

Today I am taking a break from the traditional literature review to give you my update on the state of the pandemic. Due to the length of this update, this Briefing will be provided in the attachment.

I have divided this report into the following sections:

- Introduction
- NPI
- Therapeutics
- Schools
- Thanksgiving
- Returning college student
- Final Comments

I do not expect everyone will agree with all of my observations since there is still a lot we do not fully understand, so some of what I have written is opinion.

I hope you find this “Special Edition” of value as we approach the holidays and as we enter the next phase of the pandemic. Feel free to share this report with your colleagues if you feel this will help others. As always, I welcome your comments.

Have a good Monday

Ed

COVID-19 Daily Briefing

Special Edition

The State of the Pandemic November 16, 2020

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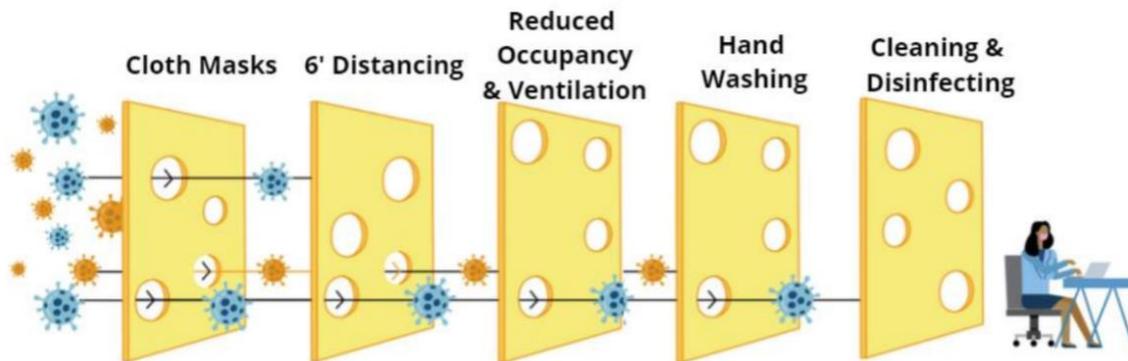
Introduction

New infections surpassed 177,224 on Friday, setting a daily record that eclipsed the highest daily case counts of previous peaks in the spring and summer. The number of new infections was lower Saturday at 166,555. At the same time hospitalizations have increased and the death toll in the US is approaching 250,000. (case fatality rates, however, are down-see section on therapeutics) Cases are more geographically widespread, reaching more remote regions than the spring and summer. More young people are among those newly infected, and they are less likely to need hospital care than the elderly. But as infections rise among the young, so does transmission to high-risk older co-workers and family.

COVID fatigue is real and may be contributing to transmission as people frustrated with months of restrictions have started to relax. It is estimated that ~70% of new cases are linked to family gatherings, weddings, indoor restaurants and bars, and crowded gyms.(not all gyms are the same-some have been able to open safely by limiting numbers, social distancing, requiring masks, improving ventilation, and enhanced disinfection). Now that SARS-CoV-2 is widespread, people are becoming infected not just at large gatherings, but when we let our guard down and not wearing a mask in smaller settings often among even their own extended family and “trusted” friends.

Halloween gatherings have contributed to current spread and Thanksgiving may be no different and probably worse. So where do we go from here as Thanksgiving approaches. Below I will try and summarize NPI, therapeutics, and what we can do about Thanksgiving especially when college students come back home. Some of my comments are opinions but I try to base this on current level of science understanding we still have knowledge gaps.

NPI (nonpharmaceutical interventions)



PolicyLab adapted this graphic from the Cleveland Clinic's "Swiss Cheese Approach to COVID Mitigation"

What about lockdowns? It is not clear that shutting down would stop or even control this spread. In fact, there is a real chance such measures could have the opposite effect, prompting more congregating indoors in household or private settings. Based on experience this spring and summer lockdowns did not "crush" the virus. They merely delay its spread until the lockdowns ended or we let our guard down. Targeted restrictions on people, businesses, and schools may be needed in an emergency in some locations to prevent hospitals from being overrun like El Paso. The costs of lockdowns are not insignificant. The U.S. is still recovering from the spring lock down when the jobless rate surged in two months to almost 15%, the highest since the Great Depression. Thousands of businesses closed, and many will never reopen. The human cost is even worse. A quarter of 18- to 24-year-olds have reported suicidal thoughts, alcohol use, and increased substance abuse. Half of them reported symptoms consistent with a depressive disorder, according to a CDC survey in June. Some 13% of Americans said they started or increased substance use to cope with the pandemic. Domestic abuse is up, people with chronic diseases have delayed care resulting in increased morbidity and mortality, and immunizations rates are down. An example, measles killed over 200,000 people worldwide, the highest in almost 25 years. In US we had > 1000 cases last year and 11 states reported immunization rates <90%. The pandemic will only make this worse. Money alone will not eliminate this harm.

So, what works? The best response to these spikes is to highlight and enforce what some have called the 3Ws: wash your hands, watch your distance, and wear your mask. Above is a "Swiss Cheese" approach to reduce SARS-CoV-2 transmission. The CDC just released a scientific brief (November 11, 2020) on the use of masks to control the spread of SARS-CoV-2. The brief reports that cloth masks not only block most large droplets (i.e., 20-30 microns and larger) but they can also block the exhalation of fine droplets and particles (also often referred to as aerosols) smaller than 10 microns ; which increase in number with the volume of speech and specific types of phonation like singing. Multi-layer cloth masks can both block up to 50-70% of

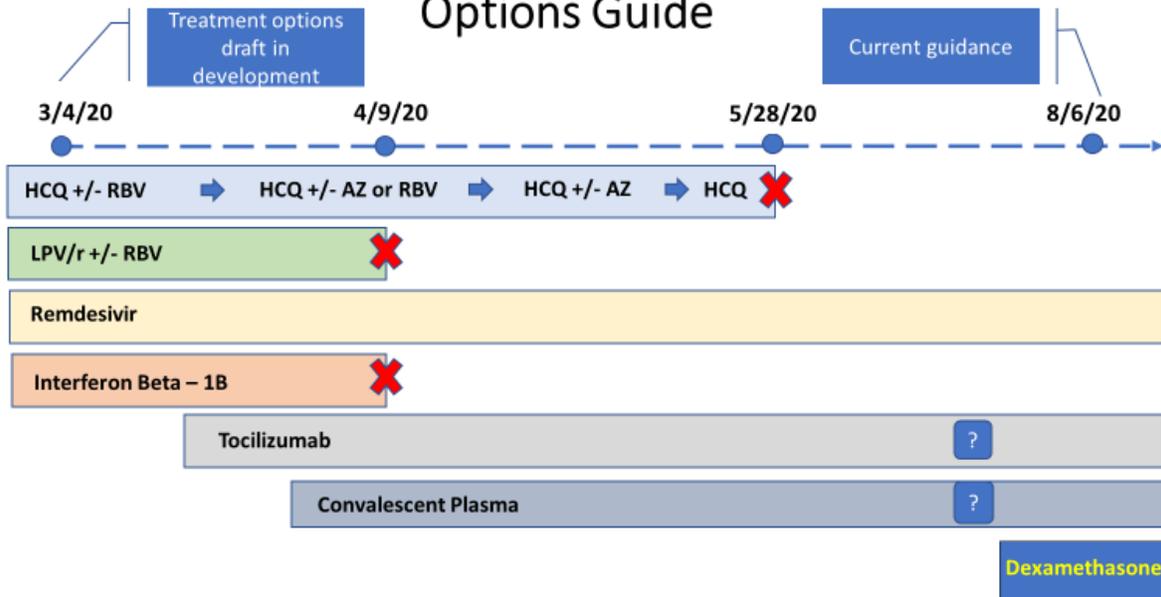
these fine droplets and particles and limit the spread of those that are not captured. Recent studies also demonstrate that cloth mask can also reduce wearers' exposure to infectious droplets through filtration, including filtration of fine droplets and particles less than 10 microns. CDC concludes that the relationship between source control and personal protection is likely complementary and possibly synergistic, so that individual benefit increases with increasing community mask use. Therefore, the adoption of a universal masking policy can help avert future lockdowns, especially if combined with other non-pharmaceutical interventions such as social distancing, hand hygiene, and adequate ventilation. I would further recommend wearing masks, regardless of distance, which is much easier to interpret and enforce. I view masks like getting a car and automatically putting on your seat belt. When we go out, we should automatically wear our masks (CORRECTLY). I also agree with new limits for the number of people who may gather in groups — up to 10-12 people indoors and 20-25 outdoors. A word of caution about outdoor events. Transmission may be lower outdoors, but close contact for long periods of time without masks can still result in transmission. Therefore, even if outside if you cannot socially distance you should wear a mask. If indoors in addition to reduce occupancy, we can improve ventilation by open windows and allowing in more outside air. Carry hand sanitizers wherever you go and disinfect high touch surfaces whenever possible.

Therapeutics

We have learned a lot in a short time about how to manage COVID-19 patients. We are much better prepared to handle this wave than in March or April. Mortalities rates and length of stay have decreased due to more medical knowledge and better therapeutics. The rest of this section will review the key therapeutics currently in use based on the current level of science.

Below outline the evolving changes in therapy.

History and Review of Treatment Options Guide



hydroxychloroquine (HCQ), ribavirin (RBV), azithromycin (AZ), lopinavir (LPV), ritonavir (r)

Slide courtesy Ardath Mitchell=modified

The graph below outlines stages of disease and potential treatment.

	Asymptomatic or Presymptomatic	Mild Illness	Moderate Illness	Severe Illness	Critical Illness
Features	Positive SARS-CoV-2 test; no symptoms	Mild symptoms (e.g., fever, cough, or change in taste or smell); no dyspnea	Clinical or radiographic evidence of lower respiratory tract disease; oxygen saturation $\geq 94\%$	Oxygen saturation $< 94\%$; respiratory rate ≥ 30 breaths/min; lung infiltrates $> 50\%$	Respiratory failure, shock, and multiorgan dysfunction or failure
Testing	Screening testing; if patient has known exposure, diagnostic testing	Diagnostic testing	Diagnostic testing	Diagnostic testing	Diagnostic testing
Isolation	Yes	Yes	Yes	Yes	Yes
Proposed Disease Pathogenesis	Viral replication				
Potential Treatment	Antiviral therapy		Antibody therapy		Antiinflammatory therapy
Management Considerations	Monitoring for symptoms	Clinical monitoring and supportive care	Clinical monitoring; if patient is hospitalized and at high risk for deterioration, possibly remdesivir	Hospitalization, oxygen therapy, and specific therapy (remdesivir, dexamethasone)	Critical care and specific therapy (dexamethasone, possibly remdesivir)

N Engl J Med 2020; 383:1757-66

1. Monoclonals. For mild illness in high risk populations the use of monoclonals hopefully will reduce progression, hospitalization, and deaths. Therefore, people in the high-risk groups with symptoms should be tested in a timely manner before they deteriorate.

Public health official need to message that COVID-19 is now treatable in the early stages of disease. Early data is promising. Logistics about where to administer safely will need to be worked out since most of these patients will be treated in the outpatient setting.

2. Remdesivir is now approved by the FDA for the treatment of COVID-19 in hospitalized adult and pediatric patients (aged ≥ 12 years and weighing ≥ 40 kg). Below summarized the ACTT-1 trial
 - a. The benefit of remdesivir for reducing time to recovery was clearest in the subgroup of hospitalized patients who required supplemental oxygenation at study enrollment (ordinal scale 5, n = 435; recovery rate ratio 1.45; 95% CI, 1.18–1.79). In a post hoc analysis of deaths by Day 15, remdesivir appeared to confer a survival benefit in this subgroup (HR for death 0.28; 95% CI, 0.12–0.66).
 - b. In patients who required high-flow oxygen or noninvasive ventilation at study enrollment (ordinal scale 6, n = 193), there was no observed difference in time to recovery between the remdesivir and placebo groups (recovery rate ratio 1.09, 95% CI, 0.76–1.57). In a post hoc analysis of deaths by Day 15, there was no evidence that remdesivir had an impact on the mortality rate in this subgroup (HR 0.82; 95% CI, 0.40–1.69).
 - c. Among the patients who were on mechanical ventilation or ECMO at study enrollment (ordinal scale 7, n = 285), there was no observed difference in time to recovery between the remdesivir and placebo groups (recovery rate ratio 0.98; 95% CI, 0.70–1.36). In a post hoc analysis of deaths by Day 15, there was no evidence that remdesivir had an impact on the mortality rate in this subgroup (HR 0.76; 95% CI, 0.39–1.50).
 - d. **Recommendation:** Remdesivir should be prescribed early when patients require supplemental oxygen before patients progress to the inflammatory stage. Patients on vapotherm and mechanical ventilation are unlikely to benefit from administration of remdesivir. Steroids should be considered the mainstay of therapy for patients in the inflammatory stage (see graph above and comments below)
3. Convalescent Plasma
 - a. Currently, there are insufficient data from well-controlled, adequately powered, randomized clinical trials to evaluate the efficacy and safety of convalescent plasma for the treatment of COVID-19.
 - b. However, >70,000 patients in the United States have received COVID-19 convalescent plasma through the Mayo Clinic's Expanded Access Program (EAP), which was designed primarily to provide broad access to investigational convalescent plasma and thus did not include an untreated control arm. The results of their analyses suggest that convalescent plasma with high antibody titers may be more beneficial than low-titer plasma in nonintubated patients, particularly when administered within 72 hours of COVID-19 diagnosis.
 - c. **Recommendation:** Like remdesivir, if considering convalescent plasma should be given early before patients progress to the inflammatory stage. When monoclonals become available they may replace convalescent plasma.
4. Corticosteroids

- a. Patients with severe COVID-19 can develop a systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. It has been proposed that the potent anti-inflammatory effects of corticosteroids might prevent or mitigate these deleterious effects.
 - b. Recommendations on the use of corticosteroids for COVID-19 are largely based on data from the RECOVERY trial, a large, multicenter, randomized, open-label trial performed in the United Kingdom. This trial compared hospitalized patients who received up to 10 days of dexamethasone to those who received the standard of care. Mortality at 28 days was lower among patients who were randomized to receive dexamethasone than among those who received the standard of care.
 - c. This benefit was observed only in patients who were mechanically ventilated or required supplemental oxygen at enrollment. No benefit of dexamethasone was seen in patients who did not require supplemental oxygen at enrollment.
 - d. **Recommendation:** Administer steroids to patients hospitalized with infection due to SARS-CoV-2 who require supplemental oxygen especially patients who require mechanical ventilation.
5. Other immunomodulators. The jury is still out of the use of drugs like tocilizumab, sarilumab, anakinra, acalabrutinib, ibrutinib, zanubrutinib and Janus kinase inhibitors (e.g., baricitinib, ruxolitinib, tofacitinib). Trials are also underway to look at combination therapy.
6. Antithrombotic therapy
- a. Infection with SARS-CoV-2 has been associated with inflammation and a prothrombotic state, with increases in fibrin, fibrin degradation products, fibrinogen, and D-dimers.
 - b. For non-hospitalized patients with COVID-19, anticoagulants and antiplatelet therapy should not be initiated for prevention of venous thromboembolism (VTE) or arterial thrombosis unless there are other indications
 - c. Hospitalized adults with COVID-19 should receive VTE prophylaxis per the standard of care for other hospitalized adults.
 - d. **Recommendation:** For adults who are admitted to a hospital with COVID-19, VTE prophylaxis, unless contraindicated (e.g., a patient has active hemorrhage or severe thrombocytopenia), should be prescribed using the recommendations for patients who have been admitted to a hospital for other indications.
7. There are insufficient data to recommend either for or against the use of vitamin C, vitamin D, or zinc for the treatment of COVID-19 in critically ill patients.

Schools

SARS-CoV-2 transmission in schools remain low. Instead infections appear to be occurring in the community not in the schools. Decision to close schools for in person learning must balance safety versus potential educational and economic damage from schooling children at home. A growing number of health experts have recommended opening more elementary schools because young children appear less prone to transmit the virus than experts had feared, and because younger students have a hard time learning online independently.

Currently, about 37% of students nationwide are attending schools that are entirely remote. Closing schools has costs on children, but there may also be health benefits for people staying at home. When millions of students returned to school with remote learning as their only option this fall, large numbers of them went missing — especially in lower-income neighborhoods. A new wave of school closures would likely renew headaches for working parents, many of whom need to work and lack childcare, and others lack internet connectivity or the resources to help students with online learning. Some have questioned the quality of remote learning. This only makes disparities greater. Should schools be closed when studies show they are not where the transmission is happening? In Europe, despite lockdowns, they have elected to keep schools open.

Thanksgiving

Thanksgiving is just around the corner, now 10 days away. Let us use the next 10 days as a time to regroup and think about our goals and the challenges facing us to keep everyone safe. Holiday plans unfortunately will be limited this year. Creating your “holiday bubble” is crucial. The safest way to celebrate Thanksgiving this year is to celebrate with people in your household and/or close family bubble. If you do plan to spend Thanksgiving with people outside your household/immediate family bubble, take steps to make your celebration safer. The CDC recommends: (1) wear a mask(except when eating); (2) stay at least 6 feet away from others who do not live with you;[I think 10 feet is better when eating] (3) wash your hands; (4) make your celebration safer: bring your own food, drinks, utensils, and plates if outside the immediate family bubble (5) if possible have meals outside if not possible make sure to open the windows (6) limit the number of guests(10 inside has been the recommendation and 20-25 outside) Remember, now that SARS-CoV-2 is widespread, people are becoming infected not just at large gatherings, but when we let our guard down and not wearing a mask in smaller settings often among even their own extended family and “trusted” friends.

Returning college students

If you have not thought about guidance for return of college students, I have put together what I think are a few commonsense recommendations

1. Some students may already have had COVID-19 during this semester. If so testing and quarantining may not be necessary, however, they should still adhere to safe practices outside the “family bubble” since we know, although rare, they can be reinfected after 3-4 months.
2. For those not infected, students should quarantine themselves before traveling for at least a week or more if possible and receive one or more negative coronavirus test results within three days of departure from school to home.

3. Students should stop eating together indoors and/or in proximity. This has been **the number one source of exposures on many college campuses**. Always sit at least 6 feet apart when not wearing masks and farther when eating a meal. [I recommend 10 feet] Consider eating outside whenever possible. Avoid small rooms and limit the amount of time around others not wearing masks. Insist on compliance. Do not be afraid to speak up.
4. Upon arrival home, you should initially quarantine until you have been retested ideally in the first week after arrival.
5. Those who do not test should quarantine for 14 days before and after traveling.

Final Comments

NPIs can reduce the transmission of SARS-CoV-2. If we execute these strategies consistently well, we can allow schools to remain open and our economy to continue functioning. Further, these measures permit the careful daytime socialization in schools and communities that can help deter the riskier gatherings that might otherwise ensue and reduce the non-COVID medical consequences outlined above. These strategies help balance the public health benefits of keeping the population safe — and in school — with the need to maintain a strong economy to support all the residents in the US. It is up to all of us to be good citizens to keep our homes safe, our gatherings limited, and to ensure that those entering your home who aren't household members remain masked and distanced at all times, especially through the holiday season.

With better therapeutics including monoclonals we can improve outcomes in patients infected with SARS-CoV-2. Vaccines should be available at the end of this year for high risk people and hopefully by the end of the first quarter 2021 for the general population. There is light at the end of the tunnel (seems like a long tunnel) if we can just do the right things for the next 3-4 months. We cannot afford to let our guard down.

