COVID-19 Update: Where are we now?

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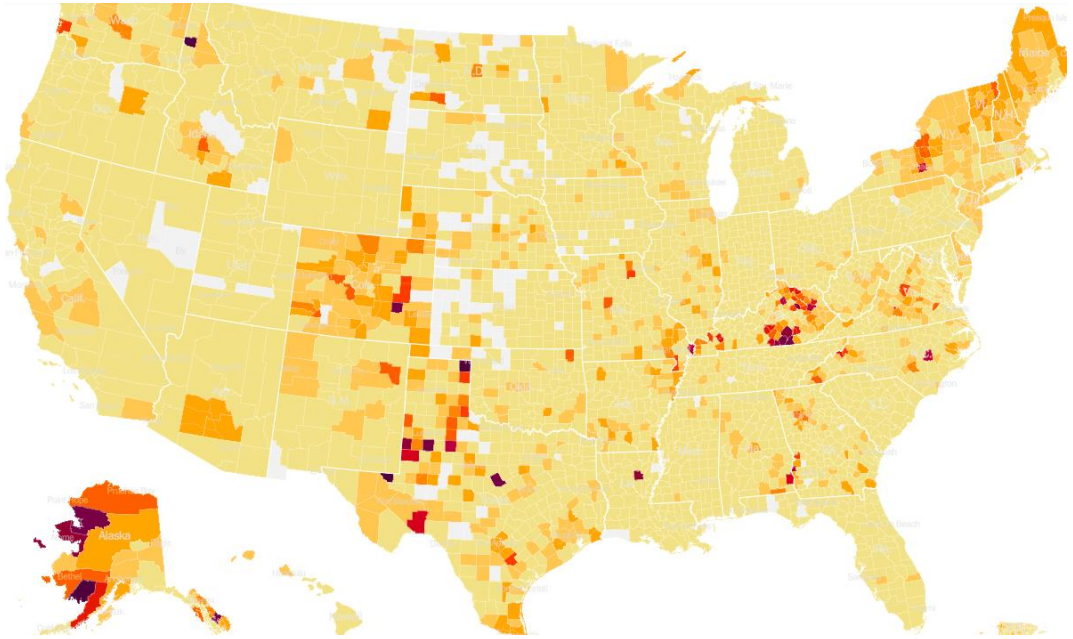
Disclosures

- I have no financial disclosures.
- I served as an unpaid co-investigator for COVID-19 clinical trials from Gilead, Regeneron, and the NIH.
- I will be discussing off-label and emergency use authorized treatments for COVID-19.

Outline

- COVID-19 Epidemiology and Emerging Variants
- COVID-19 Management and Prevention Updates
- COVID-19 Vaccination Updates

COVID-19 in the United States

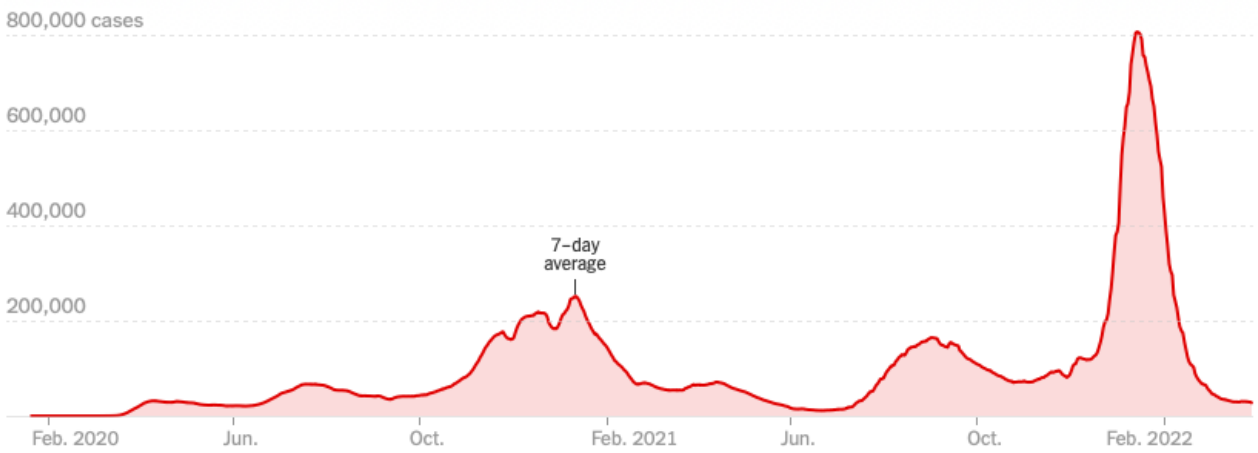


Vaccinations

	AT LEAST ONE DOSE	FULLY VACCINATED
All ages	77%	65%
5 and up	82%	70%
65 and up	95%	89%

New reported cases

All time | Last 90 days

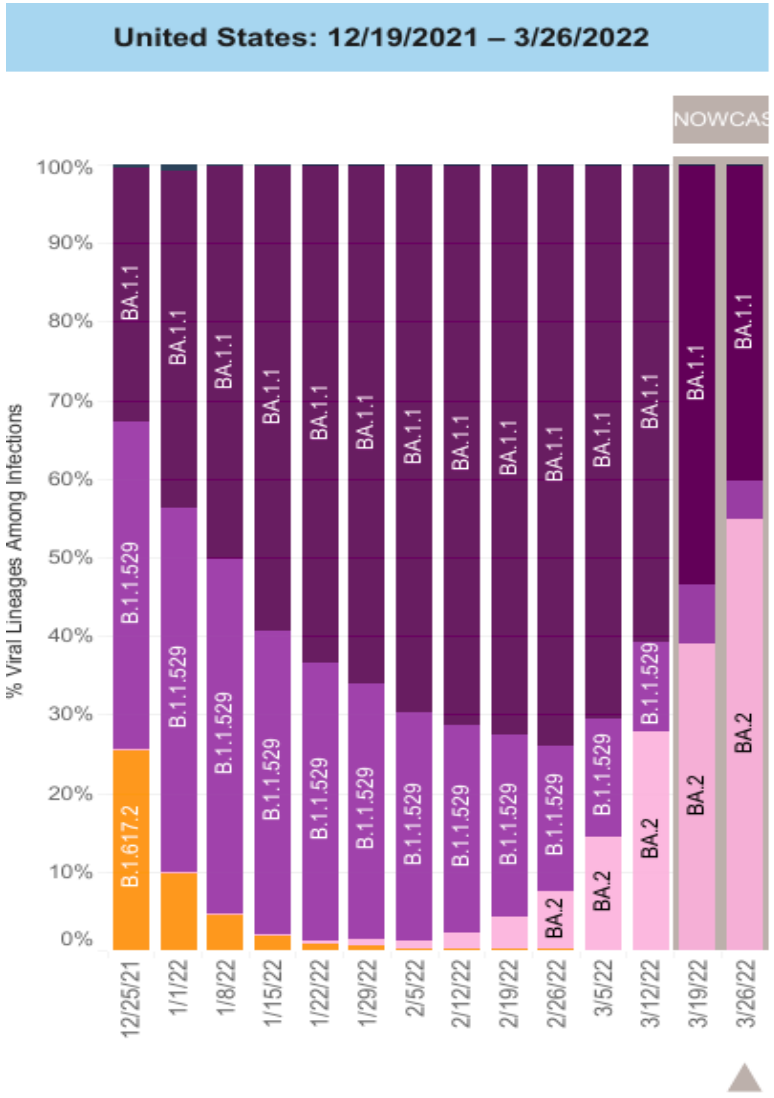


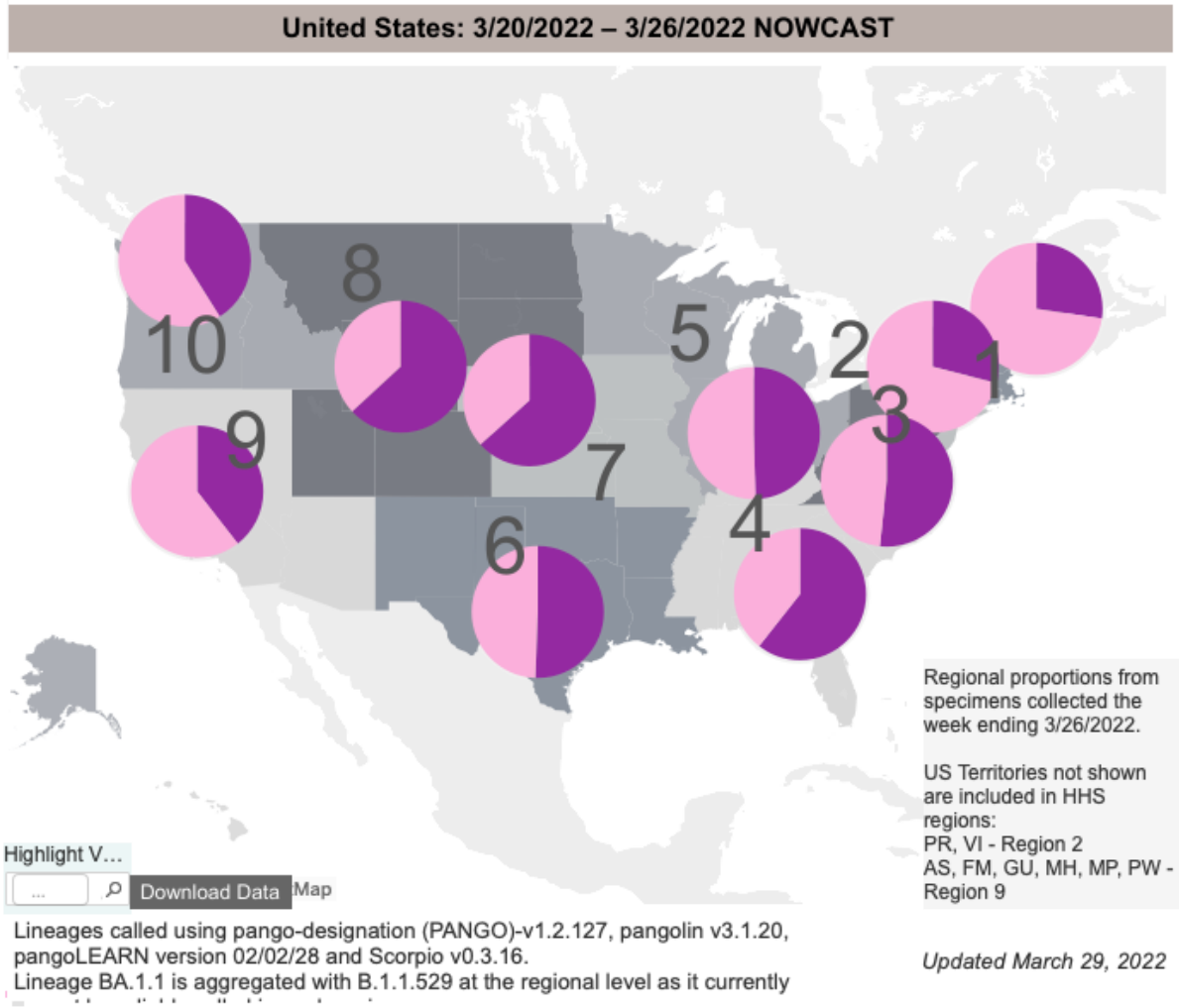
	DAILY AVG. ON MAR. 30	14-DAY CHANGE	TOTAL REPORTED
Cases	27,621	−12%	79,969,941
Tests	888,308	+7%	—
Hospitalized	17,092	−33%	—
In I.C.U.s	2,700	−40%	—
Deaths	702	−44%	978,387

▶ About this data

New York Times COVID-19 Tracker https://www.nytimes.com/interactive/2021/us/covid-cases.html Accessed 3/31/22

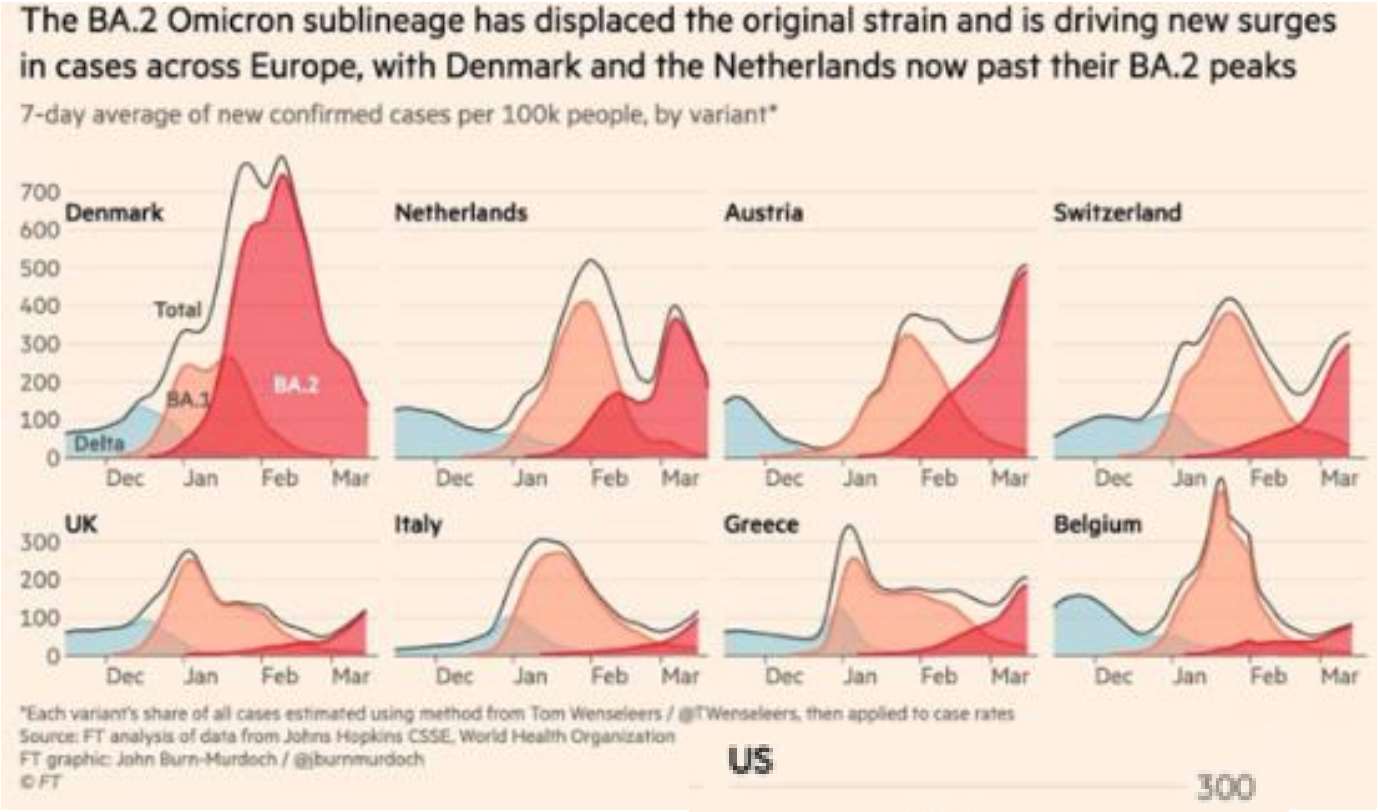
COVID-19 Variants in the US





CDC COVID-19 Variant Tracker https://covid.cdc.gov/covid-data-tracker/#variant-proportions

Omicron Subvariants: BA.1 vs. BA.2



BA.2: More transmissible, similar disease severity and vaccine efficacy to BA.1

Feature	BA.1	BA.2
Transmission (infectiousness)	Reference	30% higher
Viral Load	Reference	Nearly 2-fold
Mutations in Spike	Reference	8 different, not shared
Neutralizing antibodies median titer	Reference	Lower level, ~70%
Disease-causing potential (virulence)	Reference	Same, but infects many more people
2-shot effectiveness vs hospitalizations*		
Up to 6 months	63% (95% CI 47,75)	69% (95% CI 27,87)
Past 6 months	32% (95% CI 11,49)	50% (95% CI 7,73)
3-shot effectiveness vs hospitalizations *		
Up to 70-days	81% (95% CI 75,85)	83% (95% CI 71,91)
Past 70-days	73% (95% CI 65,79)	70% (95% CI 50,82)

*data from UKHSA March 24 report using Emergence Care dataset, includes "for" and "with" Covid so under-estimates effectiveness

@erictopol

Eric Topol Substack https://erictopol.substack.com/p/a-new-wave-and-a-new-booster?s=r

Outline

- COVID-19 Epidemiology and Emerging Variants
- **COVID-19 Management and Prevention Updates**
- COVID-19 Vaccination Updates

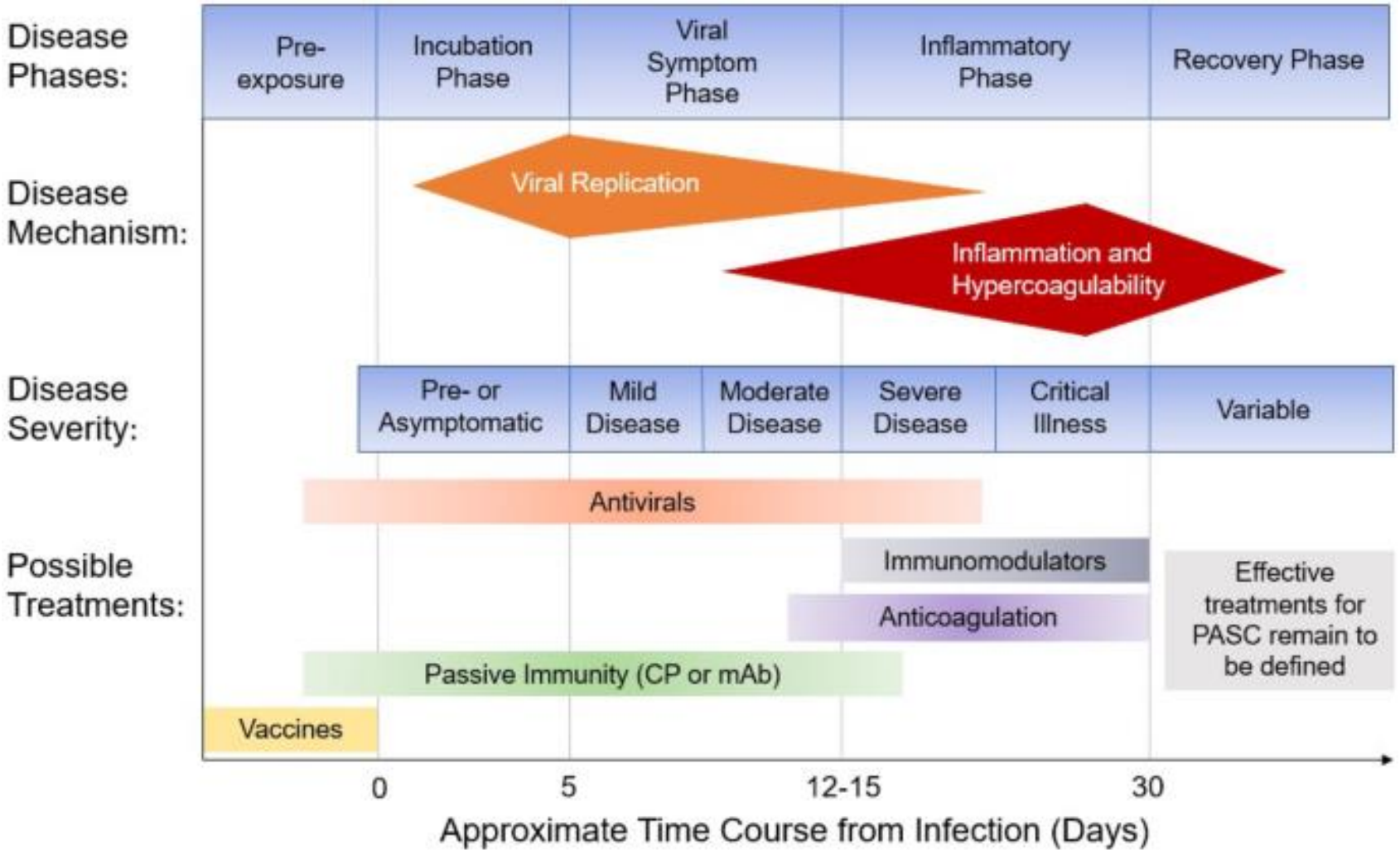
COVID-19 Disease Severity Classification

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

NIH COVID-19 Treatment Guidelines https://www.covid19treatmentguidelines.nih.gov

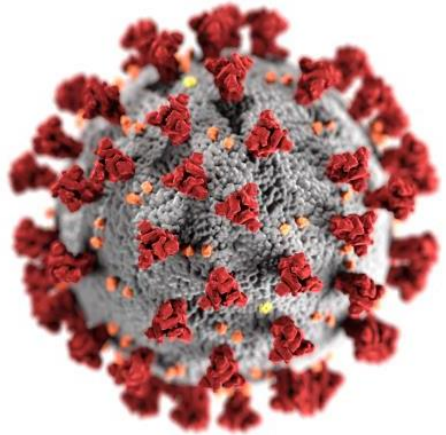
COVID-19 Therapeutics: Where are we now?



EY Bae, et al. *Curr Infect Dis Reports* 2021

Antivirals

- Agents directly targeting SARS-CoV-2 replication
- Likely work best in early viral phase or as prophylaxis
- Example Agents
  - Remdesivir (RDV)
  - Nirmatrelvir/ritonavir (Paxlovid)
  - Molnupiravir



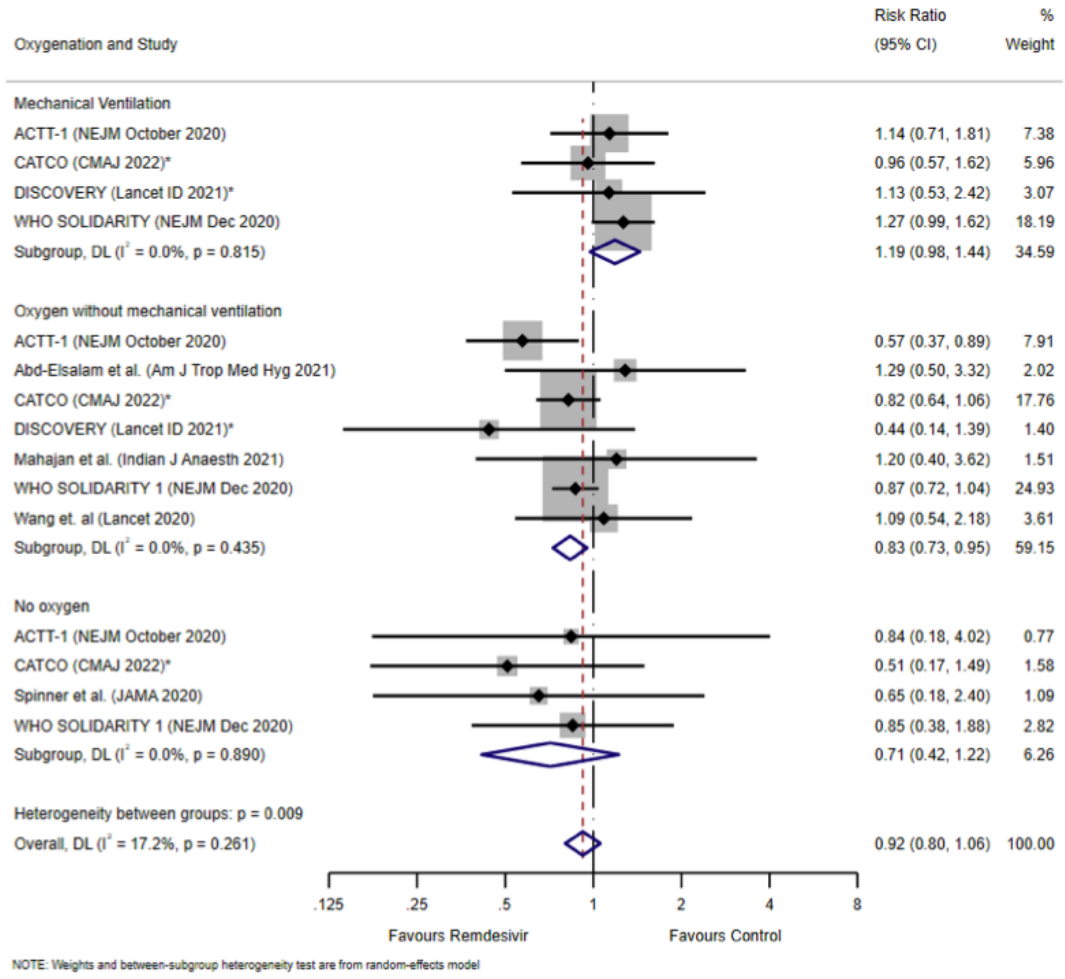
Updated Remdesivir Meta-Analysis

- Updated RDV meta-analysis including 8 RCTs (latest CATCO trial), 9157 patients

- Risk ratio for mortality based on baseline oxygen needs:

- MV: 1.19 (0.98-1.44)
- On O_2: **0.83 (0.73-0.95)**
- No O_2: 0.71 (0.42-1.22)

Figure 1 – Random Effects Meta-Analysis



*Excludes patients already included in SOLIDARITY (NEJM 2020)

Lee TR, et al. MedRxiv 2022; https://www.medrxiv.org/content/10.1101/2022.01.22.22269545v1.full.pdf

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Outpatient Short-course Remdesivir

- PINETREE trial: High-risk symptomatic outpatients ≤ 7 days of symptom onset received 3 days of RDV
- Inclusion: ≥ 60 years old or at least one high risk factor
- Exclusion: **Vaccinated, Requiring O_2 or hospitalization**
- 562 patient enrolled; Mean age 50, median sx duration 5 days; 62% DM2, 55% Obesity, 58% HTN, 4% immune compromised
- Primary outcome: Risk of hospitalization or death due to COVID-19 was 87% lower in RDV group
- Similar rate of ADEs in RDV and Placebo groups

Outcome	RDV group	Placebo group	P-value
COVID-19 hospitalization or death, day 28	**2 (0.7%)**	**15 (5.3%)**	**0.008**
Any death, day 28	0	0	
Any hospitalization, day 28	5 (1.8%)	18 (6.4%)	

Gottlieb RL, et al. N Engl J Med; 2021 Dec 22

Applying the Evidence: Remdesivir

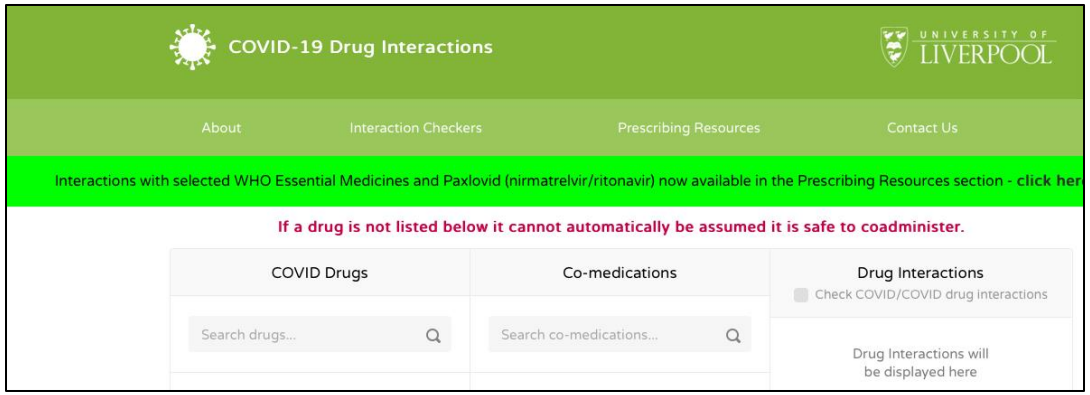
- Best evidence in patients with severe COVID-19 but not intubated (low flow O_2 > high flow or noninvasive ventilation); no clear benefit in critical disease (mechanical ventilation)
- Compelling data in very early outpatient use but logistically challenging
- **Modest clinical benefit, may reduce mortality in those on O_2**
- **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, 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.

COVID-19 Oral Antivirals

- Two new EUA oral antivirals: Nirmatrelvir/ritonavir (Paxlovid) and Molnupiravir
- Demonstrated reduction in hospitalization in high-risk outpatients (89% for Paxlovid, ~30% for Molnupiravir)
- Approved for outpatient treatment of symptomatic patients with mild to moderate disease **within 5 days of symptom onset**
- Not approved for hospitalized patients
- Watch many drug-drug interactions with Paxlovid!
- Molnupiravir contraindication in pregnancy or caution in those trying to conceive

Liverpool COVID-19 Drug Interaction Checker

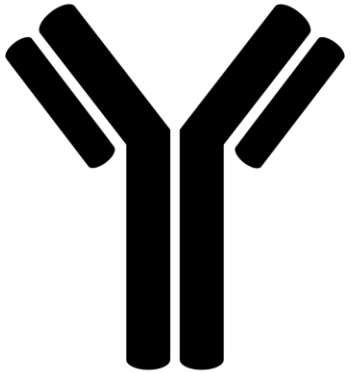


NIH COVID-19 Treatment Guidelines https://www.covid19treatmentguidelines.nih.gov
UK Liverpool COVID-19 Drug Interactions https://www.covid19-druginteractions.org/checker

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
  - SARS-CoV-2 Monoclonal Antibodies
  - Convalescent Plasma



SARS-CoV-2 Monoclonal Ab

- 4 Monoclonal Ab with EUA for **mild to moderate COVID-19 in high-risk outpatients < 7 days from symptom onset**
- NOT currently approved for patients **hospitalized due to COVID-19** (but can be used if hospitalized for non-COVID-19 and meets EUA criteria)

EUA Mab	Clinical Efficacy	Predicted Efficacy against variants	Comments
Bamlanivimab/ etesevimab	70% RRR in hospitalization or death (2% vs. 7%)	Significant reduction for Delta, Gamma, and **Omicron**	No longer in use due to Omicron
Casirivimab/imdevimab	71% RRR in hospitalization or death (1.3% vs. 4.6%)	Significant reduction for **Omicron**	No longer in use due to Omicron
Sotrovimab	85% RRR in hospitalization or death (1% vs. 7%)	Significant reduction for **Omicron BA.2 subvariant**	Recommended by NIH (AIIa); *distribution paused in some states*
Bebtelovimab	More limited clinical efficacy data from phase 2 study	Retains *in vitro* activity for circulating Omicron variants	Recommended by NIH if others not available (CIII)

NIH COVID-19 Treatment Guidelines https://www.covid19treatmentguidelines.nih.gov

SARS-CoV-2 Mab Prophylaxis: Evusheld

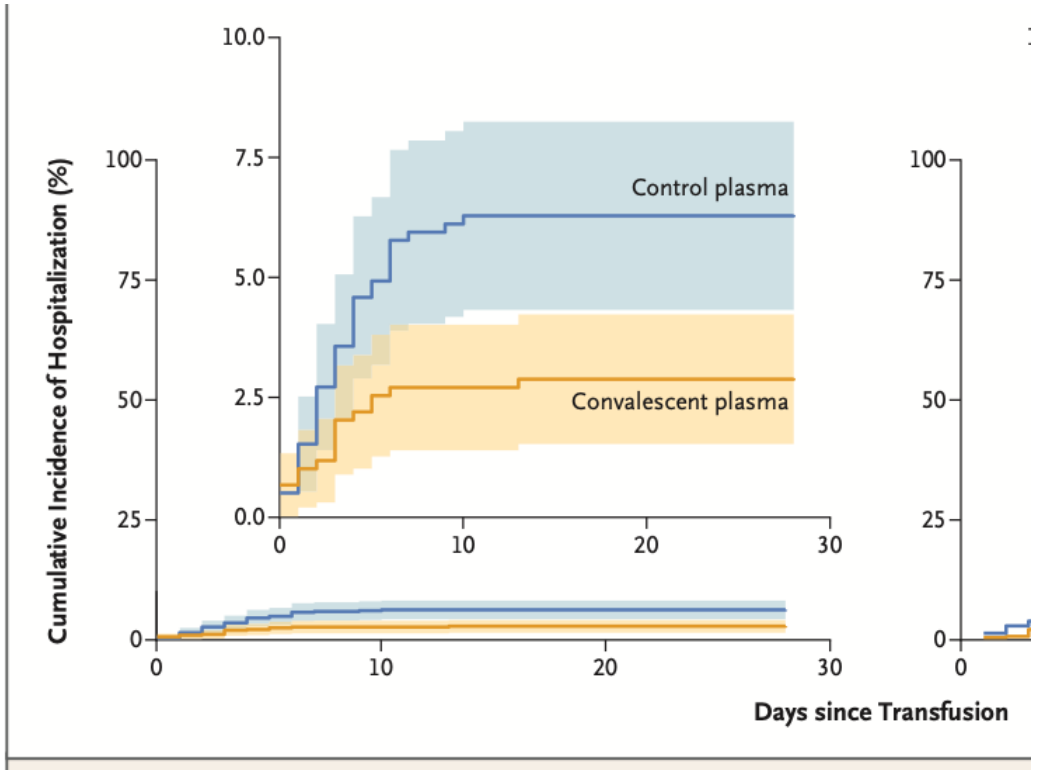
- Two long-acting Mab (tixagevimab/cligavimab) with extended half-life up to 12 months protection
- EUA for prophylaxis in **moderate/severe immunocompromised pts or those unable to be vaccinated**
- PROVENT phase 3 prophylaxis trial: 5,197 participants (2:1 randomization), 75% with high-risk comorbidities, single 300 mg IM injection or saline IM placebo
- **Recommended dose increased to 600 mg due to Omicron variants**

	AZD 7442 Arm	Placebo Arm	Relative Risk Reduction
Symptomatic PCR + disease	8	17	**77% (95% CI: 46%-90%)**
Severe disease	0	3	
Death	0	2	

https://www.astrazeneca.com/media-centre/press-releases/2021/azd7442-prophylaxis-trial-met-primary-endpoint.html

Convalescent Plasma: Comeback Kid?

- RCT of high-titer convalescent plasma in outpatient COVID-19 ≤ 8 days from sx onset
- Pre-Omicron era, 1225 enrolled, > 80% unvaccinated
- Primary outcome: 54% RRR in risk of hospitalization with CP (2.9% vs 6.3%; p=0.005)
- **Take-home message:** Early, high-titer CP may have a role in outpatient COVID-19, *particularly in unvaccinated or immunocompromised*



Sullivan DJ, et al. N Engl J Med 2022 Mar 30; **DOI: 10.1056/NEJMoa2119657**

Immunomodulators

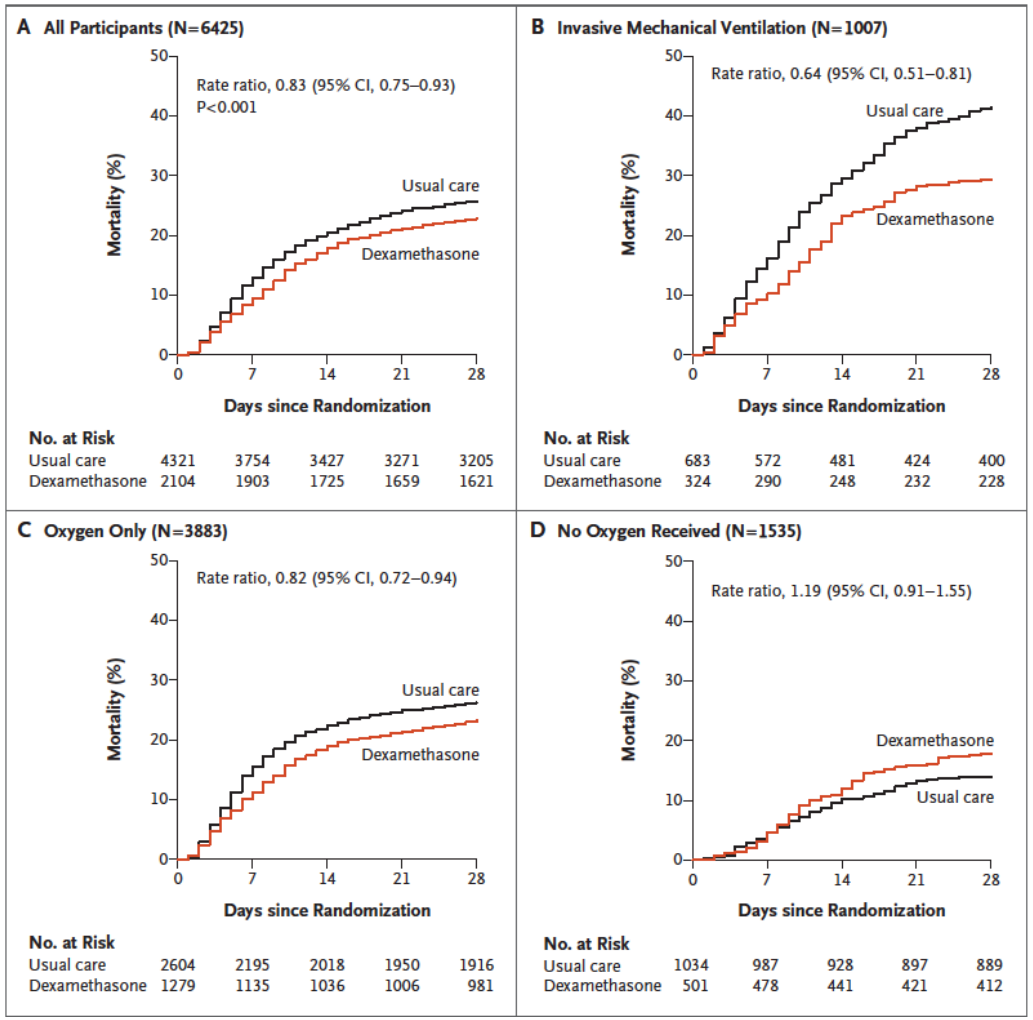
- Agents dampen the host immune and inflammatory response to SARS-CoV-2
- Likely work best during host inflammatory phase or possibly in combination with antiviral agents
- Example Agents
  - Corticosteroids
  - Cytokine Inhibitors (e.g. IL-6)
  - JAK Pathway Inhibitors (e.g. baricitinib)

Corticosteroids: RECOVERY Trial

- Open-label, adaptive COVID-19 trial in UK
- Dexamethasone 6 mg daily up to 10d

(N=2104) vs. Usual Care (N=4321)

- 28 day Mortality Rate Ratios:
  - Overall: **0.83**
  - On MV: **0.64 (Absolute RR ≅ 12%)**
  - On O_2: **0.82 (Absolute RR ≅ 3%)**
  - No O_2 : 1.19



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

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Applying the Evidence: Corticosteroids

- Strongest data for critically ill COVID-19
  - Give to all unless clear contraindication; optimal dosing less clear
  - Dexamethasone or IV methylprednisolone (2 mg/kg x 5 days, then taper for total of 10 days)
- Strong data for severe COVID-19 on O_2 (RECOVERY)
  - Give to most unless clear contraindication, usually combined with antiviral
- **Do NOT use systemic steroids in those who are outpatient or not on O_2**
- Small trial supporting **inhaled** budesonide 800 mg BID in symptomatic outpatients

IDSA COVID-19 Real Time Learning Network https://www.idsociety.org/covid-19-real-time-learning-network/therapeutics-and-interventions/immunomodulators/#CorticosteroidsDosing

Applying the Evidence: IL-6 and JAK inhibition

- Both IL-6 receptor and JAK inhibitors have shown mortality benefit in addition to standard of care (corticosteroids +/- remdesivir)
- **How to use and who is the right patient population?**
- IL-6R antagonists: Tocilizumab, weight-based dosing, single dose
- Use in those progressing to higher O_2 or intubation (< 24h) despite steroids, especially if CRP > 75
- JAK Inhibitors (baricitinib): 4 mg PO daily up to 14d, dose reduce in CKD
- Can use either as alternative if steroids contraindicated OR in addition to steroids in those progressing to higher O_2 or mechanical ventilation

COVID-19 Anticoagulation (NIH Guidelines)

Patient Population	Therapeutic Dose Anticoagulation (LMWH preferred)	Prophylactic Dose Anticoagulation
Clinically suspected or diagnosed VTE/PE (AI)	✓	
Hospitalized nonpregnant patients on low-flow O_2 AND D-Dimer > ULN*(CIIa)	✓	
Hospitalized patients requiring ICU level care or high-flow O_2/NIV (AI)		✓
All other hospitalized patients (including all pregnant patients) (BIII)		✓

* Contraindications to therapeutic anticoagulation include: Platelets < 50k, Hgb < 8 mg/dL, Need for dual antiplatelet, ED visit or hospitalization for major bleeding in last 30 days, Inherited or known history of bleeding disorder.

NIH COVID-19 Treatment Guidelines https://www.covid19treatmentguidelines.nih.gov

What is NOT currently recommended

- Routine bacterial antibiotics
- Hydroxychloroquine
- HIV protease inhibitors
- Ivermectin
- Colchicine
- IVIG
- Azithromycin (for COVID-19)
- Zinc, Vitamin C, Vitamin D (for COVID-19)

Case #1

- 45 year old male with PMHx of NYHA III CHF, obesity, DM type 2 contacts the clinic with 2 days of fevers, cough, fatigue. His home pulsox is reading 96% on room air. He received 2 doses of Moderna vaccine in May. He had a prolonged exposure to a family friend last week who is now COVID+. **What do you recommend?**

- Immediate COVID-19 rapid Ag +/- PCR testing, Isolation
- Counsel and strongly recommend one of the following:
  - Monoclonal Ab treatment (Bebtelovimab or Sotrovimab)
  - Oral nirmatrelvir/ritonavir (Paxlovid)
  - Outpatient IV Remdesivir x 3 days

Case #1: Outpatient COVID-19

- Key Pearls: Prioritize early outpt therapy in high risk patients; **Every high risk patient should have Mab action plan**
- Selling Point: 70-85% reduction in risk of hospitalization or death
- Oral nirmatrelvir/ritonavir also a good option if within 5 days of sxs and no drug-drug interactions
- IV Remdesivir x 3 days also a choice but outpatient logistics more challenging

Mab EUA Criteria:

Sx onset < 7 days
Not hospitalized **due to COVID**
No new or ↑ oxygen
"High risk for progression"

Mab High Risk Criteria:

Age > 65
BMI > 25
DM, CKD, Chronic heart/lung dz
Immunosuppressed
Others….

Case #2

- 63 year old male with PMHx of obesity, COPD, HTN admitted with 6 days of fevers, HA, rhinorrhea, SOB. He was unvaccinated. COVID-19 PCR positive on admission, CXR shows bilateral interstitial infiltrates. O_2 sat 94% on 3L NC. LFTs 2x ULN. CRP 25 mg/L. **What do you recommend?**
- Dexamethasone 6 mg daily up to 10 days plus IV Remdesivir x 5 days
- At least ppx anticoagulation, possibly therapeutic
- Trend O_2 sats, LFTs, D-dimer, CRP
- No antibacterial antibiotics; Awake proning

Case #2: Severe COVID-19 on low flow O2

Key Pearls:

- Dexamethasone and Remdesivir mainstay of Rx
- Secondary bacterial infection rare, no abx needed in most cases
- Assess anticoagulation level based on bleeding risk
- Awake proning may benefit, no cost intervention
- Trend O2, LFTs, D-dimer and CRP
- If O_2 needs progressing rapidly, can consider adding baricitinib or tocilizumab
- Cannot use Mab via EUA but can consider compassionate use if Ab negative

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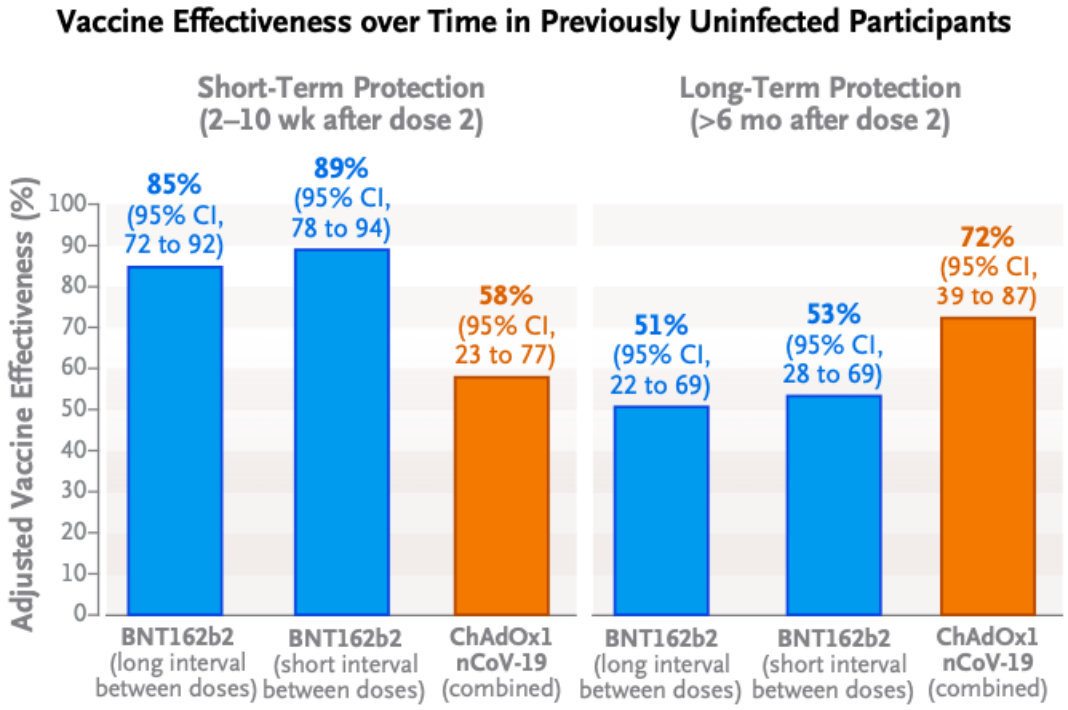
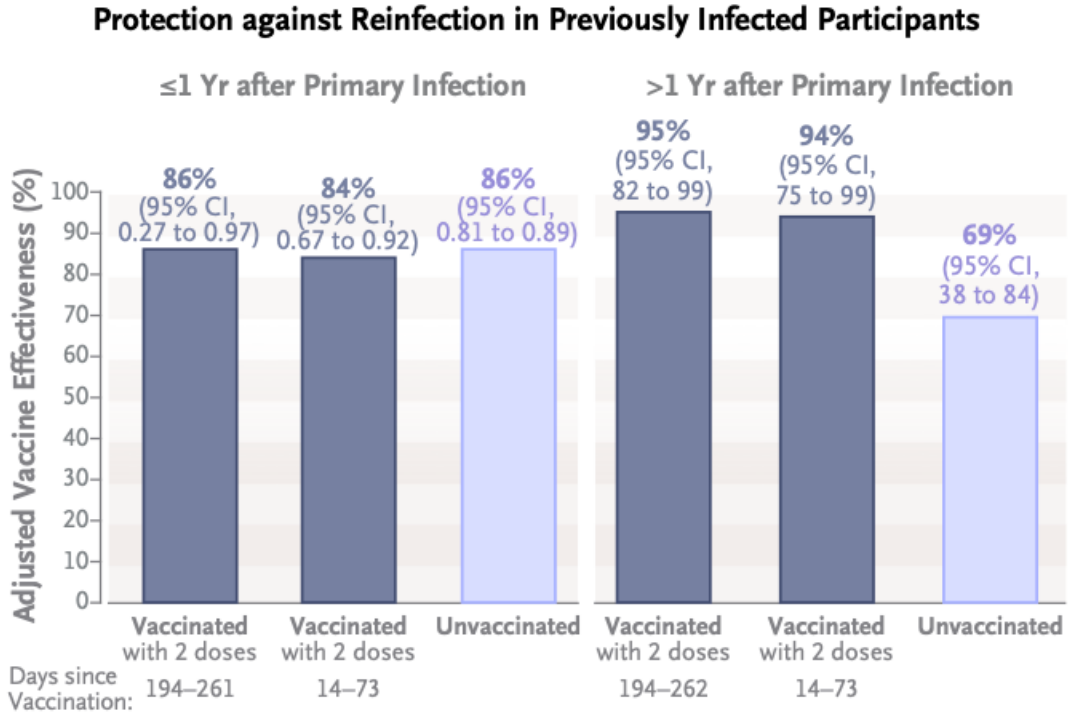
- COVID-19 Epidemiology and Emerging Variants
- COVID-19 Management and Prevention Updates
- **COVID-19 Vaccination Updates**

Vaccine and Infection-induced Immunity

Prospective UK cohort of > 35,000 HCWs from Dec 2020-Sept 2021 (pre-Omicron)





Robust vaccine immune protection against infection (esp. mRNA) that wanes > 6 months

Robust infection-induced immune protection that is further boosted with vaccination

Hall V, et al. N Engl J Med 2022 Mar 31; DOI: 10.1056/NEJMoa2118691

CDC Vaccine Recs: Non-Immunocompromised

COVID-19 Vaccination Schedule*

Vaccine	0 month	1 month	2 month	3 month	4 month	5 month	6 month	7 month	8 month	9 month	10 month	11 month
Pfizer-BioNTech (ages 5-11 years)	1st Dose	2nd Dose (3 weeks after 1st dose)										
Pfizer-BioNTech (ages 12 years and older)	1st Dose	2nd Dose[1] (3–8 weeks after 1st dose)					Booster Dose[2] (at least 5 months after 2nd dose)				2nd Booster Dose[3] (See footnote)	
Moderna (ages 18 years and older)	1st Dose	2nd Dose[1] (4–8 weeks after 1st dose)					Booster Dose[2] (at least 5 months after 2nd dose)				2nd Booster Dose[3] (See footnote)	
Janssen (ages 18 years and older)	1st Dose		Booster Dose[2] (at least 2 months after 1st dose)				2nd Booster Dose[3] (See footnote)					

Note: Timeline is approximate. Intervals of 3 months or fewer are converted into weeks per the formula "1 month = 4 weeks." Intervals of 4 months or more are converted into calendar months.

2nd Booster Dose now an option for those ≥ 50 years old

- Greatest likely benefit in those ≥ 65 years old or with chronic medical conditions
- Those with recent Omicron infection can likely delay booster shot

CDC Vaccine clinical considerations https://www.cdc.gov/vaccines/covid-19/index.html
Michigan DHHS https://www.michigan.gov/coronavirus/0,9753,7-406-98178_103214---,00.html

CDC Vaccine Recs: Immunocompromised

COVID-19 Vaccination Schedule

For Those who are Moderately or Severely Immunocompromised

Vaccine	0 month	1 month	2 month	3 month	4 month	5 month	6 month	7 month	8 month	9 month
Pfizer-BioNTech (ages 5-11 years)	**1st Dose**	**2nd Dose** (3 weeks after 1st dose)	**3rd Dose** (At least 4 weeks after 2nd dose)							
Pfizer-BioNTech (ages 12 years and older)	**1st Dose**	**2nd Dose** (3 weeks after 1st dose)	**3rd Dose** (At least 4 weeks after 2nd dose)			**Booster Dose[1]** (at least 3 months after 3rd dose)				**2nd Booster Dose[3]** (See footnote)
Moderna (ages 18 years and older)	**1st Dose**	**2nd Dose** (4 weeks after 1st dose)	**3rd Dose** (At least 4 weeks after 2nd dose)			**Booster Dose[1]** (at least 3 months after 3rd dose)				**2nd Booster Dose** (See footnote)
Janssen (ages 18 years and older)	**1st Dose**	**2nd (Additional) Dose[2] using an mRNA COVID-19 Vaccine** (At least 4 weeks after 1st dose)		**Booster Dose[1]** (at least 2 months after additional dose)				**2nd Booster Dose[3]** (See footnote)		

Note: Timeline is approximate. Intervals of 3 months or fewer are converted into weeks per the formula "1 month = 4 weeks." Intervals of 4 months or more are converted into calendar months.

CDC Vaccine clinical considerations https://www.cdc.gov/vaccines/covid-19/index.html
Michigan DHHS https://www.michigan.gov/coronavirus/0,9753,7-406-98178_103214---,00.html

Conclusions

- Cases and hospitalizations are currently at nadir after Omicron surge but likely to see a new wave in the summer due to new variants, waning immunity
- Outpatient therapies focus on early initiation of oral antivirals, Mabs, or short course IV Remdesivir (if available)
- Cornerstone of inpatient treatment for those with severe disease (on O2) remains IV remdesivir plus steroids (+/- other immunomodulators)
- Vaccine recommendations on boosters continue to evolve with changing science and new variants

Questions?


Winning shot.
Let's get the vaccine.
utswmed.org/taketheshot
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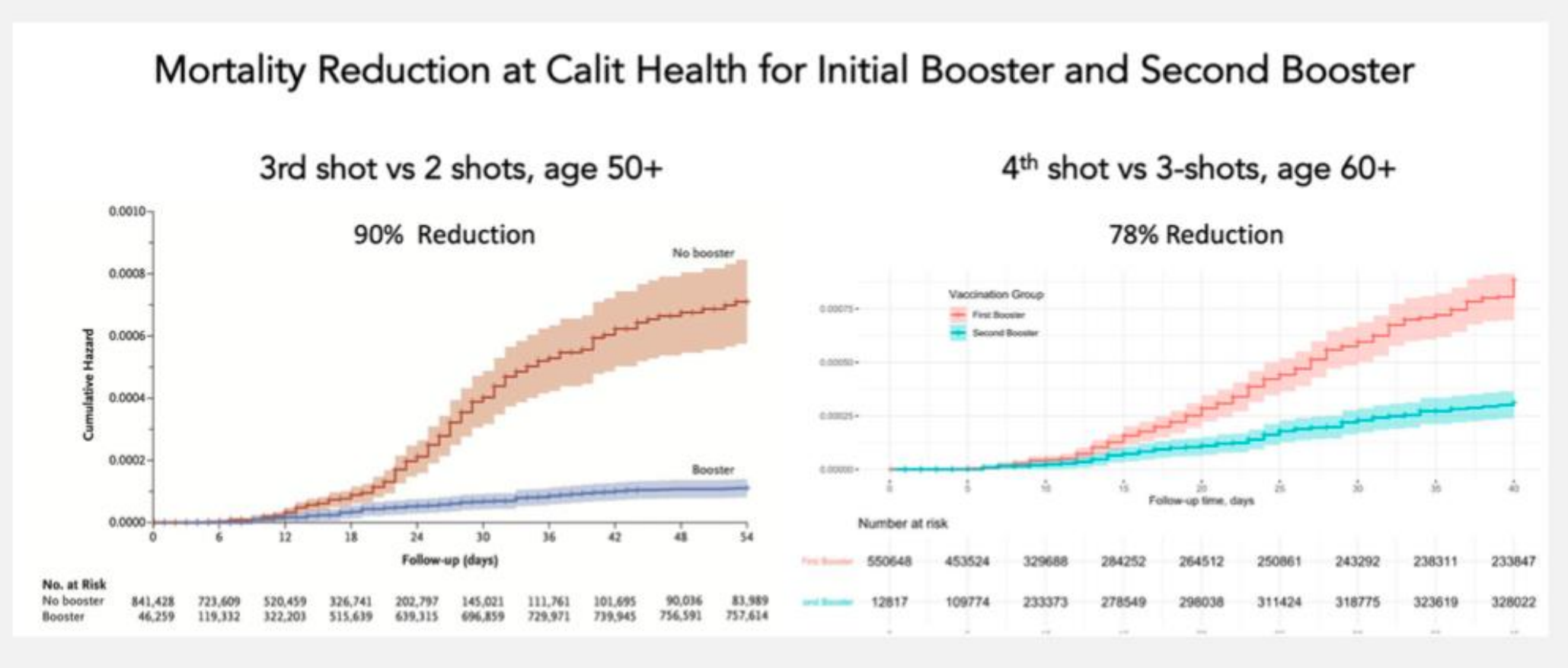
Extra Slides

4th Dose COVID-19 Booster: Israel Clalit Health

Pre-print retrospective cohort of > 560k patients > 60 yo in large Israeli Health System



Eric Topol Substack https://erictopol.substack.com/p/a-new-wave-and-a-new-booster?s=r

TOGETHER Ivermectin COVID-19 Trial

Largest and most rigorous RCT of early ivermectin treatment in COVID-19 showed no benefit in reducing disease progression

METHODS

We conducted a double-blind, randomized, placebo-controlled, adaptive platform trial involving symptomatic SARS-CoV-2–positive adults recruited from 12 public health clinics in Brazil. Patients who had had symptoms of Covid-19 for up to 7 days and had at least one risk factor for disease progression were randomly assigned to receive ivermectin (400 μg per kilogram of body weight) once daily for 3 days or placebo. (The trial also involved other interventions that are not reported here.) The primary composite outcome was hospitalization due to Covid-19 within 28 days after randomization or an emergency department visit due to clinical worsening of Covid-19 (defined as the participant remaining under observation for >6 hours) within 28 days after randomization.

RESULTS

A total of 3515 patients were randomly assigned to receive ivermectin (679 patients), placebo (679), or another intervention (2157). Overall, 100 patients (14.7%) in the ivermectin group had a primary-outcome event, as compared with 111 (16.3%) in the placebo group (relative risk, 0.90; 95% Bayesian credible interval, 0.70 to 1.16). Of the 211 primary-outcome events, 171 (81.0%) were hospital admissions. Findings were similar to the primary analysis in a modified intention-to-treat analysis that included only patients who received at least one dose of ivermectin or placebo (relative risk, 0.89; 95% Bayesian credible interval, 0.69 to 1.15) and in a per-protocol analysis that included only patients who reported 100% adherence to the assigned regimen (relative risk, 0.94; 95% Bayesian credible interval, 0.67 to 1.35). There were no significant effects of ivermectin use on secondary outcomes or adverse events.

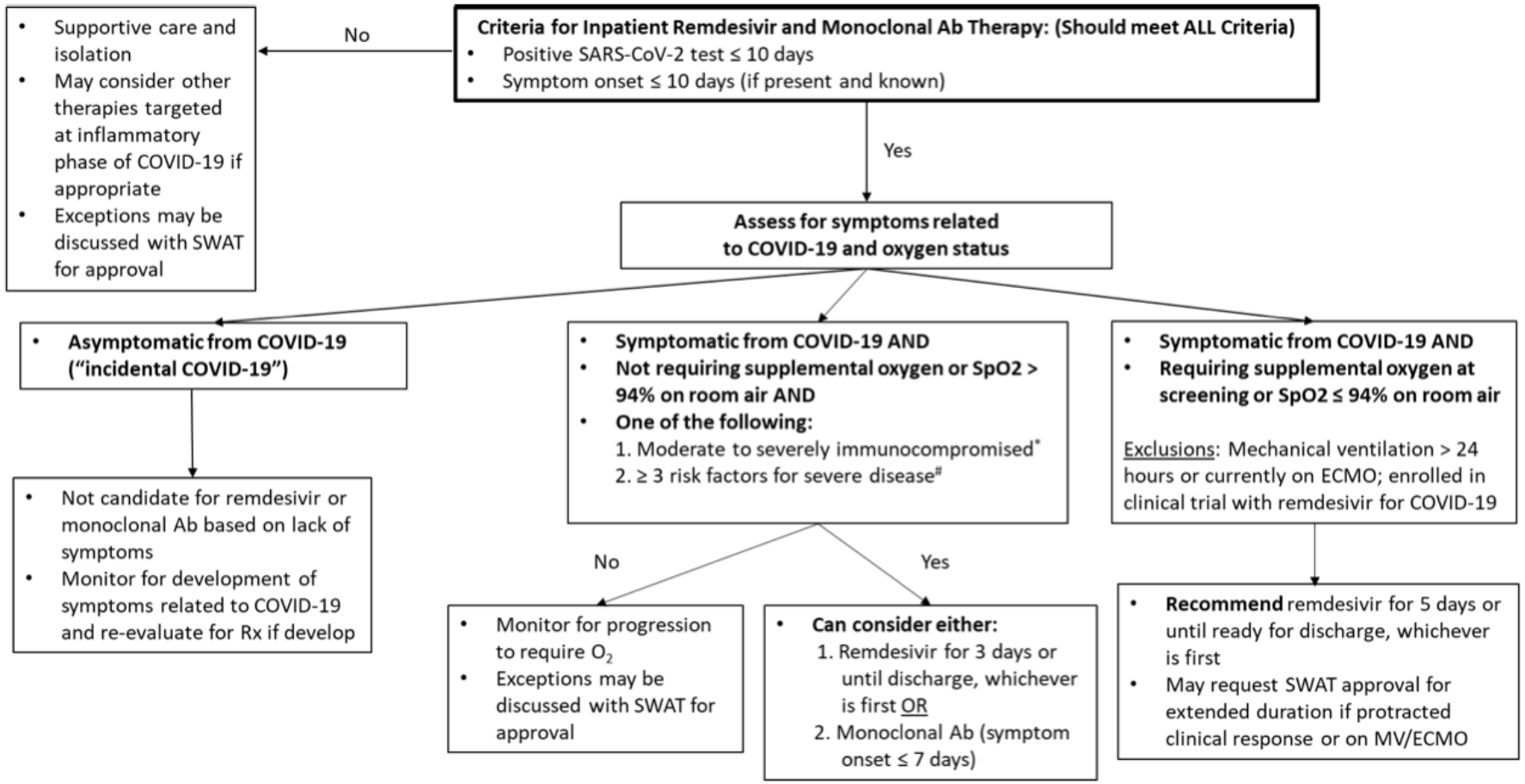
CONCLUSIONS

Treatment with ivermectin did not result in a lower incidence of medical admission to a hospital due to progression of Covid-19 or of prolonged emergency department observation among outpatients with an early diagnosis of Covid-19. (Funded by FastGrants and the Rainwater Charitable Foundation; TOGETHER ClinicalTrials.gov

Reis G, et al. N Engl J Med 2022 Mar 30; **DOI: 10.1056/NEJMoa2115869**

UTSW Inpatient RDV and Mab Algorithm

Figure 1: Algorithm for Inpatient Use of Remdesivir and Monoclonal Antibodies

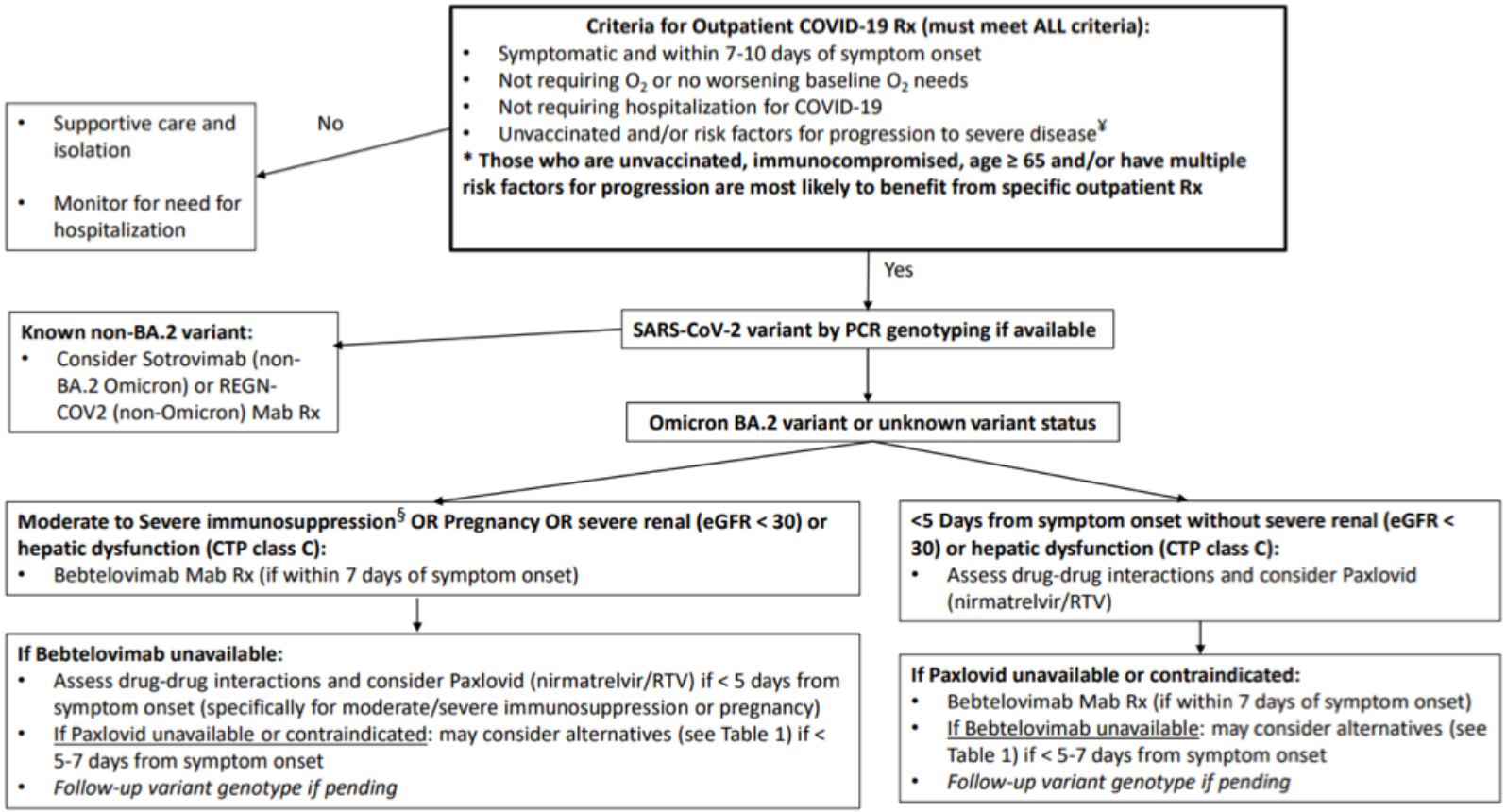


*Moderate to severely immunocompromised per CDC definitions https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html

#Risk factors for severe disease: Unvaccinated, Age ≥ 65, DM2, Obesity (BMI > 30), and Chronic cardiac, pulmonary, renal, neurologic or liver disease

UTSW Outpatient Algorithm

Figure 1. Recommended Treatment Approach for Non-Hospitalized Patients with COVID-19



¥ Risk factors for progressing to severe disease -- https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html

§ Moderate to severe immunosuppression -- https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html