

Good morning

First it is not too late to respond on your opinion about the revised CDC's definition of close contacts. Please respond by tomorrow PM so I can summarize in the Daily Briefing this Friday.

Today I will start with an editorial on whether the glass is half full or empty when it comes to COVID-19 as we approach the fall and winter.

For review I start out with a very nice paper on modeling the impact on RO aimed to understand the association of introducing and lifting NPIs with the level of transmission of SARS-CoV-2. The next paper is a patient oriented publication on safe breast feeding by COVID-19 positive mothers. The next paper is a sobering review on COVID-19 hospitalizations among HCP. Nursing-related occupations represented the largest proportion of HCP and obesity was found to be a significant risk factor. Physicians have a much lower risk. The last 2 papers are on use of tocilizumab. The first is a RCT in moderate to severe COVID-19 and the second is a retrospective non randomized review with no controls. The results of the RCT shows no benefit.

Have a wonderful day

Ed

VII Editorial: We need leaders who are honest, credible, compassionate, and can inspire people to do the right thing. We need to be able to give people hope that if they modify their behavior we can control this pandemic, but it will take all of us to protect one another by practicing the "3Ws": wash hands, wear masks, and watch your distance. Creating fear or politicizing this pandemic is not the right approach. Statements like we are about to go into a dark winter, does not give us hope or inspiration.

Yes, the uptick in certain areas of the country is profoundly serious which seems to grab the headlines. What does not get the same headlines are death rates have also fallen tremendously as treatments have improved. This includes therapeutics such as antivirals such as remdesivir and monoclonals (Regeneron), steroids to reduce the hyperinflammatory response, but also medical protocols such as prone positioning and use of high flow heated oxygen (Vapotherm) to avoid invasive ventilation, and anticoagulants to prevent blood clots. Testing is more readily available with short turnaround times which aids in isolation and contact tracing.

NYU Langone hospital system reports its mortality rate declined by 70% from March to August after accounting for age, health risks, admission vital signs and other factors and Houston Methodist hospital system reported its mortality rate significantly dropped comparing the summer wave to the initial wave in the spring. We are doing a better job of protecting the elderly and those with high-risk medical conditions. The CDC has reported that deaths in nursing homes have significantly declined.

In addition, there have been unintended consequences impacting non-COVID medical conditions. Nearly a third of the so-called excess deaths in the U.S. this year have been attributed to causes other than COVID, including cardiovascular disease, diabetes, opioid and alcohol related, depression suicides etc. Pediatric immunization rates have fallen.

On the positive side vaccines continue to progress, and four in the U.S. have entered Phase 3 trials, that have shown evidence of generating antibodies in vaccinated patients including the elderly and minority

populations. It is hoped that some vaccines will be available before the end of the year prioritized for healthcare workers and high-risk people. Projections if all goes as planned that by the spring vaccines will be available to the public providing the vaccines continue to show they are safe and effective. Politicians explicitly stating they do not trust the process only discourage people for being vaccinated which may prolong the pandemic resulting in excess of preventable deaths.

Yes, cases are increasing, but this was predicted as cooler weather arrives and Americans go indoors. But the good news is that the US is better prepared to handle another virus surge, and progress toward a vaccine continues along with better therapeutics. Yes, I believe there really is something called COVID fatigue, but this is not the time to let our guard down. We can live with this virus and protect the most vulnerable if we follow the simple “3Ws”. I ask you: Is the glass half full or half empty?

The Temporal Association of Introducing and Lifting Non-Pharmaceutical Interventions with the Time-Varying Reproduction Number (R) of SARS-CoV-2: A Modelling Study Across 131 Countries

Lancet Infect Dis published online October 22, 2020

Non-pharmaceutical interventions (NPIs) were implemented by many countries to reduce the transmission of SARS-CoV-2. The investigators aimed to understand the association of introducing and lifting NPIs with the level of transmission of SARS-CoV-2, as measured by the time-varying reproduction number (R), from a broad perspective across 131 countries. In this modelling study, they linked data on daily country-level estimates of R from the London School of Hygiene & Tropical Medicine with data on country-specific policies on NPIs from the Oxford COVID-19 Government Response Tracker, available between Jan 1 and July 20, 2020.

They found that reopening schools, lifting bans on public events, lifting bans on public gatherings of more than ten people, lifting requirements to stay at home, and lifting internal movement limits were associated with an increase in R of 11–25% on day 28 following the relaxation. However, the effects of introducing and lifting NPIs were not immediate; it took a median of 8 days (IQR 6–9) following the introduction of NPIs to observe 60% of their maximum reduction in R and even longer (17 days [14–20]) following the relaxation to observe 60% of the maximum increase in R .

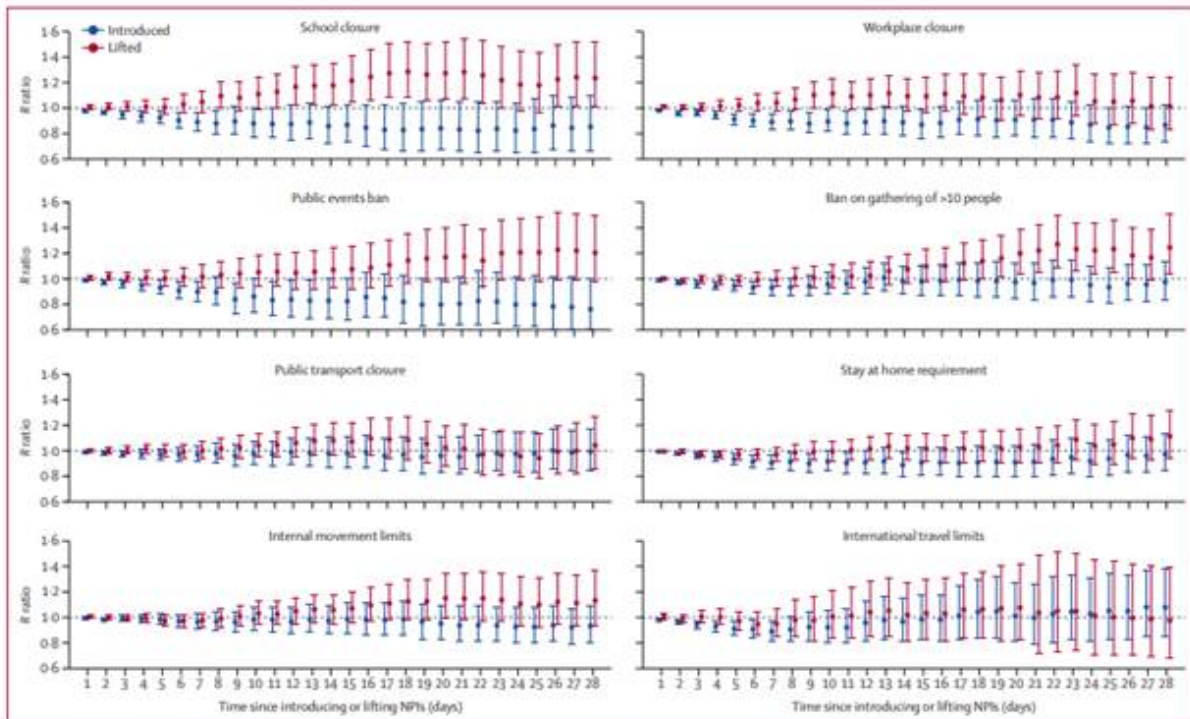


Figure 3: Change over time in the R ratio following the introduction and relaxation of individual NPIs

Comment: The authors acknowledged that the estimations come with some limitations, because differences in measure implementations could not be controlled across countries. In addition, the findings suggested that combinations of measures rather than single ones were more effective in reducing the R number for COVID-19. This model can help inform policymaker decisions on which NPIs to introduce or lift and when to expect a notable effect following the introduction or the relaxation.

Best Practices for COVID-19–Positive or Exposed Mothers—Breastfeeding and Pumping Milk

JAMA Pediatrics published online October 26, 2020

Mothers, along with their family and health care professionals, should decide whether and how to start or continue breastfeeding. Although we do not know for sure if mothers with COVID-19 can spread the virus to infants through breast milk, it is unlikely based on what we do know and what has been published. In addition, women who have had COVID-19 usually have high amounts of antibodies to the virus in their breast milk, which coat the inside of infants' noses and mouths, helping to block infection. Fresh (not frozen) milk is ideal.

If you test positive for COVID-19 and want to breastfeed or express breast milk, follow these guidelines: (1) Wash your hands before and after touching your infant or any pump or bottle parts. (2) Avoid using a pump that is shared by others. (3) Wear a mask or cloth face covering during breastfeeding or pumping. (4) If possible, pumped breast milk should be fed to the infant by a healthy caregiver who does not have COVID-19, is not at high risk for severe illness from COVID-19, and is living in the same home.

If you are breastfeeding and may have been exposed to COVID-19 and/or work in a setting with increased risk of exposure to the virus, such as a health care professional or first responder, limiting duties or isolating from your family are not currently recommended. Clean your hands routinely, whether breastfeeding or pumping milk. Some women may wish to follow the guidelines above for those who have COVID-19, in addition to these suggestions: (1) Upon returning home, you may choose

to take off shoes, immediately wash work clothing, and shower. (2) You can continue your usual work while following workplace guidelines. (3) You may wish to work with supervisors to limit high-risk situations, especially with people testing positive for COVID-19.

Mothers who are COVID-19-positive and want to breastfeed:

- Wash hands before and after touching the infant or feeding equipment
- Avoid using a pump shared by others
- Wear a mask or face covering during breastfeeding and pumping
- Follow manufacturer instructions to clean pump parts after each use
- Try to have a healthy caregiver (who does not have COVID-19 and lives in the same home) feed pumped breast milk to the infant

 *L. Kethu*

 Breastfeeding mothers who have been exposed to COVID-19 should also follow the suggestions above

Breastfeeding mothers who work in settings with high risk of exposure:

- Talk to supervisors at work about limiting exposure to situations involving COVID-19-positive individuals
- Clean shared surfaces in lactation rooms before and after use
- After coming home, take off shoes, wash work clothes, and take a shower
- If the infant is high risk for COVID-19, consider isolating from the infant while providing breast milk



Comment: These are common sense recommendations. We know in the hospital setting if mother follows the steps above, infants can be safely breast fed. The Daily Briefing as reviewed multiple articles indicating breast feeding in the hospital is safe. We also think if mothers follow the guidance above, they can continue to breast feed their infants safety after they leave the hospital.

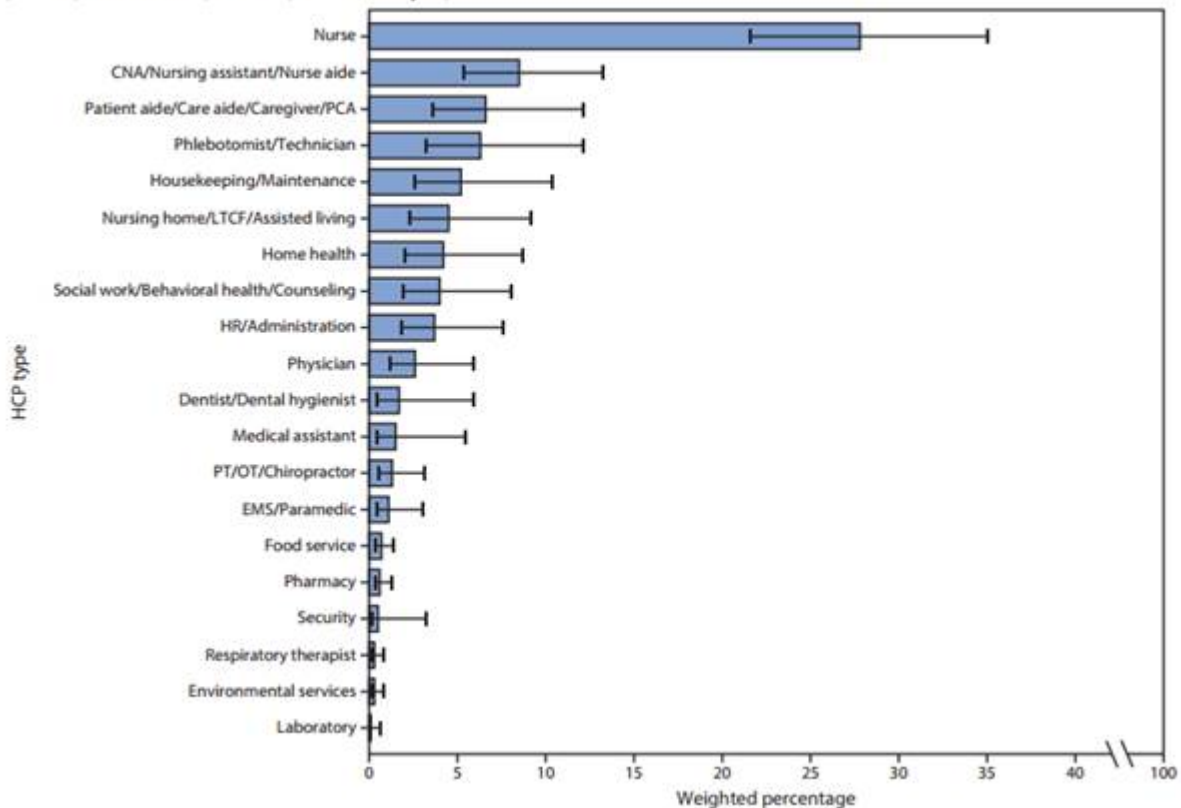
COVID-19–Associated Hospitalizations Among Health Care Personnel — COVID-NET, 13 States, March 1–May 31, 2020

MMWR published online October 26, 2020

Among 6,760 adults hospitalized during March 1–May 31, 2020, for whom HCP status was determined by the COVID-19–Associated Hospitalization Surveillance Network (COVID-NET), 5.9% were HCP.

Nursing-related occupations (36.3%) represented the largest proportion of HCP hospitalized with COVID-19. [physicians much lower] Median age of hospitalized HCP was 49 years, and 89.8% had at least one underlying medical condition, of which obesity was most commonly reported (72.5%). A substantial proportion of HCP with COVID-19 had indicators of severe disease: 27.5% were admitted to an intensive care unit (ICU), 15.8% required invasive mechanical ventilation, and 4.2% died during hospitalization.

FIGURE 2. Weighted percentage of personnel types*¹ among reported health care personnel (HCP) with COVID-19-associated hospitalizations (N = 438) — COVID-NET, 13 states,⁵ March 1–May 31, 2020



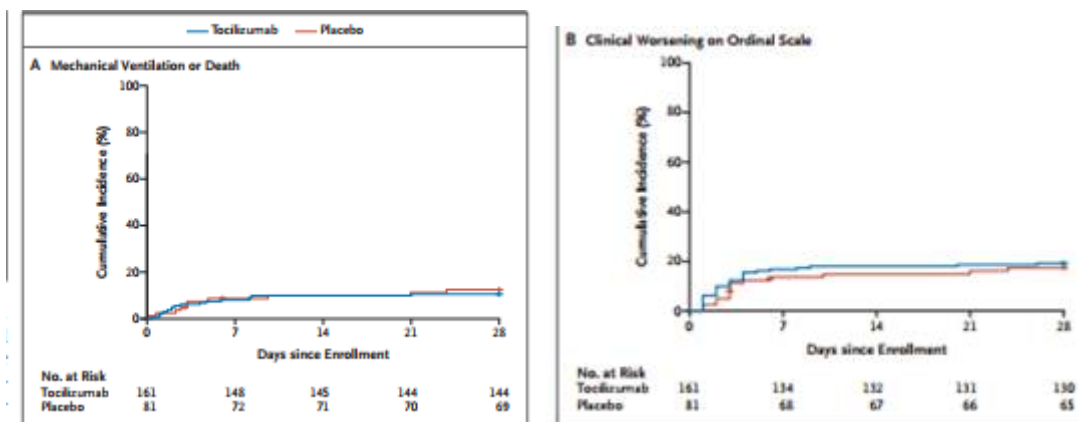
Comment: As this report confirms HCP can have severe COVID-19-associated illness, highlighting the importance for continued infection prevention in health care settings as well as community mitigation efforts to reduce SARS-CoV-2 transmission. The findings in this report confirms the need for prevention and management of obesity through evidence-based clinical care as well as policies, systems, and environmental changes to support HCP in healthy lifestyles to reduce their risk for poor COVID-19-related outcomes. This also highlight the prevalence of severe COVID-19-associated illness among HCP and potential for transmission of SARS-CoV-2 among HCP, which could also decrease the workforce capacity of the health care system which is critical in areas experiencing the current surge. Lastly, findings from this analysis are comparable to those reported among HCP with COVID-19 in China, which found that nursing-related occupations accounted for the largest proportion of COVID-19 cases among HCP. [JAMA Netw Open 2020;3:e209666]

Efficacy of Tocilizumab in Patients Hospitalized with Covid-19

N Engl J Med published online October 21, 2020

The investigators performed a randomized, double-blind, placebo-controlled trial involving patients with confirmed moderate to severe SARS-CoV-2 infection, hyperinflammatory states, and at least two of the following signs: fever (body temperature >38°C), pulmonary infiltrates, or the need for supplemental oxygen in order to maintain an oxygen saturation greater than 92%. Patients were then randomly assigned in a 2:1 ratio to receive standard care plus a single dose of either tocilizumab (8 mg per kilogram of body weight) or placebo. The primary outcome was intubation or death, assessed in a time-to-event analysis. The secondary efficacy outcomes were clinical worsening and discontinuation of supplemental oxygen among patients who had been receiving it at baseline, both assessed in time-to-event analyses.

The investigators enrolled 243 patients; 141 (58%) were men, and 102 (42%) were women. The median age was 59.8 years (range, 21.7 to 85.4), and 45% of the patients were Hispanic or Latino. The laboratory findings were the same in both groups (e.g. CRP, IL-6, D-dimer, LDH, PCT etc.). The hazard ratio for intubation or death in the tocilizumab group as compared with the placebo group was 0.83 (95% confidence interval [CI], 0.38 to 1.81; P=0.64), and the hazard ratio for disease worsening was 1.11 (95% CI, 0.59 to 2.10; P=0.73). At 14 days, 18.0% of the patients in the tocilizumab group and 14.9% of the patients in the placebo group had had worsening of disease. The median time to discontinuation of supplemental oxygen was 5.0 days (95% CI, 3.8 to 7.6) in the tocilizumab group and 4.9 days (95% CI, 3.8 to 7.8) in the placebo group (P=0.69). At 14 days, 24.6% of the patients in the tocilizumab group and 21.2% of the patients in the placebo group were still receiving supplemental oxygen. Patients who received tocilizumab had fewer serious infections than patients who received placebo.



Comment: The results does not provide support for the concept that early IL-6 inhibitors is an effective treatment strategy in moderately ill patients hospitalized with COVID-19. Only 243 patients were enrolled. The explanation for the failure of tocilizumab to affect clinical outcomes in this trial is not clear. The results, however, confirmed the relationship between older age and poor outcomes in COVID-19 but did not identify separate effects of sex, diabetes, obesity, or Hispanic or Latino ethnic group on prognosis. [surprised] They also confirmed that patients with higher serum IL-6 concentrations at baseline were more likely to have a poor outcome even though IL-6 levels were modestly elevated and not extremely high. The primary event rate they observed was lower than anticipated, perhaps because of evolving standards of care during the trial. [meaning trial may have been underpowered] Remdesivir became available early in the trial, and general approaches to management were evolving. There was also an imbalance in the percentage of older patients between the treatment groups. Will patients

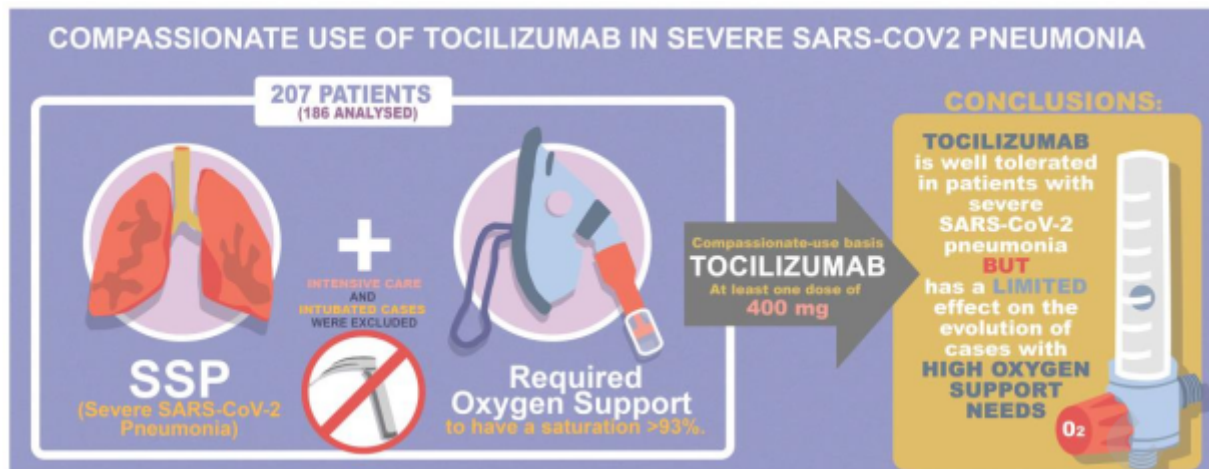
with IL inhibitors with higher IL-6 levels and patients on mechanical ventilators benefit and will combination therapy with steroids improved outcomes.

Compassionate Use of Tocilizumab in Severe SARS-CoV2 Pneumonia

Int J Infect Dis published online October 25, 2020

The investigators provided tocilizumab on a compassionate-use basis to patients with severe SARS-CoV-2 pneumonia (SSP) hospitalized (excluding intensive care and intubated cases) who required oxygen support to have a saturation >93%. Primary endpoint was intubation or death after 24 hours of its administration. Patients received at least one dose of 400 mg tocilizumab. This was a retrospective review.

A total of 207 patients were studied and 186 analyzed. The mean age was 65 years and 68% were male. A co-existing condition was present in 68 % of cases. Mortality prognostic factors were older age, higher IL-6, D-dimer and high CRP, lower total lymphocytes and severe disease requiring higher oxygen support. The primary endpoint (intubation or death) was significantly worse (37% vs 13% $p < 0.001$) in those receiving the drug when the oxygen support was high (FiO₂ >0.5%). There were limited side effects and secondary infections. A significant decrease in the median serum ferritin and the median CRP was observed.



Comment: This admittedly is not nearly as robust as trial reviewed above. There are several significant limitations in my opinion. First this was a retrospective review with no control group. Second, the decision to administer tocilizumab was made by the medical team responsible for each patient. Therefore, the clinical status of patients and the timing of drug administration after the onset of COVID-19 symptoms were variable. Total amount of drug and number of doses that patients received were not uniform, due, as previously mentioned, to a shortage of the drug in the country during the peak of the epidemic. Thirdly, most patients had received previous and/or concomitant drugs, including systemic corticosteroids and hydroxychloroquine which have anti-inflammatory properties. Therefore, they could not control for the impact of these drugs on the overall response of patients treated with tocilizumab. Bottom line this is why we do need RCTs such as article above. Both articles treated only the moderate to severe group and not patients in ICU or on mechanical ventilation.