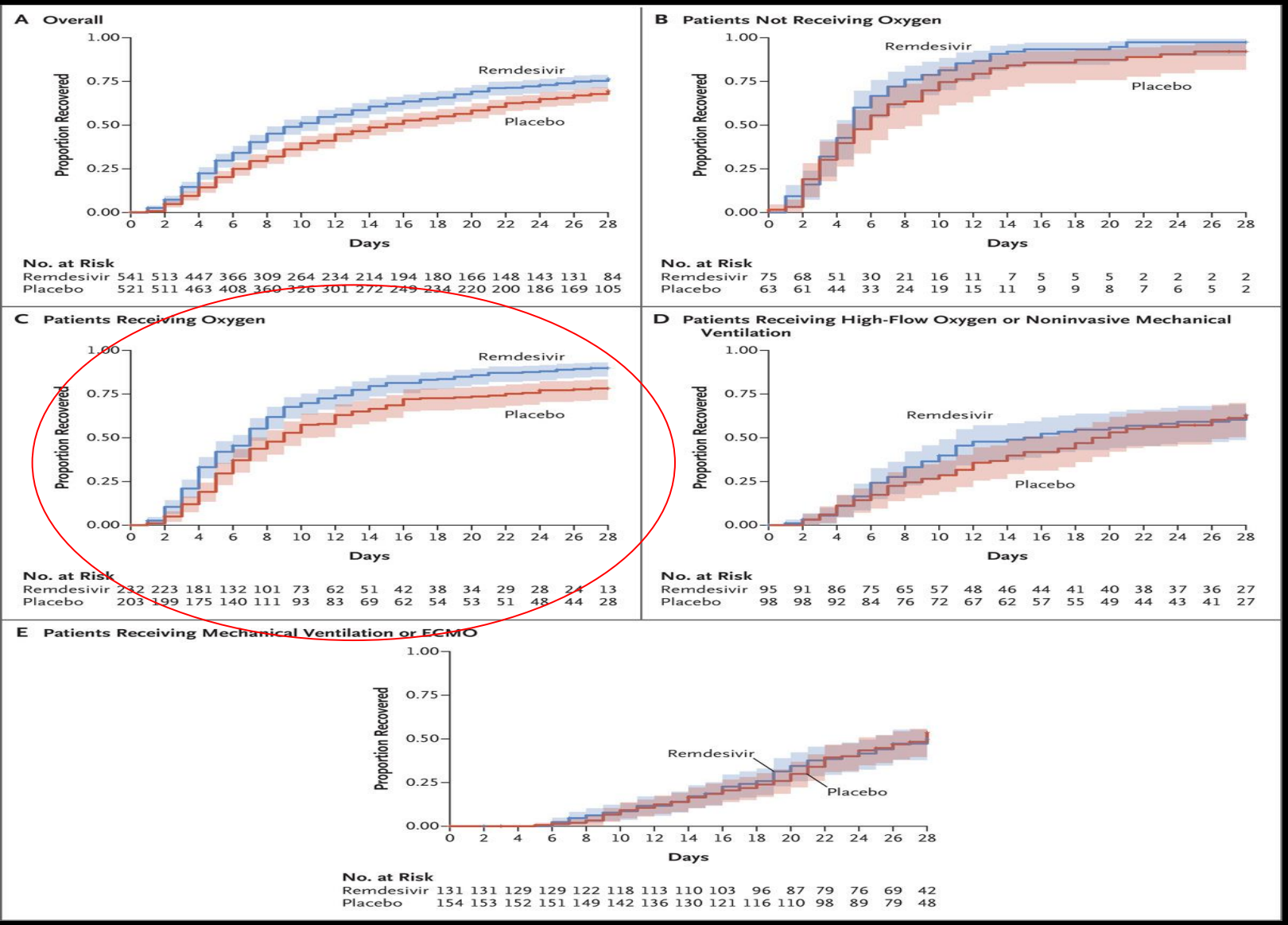
ORIGINAL ARTICLE

Remdesivir for the Treatment of Covid-19 — Final Report

- November 5, 2020
  - Double blind placebo controlled; 1063 patients underwent randomization.
    - 60 trial sites, 13 in the US
- 50% assigned to remdesivir and 50% to placebo

	Remdesivir	placebo
Median recovery time	10	15
15 day mortality (estimates)	6.7%	11.9%
29 day mortality	11.4%	15.2%
Serious Adverse events	24.6%	31.6%

Kaplan–Meier Estimates of Cumulative Recoveries.



Remdesivir chould be considered for COVID -19 positive patients who are hospitalized and meet all the following criteria:

1.Hypoxia (but not ventilated)
2.< 7-10 days from diagnosis/symptoms
3.Cr Cl > 30
4.ALT < 5 ULN (or < 250)

CMP to be monitored every day on Remdesivir

JH Beigel et al. N Engl J Med 2020;383:1813-1826.

The NEW ENGLAND JOURNAL of MEDICINE

Corticosteroids- IDSA **Recommendation**

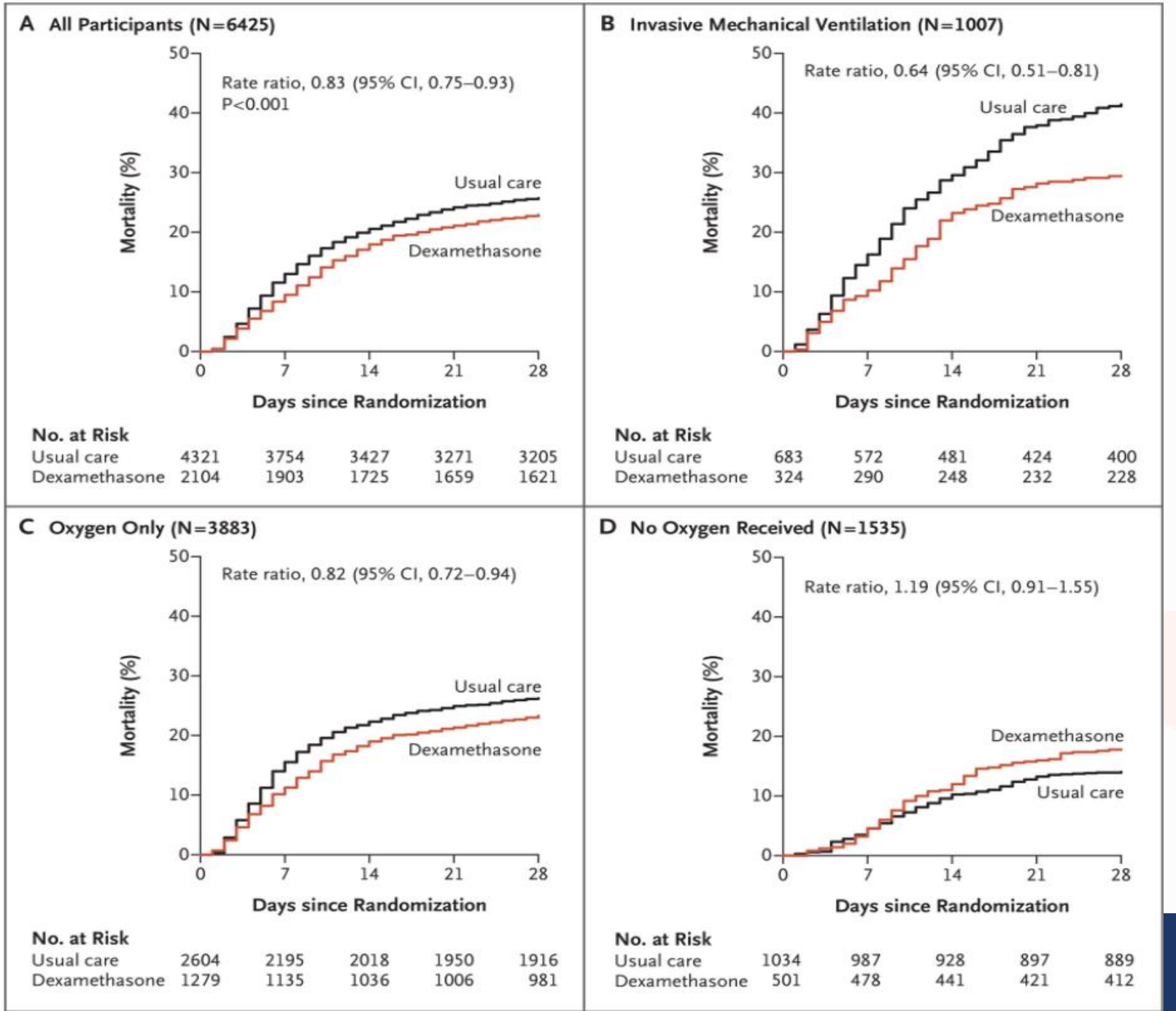
- **Yes** in hospitalized, critically ill patients
  - Odds of mortality at 28 days is 34% lower in the dexamethasone group
- **Yes** in hospitalized patients with severe COVID-19
  - 28-day mortality was 17% lower in the dexamethasone group
- **No** in hospitalized patients with COVID-19 without hypoxemia

- Dose
  - Dexamethasone 6 mg IV or PO for 10 days (or until discharge if earlier)
    - Or Equivalent total daily doses of alternative glucocorticoids
      - methylprednisolone 32 mg and prednisone 40 mg.

Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial out of the United Kingdom

	Dexamethasone 6 mg daily + SOC	Standard care
Number of patients	2104	4321
28 day all cause mortality	21.6%	24.6%
those requiring mechanical ventilation	29.3 %	41.4%
Discharged from hospital within 28 days	67.2 %	63.5%

- The benefit was greatest in
  - patients with symptoms > 7 days
  - patients who required mechanical ventilation.
  - No benefit among patients with shorter symptom duration or no supplemental O2



Increased mortality with steroids if given to non hypoxic patients

Hydroxychloroquine – no benefit in treatment and has excess mortality

- RECOVERY trial (UK)- used high doses of hydroxychloroquine
  - HCQ mortality- 25.7%
  - Usual Care- 23.5%
- Observational study (New York)
  - Increased risk of cardiac arrest with hydroxychloroquine -1·91
  - Risk increased further if hydroxychloroquine was combined with azithromycin (2·13 [1·12–4·05])

    *JAMA. 2020; **323**: 2493-2502*

Convalescent plasma

- Convalescent plasma has been used as passive immunotherapy for prevention and treatment of infections for over 100 years
  - Use of passive antibody therapy using the serum of recovered patients
  - no residual virus, high titers of neutralizing antibodies (hopefully)

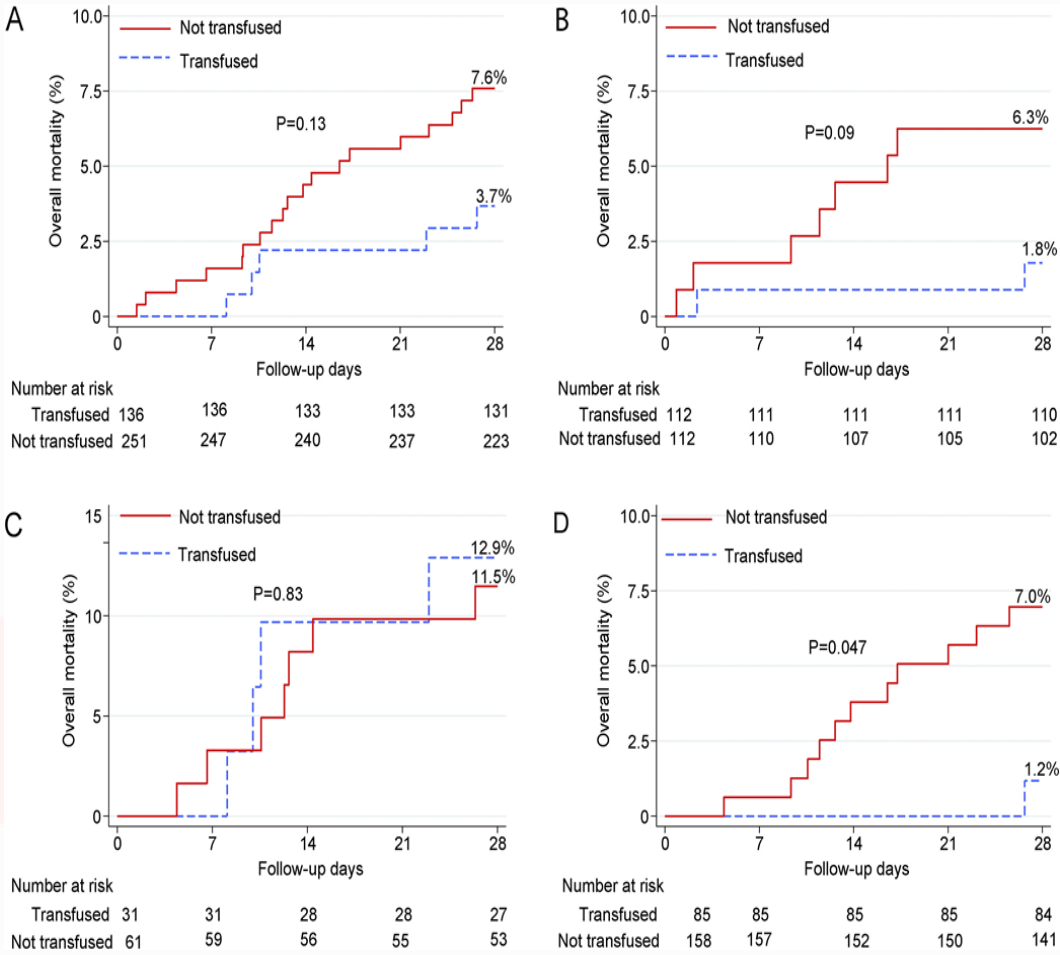
  We had great hopes in the beginning of the COVID pandemic

  I transfused the first patient in South Carolina in March 2020
    - We had to get that one from Tennessee
    - Within 12 hours her taste and smell returned, discharged 2 days later
    - She has been on television multiple times as the first recipient in the state.
- However, over the last 10 months the data on its efficacy has been disappointing and it is being used less and less

Treatment of COVID-19 Patients with Convalescent Plasma Reveals a Signal of Significantly Decreased Mortality

Eric Salazar • Paul A. Christensen • Edward A. Graviss • ... David W. Bernard • Jimmy Gollihar •

- Prospective, propensity score-matched study
  - Compared COVID-19 CP to SOC
- Interim analysis at Houston hospitals
  - March 28 to July 6, 2020
- 316 transfused patients
  - 36 met a 28-day outcome
  - Matched to 251 non-transfused contros.
- Significant reduction (*P* = 0.047) in mortality within 28 days
  - Specifically in patients transfused < 72 h of admission with plasma



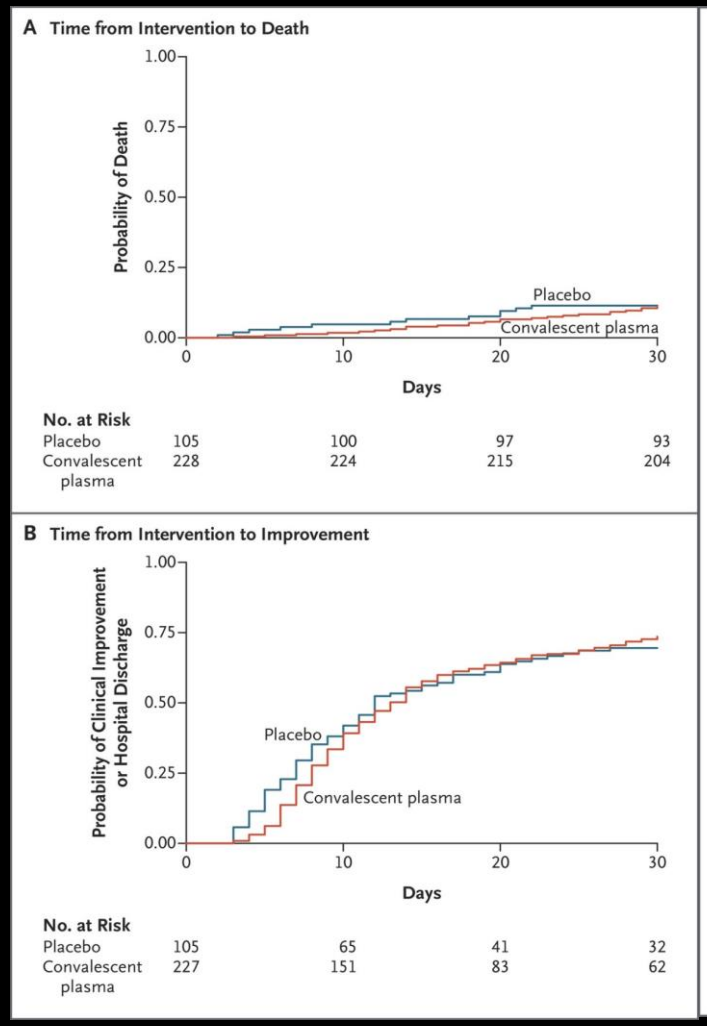
ORIGINAL ARTICLE

A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia

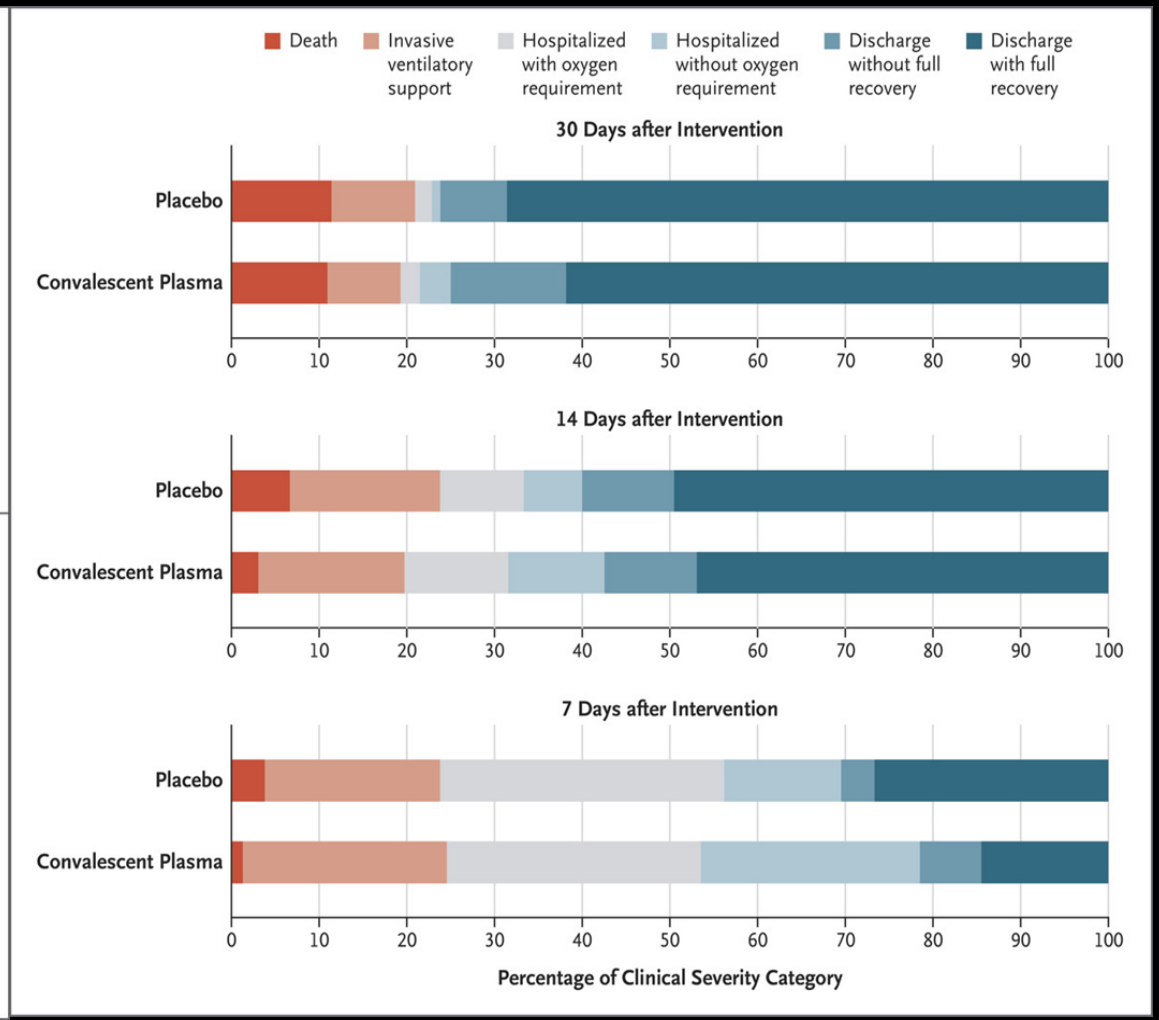
Ventura A. Simonovich, M.D., Leandro D. Burgos Pratx, M.D., Paula Scibona, M.D., María V. Beruto, M.D., Marcelo G. Vallone, M.D., Carolina Vázquez, M.D., Nadia Savoy,

- Published NEJM Nov 24, 2020
  - Randomized multicenter trial in Argentina
  - Hospitalized adult patients with severe Covid-19 pneumonia
- Inclusion Criteria: At least one of the following
    - SaO_2 below 93% on room air
    - PaO_2/FiO_2 <300 mm Hg
    - SOFA or modified SOFA (mSOFA) score of two or more points above baseline status
  - 228 patients were assigned to receive CP & 105 to receive placebo.
    - The median time from the onset of symptoms to enrollment in the trial - 8 days
  - Infused convalescent plasma had a median titer of 1:3200 of total SARS-CoV-2 antibodies
- Overall mortality
  - CP arm- 10.96%
  - Placebo- 11.43%
- Adverse events and serious adverse events were similar in the two groups.

Time to Death or to Improvement after Treatment with CP or Placebo.



Clinical Outcomes among Patients Treated with Convalescent Plasma as Compared with Placebo.



VA Simonovich et al. N Engl J Med 2020. DOI: 10.1056/NEJMoa2031304

The NEW ENGLAND JOURNAL of MEDICINE

NIH Update October, 2020

- Recommendation
- There are **insufficient data** to recommend either for or against the use of convalescent plasma for the treatment of COVID-19.
  - Serious adverse reactions are infrequent
- The long-term risks of treatment with COVID-19 convalescent plasma are unknown
- Convalescent plasma should not be considered standard of care for the treatment of patients with COVID-19.
- Prospective, well-controlled, adequately powered randomized trials are needed

COVID-19 and increased thromboembolism

- French prospective multicenter cohort of 150 ICU patients
  - 16.7% had pulmonary embolism despite prophylactic anticoagulation
- A Dutch study of 184 ICU patients
  - Cumulative incidence of Thromboembolism - 31%
  - CTPA and/or ultrasonography confirmed VTE - 27%
  - Arterial thrombotic events - 3.7% (95%CI 0-8.2%)
- An Italian study found VTE rate - 22%

Registry of Arterial and Venous Thromboembolic Complications in Patients With COVID-19

- JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY; Aug 2020
  - Mass General and Brigham hospitals
  - Prophylactic anticoagulation was prescribed in 89.4%
  - Thrombotic complications
    - non–critically ill hospitalized patients- 2.6**%**
    - hospitalized critically ill patients – **35.3%**
  - Elevated levels of the following markers have been identified
    - D-dimer- 100%; Fibrinogen ; factor VIII – 100%
    - Antiphospholipid antibodies - 53% of participants
    - Decreased protein C, protein S, and antithrombin levels – 100%

NIH Guidelines for Anticoagulant and Antiplatelet Therapy

- Chronic Anticoagulant and Antiplatelet Therapy
  - Patients who are on anticoagulant or antiplatelet therapies should continue these medications
- Venous Thromboembolism Prophylaxis and Screening
  - For nonhospitalized patients with COVID-19, anticoagulants and antiplatelet therapy should not be initiated
- Hospitalized nonpregnant adults with COVID-19 should receive prophylactic dose anticoagulation
- Hospitalized patients with COVID-19 should not routinely be discharged n VTE prophylaxis unless there are other reasons.
  - Continuing anticoagulation with for extended VTE prophylaxis after hospital discharge can be considered in patients who are at low risk for bleeding and high risk for VTE
- For hospitalized COVID-19 patients who experience rapid deterioration of pulmonary, cardiac, or neurological function
  - Consider the possibility of thromboembolic disease

The COVID-19 Outpatient Thrombosis Prevention Trial

- Multi-center adaptive randomized, double-blind, placebo-controlled
  - Compare the effectiveness of anti-coagulation vs anti-platelet agents vs placebo
  - Non-hospitalized patients who have evidence of elevated D-dimer and hsCRP.
- Will compare
  - Apixiban 2.5 mg PO BID
  - Apixiban 5 mg PO BID
  - Aspirin PO BID
  - Or Placebo

Tocilizumab- IL-6 antagonist

- **Studies showing no benefit**
- RCT-TCZ-COVID-19 (n=126)
  - Primary end point- hypoxia, ICU admission or death- Stopped early due to lack of benefit
- CORIMUNO-19-TOCI(n=131)
  - Toci may have reduced need for mechanical ventilation but no impact on mortality
- BACC Bay Trial(n=243)- 7 Boston hospitals
  - Placebo controlled; Toci did not reduce requirement for intubation or reduce mortality
- COVACTA trial
  - First global, randomised, double-blind, placebo-controlled phase III study
    - No difference in patient mortality at week 4
- Empacta (n=389)
  - Placebo controlled; Toci reduced need for mechanical ventilation but mortality did not improve
- **Studies showing benefit**
- REM-CAP Trial (n =800)- very recently published
  - Patients started on IL-6 antagonist within 24 hours of ICU admission

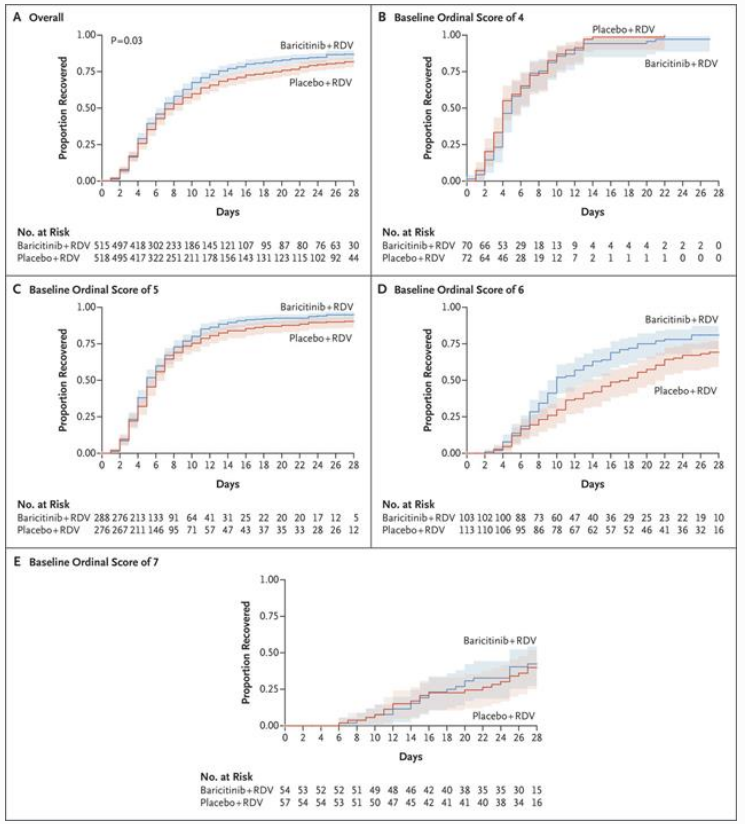
  Reduced mortality in IL-6 arm

NIH Guidelines

- The Panel recommends against the use except in a clinical trial:
  - Anti-IL-6 receptor monoclonal antibodies (e.g., sarilumab, tocilizumab, siltuximab
  - Interferons (alfa or beta)
  - Bruton's tyrosine kinase inhibitors (e.g., acalabrutinib, ibrutinib, zanubrutinib)
  - Janus kinase inhibitors (e.g., baricitinib, ruxolitinib, tofacitinib)

ACTT-2: Remdesivir + baricitinib

- Baricitinib: Oral Janus kinase 1 & 2 inhibitor
- Double blind, randomized, placebo-controlled trial
  - Remdesivir + baricitinib OR remdesivir + placebo
- Primary outcome: time to recovery
  - Combination: recovered 1 day faster
    - 7 day vs 8 days, RR 1.16, 95% CI: 1.01-1.32, p=0.03

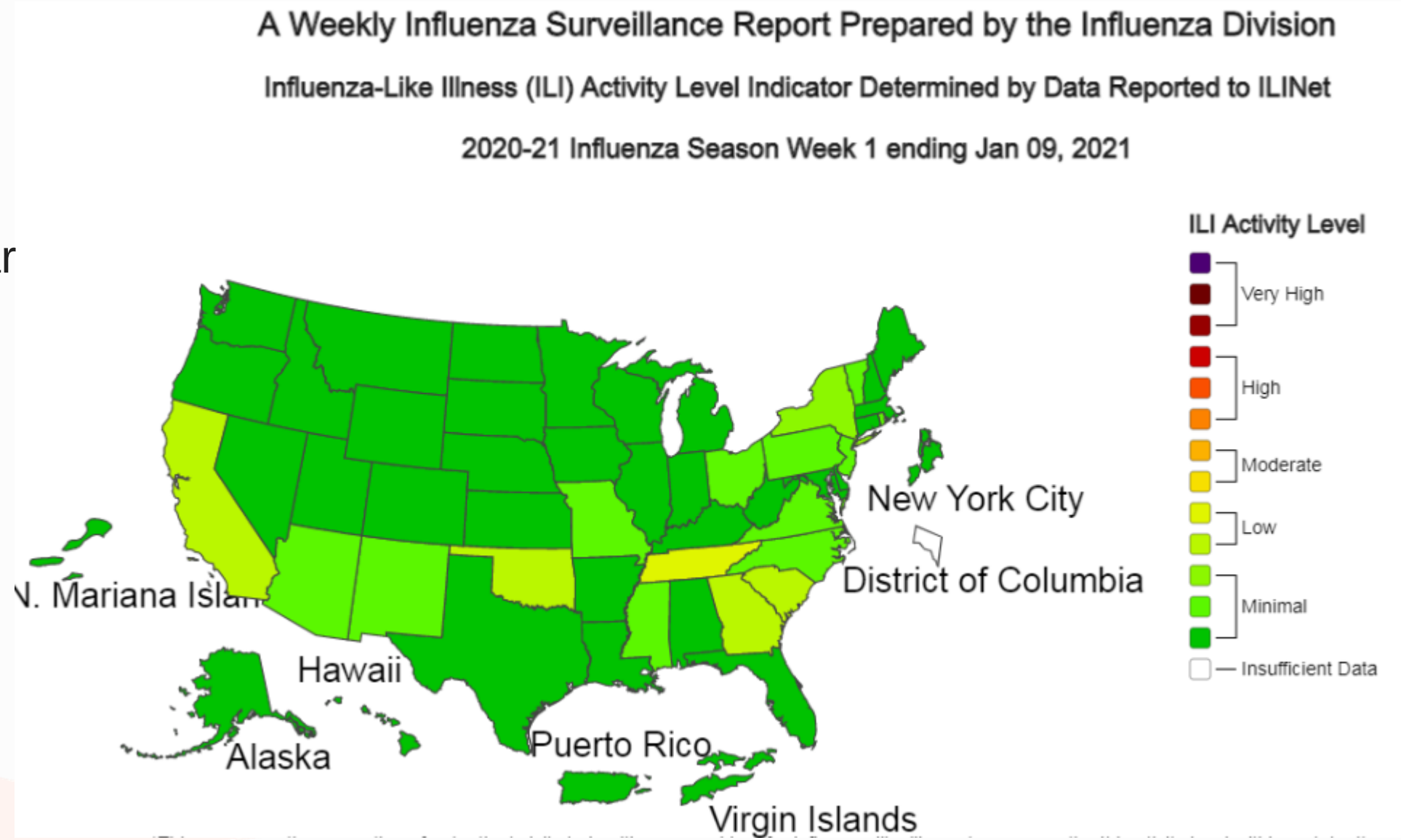


- Mortality
  - Day 28: 5.1% in combination, 7.8% in control (HR 0.65, 95% CI 0.39-1.09)
    - Greatest numerical difference in mortality was those at ordinal 5 or 6
  - 14 day mortality: 1.6% in combination group, 3.0% control group

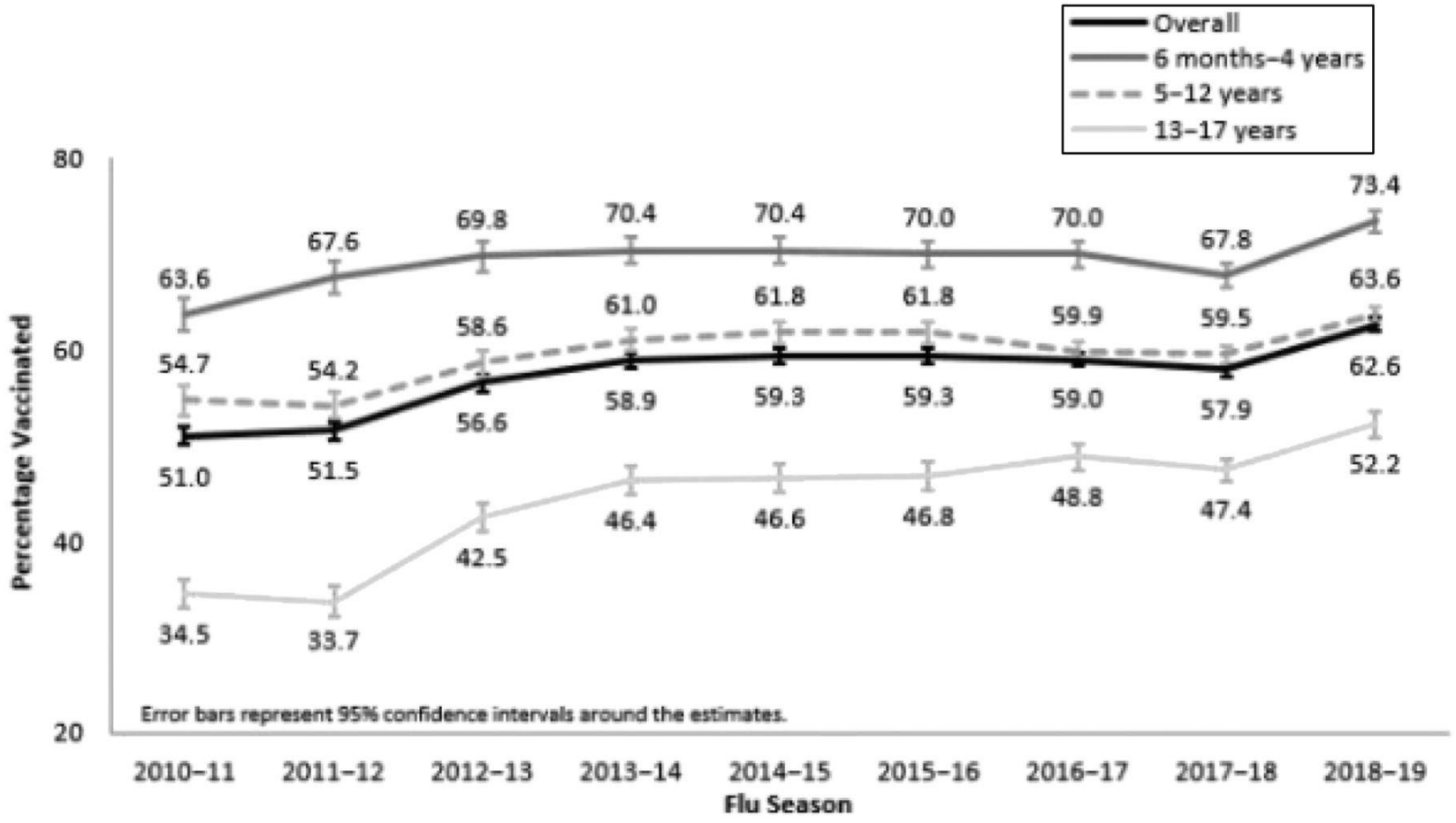
Long COVID syndrome

- Sequelae that extend beyond 4 weeks after initial infection.
- CDC telephone survey
  - 274 symptomatic respondents
    - 35% reported not having returned to their usual state of health 2 weeks or more after testing; 26% of these patients were aged 18 - 34 years
- Myriad manifestations but common ones are
  - Fatigue- 52% in a study from Ireland
  - Cardiopulmonary- Fatigue, dyspnea
    - In two studies there were Cardiac MRI abnormalities in > 50 % of patients.
  - Neuropsychiatric:
    - headaches, vision changes, hearing loss, loss of taste or smell, impaired mobility, numbness in extremities, tremors, myalgia, memory loss, cognitive impairment, (brain fog), mood change

- Lower than usual flu activity this year



Influenza vaccination coverage in children 6 months to 17 years of age in the United States, 2010 to 2019.



Committee on Infectious Diseases Pediatrics
doi:10.1542/peds.2020-024588

PEDIATRICS®

Persons at higher risk for influenza complications, recommended for antiviral Rx

- children < 2 years
- adults > 65 years
- COPD, (including asthma)
- Cardiovascular/ renal/hepatic/hematological (including sickle cell disease), DM
- Immunosuppression including HIV
- Pregnant or postpartum (within 2 weeks after delivery)
- American Indians/Alaska Natives;
- BMI> 40
- Residents of nursing homes

Anti viral agent	Activity against	use	Recommended for treatment within 2 days of illness onset	Adverse events
Oseltamivir	Influenza A and B	Treatment Chemopro phylaxis	Any age 3 months and older	Nausea, vomiting, headache
Inhaled Zanamivir	Influenza A and B	Treatment chemopro phylaxis	7 years and older 5 years and older	Not recommended in underlying respiratory disease
Intravenous Peramivir	Influenza A and B	Treatment only	Treatment of acute uncomplicated influenza	
Oral Baloxavir	Influenza A and B	Treatment Chemopro phylaxis	12 years or older Approved for > 12 years of age	

AETC AIDS Education & Training Center Program Southeast

Monthy 1st and 3rd Wednesday and
12:00pm-1:00pm EST
11:00am-12:00pm CST
09:00am-10:00am PST

4th Wednesday
12:00pm-1:00pm CST
01:00pmpm-2:00pm EST
10:00am-11:00am PST

South East Viral Hepatitis Interactive Case Conference

Free, CME Accredited case discussion , three times a month
Present your cases!!!