Dear colleagues and friends

Today I am devoting the first half of the Briefing to outline what I believe is the most current science around the delta, vaccines, and masks. I have done my best to be objective devoid of politics and fear mongering. I have shared an earlier version with some of you yesterday and I have updated based on new information from CDC and Israel. I hope you find this perspective valuable understanding that the science continues to evolve.

In addition to this update, I am also reviewing 4 articles. The first article is a meta-analysis on the use of IL-6 antagonists. The next two articles looks at high flow nasal oxygen for management of respiratory failure. The last article is another reminder of long-term symptoms 1 year after Covid-19 infection.

I hope everyone has a good weekend-stay vigilant, but stay positive. Despite the challenges of delta, we are in a much better place than 1 year ago! Your feedback is always welcomed so I can publish information that is useful and relevant to your work.

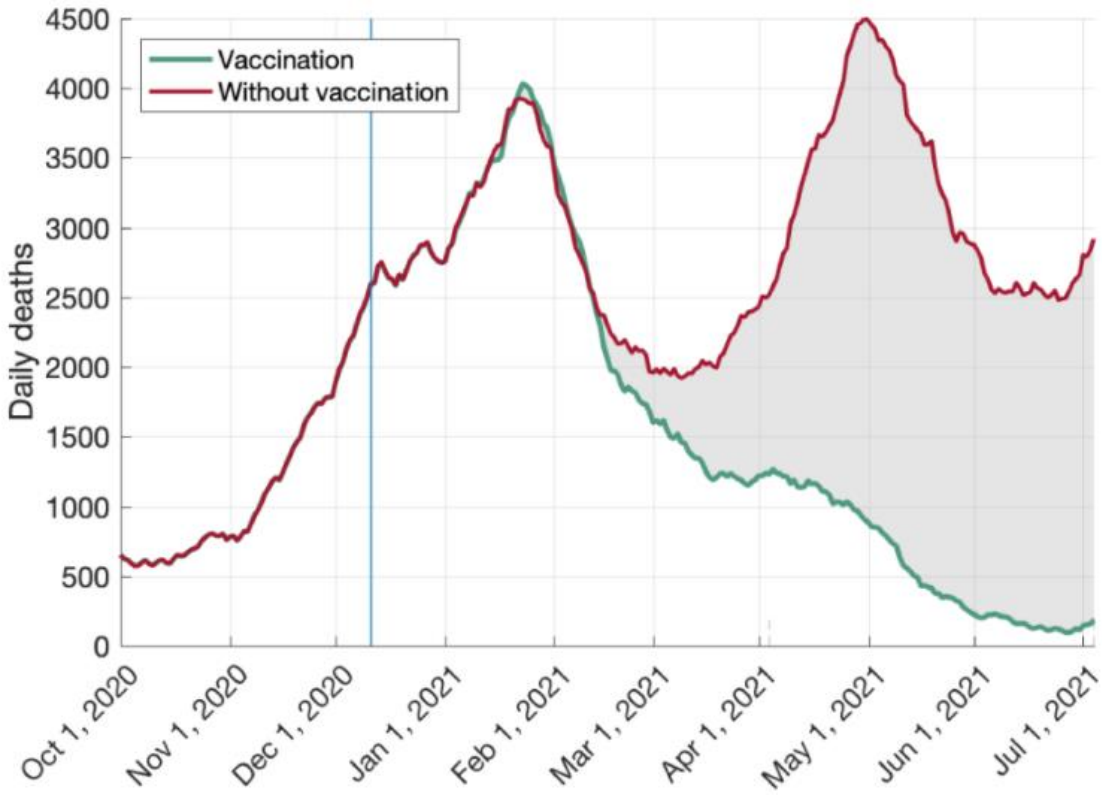
Ed

VII Comments: Delta Update, Vaccinations, and Masking

By now you have probably heard the "headline": Pfizer vaccine less effective against the Delta variant. Let us take a deep breath and take a dive into the data. Results from Israel suggest Pfizer' vaccine is less effective at protecting against infections caused by the Delta variant of Covid-19 but here is the key, it retains its potency to prevent severe illness if you have been fully immunized. To date the Delta variant does not appear to be more deadly, but is more transmissible. The vaccine protected 64% of vaccinated people from infection during an outbreak of the Delta variant, down from 94% before, according to Israel's Health Ministry. It was 94% effective at preventing severe illness in the same period, compared with 97% before, the ministry said. Numbers show that 2.5% of all people confirmed with COVID-19 became seriously ill during previous waves (20-30 people per 1,000 cases). In this wave, no more than 0.5% (3-5 per 1,000) have fallen seriously ill. The network is also reporting that 90% of current infections in Israel are of the Delta variant. The variant has also taken hold in other countries with higher vaccination rates like the UK and the U.S., spreading primarily among unvaccinated populations. Expectations have been high because the mRNA vaccines are in fact incredibly effective. People may have unrealistic expectations regarding breakthrough infections. These vaccines are not 100% effective (no vaccine is 100%-MMR is 95%) It seems that people are almost expecting sterilizing immunity from these vaccines. In addition, the higher the number of vaccinated people, the more breakthrough cases. Interpretation is also important. In Israel it has been reported 55% of the newly infected cases had been vaccinated. However, this is quite different than half of vaccinated people were infected. So, if almost 6 million people in Israel are fully vaccinated and 55% of them experienced breakthrough infections, the number would be much higher – more than 3 million! Remember the positive news is these vaccines are still 94% effective against severe disease or mortality.

In a recent study it is projected, that in the US without a vaccination program, by the end of June 2021 there would have been approximately 279,000 additional deaths and up to 1.25 million additional hospitalizations. [Deaths and Hospitalizations Averted by Rapid U.S. Vaccination Rollout (Commonwealth Fund, July 2021). https://doi.org/10.26099/wm2j-mz32] Preliminary data collected from a set of US states over the past 6 months showed that 99% of people who died from Covid-19 were unvaccinated. See below

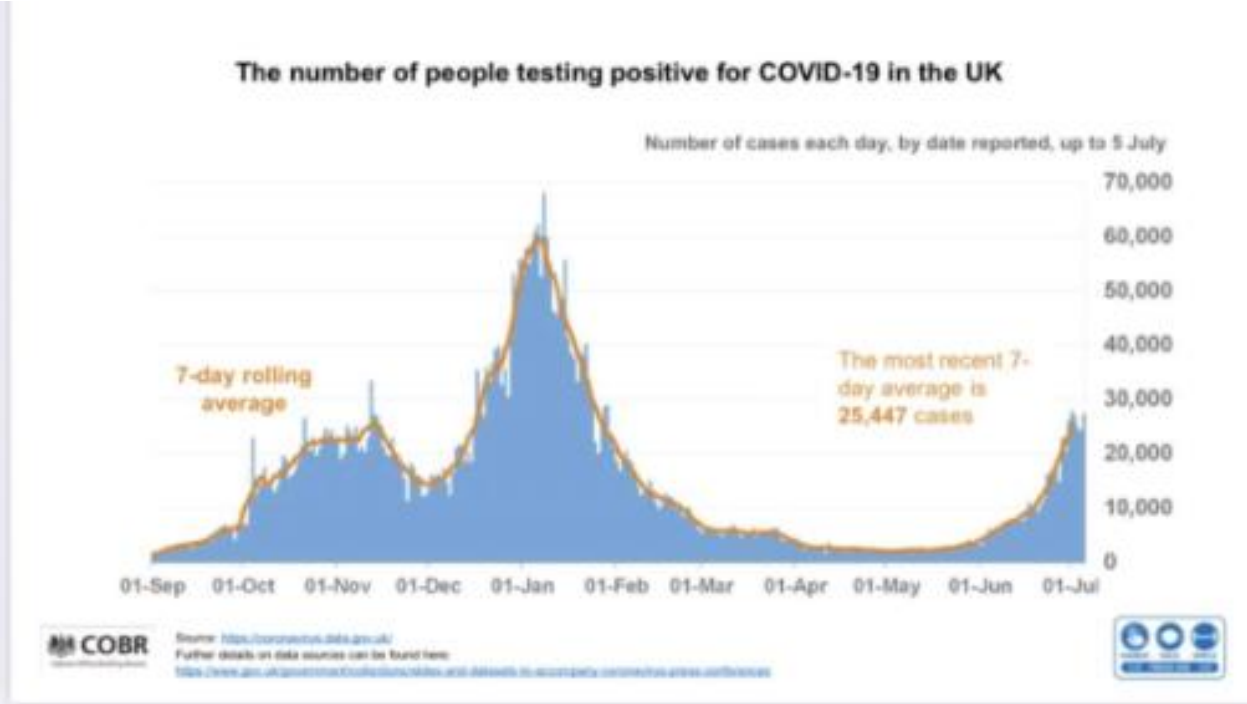
Estimated U.S. seven-day rolling average of daily deaths with and without vaccination

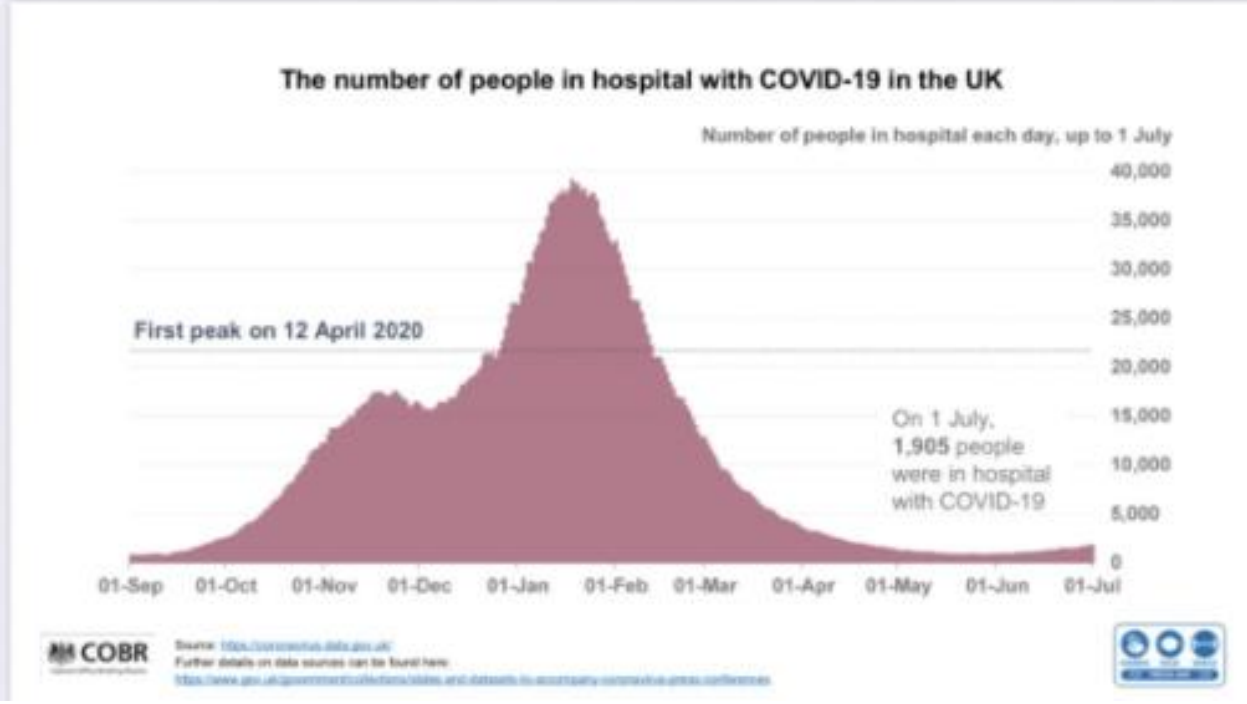


Source: Alison Galvani, Seyed M. Moghadas, and Eric C. Schneider, *Deaths and Hospitalizations Averted by Rapid U.S. Vaccination Rollout* (Commonwealth Fund, July 2021). https://doi.org/10.26099/wm2j-mz32

In recent weeks Delta is has become the most common variant in the US. [51.7%] Infections from the Delta strain contributed to a 10% rise in daily Covid-19 cases to around 12,600 late last month, according to the CDC late last week. That is still a 95% drop from peak levels in the U.S. in January, but hospital admissions are increasing in over 25 states. In fact, yesterday the CDC reported the 7-day average of new daily cases jumped 11%, and hospitalizations increased 7%. However, where vaccination rates are high, new cases and hospitalizations are declining, but where vaccinations rates are low, new cases and hospitalizations are up. Vaccines

available in the U.S. protect against the Delta variant and cases of breakthrough infection in the fully vaccinated appear to rarely result in severe illness as has been reported in Israel. Delta variants poses the greatest threat to those who are unvaccinated. Worldwide variants are currently winning the race against vaccines because of inequitable vaccine production and distribution. Data from the UK, a highly vaccinated country, shows the uncoupling of cases from hospitalizations/deaths. The case counts are no longer a reliable indicator of severe disease and hospitalizations in a country with high vaccination rates. see below





Next we have heard conflicting guidance about wearing a mask after you're fully vaccinated against COVID-19. The WHO recently urged vaccinated people to wear one indoors. Los Angeles Country has advised the same. However, the CDC stood by its recommendation and continues to advise that people fully vaccinated do not need to wear masks in most situations. Dr. Fauci initially agreed. However, Sunday, he added an addendum to his thinking; or, as critics may say, he changed his mind. As a vaccinated person, he would wear his mask in certain situations in areas with low vaccination rates. To be fair to the WHO, their guidance is for the whole world where vaccination rates may be low and in areas where the Delta variant is dominant. Remember mask mandates are intended to primarily protect the unvaccinated. People who are fully vaccinated are well protected and breakthrough infections are still uncommon. When infection does occur, they are generally mild and severe disease is rare. Remember if you are fully vaccinated you are 94% less likely to be hospitalized even with the Delta variant. I think it is reasonable to move to a more select mask policy (vs universal) suggesting persons wear a mask indoors if exposed, at greater risk even if vaccinated [e.g., immune-compromised], high local level of new infections, or have symptoms. We should continue to monitor local infection rates, variants, vaccination rates, and adjust recommendations based on conditions on the ground. One size may not fit all. Bottom line being fully vaccinated remains the best protection for you and your community.

Lastly, it is time for the FDA to fully approve the mRNA vaccines. So far more than 180 million doses of the Pfizer vaccine and 133 million of Moderna's have been administered in the US, with millions more doses distributed worldwide. In all my years in medicine (>45), very few vaccines or medicines have had their safety and efficacy scrutinized to this degree. Clinical trials showed the vaccines were 95 percent effective at preventing symptomatic illness and/or severe disease. Since then, several peer-reviewed reports in top tier journals have supported the vaccines' safety and efficacy. Serious side effects are rare. In other words, the mRNA vaccines have overwhelmingly been proved safe and effective by clinical trials, independent research, and the experience of millions of people around the world. The urgency of full approvals cannot be overstated. This will hopefully remove a barrier to some who are vaccine hesitant. Lastly, increasing vaccinations of the US population have given rise to the hope that we can return to prepandemic life. However persistent vaccine hesitancy, emerging viral variants, and global disease surges may stand in our way.

Journal Review

Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19 A Meta-analysis JAMA published online July 6, 2021. [WHO Rapid Appraisal for Covid-19 Therapies (REACT)]
doi:10.1001/jama.2021.11330

Eligible trials randomly assigned patients hospitalized for COVID-19 to a group in whom IL-6 antagonists were administered and to a group in whom neither IL-6 antagonists nor any other immunomodulators except corticosteroids were administered. Among 72 potentially eligible trials, 27 (37.5%) met study selection criteria. The primary outcome measure was all-cause mortality at 28 days after randomization. There were 9 secondary outcomes including progression to invasive mechanical ventilation or death and risk of secondary infection by 28 days.

The meta-analysis of 27 randomized trials included 10 930 patients, of whom 2565 died by 28 days. The 28-day all-cause mortality was lower among patients who received IL-6 antagonists compared with those who received usual care or placebo (summary odds ratio, 0.86). The summary odds ratios for the association of IL-6 antagonist treatment with 28-day all-cause mortality were 0.78 with concomitant administration of corticosteroids vs 1.09 without administration of corticosteroids. The ORs for the association with progression to invasive mechanical ventilation (MV) or death, compared with usual care or placebo, were 0.77 (95% CI, 0.70-0.85) for all IL-6 antagonists, 0.74 (95% CI, 0.66-0.82) for tocilizumab, and 1.00 (95% CI, 0.74-1.34) for sarilumab. There was no increase in secondary infections.

Comment: Administration of IL-6 antagonists, compared with usual care or placebo, was associated with lower 28-day all-cause mortality in patients hospitalized for COVID-19 and reduced progression to MV. Importantly, a significant mortality benefit was only found when IL- 6 antagonist was coadministered with glucocorticoids. There was limited reporting on the level of respiratory support at the time of randomization, which precludes a more granular understanding of how IL-6 efficacy is affected by oxygen requirements. For example, in this study, the use of noninvasive ventilation and high-flow nasal oxygen was combined as 1 analytic category. How should the level of respiratory support guide the use of IL-6 antagonists? The mortality benefit associated with IL- 6 use was lower among patients who received MV vs those who did not receive MV. IL-6 for critically ill patients may be most effective when given early in the disease course, whereas benefit may be unlikely when patients have received ventilatory support for several days or more. For example, REMAP-CAP demonstrated a hazard ratio of 1.6 for improved 90-day survival in patients who received IL-6 in the first 24 hours after admission to the intensive care unit. [N Engl J Med. 2021;384:1491-1502]. In addition, appropriate use of IL-6 inhibition in patients with low oxygen requirements is not clear. The WHO now recommends IL-6 inhibitors with steroids for hospitalized severe Covid-19 patients.

Effectiveness and Harms of High-Flow Nasal Oxygen (HFNO) for Acute Respiratory Failure(ARF): An Evidence Report for a Clinical Guideline From the American College of Physicians

Ann Intern Med published online April 27, 2021
doi:10.7326/M20-4675

29 randomized controlled trials evaluated HFNO versus NIV (noninvasive ventilation) (k = 11) or COT(conventional oxygen) (k = 21).
Compared with NIV, HFNO may reduce all-cause mortality, intubation, and hospital-acquired pneumonia and improve patient comfort in initial ARF management (low-certainty evidence) but not in postextubation management. Compared with COT, HFNO may reduce reintubation and improve patient comfort in postextubation ARF management (low-certainty evidence)

Comment: This review of HFNO versus NIV or COT found that, compared with NIV, HFNO may reduce intubation, all-cause mortality, and hospital-acquired pneumonia and improve patient comfort in initial

ARF management. However, compared with NIV, HFNO may increase reintubations and mortality in postextubation ARF management. Compared with COT, HFNO may reduce reintubation and improve patient comfort in postextubation ARF management. Benefits of HFNO were less clear than those of COT in initial ARF management. In addition, HFNO may reduce facial skin breakdown compared with NIV and decrease treatment escalation. See below

Appropriate Use of High-Flow Nasal Oxygen in Hospitalized Patients for Initial or Postextubation Management of Acute Respiratory Failure: A Clinical Guideline From the American College of Physicians Ann Intern Med published online April 27, 2021
doi:10.7326/M20-7533

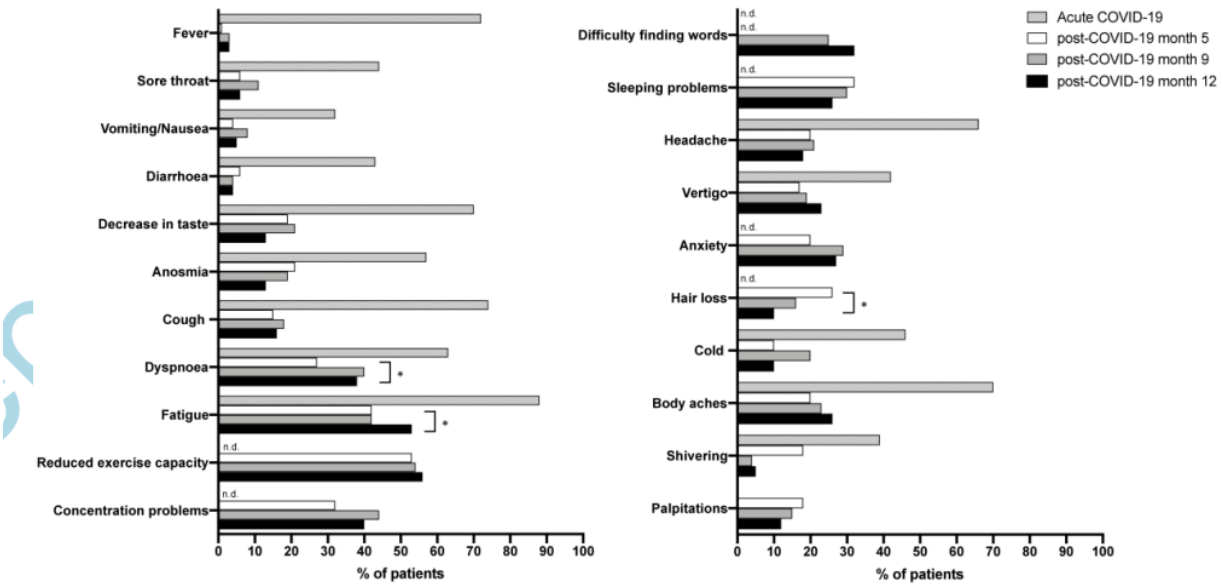
Recommendation 1a: ACP suggests that clinicians use high-flow nasal oxygen rather than noninvasive ventilation in hospitalized adults for the management of acute hypoxemic respiratory failure (conditional recommendation; low-certainty evidence).

Recommendation 1b: ACP suggests that clinicians use high flow nasal oxygen rather than conventional oxygen therapy for hospitalized adults with postextubation acute hypoxemic respiratory failure (conditional recommendation; low-certainty evidence).

Persistent symptoms in adult patients one year after COVID-19: a prospective cohort study Clin Infect Dis published online July 4, 2021.
doi/10.1093/cid/ciab611/6315216

Long term Covid-19 is defined as persistent symptoms beyond 3 months of SARS-CoV-2 infection. The investigators included patients at 5 months after acute infection in this perspective follow-up study. Patients were followed until 12 months after initial Covid-19 symptom onset. Quality of life survey (SF-12), lab values, including ANA, and SARS-CoV-2 antibody levels.
At 12 months, only 23% of patients were completely free of symptoms. The most frequent symptoms were reduced exercise capacity (56%), fatigue (53%), dyspnea (37.5%), concentration problems (40%) and, sleeping disorders (27%). ANA titers ≥1:160 was demonstrated in 43.6% of patients at 12 months and neurocognitive symptoms frequency was significantly higher in groups with ANA titer ≥1:160 compared <1:160. They did not differ in their SARS-CoV-2 antibody levels.

Figure 2



Comment: In this cohort, the most likely symptoms to persist until 12 months were reduced exercise capacity, fatigue, dyspnea, concentration problems, problems finding words, and sleeping problems. Patients reporting at least one long COVID symptom had a significantly reduced physical and mental life quality. Neurocognitive long COVID symptoms can persist at least for one year after COVID-19 symptom onset and reduce life quality significantly. Several neurocognitive symptoms were associated with ANA titer elevations. This may indicate autoimmunity as cofactor in etiology of long COVID. The strength of this study is the long-term follow-up of patients with examination of all reported patients at 5 and 12 months. In addition, this study may be the longest follow-up of patients post COVID-19. This is an observational study, so increasing willingness of symptomatic patients to take part in a follow up study is a potential confounding factor.

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