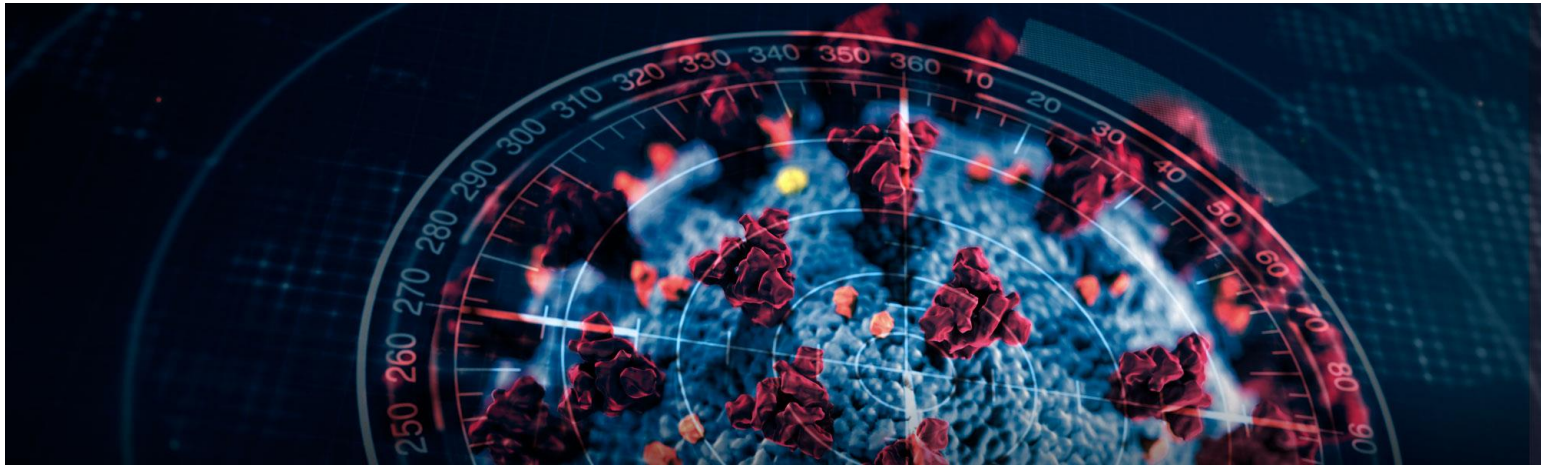
Update in COVID-19 Management: Treatments and Vaccines

Update in Internal Medicine 2021

Saturday, April 10th, 2021



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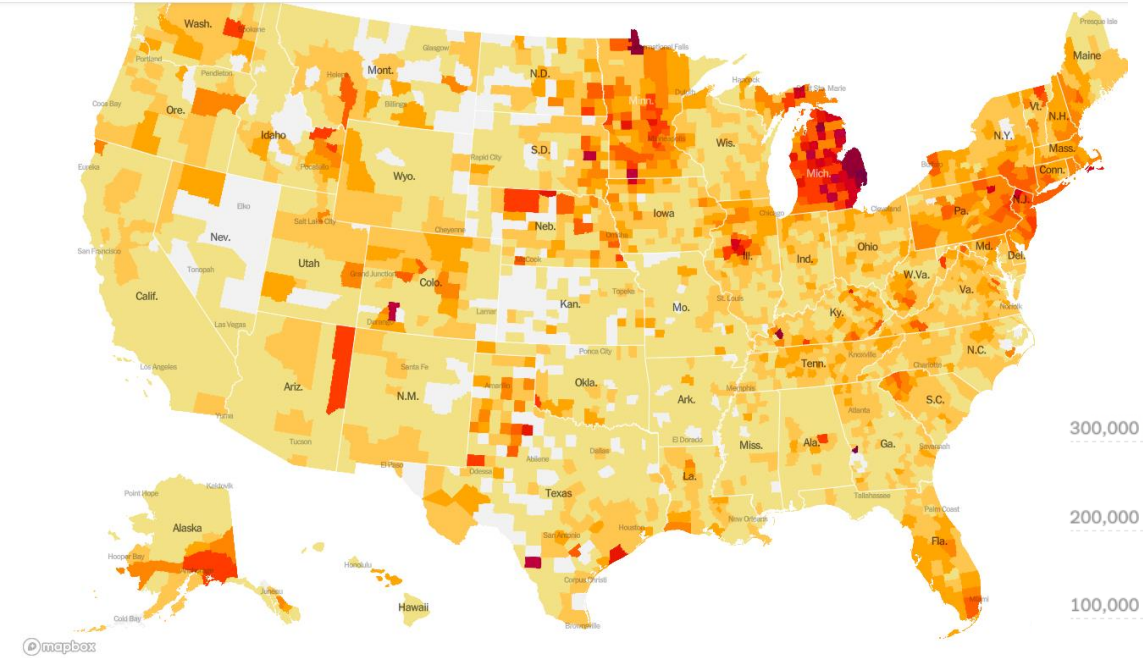
Disclosures

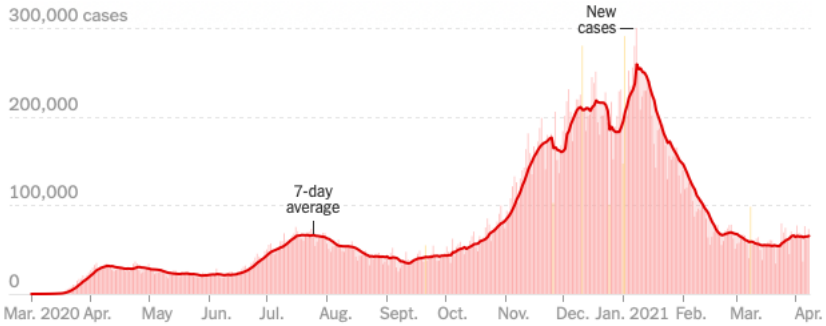
- I have no financial disclosures.
- I have served as an unpaid site Co-investigator for COVID-19 clinical trials sponsored by the NIH, Gilead, Regeneron, and Genentech.
- I will be discussing off-label investigational treatments for COVID-19.

COVID-19 Trends in the United States



Average daily cases per 100,000 people in past week

10 30 50 70 100 250 Few or no cases



	TOTAL REPORTED	ON APRIL 7	14-DAY CHANGE
Cases	31 million+	73,200	+14% ↗
Deaths	559,450	2,564*	−31% ↘
Hospitalized		43,780	+6% →

Source: New York Times; Data as of April 8, 2021

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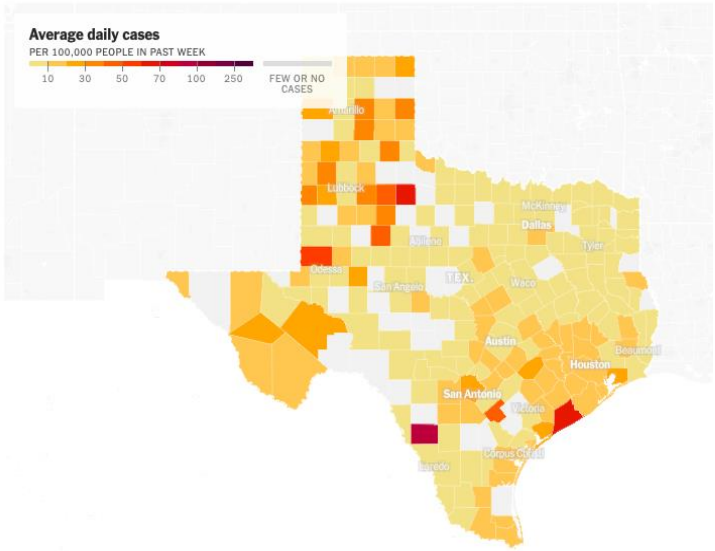
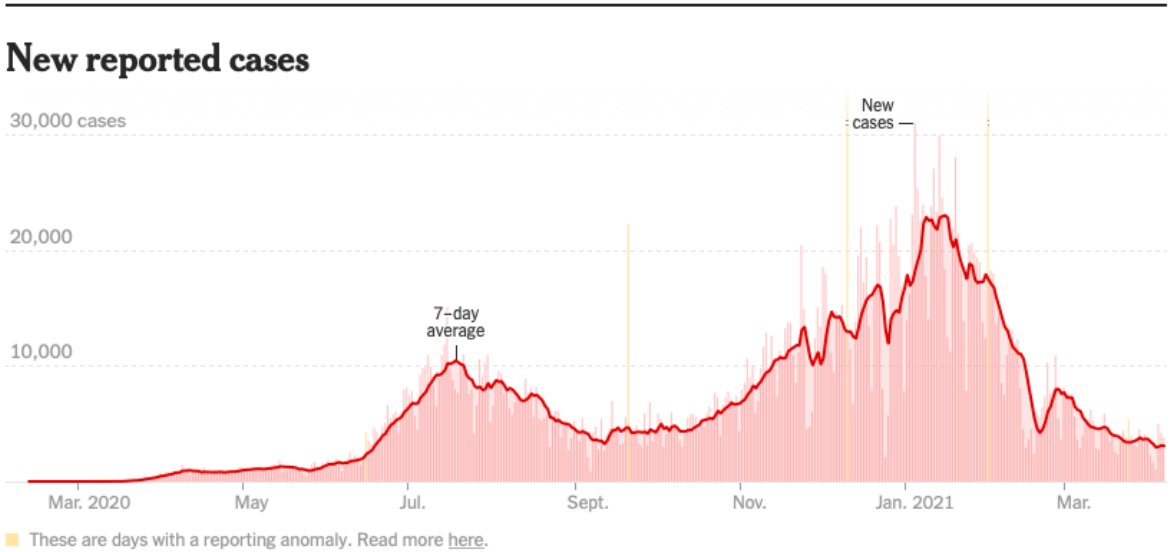
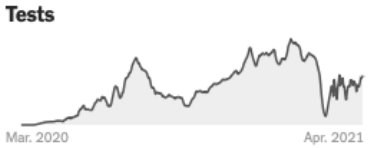
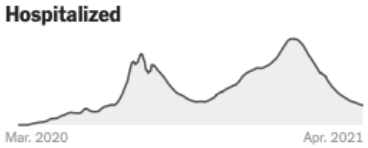
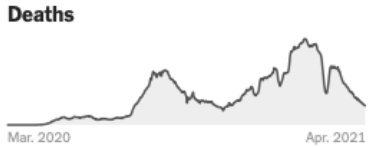
COVID-19 Trends in Texas











	AVG. ON APR. 7	14-DAY CHANGE	TOTAL REPORTED
Cases	3,072	−10%	2,819,388
Deaths	76	−38%	49,167
Hospitalized	3,373	−17%	—
Tests	73,373	+8%	—

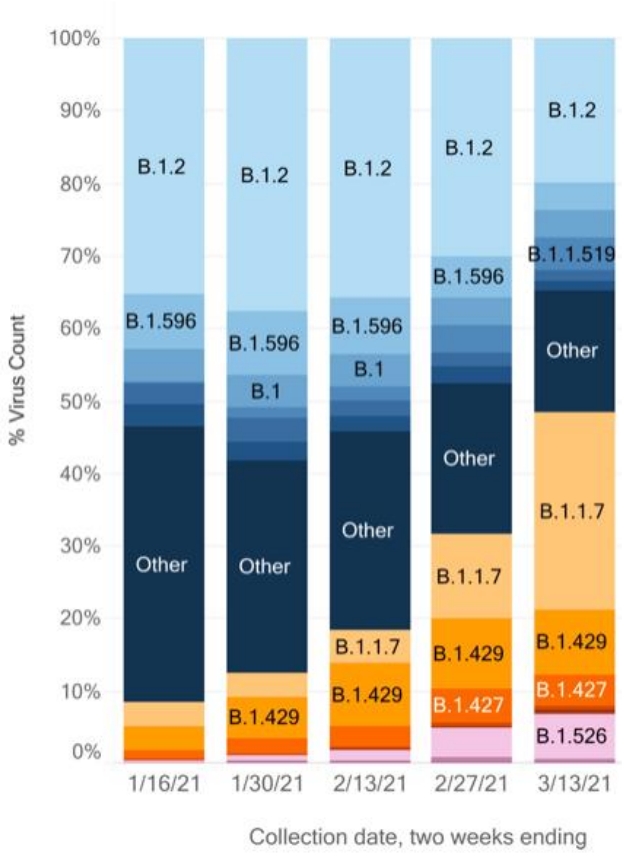
Source: New York Times; Data as of April 8, 2021

SARS-CoV-2 Variants of Concern

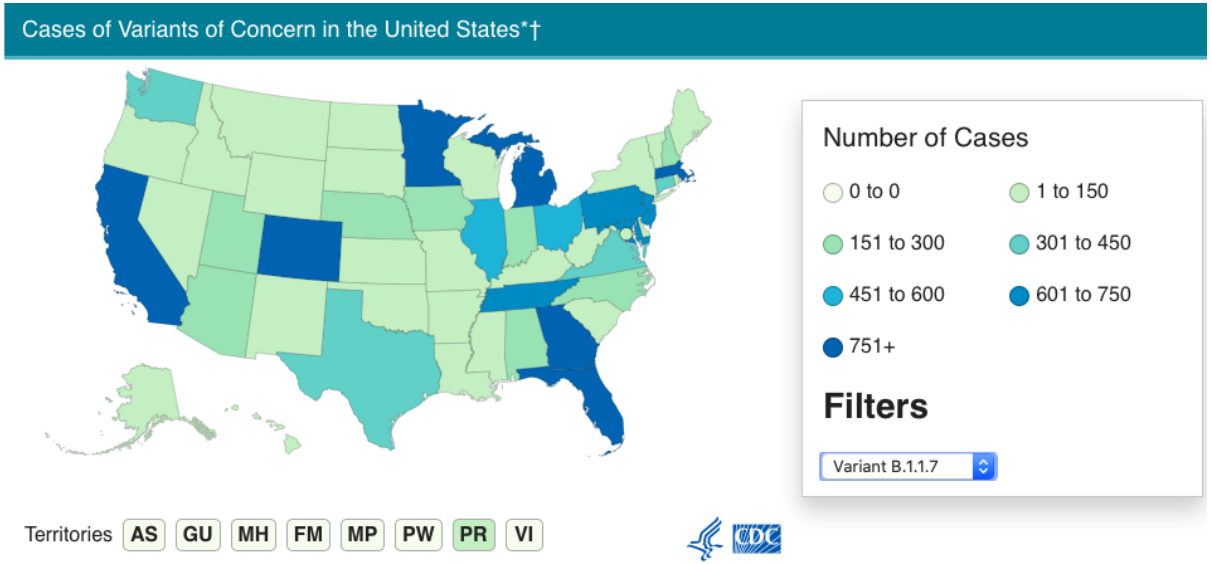
Key SARS-CoV-2 variants of concern	B.1.1.7	B.1.351	P.1	B.1.427/ B1.429
Location/Date first identified	**United Kingdom**, Sep 2020	**South Africa**, Oct 2020	**Brazil** and Japan, Jan 2021	**California,** July 2020
Identified in US to date	Yes	Yes	Yes	Yes
Impact on vaccine efficacy?	No	Some reduced efficacy	Likely some reduced efficacy	Possible some impact
Impact on monoclonal antibody therapies?	No	Reduced efficacy to some but not all Ab products	Reduced efficacy to some but not all Ab products	Reduced efficacy to some but not all Ab products
Primary Concerns	Increased spread by ~ 50%, more severe disease	Increased spread, some antibody escape	Increased spread, some antibody escape	Increased spread by 20%, some antibody escape

https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html#Concern

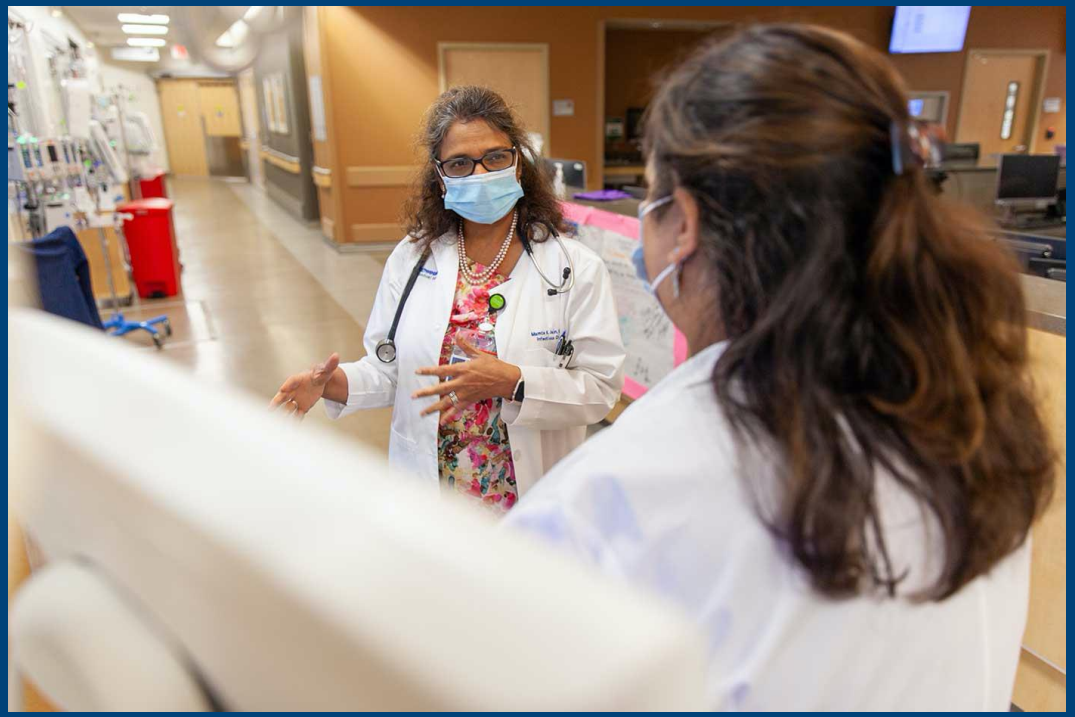
SARS-CoV-2 Variants of Concern in US



B.1.1.7 ("UK variant") now dominant variant in US but distributed heterogeneously across the country



https://www.cdc.gov/coronavirus/2019-ncov/transmission/variant-cases.html



Treating COVID-19

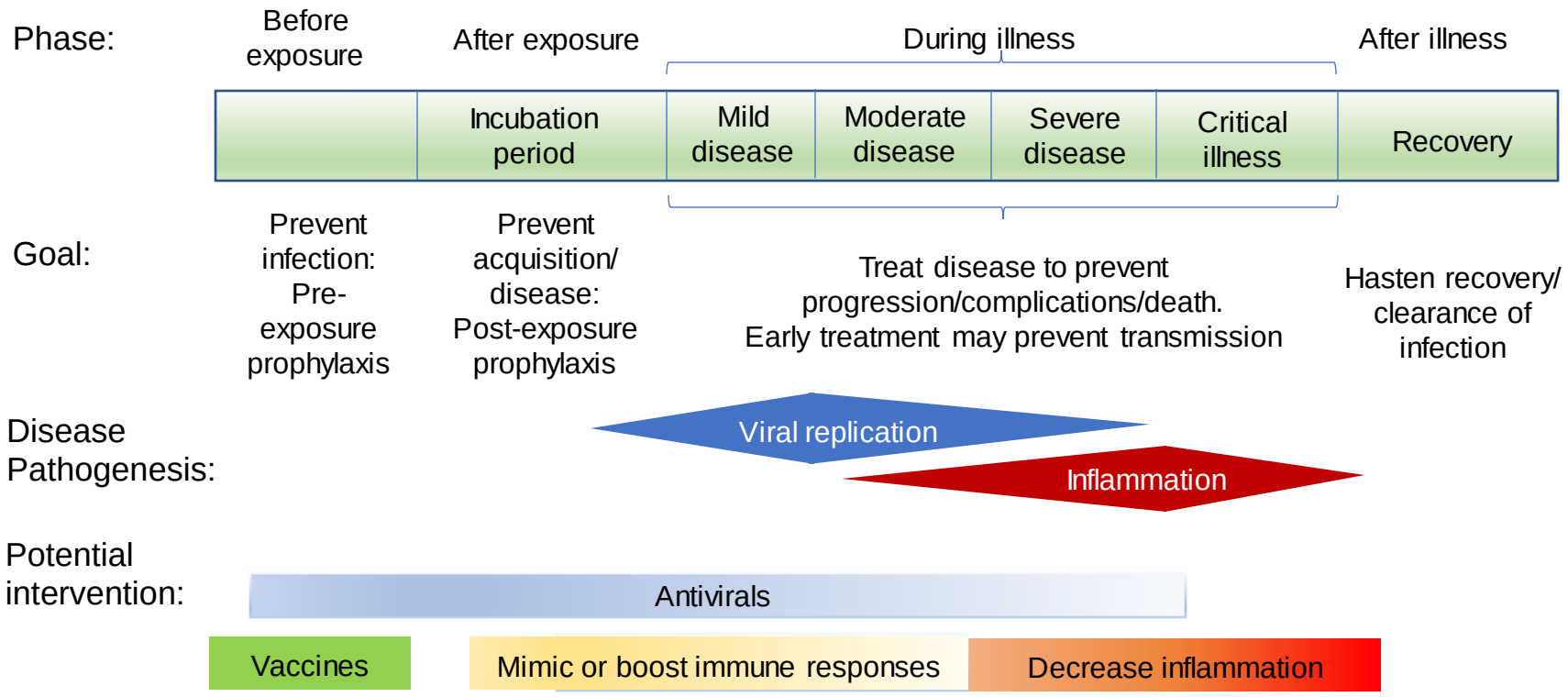
Pharmacologic Treatments

Disease Severity in COVID-19

Disease Category	Clinical Definition
Asymptomatic COVID-19	Viral replication without symptoms
Mild COVID-19	Symptomatic, no hypoxia or signs of PNA, no ongoing medical care
Moderate COVID-19	Symptomatic, signs of PNA or ongoing medical care **but no hypoxia at rest (O_2 ≥ 94% on room air)**
Severe COVID-19	**Hypoxic at rest (O_2 < 94% on room air),** RR > 30, P/F ratio < 300, >50% lung infiltrates; some subdivide between low-flow vs. high-flow O_2/NIV
Critical COVID-19	ARDS or septic shock; requiring Mechanical ventilation or ECMO

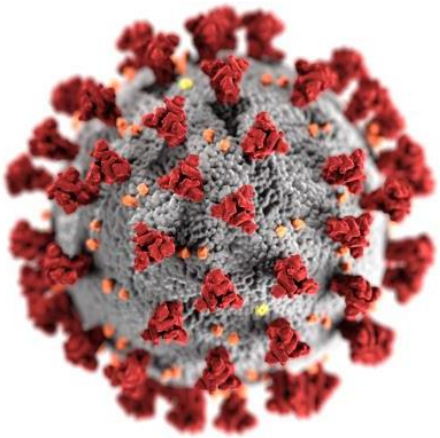
Must pay attention to trial methods because some define these categories differently, particularly severe disease

Goals of Treatment Across COVID-19 Spectrum



Antivirals

- Agents directly targeting SARS-CoV-2 replication
- Likely work best in early viral phase or as prophylaxis
- Example Agents
  - **Remdesivir (RDV)**
  - Hydroxychloroquine/Chloroquine
  - Lopinavir-Ritonavir
  - Ivermectin
  - Favipiravir
  - Molnupiravir (MK-4482)

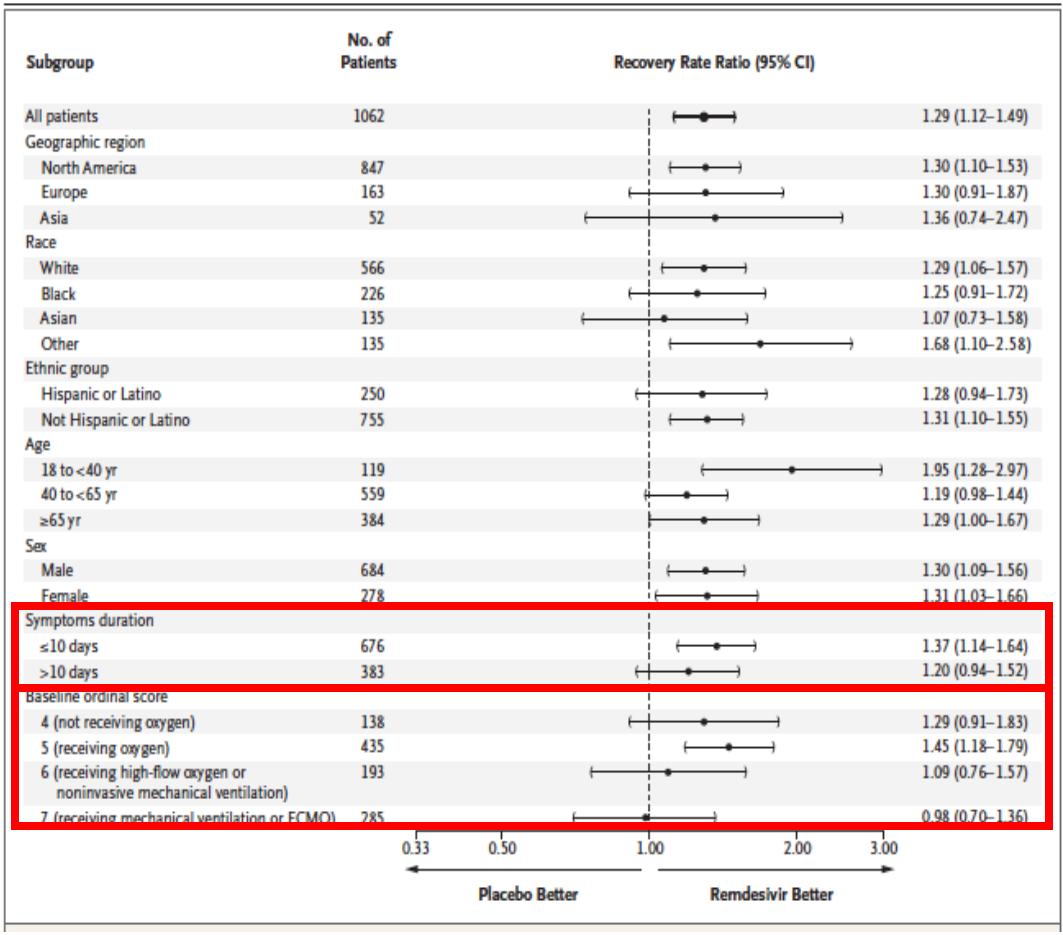


Not recommended due to lack of proven benefit in RCT(s)

Inconclusive or lacking adequate RCT(s), only use in clinical trials

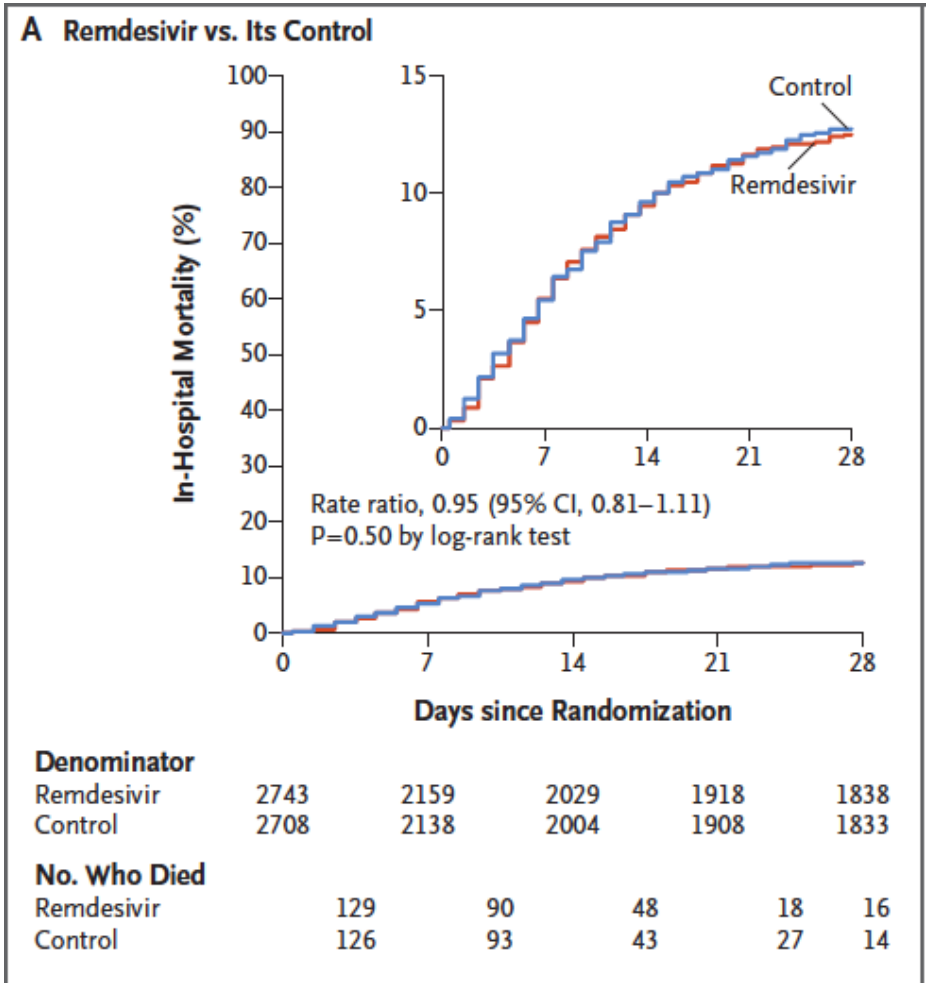
ACTT-1 Trial (RDV vs. Placebo)

- Double-blind, placebo-controlled RCT, mostly in North America
- RDV x 10 days (N=541) vs. Placebo (N=521)
- Primary Outcome: Median time to recovery 10d vs. 15d (RR 1.29; p<.001)
- **Limitations:** Not powered for mortality, ? relevance of ordinal scale, may have started too late (9d)



SOLIDARITY: RDV Arm

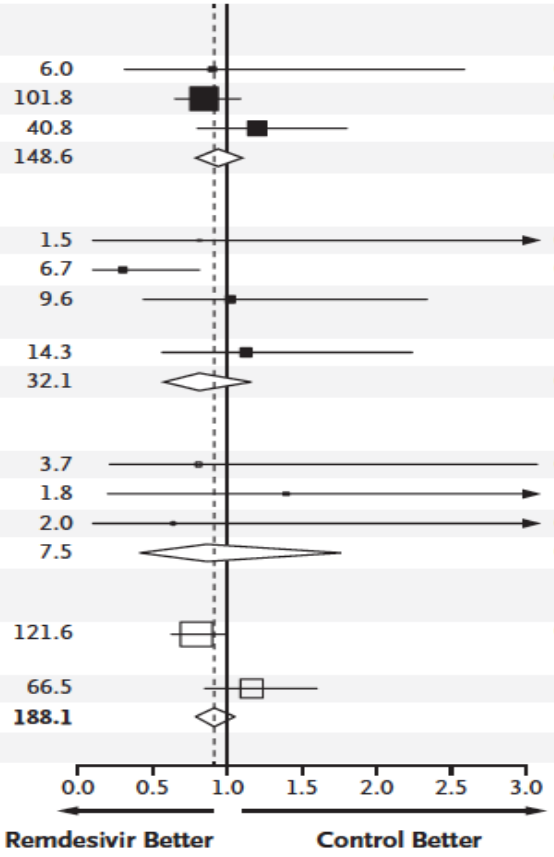
- Open-label, RCT of RDV x 10 days (N=2743) vs. local std care (N=2708)
- 63% on O_2, 8% on MV
- In-hospital Mortality: 11.8%; No diff between groups
- No difference in need for MV or time to discharge
- **Limitations:** Open label design, Time from Sx onset and O_2 level not reported



Solidarity Trial: Pan H, et al. NEJM 12/2/2020.

RDV Meta-Analysis: No Mortality Benefit

Subgroup	Remdesivir	Control	Observed–Expected No. of Deaths in Remdesivir Group: Value	Observed–Expected No. of Deaths in Remdesivir Group: Variance	Rate Ratio for Death (99% CI; 95% CI for totals)
	no. of deaths reported/no. of patients (%)				
Solidarity (stratified according to oxygen use and ventilation)					
No supplemental oxygen	11/661 (2.0)	13/664 (2.1)	−0.6	6.0	0.90 (0.31–2.58)
Low-flow or high-flow oxygen	192/1828 (12.2)	219/1811 (13.8)	−16.9	101.8	0.85 (0.66–1.09)
Ventilation	98/254 (43.0)	71/233 (37.8)	7.6	40.8	1.20 (0.80–1.80)
Stratified total: Solidarity	301/2743 (12.5)	303/2708 (12.7)	−10.0	148.6	0.94 (0.80–1.10)
ACTT-1 (stratified according to 4 ordinal score levels)					
No supplemental oxygen	3/75 (4.1)	3/63 (4.8)	−0.3	1.5	0.82 (0.10–6.61)
Low-flow oxygen	9/232 (4.0)	25/203 (12.7)	−8.0	6.7	0.30 (0.11–0.81)
High-flow oxygen or noninvasive ventilation	19/95 (21.2)	20/98 (20.4)	0.2	9.6	1.02 (0.44–2.34)
Invasive ventilation	28/131 (21.9)	29/154 (19.3)	1.8	14.3	1.13 (0.57–2.23)
Stratified total: ACTT-1	59/533 (11.1)	77/518 (14.9)	−6.4	32.1	0.82 (0.58–1.16)
Trials with few deaths (and randomization ratio of 2:1)					
Wuhan: low-flow oxygen	11/129 (8.5)	(7/68)×2 (10.3)	−0.8	3.7	0.81 (0.21–3.07)
Wuhan: high-flow oxygen or ventilation	11/29 (37.9)	(3/10)×2 (30.0)	0.6	1.8	1.40 (0.20–9.52)
International: no supplemental oxygen	5/384 (1.3)	(4/200)×2 (2.0)	−0.9	2.0	0.64 (0.10–3.94)
Stratified total: 2:1 trials	27/542 (5.0)	(14/278)×2 (5.0)	−1.1	7.5	0.86 (0.42–1.77)
Risk groups (calculated by summation of relevant strata)					
Lower risk: strata with no ventilation	231/3309 (7.0)	282/3277 (8.6)	−27.6	121.6	0.80 (0.63–1.01)
Higher risk	156/509 (30.6)	126/505 (25.0)	10.1	66.5	1.16 (0.85–1.60)
Stratified total	**387/3818 (10.1)**	**408/3782 (10.8)**	**−17.5**	**188.1**	**0.91 (0.79–1.05)**
Heterogeneity between trials (Solidarity vs. ACTT-1 vs. 2:1 trials): χ^2_2=0.5					P=0.20



Solidarity Trial: Pan H, et al. NEJM 12/2/2020.

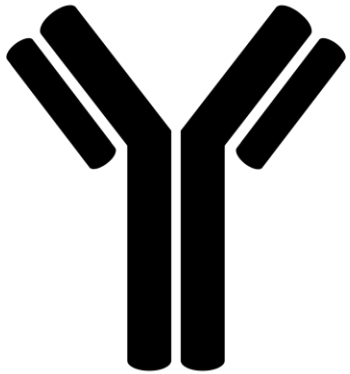
Applying the Evidence: Remdesivir

- Strongest evidence of benefit in patients with severe COVID-19 but not intubated (Low flow O_2 > high flow or noninvasive ventilation)
- Less clear if any clinical benefit in moderate disease (no O_2) or critical disease (mechanical ventilation)
- **Modest clinical benefit, does not appear to reduce mortality**
- **Practical considerations with RDV:**
  - Default duration 5 d, might extend in MV/ECMO
  - Monitor LFTs daily, stop for ALT/AST > 10x upper limit of normal
  - Limited data in CKD (GFR < 30), however, growing consensus suggest can be used if benefit outweighs risk[1]
  - **FDA-approved for COVID-19 hospitalized adults/teens, kids (<12 or <40 kg) via EUA**

1. Adamsick ML, et al. JASN 2020; 31(7):1384-86.

Immune System Mimics

- Agents mimic the immune system's response to SARS-CoV-2
- Likely work best early prior to body's own immune response or as prophylaxis
- Example Agents
  - **Monoclonal Antibodies**
  - Convalescent Plasma
  - Interferons
  - Hyperimmune Immunoglobulins



Not recommended due to lack of proven benefit in RCT(s)

Inconclusive or lacking adequate RCT(s), only use in clinical trials

SARS-CoV-2 Monoclonal Ab

- 3 Monoclonal Ab targeting spike protein granted emergency use authorization (EUA) for **mild to moderate COVID-19 in outpatients at high-risk for progression within 10 days of symptom onset**
- NOT approved for patients hospitalized due to COVID-19
- Due to concerns re: *in vitro* susceptibility with new variants, only combination Mabs are currently recommended for use by NIH

EUA Mab	Company	Clinical Efficacy	Predicted Efficacy against variants	Comments
Bamlanivimab	Eli Lilly	75% RRR in ED visit or hospitalization (1.6% vs. 6.3%)	Significant reduction for B.1.351, P.1, B.1.429/427, B.1.529	NOT recommended by NIH (AIII)
Bamlanivimab/ etesevimab	Eli Lilly	70% RRR in hospitalization or death (2% vs. 7%)	Significant reduction for B.1351, P.1	Recommended by NIH (AIIa)
Casirivimab/ imdevimab	Regeneron	71% RRR in hospitalization of death (1.3% vs. 4.6%)	Retains *in vitro* activity	Recommended by NIH (AIIa)

https://www.covid19treatmentguidelines.nih.gov/statement-on-anti-sars-cov-2-monoclonal-antibodies-eua/

Immunomodulators

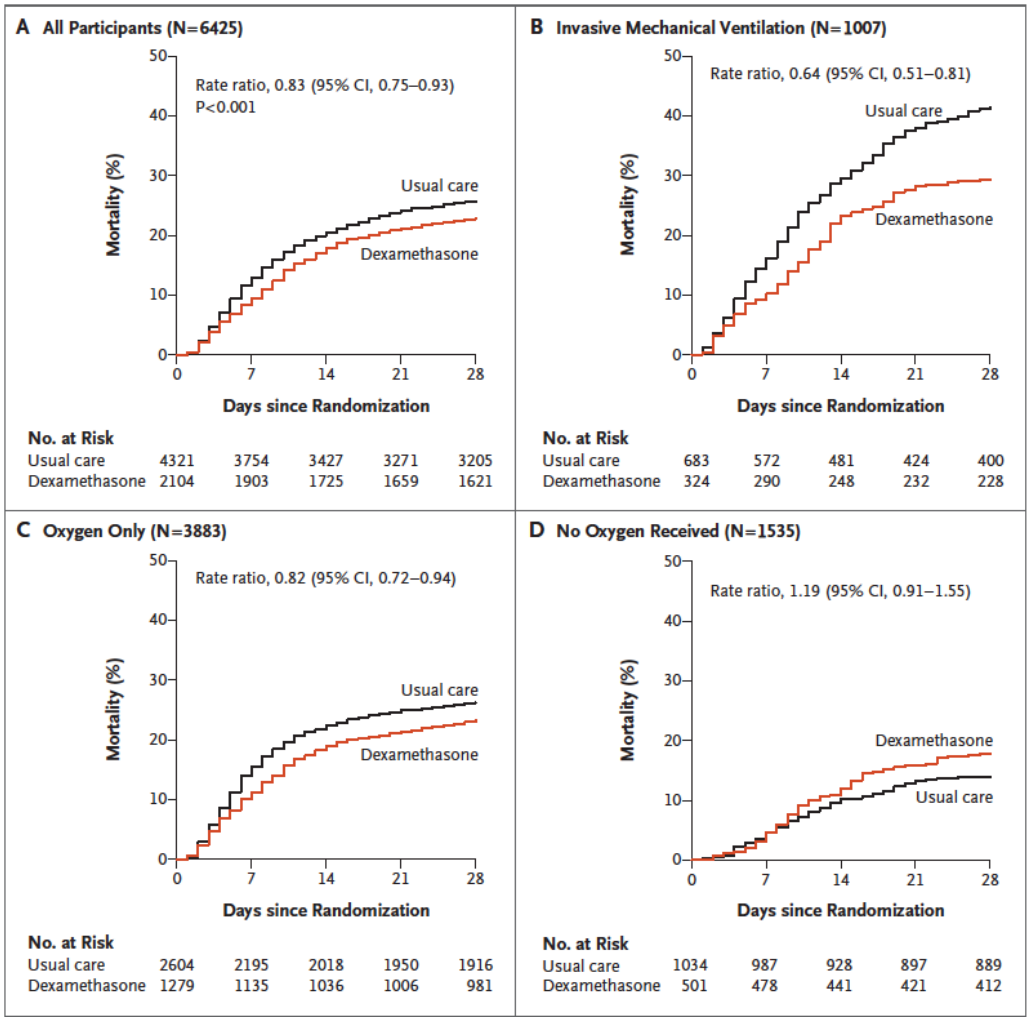
- Agents dampen the host immune and inflammatory response to SARS-CoV-2
- Likely work best during host inflammatory phase or possibly in combination with antiviral agents
- Example Agents or Therapies
  - **Corticosteroids**
  - **Cytokine Inhibitors** (e.g. IL-6)
  - **JAK Pathway Inhibitors** (e.g. baricitinib)
  - Colchicine 
  - Fluvoxamine 

 Not recommended due to lack of proven benefit in RCT(s)

 Inconclusive or lacking adequate RCT(s), only use in clinical trials

Steroids: RECOVERY Trial

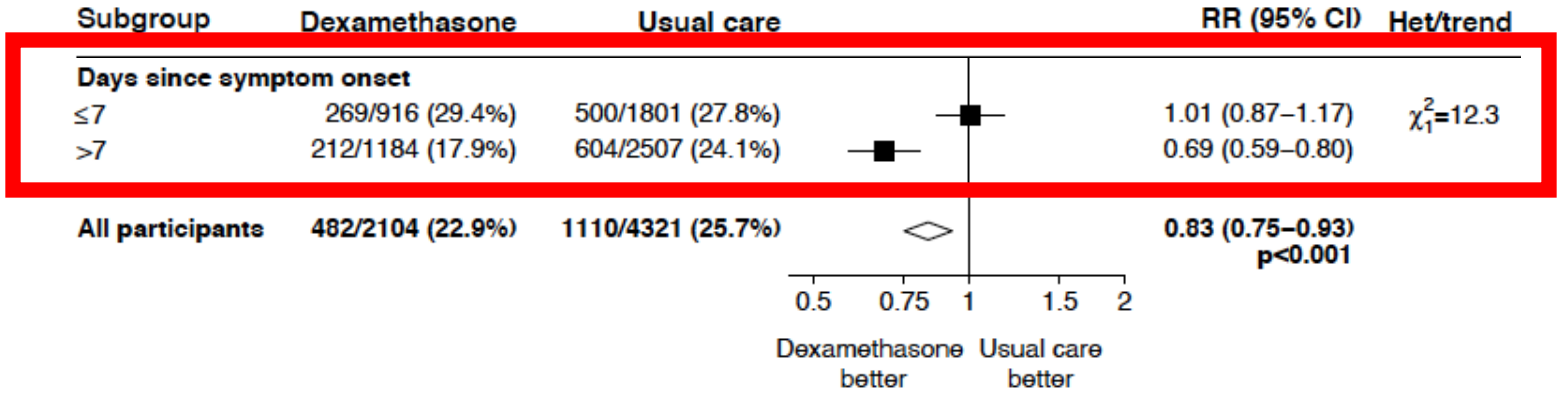
- Open-label, adaptive trial of COVID-19 Rx in UK
- Dexamethasone 6 mg daily up to 10d (N=2104) vs. Usual Care (N=4321)
- 28d Mortality Rate Ratios:
  - Overall: **0.83**
  - On MV: **0.64 (ARR ≅ 12%)**
  - On O_2: **0.82 (ARR ≅ 3%)**
  - No O_2 : 1.19



Horby P, et al .NEJM 2020; Online 7/17/2020.

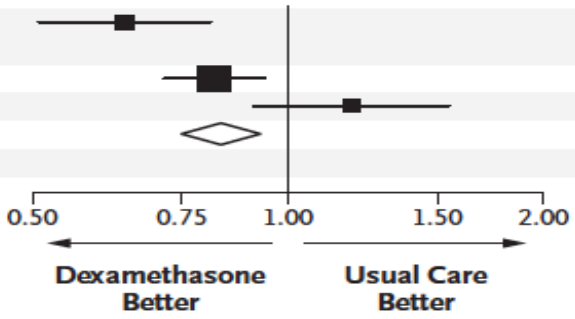
Steroids: RECOVERY Trial- Impact of Sx Onset Timing and Level of O_2

Figure S1: Effect of allocation to dexamethasone on 28–day mortality by other pre–specified baseline characteristics



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



Horby P, et al. NEJM 2020; Online 7/17/2020.

Applying the Evidence: Corticosteroids

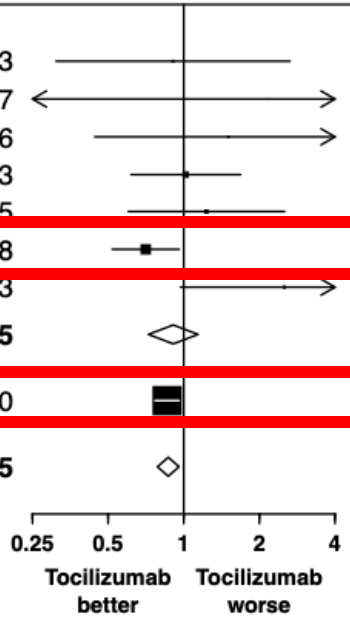
- Strongest data for critically ill COVID-19
  - Give to all unless clear contraindication
  - Dexamethasone (1st) or hydrocortisone (2nd); Best dose unknown so use RECOVERY dose unless in shock (?)
- Solid data for severe COVID-19 on O_2 (RECOVERY)
  - Give to most unless clear contraindication
  - If on low flow O_2 and early in disease (<7d), can possibly wait to see if progresses
- **Do NOT use steroids in those who are outpatient or not on O_2**

Meta-Analysis: IL-6 Inhibitors in COVID-19

Figure 4: Tocilizumab vs usual care in patients hospitalised with COVID – Meta–analysis of mortality in RECOVERY and other trials

	Deaths / Patients randomised (%)		Observed–Expected		Ratio of death rates, RR (95% CI)
	Tocilizumab	Usual care	(O–E)*	Var(O–E)	
COR–IMUNO TOCI	7/64 (10.9)	8/67 (11.9)	–0.3	3.3	0.91 (0.31–2.65)
RCT–TCZ–COVID–19	2/60 (3.3)	1/66 (1.5)	0.6	0.7	2.17 (0.22–21.3)
BACC Bay	9/161 (5.6)	(3/82) x2† (3.7)	1.0	2.6	1.51 (0.44–5.13)
COVACTA	58/294 (19.7)	(28/144) x2† (19.4)	0.3	15.3	1.02 (0.62–1.68)
EMPACTA	26/249 (10.4)	(11/128) x2† (8.6)	1.6	7.5	1.23 (0.60–2.52)
REMAP–CAP	98/353 (27.8)	142/402 (35.3)	–14.2	40.8	0.71 (0.52–0.96)
TOCIBRAS	14/65 (21.5)	6/64 (9.4)	3.9	4.3	2.51 (0.97–6.50)
Subtotal: 7 trials	**214/1246 (17.2)**	**241/1307 (18.4)**	**–7.2**	**74.5**	**0.91 (0.72–1.14)**
RECOVERY	596/2022 (29.5)	694/2094 (33.1)	–48.2	316.0	0.86 (0.77–0.96)
All trials	**810/3268 (24.8)**	**935/3401 (27.5)**	**–55.4**	**390.5**	**0.87 (0.79–0.96) p=0.005**

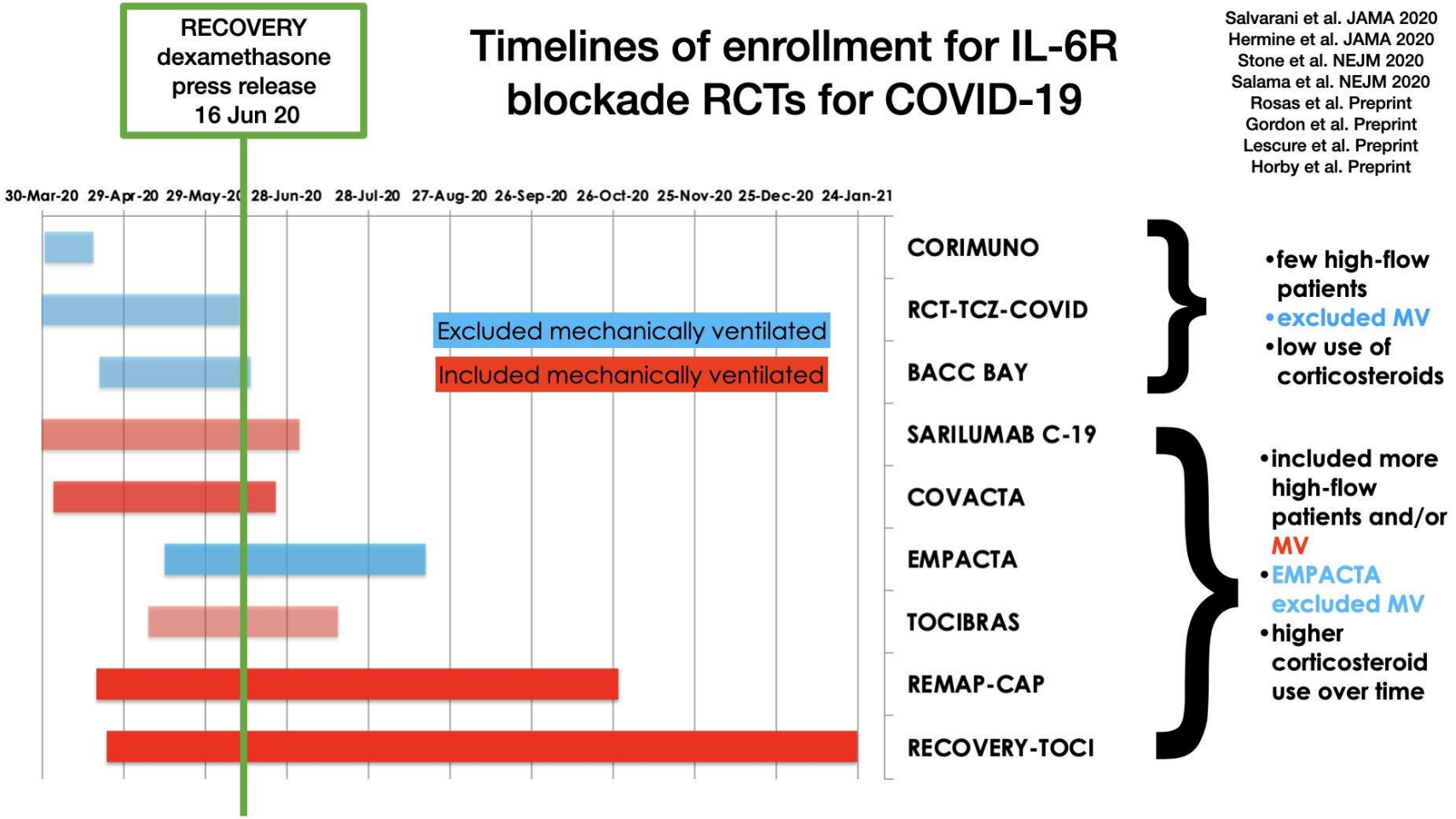
Heterogeneity between RECOVERY and previous trials: χ^2_1=0.2



* Log–rank O–E for RECOVERY, O–E from 2x2 tables for the other trials. RR is calculated by taking ln RR to be (O–E)/V with Normal variance 1/V. Subtotals or totals of (O–E) and of V yield inverse–variance–weighted averages of the ln RR values.

Horby P, et al. medRxiv preprint doi: https://doi.org/10.1101/2021.02.11.21249258

Differences and Timelines of IL-6 Trials

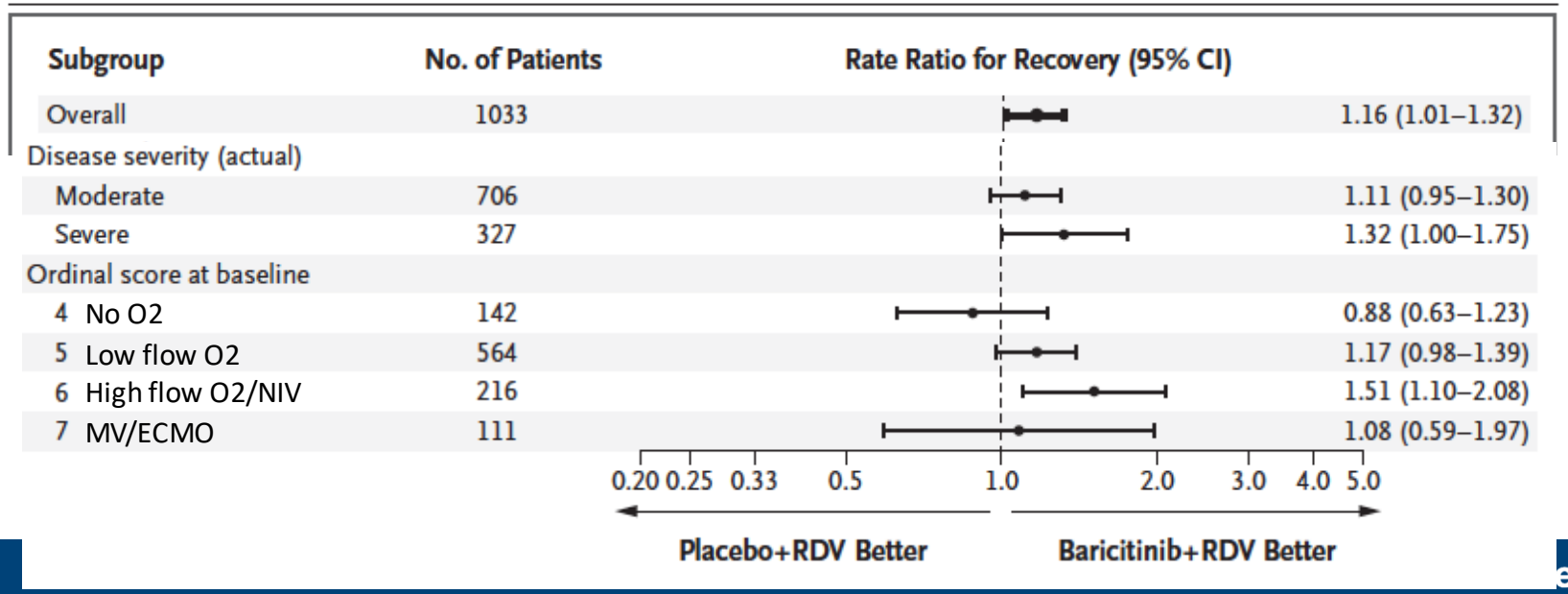


Consider IL-6 inhibitors in pts progressing to high-flow O_2 or MV despite being on steroids

Adapted from Twitter: @Arthur_Kim_ID (2/11/21)

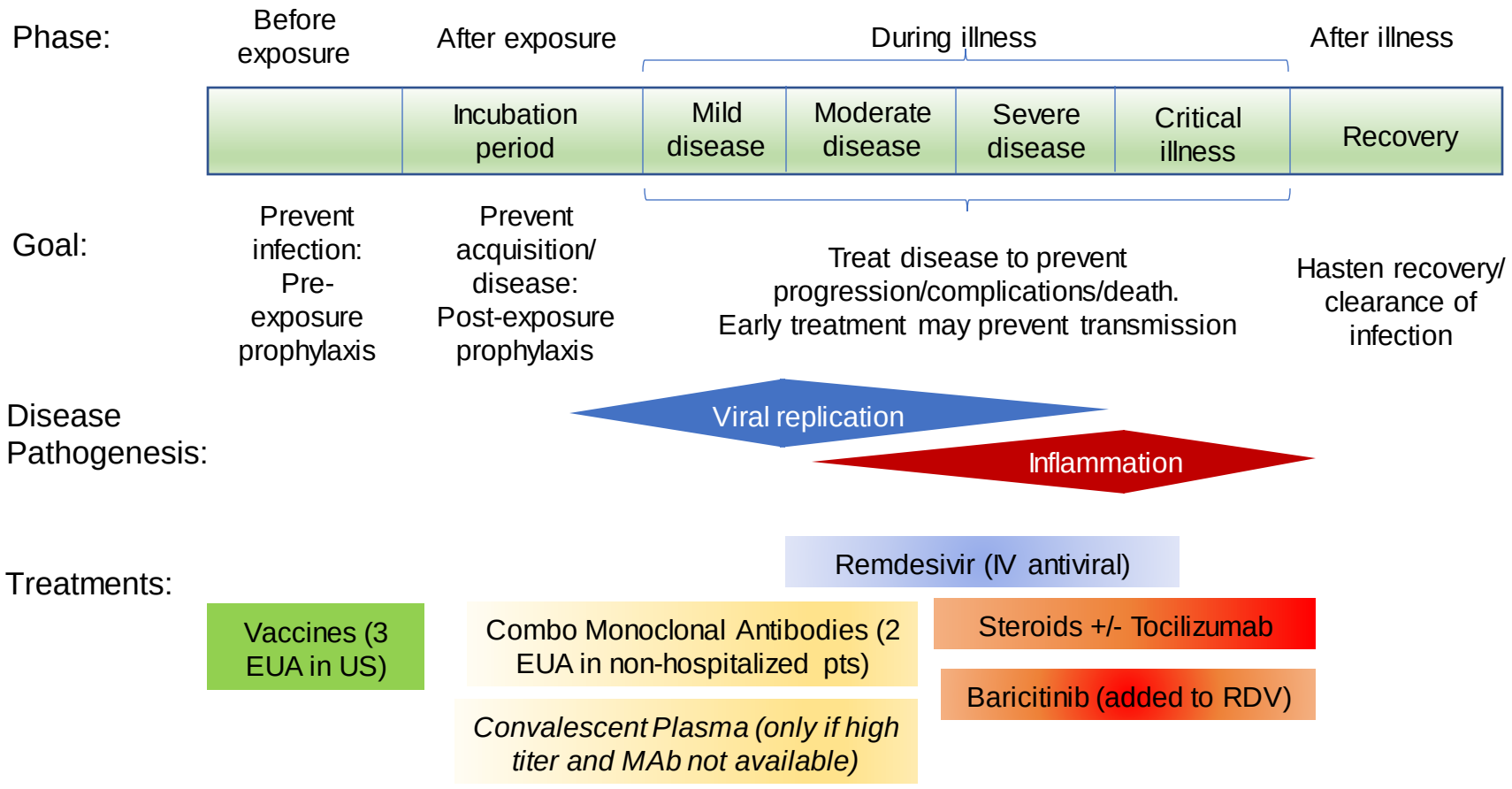
ACTT-2: JAK Inhibitors

- Oral inhibitors of Janus Kinase (JAK) 1 and 2 (e.g. baricitinib)
- **NIH ACTT-2 trial**: Combination of RDV + baricitinib significant 1 day faster median time to recovery, non-significant 35% reduction in mortality compared to RDV alone; **Benefit greatest in those on high flow/NIV but not intubated**
- NIH ACTT-4 trial ongoing: RDV + baricitinib vs. RDV + steroids



Kalil A, et al. NEJM 12/11/2020

Current Recommended COVID-19 Rx: April 2021

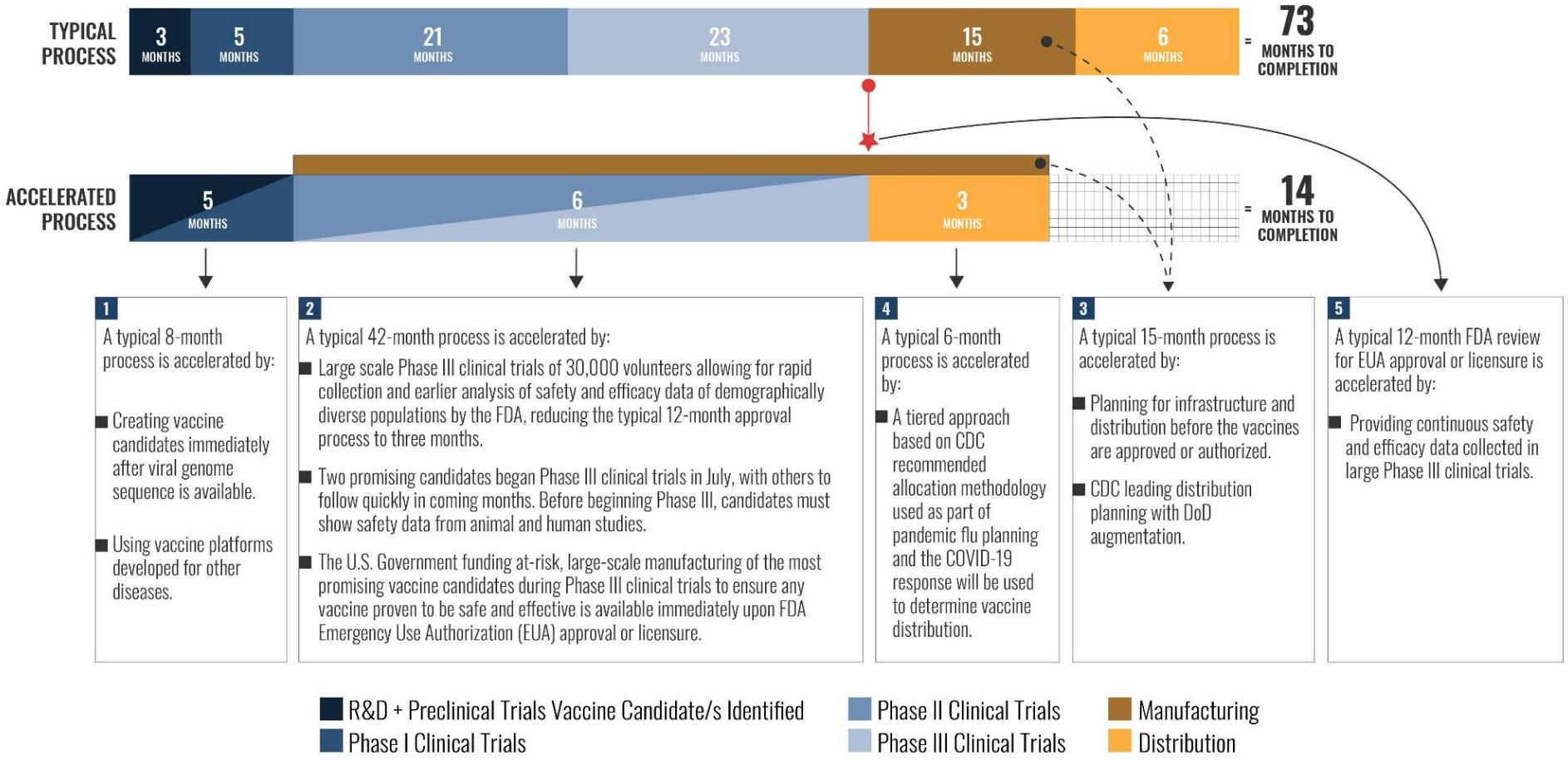


EUA: Emergency Use Authorization

Defeating COVID-19

Vaccines

How Did We Get Here So Fast: Operation Warp Speed



Financial and government risk increased, not product or safety risk

https://media.defense.gov/2020/Aug/13/2002476369/-1/-1/0/200813-D-ZZ999-100.JPG

COVID-19 Vaccines Tested in Diverse Populations

Vaccine	Pfizer mRNA	Moderna mRNA	Johnson and Johnson viral vector
Trial participants	N= 43,448	N=30,351	N= 43,783
Female Gender (%)	49.1%	47.4%	45%
Age > 65 (%)	20.9%	24.8%	19.5%
Race: Non-white (%)	17.9%	20.8%	41%
Ethnicity: Hispanic or Latino (%)	26.1%	20.5%	46%
Medical Comorbidities (%)	46%	42%	40.8%

Similar efficacy generally seen across all subgroups based on age, gender, race, ethnicity and medical conditions.

Pfizer FDA VRBPAC Presentation 12/10/20; Moderna FDA VRBPAC Presentation 12/17/20; J&J FDA VRBPAC Presentation 2/26/21

Summary of COVID-19 Vaccine Trials

Company	Platform	Doses	Number in trial vaccinated	Protection from Hospitalized COVID-19	Protection from severe COVID-19	Protection from all sx COVID-19
Pfizer/ BioNTech	mRNA	2	~18,600	100%	100%	95% (>90% out to 6 mos)
Moderna	mRNA	2	~15,000	97% (1 after 2nd dose)	97%	94.1% (Ab levels out to 6 mos)
J&J/ Janssen	Human adeno vector	1	~22,000	100%	85% (none hospitalized)	72% US, 66% Latin America, 57% S Africa
Oxford/ AstraZeneca	Chimp adeno vector	2	~28,588	100%	100%	76% US; 70% UK; S Africa trial halted for mild
Novavax	Protein + Adjuvant	2	~8800	100%	100%	96% UK; 55% S. Africa

Adapted from @MonicaGandhi9 (Twitter 4/2/21)

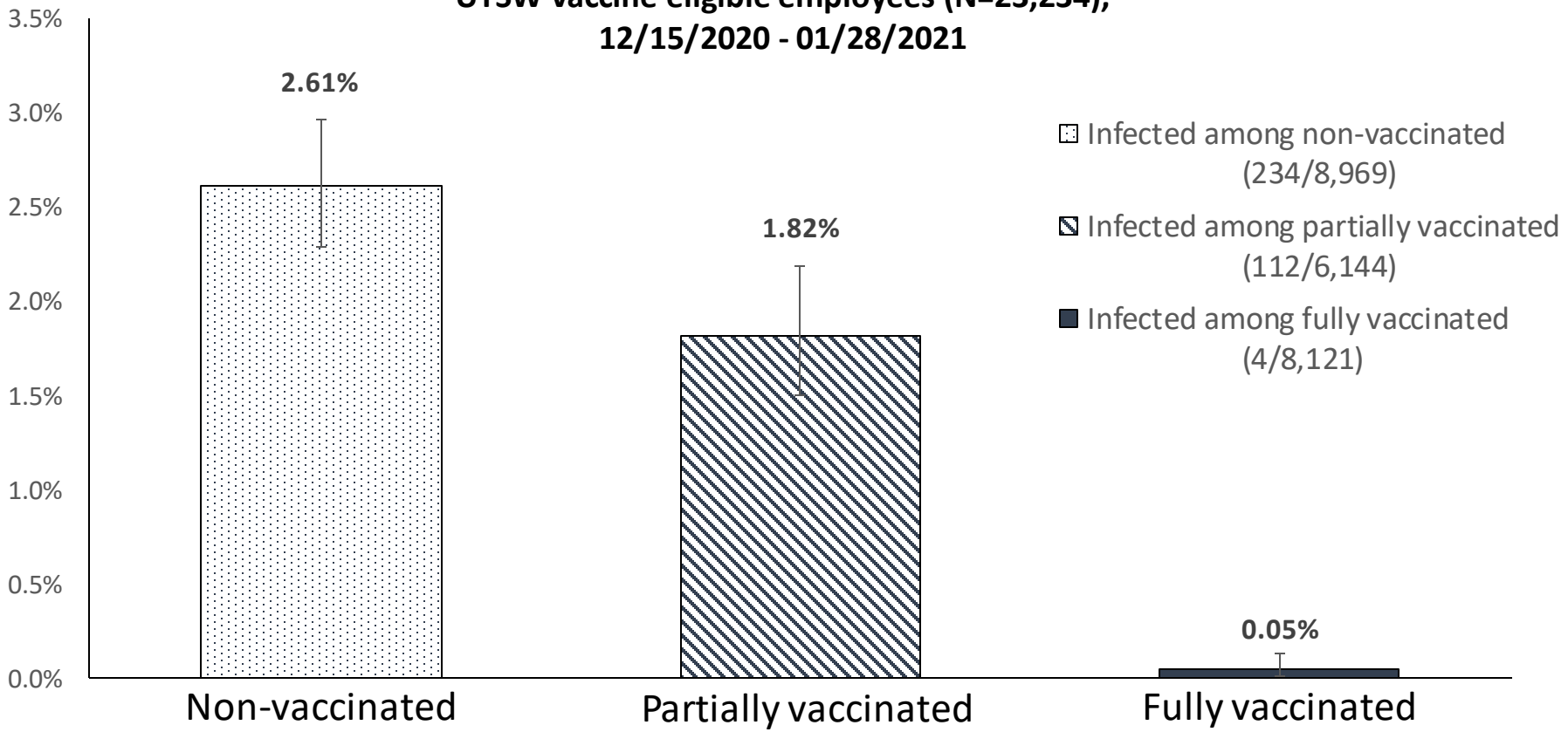
Reactogenicity: Comparison to Other Vaccines

(After dose #2 for the two-dose regimens, age <60 – the highest side effect group found)

	SHINGRIX (ZOSTER VACCINE RECOMBINANT, ADJUVANTED) Shingrix	moderna messenger therapeutics COVID-19 mRNA-1273	Pfizer COVID-19 BNT162b2	Johnson & Johnson Ad26.COV2.S	Influenza Vaccine FLUCELVAX QUADRIVALENT Flu
Local Pain	88.4%	90.1%	77.8%	58.6%	45.4%
Redness	38.7%	9.0%	5.9%	9.0%	13.4%
Swelling	30.5%	12.6%	6.3%	7.0%	11.6%
Myalgia	56.9%	61.3%	37.3%	39.1%	15.4%
Fatigue	57%	67.6%	59.4%	43.8%	17.8%
Headache	50.6%	62.8%	51.7%	44.4%	18.7%
Chills	35.8%	48.3%	35.1%	2%* (unsolicited)	6.2%
Fever	27.8%	17.4%	15.8%	12.8%	0.8%
Overall Grade 3%	5.2%	4.1%	1.5%	0.54%	0.45%
Overall SE %	48%	46%	36%	27% *31% not counting chills	15%
	1	2	3	4	5

Impact of COVID-19 Vaccination on UTSW Employees

Percent newly testing positive for COVID-19 on or after UTSW COVID-19 employee vaccination distribution began, stratified by vaccination status*, UTSW vaccine eligible employees (N=23,234), 12/15/2020 - 01/28/2021



*Vaccination status is determined at date of positive COVID-19 test showing new infection 12/15/20 or later, and if no infection, vaccination status as of 1/28/21. Non-vaccinated include those with no record of vaccine received at UTSW. Partially vaccinated include those who received one dose, or who received their second dose less than 7 (Pfizer) or 14 (Moderna) days ago. Fully vaccinated include those who received their second dose at least 7 (Pfizer) or 14 (Moderna) days ago

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CDC Real-World Effectiveness Study: mRNA Vaccines

TABLE 2. Person-days, SARS-CoV-2 infections, and vaccine effectiveness among health care personnel, first responders, and other essential and frontline workers, by messenger RNA immunization status — eight U.S. locations, December 14, 2020–March 13, 2021

Return

COVID-19 immunization status	Person-days	SARS-CoV-2 infections		Unadjusted vaccine effectiveness*	Adjusted vaccine effectiveness*,†
		No.	Incidence rate per 1,000 person-days	% (95% CI)	% (95% CI)
Unvaccinated	116,657	161	1.38	N/A	N/A
Partially immunized	41,856	8	0.19	82 (62–91)	80 (59–90)
≥14 days after receiving first dose only§	15,868	5	0.32		
≥14 days after first dose through receipt of second dose	25,988	3	0.12		
Fully immunized					
≥14 days after second dose	78,902	3	0.04	91 (73–97)	90 (68–97)

Abbreviations: CI = confidence interval; N/A = not applicable.

* Vaccine effectiveness was estimated using a Cox proportional hazards model accounting for time-varying immunization status.

† Hazard ratio is adjusted for study site.

§ Participants received first dose but had not received second dose by the end of the study period.

https://www.cdc.gov/mmwr/volumes/70/wr/mm7013e3.htm#T2_down

Special Populations: Prior COVID-19 Infection

- CDC recommends vaccination be offered to people regardless of history of COVID-19 infection
  - Vaccine trials show safety
  - Vaccines provide added protection even in those with prior COVID
- Antibody testing not recommended prior to vaccination
- If you currently have COVID-19, it is recommended to wait until acute illness over and cleared to work; if desired, you can wait for almost 90 days to get the vaccine
- Wait at least 90 days for vaccine if you received convalescent plasma or monoclonal Ab treatments

www.cdc.gov/vaccines/covid-19/info-by-product/pfizer/clinical-considerations.html#contraindications-precautions

Special Populations: Pregnancy and Immunocompromised Patients

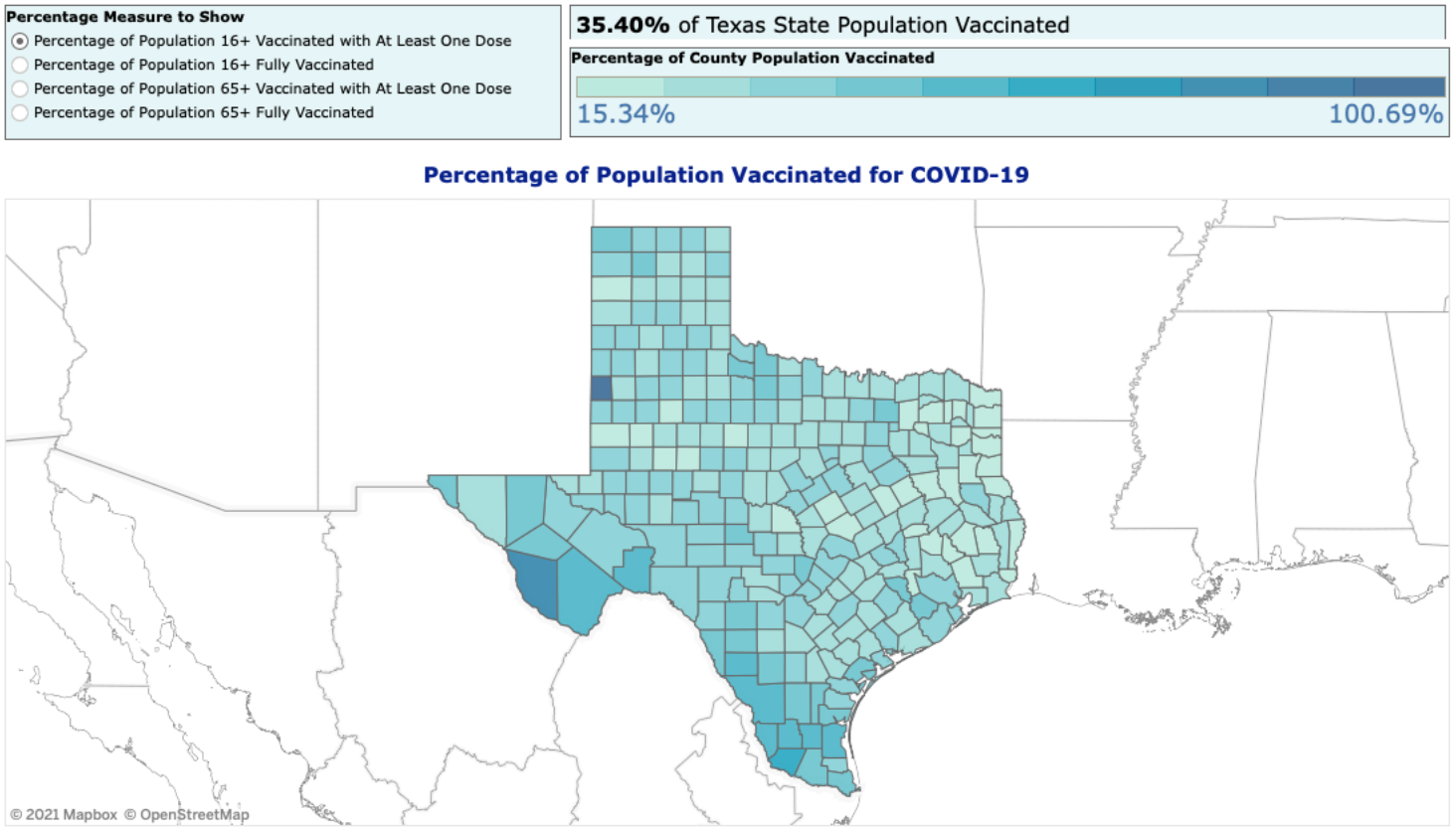
Pregnancy and Breastfeeding:

- Women known to be pregnant were excluded from vaccine trials
- **No safety concerns identified from > 30,000 pregnant women vaccinated with mRNA vaccines**
- Registry of > 1,800 pregnancies, 275 completed showed miscarriage rate same as baseline community rate
- Data now shows immunity passed via placenta and breastfeeding
- OB/Gyn groups recommend that pregnant/lactating females should be offered vaccine when eligible

Immunocompromised Patients:

- Such patients may have reduced immune response to vaccine but are still recommended to receive the vaccine

COVID-19 Vaccine Efforts in Texas



This dashboard is updated by 4:00 pm each day with data as of 11:59 pm the previous night. See the About the Data tab for more information on data sources.

Doses Administered
13,268,799

People Vaccinated
8,591,350

People Fully Vaccinated
5,063,173

Total Doses Allocated
19,397,865

State Doses Shipped
14,527,505

Last Updated:
4/8/2021 2:00 pm

Texans age 65+: 66% have received at least one dose and 50% fully vaccinated

Source: Texas DSHS; Data updated as of 4/8/2021

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UTSW COVID-19 Resources to Address Vaccine Hesitancy

UTSW COVID-19 MedBlogs and Vaccine Website

Recent MedBlogs:

- Life After COVID-19 Vaccines
- COVID-19 Vaccine Hesitancy: How to Overcome the Culture of Mistrust
- COVID-19 Vaccines: Separating Myths From Reality
- COVID-19 Vaccines: The Tough Questions Answered By a Frontline Doctor

UTSW "What to Know" Videos

Life After COVID-19 Vaccination

Building Confidence in COVID-19 Vaccines

https://utswmed.org/medblog/topic/covid/
https://utswmed.org/whattoknow/

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Key Take-Home Messages

- COVID-19: Reminder of potential impact of emerging infectious diseases on public health and society at large
- Treatments for COVID-19 only modestly effective to date, still need clinical trials for better targeted approaches
  - Early monoclonal Ab (combo) can reduce hospitalization and death in high-risk outpatients
  - Remdesivir (+/- baricitinib) can shorten hospitalization and time to recovery, unclear if reduces mortality
  - Steroids (+/- IL-6 inhibitors) can reduce mortality in severe and critically ill COVID-19
- COVID-19 vaccines are effective and safe
  - Strongly protective against severe disease and death
  - Provide protection even against new variants
  - Currently 3 available in U.S.: Pfizer and Moderna (mRNA), J&J (viral vector)
- Non-pharmacologic interventions (NPIs) like masking and physical distancing still important in public while the vaccine rollout proceeds