Week in Review: 11-15 May 2020

BRIEF19

A daily review of covid-19 research and policy.

RESEARCH BRIEFING

Briefing from the editor: This is not the flu. In a *JAMA Internal Medicine* Viewpoint, Carlos del Rio (Emory University) and I argue that the method by which seasonal influenza deaths are estimated render them inappropriate for comparisons with covid-19. The CDC uses complicated algorithms to generate their yearly flu death estimates, which range from 24,000 to 60,000 annually. Meanwhile, covid-19 deaths are being counted directly and in just over two months have caused over 80,000 deaths in the United States. What hospitals are seeing today does not comport with numbers that make flu and covid-19 appear remotely similar. Comparing raw counts to raw counts is more appropriate. In so doing, we reveal that covid-19 killed on average around 20 times more Americans in a week in late April than seasonal influenza killed during the peak week of the last seven seasons (range 9.5 to 44.1-fold increase). While adult influenza is not required to be reported, as covid-19 currently is, raw influenza counts may still overstate the case, as many of the death certificates where influenza appears also contain other causes of death which may have been the proximate cause. *15 May 2020.* *–Jeremy Samuel Faust, MD, MS*

New triple therapy for covid-19 infection. A recent randomized clinical trial was published in *The Lancet* assessing the safety and effectiveness of a combination of medicines comprised of interferon beta-1b, lopinavir-ritonavir, and ribavirin given to hospitalized patients in Hong Kong with SARS-CoV-2 infection. Patients received either a complex regimen of interferon beta-1b, lopinavir-ritonavir, and ribavirin ("triple therapy group") or lopinavir-ritonavir alone ("control group"). A recent trial in *NEJM* found lopinavir-ritonavir to have no benefit in covid-19 patients. The researchers monitored how long it was before patients produced negative nasopharyngeal swabs for SARS-Cov-2 and how long symptoms lasted. Between February 10 and March 20, 2020, 127 patients were recruited to the trial. The triple therapy group had a shorter average time from starting the medication until they produced negative nasopharyngeal swabs, compared to the control group at 7 days and 12 days. The triple therapy group also had faster resolution of symptoms compared to the control group (4 days versus 8 days) and stayed in the hospital less long (9 days vs 14.5 days in the control group). Side effects like nausea and diarrhea occurred similarly in both groups. **Analysis:** Have we found a therapy that is finally useful for covid-19? Maybe. The patients assessed and described in this *The Lancet* paper were not among the sickest when compared to patients studied in other published studies. The recent *NEJM* study that looked at lopinavir-ritonavir alone used slightly stricter inclusion criteria to capture "sicker" patients. This current *Lancet* paper also looked at "patient-oriented" outcomes, including resolution of symptoms and length of hospital stay. The results were wide ranging, and statistically speaking, difficult to interpret. Nevertheless, this new "triple therapy" warrants further investigation via trials that are specifically designed to assess patient-oriented outcomes as the main objective. *Abbreviated from Brief19 for 11 May 2020.* *–Joshua Niforatos, MD*

Is covid-19 triggering Kawasaki-like disease? A case series appearing *The Lancet* describes 8 children (ages 4-14) in England who had features of so-called "hyperinflammatory shock," similar to the complications sometimes seen in an inflammatory condition known as Kawasaki Disease (KD), or mucocutaneous lymph node syndrome. The authors state that 8 children

presenting in such a short span represents a four-fold increase over their usual numbers. Two of the children tested positive for SARS-CoV-2, including one from the autopsy of the single child who died. However, the authors later state that all eight patients were eventually found to have positive antibodies to SARS-CoV-2, though these data were not presented in results of the paper. The findings raise concerns that covid-19 may occasionally trigger a KD-like syndrome. KD is rare with fewer than 20,000 diagnosed cases per year in the United States. It is characterized by a fever for five or more days, red eyes, changes to the mucous membranes, a red rash, and swollen glands in the neck. Of patients with suspected KD, only a small number develop "complete" KD, and fewer still develop signs of "shock" from KD. Of the 8 children described in the paper, 5 required mechanical ventilation, two required non-invasive ventilation, and one required high flow oxygen through the nose. The cause of KD is unknown, but some theories propose that children who have recently recovered from infections are more likely to develop it. It is unknown whether SARS-CoV-2 in particular is more likely to cause this KD-like condition. It could be unrelated, but these findings hint at the fact that the virus may either be directly causing the condition, or that the virus might be more prevalent in some areas than commonly appreciated and, in reality, any widespread infection moving through a community would cause small spikes like this to occur. *Abbreviated from Brief19 for 11 May 2020.* *–Lauren Westafer DO, MPH*

More studies show hydroxychloroquine is not effective for treating covid-19. A new study published in JAMA assessed 1,438 hospitalized patients with covid-19 who received hydroxychloroquine and azithromycin (HCQ+AZ), HCQ alone, AZ alone, or neither drug. These 1,438 patients represent 88.2% of all covid-19 patients admitted across 25 hospitals in the New York metropolitan region between March 15 and 28, 2020 with a final follow-up date of April 24. The authors compared in-hospital mortality, cardiac arrest, and abnormal ECG findings. During the study period, 20.3% of all admitted patients died. The probability of dying from covid-19 after receiving HCQ+AZT was 25.7%; after receiving HCQ alone, 19.9%; after receiving AZ alone, 10%, and after receiving neither drug, 12.7%. After statistical correction for patient differences, there were no significant differences in mortality among any of the groups. Many side effects were reported in this study. Patients receiving HCQ+AZ were more likely to suffer from cardiac arrest compared with those in the other groups. However, some caveats are worth noting. This study was an observational study and not a randomized clinical trial. The patients who received HCQ+AZ were notably sicker than the other groups. Of note, 13% of HCQ+AZ patients were mechanically ventilated in less than a day compared to 5% of patients who did not receive any drug. There has been a steady stream recently of negative studies on HCQ. However, the largest ones have been observational studies. An important randomized clinical trial that included patients receiving HCQ is expected to be published this week. *Abbreviated from Brief19 for 12 May 2020.*

–Joshua Niforatos, MD Research Section Editor and Lauren Westafer, DO, MPH

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Brief19 is a daily executive summary of covid-19-related medical research, news, and public policy. It was founded and created by frontline emergency medicine physicians with expertise in medical research critique, health policy, and public policy.