TGIF – a short week, but a very important week in our fight against this pandemic.

I start with a tribute and commentary as we approach the 20th anniversary of 9/11.

Under Covid-19 News, a few graphs which update where we are in the pandemic in the US. Next is my review and thoughts about the President's initiative announced yesterday. Would love your thoughts on the questions I raised. Last, I review some facts about Mu which has been the news lately.

Under Journal Review a lot to share. The first two articles examine a few recent CDC reports on hospitalizations and ED visits among children and adolescents. The next article is an animal model on the potential use of the antiviral molnupiravir including activity against variants. In my comments I also mention the potential of fluvoxamine and the controversy surrounding the use of ivermectin. The last 2 articles are on JAK inhibitors which demonstrate a clear benefit with JAK inhibitors in select patients with severe disease.

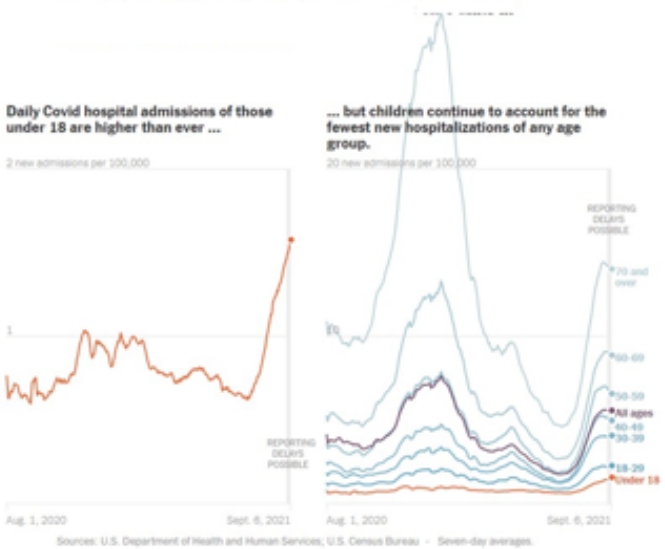
Have a wonderful weekend.

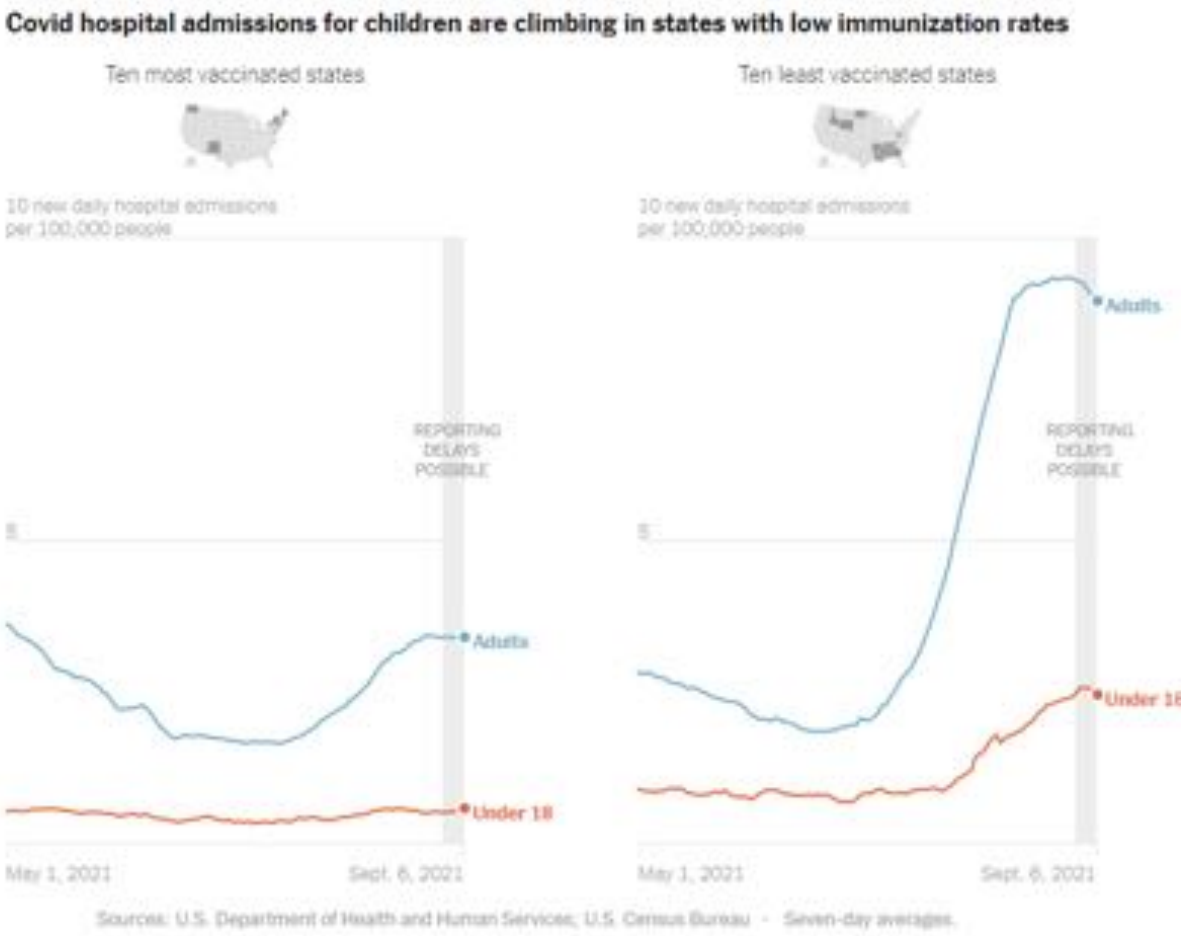
Ed

Tomorrow is the 20th anniversary of 9/11. Tomorrow we should reflect on this horrifying day which was an attack on all humanity. We should also remember the victims including the courage of the first responders who lost their lives trying to save others. Despite the chaos in the world, we are still fortunate to live a in country that values life and human dignity. Throughout American history, national crises have generally brought us together. However, this pandemic has become politicized leading to distrust of one another and to vehement disagreements along partisan lines. This is not who we are, and this must stop! However, on the positive side the pandemic also produced some remarkable examples of what we can do when we work together—from healthcare workers caring for the sick, to scientists, supported by businesses and government, who produced the miraculous vaccines that have saved millions of lives. I am reminded of a quote from Paulo Coelho: "It's the simple things in life that are the most extraordinary." Let us remember how fortunate we are and try to work together for a better tomorrow. **VII**

COVID-19 News

COVID-19 Data Update





Comment: The graphs above speak for themselves. One fact that may be a surprise to some is the recent rise in persons >65. The correlation of new infection and most vaccinated versus lowest vaccinated has been reported.

President's New Mandates

As most of you know President Biden announced new vaccination requirements. There will be a 75-day grace period.

- To increase the number of Americans vaccinated, the Labor Department will develop emergency rules which will require all private-sector businesses with more than 100 employees to require that their workforces be fully vaccinated or test negative at least once a week. The rule would affect an estimated 80 million workers.
- Mr. Biden pointed to booster shots as a crucial way to continue to protect vaccinated Americans from the coronavirus. Last week, top federal health officials told the White House to scale back a plan to offer coronavirus booster shots this month to the general public, saying that their agencies needed more time to collect and review all the necessary data.
- Mr. Biden announced a string of measures intended to keep the coronavirus from spreading in schools and infecting children under the age of 12, who are not yet eligible for a vaccine. For parents, he urged that they ensure children ages 12 and older are vaccinated; for states, he urged mandating school staff and teachers to be inoculated. Mr. Biden also said that nearly 300,000 educators who work in federally run school programs would be required to be

vaccinated. [Latest information about 90% of school staff and teachers are already vaccinated] LA just announced vaccine mandates for eligible students taking classes in person.
- Increased testing and masking

Comment: I commend the President for highlighting the importance of vaccination as our way to control this pandemic. I have a few questions and suggestions to add to this discussion.

1. There is no mention of natural immunity. Should vaccines be required for this population? If vaccination is recommended, does this population need 1 dose versus 2 doses?
2. What about spacing of vaccination? Some data suggests dosing interval may be more important than we thought. One suggestion is 2 doses 90 days apart which may negate the need for a 3rd dose or booster dose. Another idea is to administer the vaccine like hepatitis B vaccine: 0, 1, 6 months.
3. Do children need 2 doses?

By the time this new mandate is fully implemented this surge hopefully will be behind us, so we still need to use all the tools in our toolbox to reduce spread NOW. That means the 3-Ws: wear masks indoors regardless of vaccination status as long as the transmission rate in your community is high or substantial, watch your distance, and wash your hands. As we approach the traditional respiratory virus season, we also need to make sure we get vaccinated for influenza.

What we know about Mu

The Mu variant (also known as B.1.621) is the latest form of SARS-CoV-2 to be designated a "Variant of Interest" by the World Health Organization. The agency announced the designation had been made in last week's epidemiological update, citing an uptick in Mu infections in Ecuador and Colombia, where the variant was first identified in January. In Colombia, it accounts for nearly 40% of cases, according to WHO data.

According to *Public Health England*, the variant shares mutations with other variants, most notably the Beta (B.1.351) variant first identified in South Africa. These include the E484K and K417N mutations, which researchers have linked to immune escape. K417N is also seen in the "Delta plus" variant. Additionally, Mu has the P681H mutation seen in the Alpha (B.1.1.7) variant, which is associated with increased transmissibility.

Detailed studies of the Mu variant's characteristics have yet to be conducted, but it exhibited Beta-like escape of vaccine-induced immune protection in preliminary data presented to the WHO's Virus Evolution Working Group. Studies suggest the variant is more transmissible than the ancestral SARS-CoV-2, and Mu has outcompeted Gamma and Alpha in Ecuador and Colombia. Importantly, real-world data and laboratory studies of the vaccine see no evidence that the virus or circulating variants of concern regularly escape vaccine protection.

Mu has been detected in at least 46 countries as of September 7, 2021 including the US, where Delta continues to dominate but more than 2,100 cases of Mu have been reported. Mu has been detected in every US state except Nebraska.

United States: 8/29/2021 – 9/4/2021 NOWCAST

USA

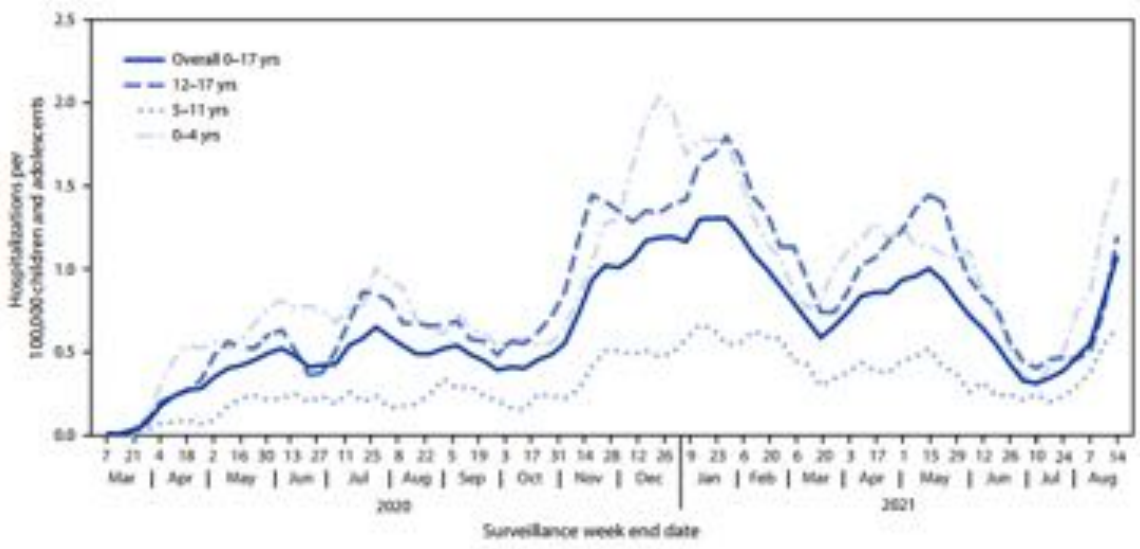
WHO label	Lineage #	Type	%Total	95%PI
Alpha	B.1.1.7	VOC	0.1%	0.0-0.2%
Beta	B.1.351	VOC	0.0%	0.0-0.2%
Gamma	P.1	VOC	0.0%	0.0-0.2%
Delta	B.1.617.2	VOC	98.9%	97.8-99.8%
	AY.2	VOC	0.1%	0.0-0.5%
	AY.1	VOC	0.1%	0.0-0.5%
Eta	B.1.525	VOI	0.0%	0.0-0.2%
Iota	B.1.526	VOI	0.0%	0.0-0.2%
Kappa	B.1.617.1	VOI	0.0%	0.0-0.2%
Mu	B.1.621		0.1%	0.0-0.5%
N/A	B.1.617.3	VOI	0.0%	0.0-0.2%
Other	Other*		0.7%	0.0-1.7%

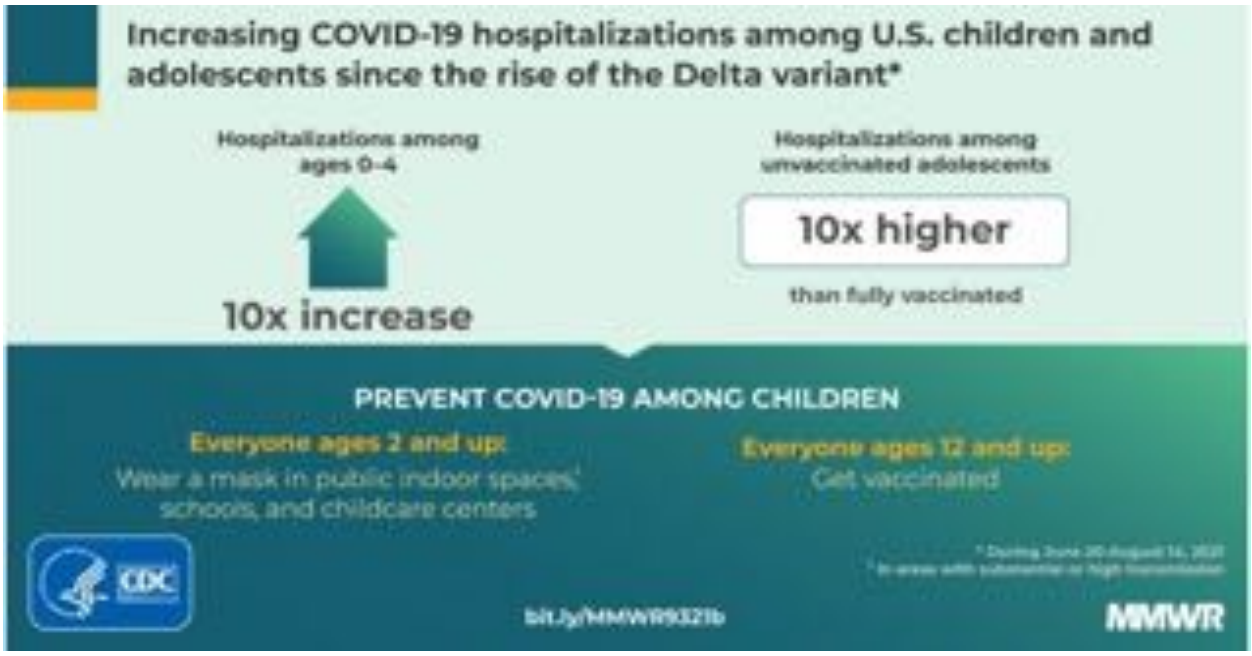
Comment: As you can see Mu is <1% of variants in the US last week. However, in Alaska Mu makes up 4% of cases. We should keep a close eye on the Mu variant, but currently it does not pose an immediate threat in the US. Can Mu outcompete other variants in US or across the world only time will tell, but to date only Columbia has significant cases and only 40%. Remember this is a VOI, not VOC. Delta is the "superstar" of variants.

Journal Review

Hospitalizations Associated with COVID-19 Among Children and Adolescents — COVID-NET, 14 States, March 1, 2020–August 14, 2021
MMWR September 3, 2021
This analysis uses Coronavirus Disease 2019-Associated Hospitalization Surveillance Network (COVID-NET) data to describe COVID-19-associated hospitalizations among US children and adolescents aged 0-17 years.

Weekly COVID-19-associated hospitalization rates among children and adolescents rose nearly five-fold during late June-mid-August 2021, coinciding with increased circulation of the highly transmissible SARS-CoV-2 Delta variant. The proportions of hospitalized children and adolescents with severe disease was similar before and during the period of Delta predominance. Hospitalization rates were 10 times higher among unvaccinated than among fully vaccinated adolescents.





Comment: Preventive measures to reduce transmission and severe outcomes in children and adolescents are essential, including vaccination of eligible children, universal masking in schools, and masking by persons aged ≥2 years in other indoor public spaces and childcare centers. The COVID-NET catchment areas include ~ 10% of the US population; thus, findings might not be nationally generalizable.

Trends in COVID-19 Cases, Emergency Department Visits, and Hospital Admissions Among Children and Adolescents Aged 0-17 Years — United States, August 2020-August 2021
MMWR September 3, 2021
Daily hospital admission data were obtained from the HHS Unified Hospital Data Surveillance System. The number of daily cases, ED visits, and hospital admissions were averaged over a 7-day period to obtain a 7-day average. The state-specific percentage of the population aged ≥12 years who had completed the COVID-19 vaccination series as of July 31, 2021, was used to group states into vaccination coverage quartiles. Results were also examined by HHS Region. US Census Bureau midyear 2019 population estimates were used to calculate vaccination coverage and cases and hospital admissions per 100,000 persons. COVID-19-associated ED visits were assessed as a percentage of all ED visits.

COVID-19 cases, emergency department visits, and hospital admissions increased from June to August 2021 among persons aged 0-17 years. Emergency department visits and hospital admissions in a 2-week period in August 2021 were higher in states with lower population vaccination coverage and lower in states with higher vaccination coverage.

State vaccination coverage quartile[§]	ED visits				Hospital admissions
	0–17 yrs	0–4 yrs	5–11 yrs	12–17 yrs	0–17 yrs
Highest[¶]	Ref	Ref	Ref	Ref	Ref
Second highest[**]	0.99 (0.94–1.05)	1.02 (0.93–1.12)	0.99 (0.90–1.10)	0.96 (0.89–1.05)	1.40 (0.87–2.25)
Second lowest[††]	2.65 (2.55–2.76)	2.31 (2.15–2.47)	2.64 (2.44–2.84)	2.84 (2.67–3.03)	3.46 (2.26–5.28)
Lowest[§§]	3.38 (3.24–3.52)	2.61 (2.42–2.82)	3.34 (3.08–3.61)	3.76 (3.52–4.02)	3.70 (2.32–5.90)

Comment: Community vaccination programs, in coordination with testing strategies and other prevention measures, is vital in protecting pediatric populations from SARS-CoV-2 infection and severe COVID-19 especially with Delta and the start of school. Testing rates for SARS-CoV-2 infection in persons aged 0-17 years are lower than they are in older age groups, therefore, pediatric case rates may be underreported. Admissions in the Unified Hospital Data Surveillance System could not be stratified by age and were only counted if the patient was admitted to a pediatric bed. Lastly the BD Insights Research Database represents only three children's hospitals, and the remainder of patients were mostly from community hospitals, therefore, patients with severe COVID-19 might be under- or overrepresented, which might account for some differences compared with past studies.

Molnupiravir Inhibits Replication of the Emerging SARS-CoV-2 Variants of Concern in a Hamster Infection Model

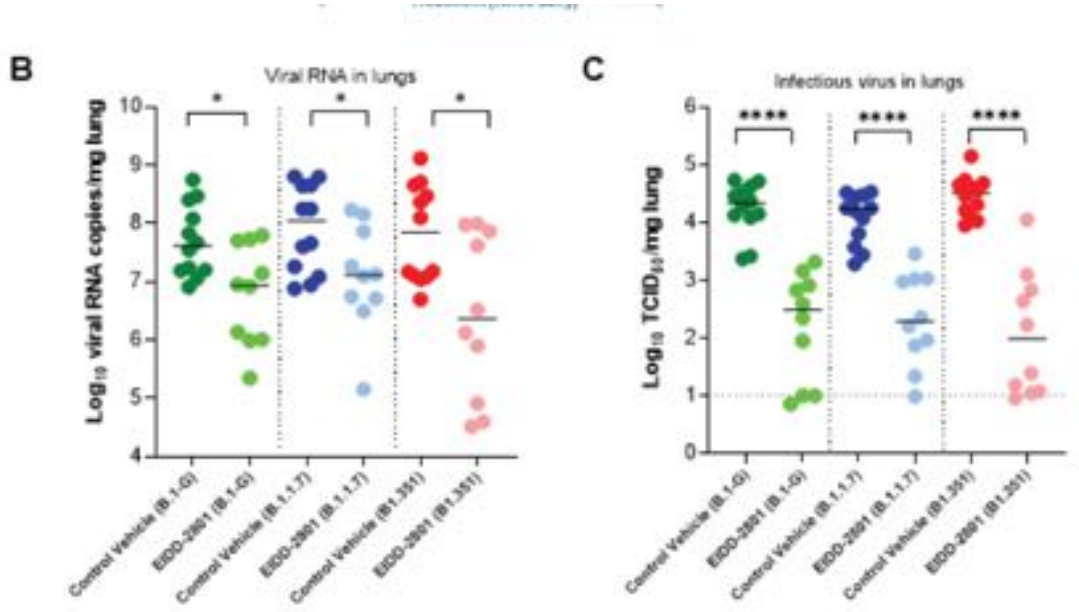
J Infect Dis 2021; 224:749–53

DOI:10.1093/infdis/jiab361

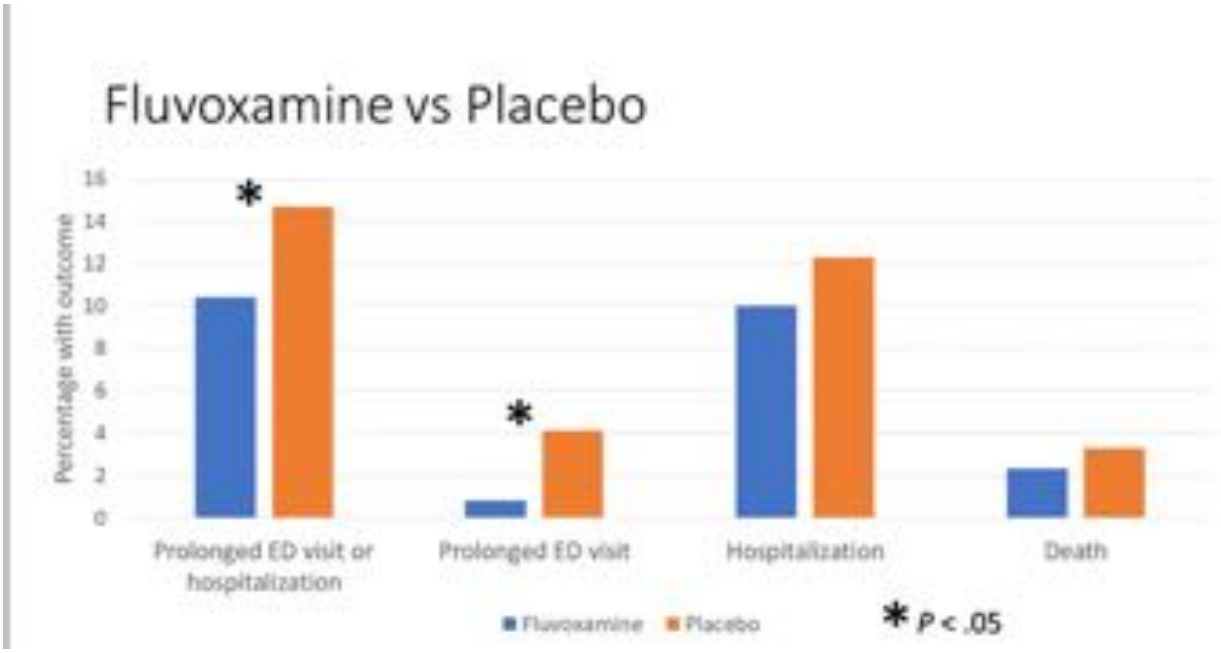
6 to 8-week-old female SG hamsters were treated orally with molnupiravir 200 mg/kg, twice a day or placebo vehicle (i.e., the control group, twice a day) for 4 consecutive days starting 1 hour before intranasal infection with 50 µL containing 1 × 105 50% tissue culture infectious dose (tCiD50) of SArS-CoV-2 Wuhan strain (BetaCov/Belgium/GHB-03021/2020; epi iSL 109 407976|2020-02-03) or hCoV-19/Belgium/rega- 12211513/2020; epi_iSL_791333, 2020-12-21 and hCoV- 19/Belgium/rega-1920/2021; epi_iSL_896474, 2021-01-11, termed in brief B.1-G, B.1.1.7, and B.1.351, respectively.

At day 4 post infection, the animals were euthanized for sampling of the lungs and further analysis by intraperitoneal injection of 500 µL Dolethal (200 mg/mL sodium pentobarbital). Lungs were collected for quantification of subgenomic viral RNA using N2 primers and probes targeting the viral nucleocapsid, infectious virus titers, and lung histopathology.

Molnupiravir treatment resulted in a statistically significant reduction in the viral RNA copies per mg of lung tissue with 0.7 (*P* = .020), 0.9 (*P* = .034), and 1.5 (*P* = .016) log10 reduction in the groups that had been infected with B.1-G, B.1.1.7, and B.1.351, respectively. Similarly, treatment significantly reduced infectious virus lung titers regardless of the SARS-CoV-2 variant used for infection. In addition to viral loads, lung pathology was assessed using histopathological examination. Significant improvement of cumulative histopathological lung scores was also observed in all the molnupiravir-treated groups.

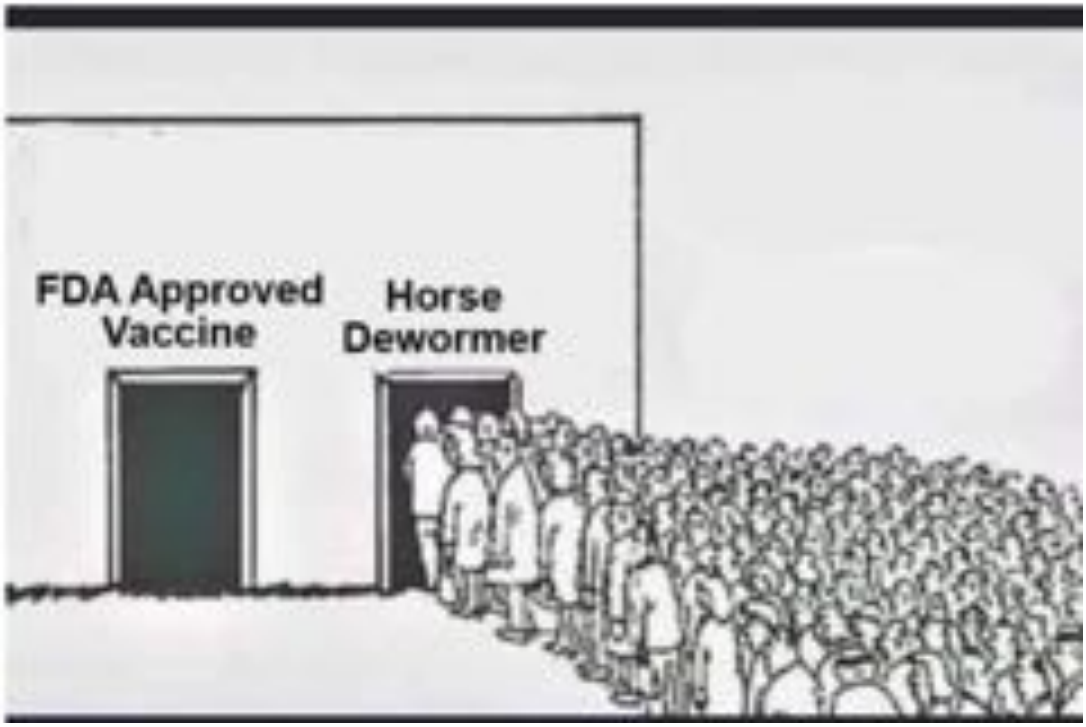


Comment: Acting at the level of viral RNA replication, molnupiravir has been able to exert its antiviral SARS-CoV-2 activity despite the mutations present in the emerging VOCs. This may be the best potential antiviral drug against SARS-CoV-2 to date. In the Briefing on July 20, 2021, I reviewed the ongoing phase 2/3, randomized, placebo-controlled, double-blind, multi-site study in evaluating the efficacy, safety, and pharmacokinetics of orally administered molnupiravir in non-hospitalized participants with a PCR confirmed case of COVID-19 which was presented at ECCMID. Findings from part 1 of the trial demonstrated that the percentage of patients who were hospitalized and/or died was lower in the combined molnupiravir-treated groups versus the placebo arm. Early molnupiravir shows promise as we await results of phase 3 trials. The other drug that shows promise is fluvoxamine. The most cited study was at a horse racing track in California during a mass outbreak of COVID-19 in Nov and Dec 2020. At 14 days, residual symptoms were present in 29 of 48 untreated patients (6 hospitalized, 2 intubated, and 1 died) and 0 of 65 treated patients. (Open Forum Infect Dis 2021 February 1) NIH guidelines state there are insufficient evidence to recommend for or against use of fluvoxamine for treatment of COVID- 19. We need more robust RCTs. In a pre-printed trial called TOGETHER, they had a decent sample size of 1472 outpatients with COVID-19. Half of them were randomized to receive 100 mg of fluvoxamine twice daily for 10 days; the rest got placebo. Below are the results.



Trials for ivermectin have created quite a stir recently. This is the same group (TOGETHER) that recently reported their results for ivermectin. Their data showed no statistical difference in outcomes among individuals randomized to ivermectin vs placebo. To remind everyone, the IDSA guidelines on the treatment and management of patients with COVID-19 also recommend against the use of ivermectin outside of a clinical trial. We must advocate for evidenced-based treatments and not give patients false hopes and potential unnecessary toxicity.

See cartoon shared by Susan Huang.



Janus Kinase Inhibitors and Major COVID-19 Outcomes: Time to Forget the Two Faces of Janus! A Meta-Analysis of Randomized Controlled Trials
Clin Rheum published online August 24, 2021
doi.org/10.1007/s10067-021-05884-4
Janus kinase (JAK) inhibitors constitute a drug class that could ameliorate the inflammatory response and enhance antibody production. The authors aimed to evaluate the efficacy of JAK inhibitors in patients with COVID-19, performing an updated meta-analysis. They searched two major databases for RCTs enrolling adult patients with documented COVID-19 in the in-hospital setting, assigned either to JAK inhibitor treatment plus standard of care or standard of care alone. They set as primary efficacy outcome the endpoint of COVID-19 death on day 28 and as secondary efficacy composite outcome that of mechanical ventilation or initiation of ECMO. They finally pooled data of interest from 4 RCTs in a total of 1338 subjects with documented COVID-19 infection, utilizing the following JAK inhibitors: baricitinib, ruxolitinib, tofacitinib, and nezulcitinib.

Treatment with JAK inhibitor compared to control resulted in a significant reduction in the risk for COVID-19 death by 43%, while it also led to a significant decrease in the risk for mechanical ventilation or ECMO initiation by 36%.

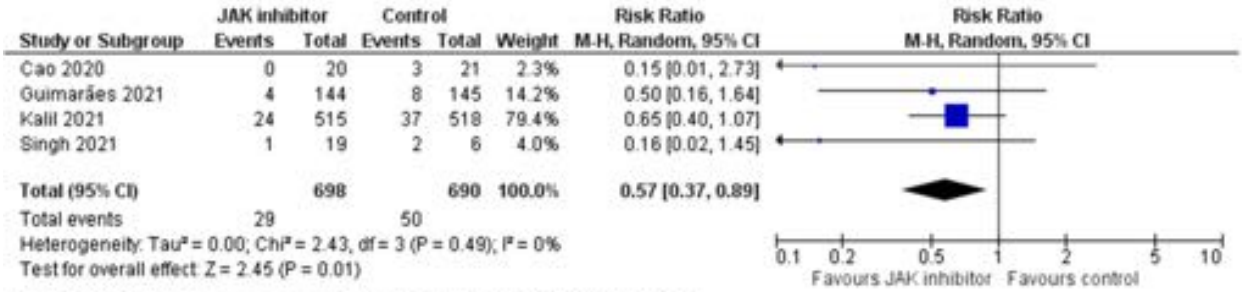
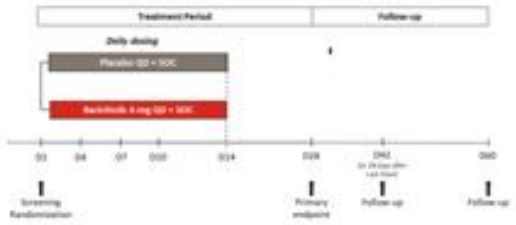


Fig. 1 Effect of JAK inhibitors compared to control on the risk for COVID-19 death

Comment: They demonstrated a clear benefit with JAK inhibitors added to standard of care in patients with COVID-19 in terms of risk reduction concerning major outcomes. The major limitations of this meta-analysis were the small number of the included trials and the lack of adequate reporting to perform additional analyses, according to baseline characteristics of interest (age, gender, comorbidities) and timing of use of JAK inhibitors. See below.

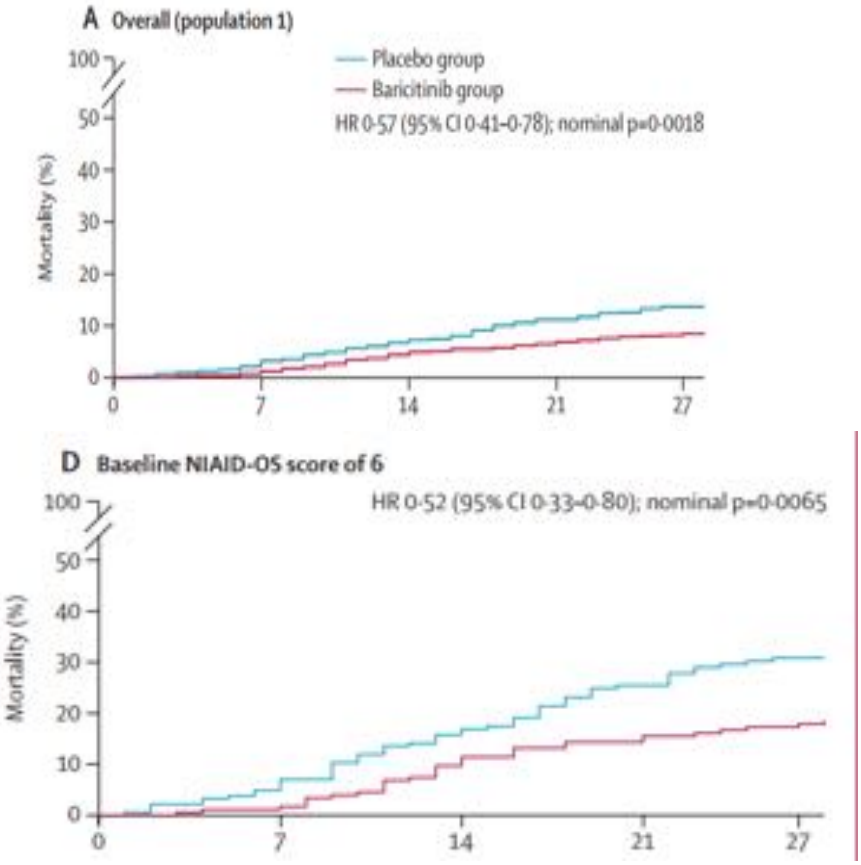
Efficacy and Safety of Baricitinib for the Treatment of Hospitalised Adults with COVID-19 (COV-BARRIER): A Randomised, Double-Blind, Parallel-Group, Placebo Controlled Phase 3 Trial
Lancet Respir Med published online September 1, 2021
doi.org/10.1016/ S2213-2600(21)00331-3
This study is a phase 3, double-blind, randomized, placebo-controlled trial. Participants were enrolled from 101 centers across 12 countries in Asia, Europe, North America, and South America. Hospitalized adults with COVID-19 receiving standard of care were randomly assigned (1:1) to receive once-daily baricitinib (4 mg) within the first two days or matched placebo for up to 14 days. Standard of care included systemic corticosteroids, such as dexamethasone, and antivirals, including remdesivir. Patients on MV were excluded. See slide below provided by Shivani Patel.

- Patient Enrollment
  - Randomized 1:1 to placebo or baricitinib 4 mg for up to 14 days or until discharge from hospital
  - Stratified according to the following baseline factors
    - Disease severity
    - Age
    - Region
    - Use of corticosteroids
- Inclusion Criteria
  - Symptomatic hospitalization for COVID-19
  - ≥1 elevated inflammatory marker (C reactive protein, D-dimer, lactate dehydrogenase, ferritin)
- Exclusion Criteria
  - Mechanical ventilation
  - No oxygen requirements



Outcome: Improvement all-cause mortality

1525 participants were randomly assigned to the baricitinib group (n=764) or the placebo group (n=761). 1204 (79·3%) of 1518 participants with available data were receiving systemic corticosteroids at baseline, of whom 1099 (91·3%) were on dexamethasone; 287 (18·9%) participants were receiving remdesivir. Overall, 27·8% of participants receiving baricitinib and 30·5% receiving placebo progressed to meet the primary endpoint (odds ratio 0·85 [95% CI 0·67 to 1·08], p=0·18), with an absolute risk difference of -2·7 percentage points (95% CI –7·3 to 1·9). The 28-day all-cause mortality was 8% (n=62) for baricitinib and 13% (n=100) for placebo (hazard ratio [HR] 0·57 [95% CI 0·41–0·78]; nominal p=0·0018), a 38·2% relative reduction in mortality. Baricitinib, however, did not reduce the incidence of a composite endpoint of disease progression. OS-6 are patients on high-flow heated oxygen.



Comment: Based on all available evidence, baricitinib is a potentially effective oral treatment option to decrease mortality in hospitalized patients with severe COVID-19. Baricitinib should be given in the first 48 hours. This was reviewed months ago in the Briefing as a pre-publication back in May 2021.