Good morning – I hope everyone had a good weekend

Under COVID-19 news I report on the preliminary findings from the RECOVERY Colchicine Trial, the updated NIH guidelines on tocilizumab, and the announcement of a promising new antiviral Molnupiravir.

In Journal Review, the first article is a CDC report on the association of state-issued mask mandates and allowing on-premises restaurant dining with COVID-19 cases. The second article is the effect of early treatment with fluvoxamine in preventing progression of COVID-19. The next article examines the effect of ivermectin in patients with mild COVID-19 disease. The last article looks at the Identification of SARS-CoV-2-specific immune alterations in acutely ill patients in JCI.

Have a wonderful day

Ed

COVID-19 News

RECOVERY Colchicine
On the advice of its independent data monitoring committee (DMC), the RECOVERY trial has stopped recruitment to the colchicine arm for lack of efficacy in patients hospitalized with COVID-19. The results showed no significant difference in the primary endpoint of 28-day mortality in patients randomized to colchicine vs usual care alone (20% vs 19%; risk ratio, 1.02; 95% CI, 0.94 - 1.11; *P* = .63).

Comment: The RECOVERY trial has already identified two anti-inflammatory drugs – dexamethasone and tocilizumab – that improve the chances of survival for patients with severe COVID-19. In Journal Review below, ivermectin showed no benefit in mild COVID-19 patients.

Updated NIH Guidance on Tocilizumab
March 5, 2021
Based on the collective evidence from the Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) and Randomized Evaluation of COVID-19 Therapy (RECOVERY) trials, the COVID-19 Treatment Guidelines Panel (the Panel) has determined the following:

- The Panel recommends the use of tocilizumab (single intravenous dose of 8 mg/kg of actual body weight, up to 800 mg) **in combination with dexamethasone** (6 mg daily for up to 10 days) in certain hospitalized patients who are exhibiting rapid respiratory decompensation due to COVID-19. The patients included in this population are:
  - Recently hospitalized patients who have been admitted to the intensive care unit (ICU) within the prior 24 hours and who require invasive mechanical ventilation, noninvasive mechanical ventilation (NIV), or high-flow nasal canula (HFNC) oxygen (>0.4 FiO_2/30 L/min of oxygen flow) (BIIa); *or*
  - Recently hospitalized patients (not in the ICU) with rapidly increasing oxygen needs who require NIV or HFNC and have significantly increased markers of inflammation (BIIa) (Note: The RECOVERY trial inclusion criterion for inflammation was C-reactive protein [CRP] ≥75 mg/L)

Comment: As reviewed last week in the Daily Briefing and now with updated NIH and IDSA guidance we have better science on how best to use tocilizumab. Tocilizumab should be given early (within 24 hours) in patients admitted to the ICU for COVID-19 pneumonia who require mechanical ventilation or who have rapidly increasing oxygen needs with vapotherm who have high CRP levels.

Experimental Drug Molnupiravir
The pill, which is being developed by Ridgeback Biotherapeutics LP and Merck MRK 1.33% & Co., demonstrated significant reduced infectious virus in subjects in a mid-stage study after five days of treatment. Unlike other drugs targeting the spike protein, molnupiravir attacks a portion of the virus that helps it reproduce. Molnupiravir is a prodrug of N4-hydroxycytidine that blocks the replication of some RNA viruses. The 182-subject Phase 2 trial studied the effect of various doses of molnupiravir in people who had developed Covid-19 symptoms within the previous week, tested positive for the disease during the most recent four days and weren't hospitalized. Tests did not detect infectious virus in any of the study volunteers who took molnupiravir twice a day after five days of treatment, while 24% of subjects who received a placebo did. This was reported at the virtual Conference on Retroviruses and Opportunistic Infections.

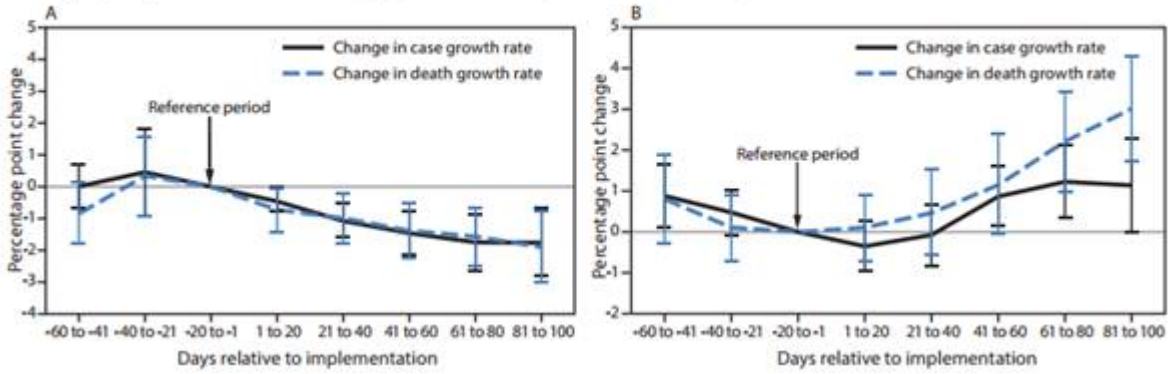
Comment: This is the first proof that an oral antiviral drug can be effective against the virus. To be clear, the finding suggests, but does not prove, that the drug can reduce illness. More studies are needed, but it is clear we need better therapeutics.

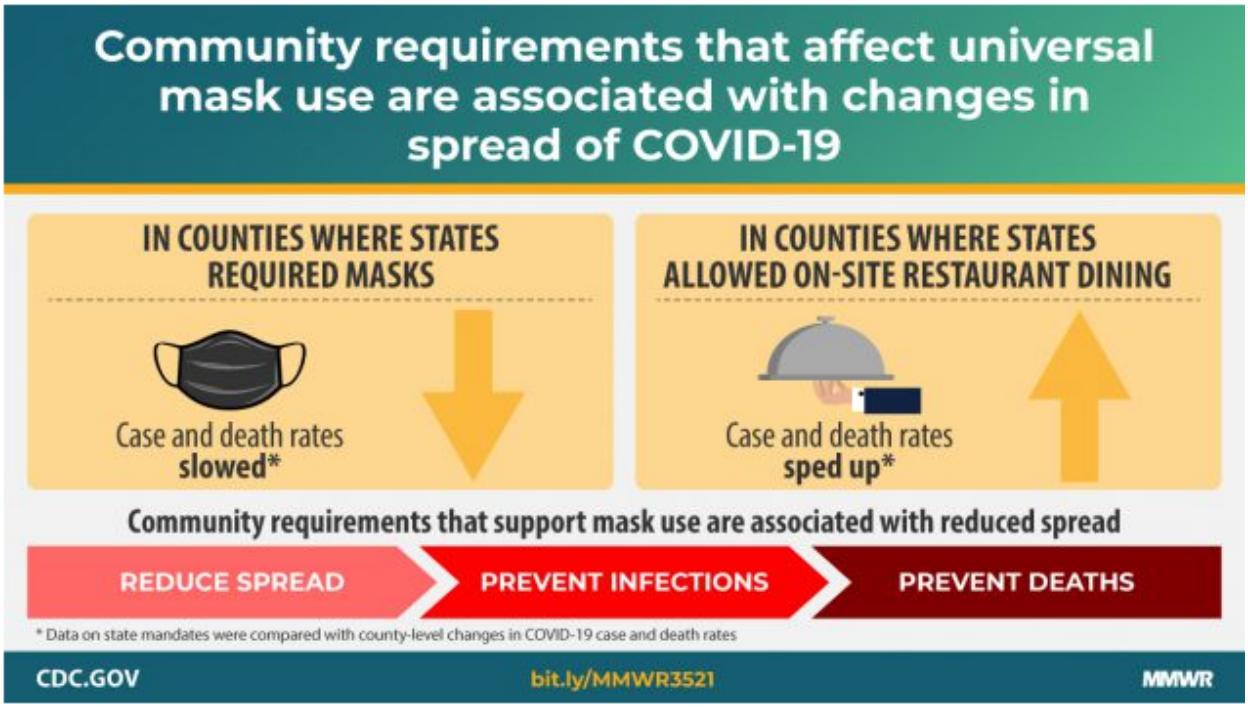
Journal Review

Association of State-Issued Mask Mandates and Allowing On-Premises Restaurant Dining with County-Level COVID-19 Case and Death Growth Rates — United States, March 1–December 31, 2020
MMWR publisher March 5, 2021
Article recommended by Patti Savrich
To examine the association of state-issued mask mandates and allowing on-premises restaurant dining with COVID-19 cases and deaths during March 1-December 31, 2020, county level data on mask mandates and restaurant reopenings were compared with county-level changes in COVID-19 case and death growth rates relative to the mandate implementation and reopening dates. Two outcomes were examined: the daily percentage point growth rate of county-level COVID-19 cases and county level COVID-19 deaths. The daily growth rate was defined as the difference between the natural log of cumulative cases or deaths on a given day and the natural log of cumulative cases or deaths on the previous day, multiplied by 100. Data on cumulative county-level COVID-19 cases and deaths were collected from state and local health department websites and accessed through U.S. Department of Health and Human Services Project.

Mask mandates were associated with decreases in daily COVID-19 case and death growth rates 1–20, 21–40, 41–60, 61–80, and 81–100 days after implementation. Allowing any on-premises dining at restaurants was associated with increases in daily COVID-19 case growth rates 41–60, 61–80, and 81–100 days after reopening, and increases in daily COVID-19 death growth rates 61–80 and 81–100 days after reopening. Implementing mask mandates was associated with reduced SARS-CoV-2 transmission, whereas reopening restaurants for on-premises dining was associated with increased transmission.

FIGURE. Association between changes in COVID-19 case and death growth rates* and implementation of state mask mandates† (A) and states allowing any on-premises restaurant dining§ (B) — United States, March 1–December 31, 2020





Comment: Policies that require universal mask use and restrict any on-premises restaurant dining can be important components of a comprehensive strategy to reduce exposure to and transmission of SARS-CoV-2. The results of this report are subject to several weaknesses. First, compliance with and enforcement of policies were not measured. Second, the analysis did not differentiate between indoor and outdoor dining, adequacy of ventilation, and adherence to physical distancing and occupancy requirements. Nonetheless, this report provides important information as states begin to relax restrictions.

Prospective Cohort of Fluvoxamine for Early Treatment of Coronavirus Disease 19
OFID published online February 1, 2021
DOI: 10.1093/ofid/ofab050
In November-December 2020, a mass outbreak of COVID-19 occurred in an occupational setting with congregate living at a horse racing track in California. On the same day as positive COVID-19 test,

patients were offered fluvoxamine. The choice was at the patient's discretion. Fluvoxamine was prescribed with a 50- to 100-mg loading dose, then 50 mg twice daily for 14 days. The facility provided the fluvoxamine at no cost. All patients were followed up in-person at 7 and 14 days.

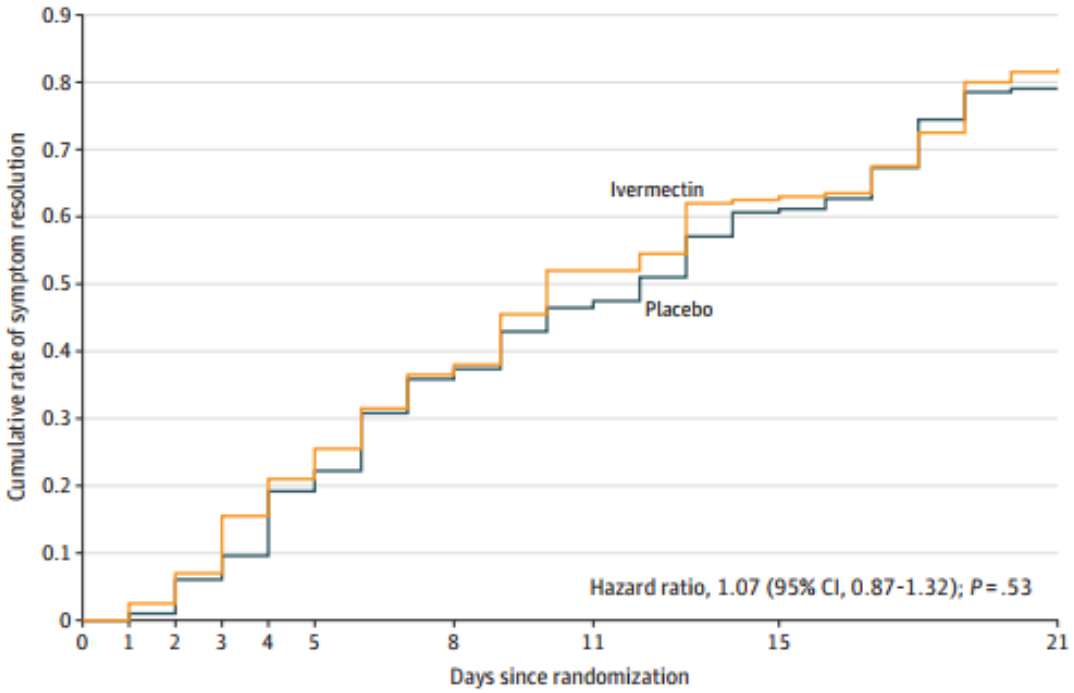
Of 113 SARS-COV-2 antigen positive persons, approximately half were asymptomatic when initially tested. The median age was 42 years (interquartile range, 33 to 56), and 75% were men; 84% were Latino, and 14% were white. In total, 65 persons opted for fluvoxamine, and 48 opted for observation alone with no therapy. Fewer patients opting for fluvoxamine were asymptomatic (38%) at time of initial diagnostic testing than those opting for observation (58%). Overall, 30% had 1 or more chronic medical comorbidities. Those opting for fluvoxamine had slightly more frequent diabetes (17% vs 8%) and slightly less treated hypertension (17% vs 35%) than those receiving observation.

The incidence of subsequent hospitalization was 0% (0 of 65) with fluvoxamine and 12.5% (6 of 48) with observation (P = .005). Two persons required intensive care unit stay with mechanical ventilation, 1 of whom died. Respiratory rates were slightly elevated at diagnosis and improved faster by day 7 with fluvoxamine (P = .001). At day 14, ongoing symptoms were present in 0% (0 of 65) with fluvoxamine compared with 60% (29 of 48) with observation alone (P < 0.001). The most common persisting symptoms were as follows: persistent anxiety (n = 19), difficulty concentrating/memory challenges (n = 18), fatigue (n = 16), insomnia (n = 12), myalgia/arthralgia (n = 10), and headache (n = 9). No serious adverse events occurred with fluvoxamine. No adverse events led to early discontinuation.

Comment: Several months ago, the Daily Briefing reported on a double-blind randomized clinical trial testing fluvoxamine for early treatment of COVID-19. In this trial, fluvoxamine decreased clinical progression. [JAMA 2020; 324:2292–300] Although fluvoxamine is a selective serotonin reuptake inhibitor, fluvoxamine also activates sigma-1 receptors present intracellularly in the endoplasmic reticulum, thereby decreasing cytokine production. Fluvoxamine seems to be promising as early treatment for COVID-19 to prevent clinical deterioration requiring hospitalization and to prevent possible long-haul symptoms persisting beyond 2 weeks. Further RCTs are needed. This is an inexpensive drug and can be given PO unlike monoclonals. This was featured on 60 Minutes last PM.

Effect of Ivermectin on Time to Resolution of Symptoms Among Adults with Mild COVID-19: A Randomized Clinical Trial
JAMA published online March 4, 2021
Article suggested by Malar Narayanan
doi:10.1001/jama.2021.3071
This is a double-blind, randomized trial conducted at a single site. Potential study participants were identified by simple random sampling from the state's health department electronic database of patients with symptomatic, laboratory-confirmed COVID-19 during the study period. A total of 476 adult patients with mild disease and symptoms for 7 days or fewer (at home or hospitalized) were enrolled.

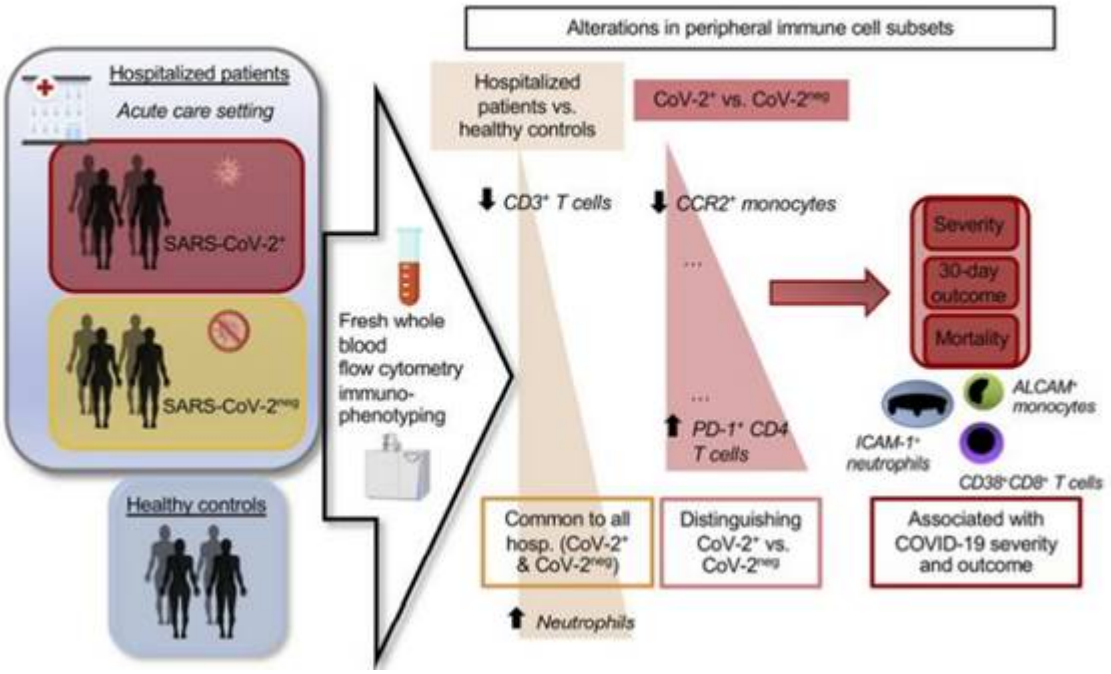
Among 400 patients who were randomized in the primary analysis population (median age, 37 years [interquartile range {IQR}, 29-48]; 231 women [58%]), 398 (99.5%) completed the trial. The median time to resolution of symptoms was 10 days (IQR, 9-13) in the ivermectin group compared with 12 days (IQR, 9-13) in the placebo group (hazard ratio for resolution of symptoms, 1.07 [95% CI, 0.87 to 1.32]; P = .53 by log-rank test). By day 21, 82% in the ivermectin group and 79% in the placebo group had resolved symptoms.

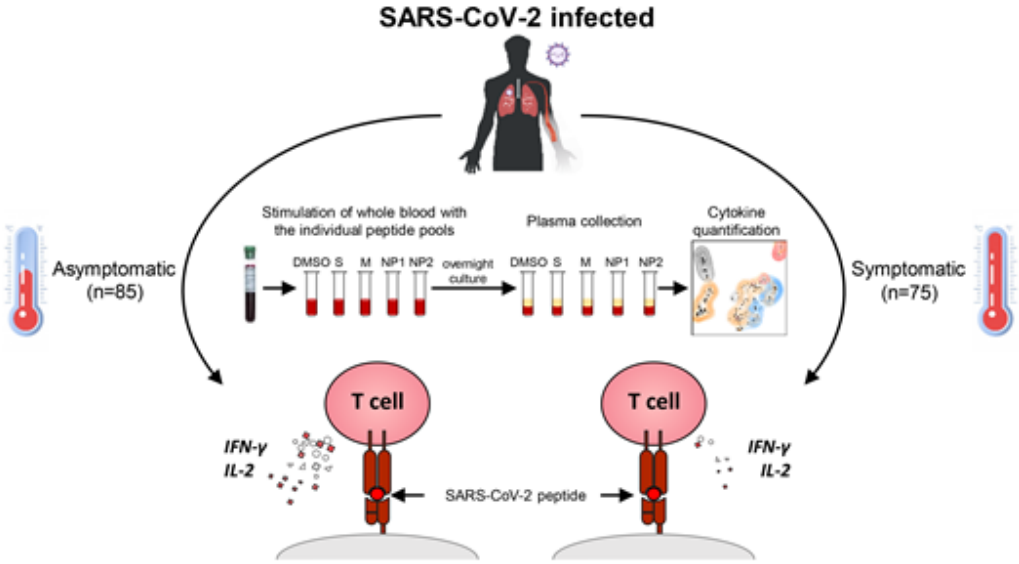


Comment: Interest in ivermectin in COVID-19 therapy began from an in vitro study that found that bathing SARS-CoV-2– infected Vero cells with 5-µM ivermectin led to an approximately 5000-fold reduction in viral RNA. However, pharmacokinetic models indicated that the concentrations used in the in vitro study are difficult to achieve in human lungs or plasma. Daily doses were used in this trial because pharmacokinetic models have shown higher lung concentrations with daily rather than intermittent dosing and have proven to be well tolerated. Despite this the study did not find any significant effect of ivermectin on other evaluated measures of clinical benefit for the treatment of COVID-19. Merck, in a press release a few weeks ago, recommended that ivermectin not be used for patients infected with SARS-CoV-2 based on current science.

Identification of SARS-CoV-2-Specific Immune Alterations in Acutely Ill Patients
JCI published online February 26, 2021
doi.org/10.1172/JCI145853
The investigators performed flow cytometry analysis on fresh peripheral blood from a consecutive cohort of i) patients hospitalized with acute SARS-CoV-2 infection; ii) patients of comparable age/sex hospitalized for other acute disease (SARS-CoV-2 negative); and iii) healthy controls using both data-driven and hypothesis-driven analyses. Based on a blood test, they were able to inventory the immune-cell populations present in 50 patients with SARS-CoV-2 and compare them to those of 22 patients of similar gender and age hospitalized for other acute illnesses, and those of 49 healthy controls.

They found several dysregulations in immune cell subsets (e.g., decreased proportion of T cells) that are similarly associated with acute SARS-CoV-2 infection and non-COVID-19 related acute illnesses. In contrast, they identified specific differences in myeloid and lymphocyte subsets that are associated with SARS-CoV-2 status (e.g., elevated proportion of ICAM-1+ mature/activated neutrophils, ALCAM+ monocytes, and CD38+CD8+ T cells). A subset of SARS-CoV-2-specific immune alterations correlated with disease severity, disease outcome at 30 days and mortality.





Comment: This immune profiling allowed the investigators to identify subsets of "dysregulated" immune cells specific to patients affected by SARS-CoV-2. Most notably, some of these immune alterations were associated with ventilation needs and mortality in these same patients. Their data provide an understanding of the immune dysregulation that are specifically associated with SARS-CoV-2 infection among acute care hospitalized patients. I believe this study lays the foundation for the development of specific biomarkers to stratify SARS-CoV-2+ patients at risk of unfavorable outcome and uncover candidate drugs to investigate from a therapeutic perspective. These markers specific to SARS-

CoV-2 could then help us to identify the patients at greatest risk and suggest new avenues for developing therapeutic targets. In addition, they confirm what has been observed in other studies: disturbances in the immune system such as neutrophilia or lymphopenia, for example, are related to the severity of the disease in hospitalized patients but are not specific to SARS-CoV-2.