Good morning. Today I start with an editorial on COVID-19 in 2021-comments are always appreciated.

Under COVID-19 News I have a recent update on current rates in USA and a Merck release on ivermectin.

Under Journal, I have tried to cover diverse topics. So today I start with a study on IL-1 and IL-6 inhibitors, followed by a nice review on use of nasal and oral antiseptics against SARS-CoV-2, ending with looking at duration of culturable virus in hospitalized patients with mild to moderate disease.

Have a great Wednesday-some great articles in the queue for Friday.

Ed

VII Editorial: COVID-19 2021

Let me start with the statement that SARS-CoV-2 will likely circulate for years, or even decades, leaving the public to coexist with COVID-19 much as it does with other endemic diseases like flu, RSV, and other coronaviruses. The ease with which SARS-CoV-2 spreads, the emergence of new strains and poor access to vaccines in large parts of the world mean COVID-19 will shift from a pandemic disease to an endemic one, which may leave lasting modifications to personal and societal behavior. Some organizations are planning for a long-term future in which prevention methods such as masking, good ventilation and testing continue in some form.

To be clear, endemic COVID-19 does not necessarily mean continuing all the current coronavirus restrictions. Vaccines will be effective at preventing severe disease and reducing hospitalizations and deaths. Still, there will be large pockets of the human population that will remain beyond the reach of a vaccine for the foreseeable future, giving the virus opportunity to continue to circulate. This will leave most of the developing world without a vaccine until later this year or next year. Currently there is no vaccine authorized for young children, but trials are underway. To complicate matters is the high rate of vaccine refusals.

On the positive side, after early challenges, vaccine delivery is keeping up with supply. But by the end of March, the monthly vaccine supply may reach 100 million doses especially if J&J get EUA from the FDA early in March. My hope is supply will start exceeding demand. The challenge will not be how to prioritize limited supply, but how to reach patients reluctant to get vaccinated. 1 in 4 in US still say they are reluctant to be vaccinated included HCWs! It is essential to emphasize in public health messaging that every adult can benefit. I personally believe people have a moral obligation to be vaccinated not only for their own wellbeing but for our community so we can stop this pandemic. We need an effective public education campaign to reduce fears and uncertainty about the vaccine's safety and benefits. We must reduce gaps in vaccination rates across race, income, and location. The COVID-19 Collaborative is working with the Ad Council and community organizations to customize messaging appropriate for different populations. Recent publications have highlighted that 20-49-year-olds are now the most common spreaders of COVID-19. Therefore, people in their 20s, 30s, and 40s need to get vaccinated when doses are available but may not show up if they are not engaged—especially as prevalence declines, they may lose a sense of urgency.

We clearly need to develop new and more effective treatments. Remdesivir is not a great drug and the only drug that has been shown to decrease mortality is dexamethasone. Combination monoclonals have been shown to decrease progression given early in high-risk individuals in the outpatient setting.

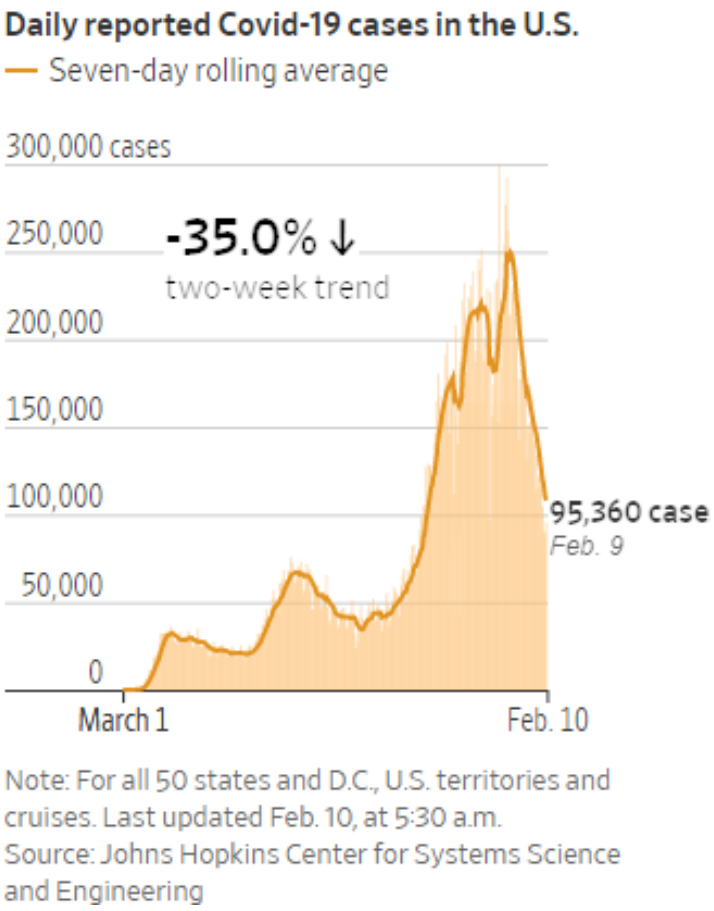
Convalescent plasma has been downgraded as an option. As such, it is not only important to develop better treatment for acute COVID-19, but also important to develop therapeutics for the persistent debilitating symptoms that many patients struggle with months after getting sick, like memory fog, and heart problems.

In the long term, we need a comprehensive overhaul of the nation's disease surveillance system, a massive upgrade of its data infrastructure and a reimagining of public health authority. We have underinvested in public health and emergency preparedness for decades. I hope we remember the lessons this pandemic has taught us.

Unfortunately, elimination of this virus is not likely, but we can get to a point where we are in control of the virus, not the virus in control of us!

COVID-19 News

Pandemic Update
Newly reported cases have dropped 56% over the past month, based on a seven-day average, marking a significantly steeper fall than the U.S. saw after the spring and summer surges. Hospitalizations have declined 38% since Jan 6. The seven-day average of Covid-19 tests returning positive fell over the past week to 6.93%, the lowest since Oct. 31.



Note: For all 50 states and D.C., U.S. territories and cruises. Last updated Feb. 10, at 5:30 a.m.
Source: Johns Hopkins Center for Systems Science and Engineering

Comment: This is encouraging news, but we cannot relax our NPIs. Vaccination rates are increasing, but emergence of variants still makes the future uncertain, but I am cautiously optimistic 2021 will be better.

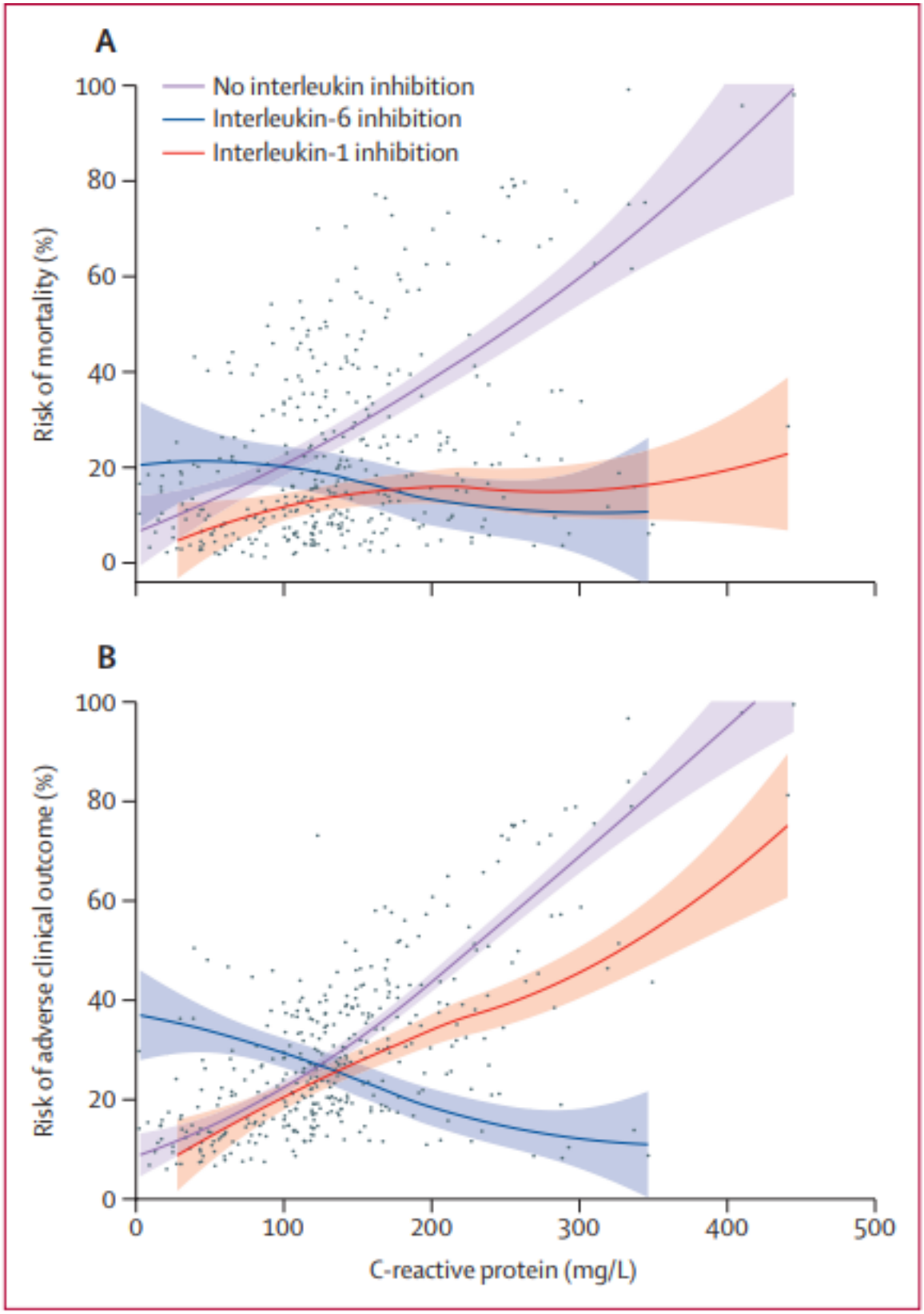
Merck Warns Against Using Ivermectin to Treat COVID-19
February 4, 2021
Merck & Co Inc said its analysis of available data does not support the safety and efficacy of its anti-parasite drug, ivermectin, for the treatment of COVID-19. The company said its analysis of existing and emerging studies of ivermectin to treat COVID-19 found no scientific basis for a potential therapeutic effect against the respiratory disease caused by the novel coronavirus.

Comment: This will probably dampen enthusiasm for the use of ivermectin. A recent study suggested it may decrease progression of disease in high-risk patients in the outpatient setting.

Journal Reviews

Interleukin-1 and Interleukin-6 Inhibition Compared with Standard Management in Patients with COVID-19 and Hyperinflammation: A Cohort Study
Lancet Rheum published online February 3, 2021
doi.org/10.1016/ S2665-9913(21)00011-4
This cohort study included patients admitted to the hospital with COVID-19, respiratory insufficiency, defined as a ratio of the partial pressure of oxygen to the fraction of inspired oxygen of 300 mm Hg or less, and hyperinflammation, defined as serum C-reactive protein concentration of 100 mg/L or more or ferritin concentration of 900 ng/mL or more. The primary endpoint was survival, and the secondary endpoint was a composite of death or mechanical ventilation (adverse clinical outcome). Multivariable Cox regression analysis was used to compare clinical outcomes of patients receiving IL-1 inhibition (anakinra) or IL-6 inhibition (tocilizumab or sarilumab) with those of patients who did not receive interleukin inhibitors, after accounting for baseline differences. All patients received standard care.

Of 392 patients included between Feb 25 and May 20, 2020, 275 did not receive interleukin inhibitors, 62 received the IL-1 inhibitor anakinra, and 55 received an IL-6 inhibitor (29 received tocilizumab and 26 received sarilumab). In the multivariable analysis, compared with patients who did not receive interleukin inhibitors, patients treated with IL-1 inhibition had a significantly reduced mortality risk (hazard ratio [HR] 0·450, 95% CI 0·204–0·990, p=0·047), but those treated with IL-6 inhibition did not (0·900, 0·412–1·966; p=0·79). In the multivariable analysis, there was no difference in adverse clinical outcome risk in patients treated with IL-1 inhibition (HR 0·866, 95% CI 0·482–1·553; p=0·63) or IL-6 inhibition (0·882, 0·452–1·722; p=0·71) relative to patients who did not receive interleukin inhibitors. However, for increasing C-reactive protein concentrations, patients treated with IL-6 inhibition had a significantly reduced risk of mortality (HR 0·990, 95% CI 0·981–0·999; p=0·031) and adverse clinical outcome (0·987, 0·979–0·995; p=0·0021) compared with patients who did not receive interleukin inhibitors.


A
No interleukin inhibition
Interleukin-6 inhibition
Interleukin-1 inhibition
Risk of mortality (%)
100
80
60
40
20
0
B
Risk of adverse clinical outcome (%)
100
80
60
40
20
0
0
100
200
300
400
500
C-reactive protein (mg/L)

Comment: IL-1 inhibition, but not IL-6 inhibition, was associated with a significant reduction of mortality in patients admitted to the hospital with COVID-19, respiratory insufficiency, and hyperinflammation. However, IL-6 inhibition was effective in a subgroup of patients with markedly high C-reactive protein concentrations. Limitations of this study are inherent to observational investigations, so use caution in interpretation of findings. Groups at baseline introduce the possibility of confounding (i.e., the risk that observed effects could be affected by clinical or demographic features besides investigational treatments), which cannot be completely excluded even after careful adjusting by multivariable regression analysis. They cannot exclude that a larger sample size or inclusion of patients at different disease stages might also have yielded a significant result for the primary outcome.

Review of the Use of Nasal and Oral Antiseptics During a Global Pandemic
Fut Microbiol published online January 19, 2021
Doi: 10.2217/fmb-2020-0286
This review explores common and/or promising antiseptic techniques and some of the ongoing clinical trials that are investigating the use of these antiseptic compounds as potential treatments and preventative measures. Currently, there are over 20 trials testing the efficacy and tolerability of PVP-I, Listerine, iota-carrageenen, hypertonic saline, chlorhexidine, baby shampoo and hydrogen peroxide.

- Povidone-iodine (betadine), ethanol and essential oils (Listerine) and a combination of xylitol and iota-carrageenan (purified from red marine algae) were shown to reduce viral load of SARS-CoV-2 *in vitro* by 3–4 log10 in 30 s.
- Chlorhexidine, a widely used oral rinse, does not act as quickly in reducing viral load in 30 s as povidone-iodineI, but binds to cell proteins, extending protection.
  • Hydrogen peroxide is not as effective as other oral rinses *in vitro* and cell toxicity is a concern.
  • Hypertonic saline is not directly virucidal, but halts replication by increasing hypochlorous acid inside the cell.

Table 2. Selected ongoing clinical trials of antiviral oral and nasal rinses against severe acute respiratory syndrome coronavirus 2.

Clinical trial #	Compounds tested	Use	EST (n)	Country	Start date	Ref.
NCT04371965	PVP-I	Gargle or nasal spray	24	France	Q3 20	[49]
NCT04341688	PVP-I, HP, neem extract and HS	Nasal lavage and gargle	50	Pakistan	Q3 20	[20]
NCT04347954	PVP-I or isotonic saline	Nasal spray	45	USA	Q3 20	[50]
NCT04410159	PVP-I, Listerine or tap water	Gargle	20	Malaysia	Q3 20	[51]
NCT04521322	IC	Nasal spray	400	Argentina	Q3 20	[52]
NCT04364802	PVP-I	Nasal spray and gargle	250	USA	Q2 20	[53]
NCT04352959	Beta-cyclodextrin and citrox	Gargle	206	France	Q2 20	[54]
NCT04449965	PVP-I	Nasal rinse and gargle	81	Canada	Q3 20	[55]
NCT04344236	Saline, PVP-I or CHX	Nasal rinse and gargle	48	USA	Q2 20	[56]
NCT04409873	Distilled water, HP, CPC, chlorine dioxide or Listerine (zero alcohol)	Gargle	150	USA	Q4 20	[57]
NCT04478019	PVP-I + CHG	PVP-I nasal swab + CHX gargle	94	USA	Q3 20	[58]
NCT04549376	PVP-I	Nasal irrigation	200	Bangladesh	Q3 20	[59]
NCT04393792	PVP-I or normal saline	Nasal rinse and gargle	40	UK	Q2 20	[60]
NCT04563689	CHG or CPC	Gargle	24	Colombia	Q2 20	[61]
NCT04337918	NORS	Nasal spray and gargle	200	Canada	Q2 20	[62]
NCT04537962	CHX, HP, CPC, zinc lactate	Mouthwash	70	Brazil	Q2 20	[63]
NCT04443868	NORS or saline	Nasal spray and nasal irrigation	300	Canada	Q3 20	[64]

CHG: Chlorhexidine gluconate; CHX: Chlorhexidine; CPC: Cetyl peridinium chloride; HP: Hydrogen peroxide; HS: Hypertonic saline; IC: Iota-carrageenan; NORS: Nitric oxide releasing solution; PVP-I: Povidone-iodine.

Comment: Several commonly used nasal antiseptics and gargles have shown activity against SARS-CoV-2 *in vitro* and clinical trials are currently underway to determine if these interventions actually impact disease course and transmission. The rapid expansion of the COVID-19 pandemic has increased interest in finding safe and effective options for protecting healthcare workers and those at greatest risk of exposure especially are variants emerge. This article is a nice review on the topic.

Duration of Culturable SARS-CoV-2 in Hospitalized Patients with Covid-19

N Engl J Med published online January 27, 2021
DOI: 10.1056/NEJMc2027040

They cultured SARS-CoV-2 in serial respiratory samples obtained from hospitalized patients with Covid-19 to assess the duration of shedding of viable virus. The data reported in this paper represent all the patients with Covid-19, as confirmed by positive PCR testing, who were hospitalized between February and June 2020. Patients were isolated until two consecutive negative or inconclusive results on real-time PCR were documented, at least 24 hours apart. They endeavored to obtain samples at approximately 2-day intervals, but this was not always possible. Viral RNA was quantitated with the use of the cycle-threshold value for the *N* gene of SARS-CoV-2. 4 Viral cultures were conducted by means of a plaque assay until at least two consecutive cultures showed no growth. They compared the time from the onset of illness to viral clearance in culture with the time to clearance in real-time RT-PCR tests. The median age of the patients was 62 years. A total of 71% of the patients had pneumonia, and 38% were receiving supplemental oxygen therapy.

SARS-CoV-2 was cultured in 29 of the 89 samples (33%) (see below). The median time from symptom onset to viral clearance in culture was 7 days (95% confidence interval [CI], 5 to 10), and the median time from symptom onset to viral clearance on real-time RT-PCR was 34 days. Viral culture was positive only in samples with a cycle-threshold value of 28.4 or less. The incidence of culture positivity decreased with an increasing time from symptom onset and with an increasing cycle threshold value.

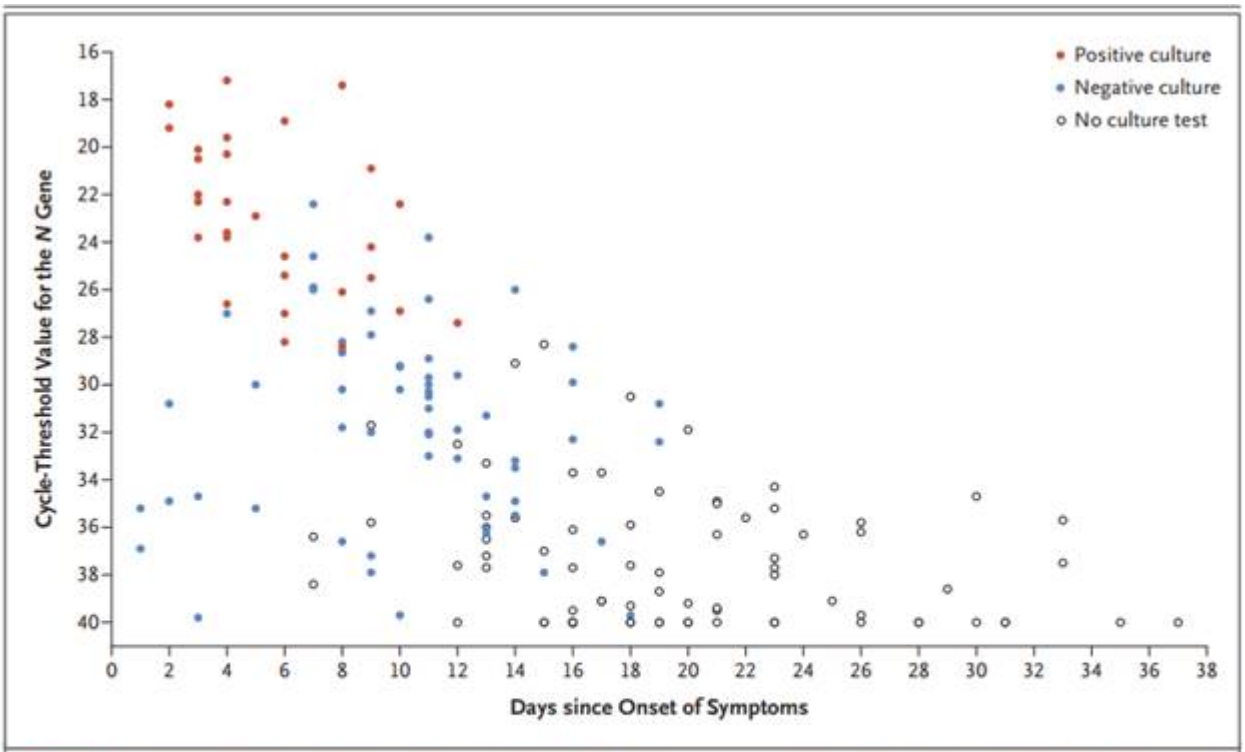


Figure 1. Timing of Presence or Absence of Viable SARS-CoV-2 on Viral Culture and Cycle-Threshold Values for 165 Serial Samples Obtained from 21 Consecutive Patients Hospitalized with Covid-19.

Viral loads were determined with the cycle-threshold value for the *N* gene of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[4] Sampling intervals ranged from 1 to 5 days (median, 2). Each circle represents a sample obtained on the specified day. Viral culture was positive only in samples with a cycle-threshold value of 28.4 or less and in those that were obtained as long as 12 days after symptom onset. Covid-19 denotes coronavirus disease 2019.

Comment: This study confirms other publications. However, small sample size, inconsistent timing of samples and relatively mild illness of the enrolled patients are weaknesses of this publication.