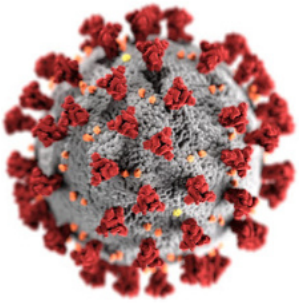


COVID-19 Action Newsletter

UT Southwestern Department of Internal Medicine
James Luby, M.D., and Robert Haley, M.D., editors

The Situation: Confirmed U.S. Cases Pass 26 Million

In the world as of February 1, 2021, 103,090,224 cases and 2,230,829 deaths have been confirmed. In the United States, there have been 26,194,662 cases, the most in the world followed in order by India, Brazil, the United Kingdom and Russia. China is now 82nd in the world with 100,097 reported cases. Deaths in the U.S. through January 25 have been estimated at 441,409.[1]

From March 10 through January 24, there have been 218,039 confirmed cases of Covid-19 reported from Dallas County with 2008 deaths, about 22% of these from long-term care facilities.[2] Sixty-eight percent of hospitalized cases in Dallas County have been under 65 years of age. Diabetes mellitus has been seen in about one-third of all hospitalized patients. More men (63%) than women (37%) have died, and 46% of the hospitalized cases have occurred in the Hispanic population. As of 1/5/2021, deaths have been analyzed by race with 25% occurring in Whites (actual White population 29%), Hispanics 46% (population 41%), Blacks 25% (population 24%), and Asians 3% (population 7%). Specimens submitted for diagnosis of respiratory viruses show continuing positivity for SARS-CoV-2 with the latest result on 1/9/21 being 25.5%, down from a peak value of 30.5% obtained during the week ending 7/4/20. Influenza A and B antigen tests and RSV antigen tests in specimens from the respiratory tract from 10/3 through 12/5/2020 have been negative. On 1/24/21, it was reported that there were 111 LTCF outbreaks which cumulatively have resulted in 3,369 resident cases and 2091 healthcare worker cases. There also were 27 outbreaks in congregate living facilities (homeless shelters, group homes and halfway houses) which have resulted in 350 resident cases and the involvement of 168 staff members.

References:

1. Covid-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) (Updated 2/01/21)
2. Dallas County Health and Human Services. Acute Communicable Disease Epidemiology Division 1/24/21

Feature Article

Cytokine Measurements in Covid-19: How often does the Cytokine Storm Syndrome occur?

Cytokines are substances secreted by the immune system that have an effect on other cells. These effects may be pro- or anti-inflammatory. Cytokine storm syndrome (CSS), according to a proposed unifying definition, is a state meeting three criteria: elevated circulating cytokine levels, acute systemic inflammatory symptoms, and secondary organ dysfunction beyond that which could be attributed to the usual response to a pathogen.[1] In the original paper describing Covid-19 from Wuhan China, investigators found that concentrations of certain cytokines were found in higher amounts in ICU patients than in normal controls and in ICU patients over that seen in non-ICU patients.[2]

Examples of conditions outside of Covid-19 in which CSS occurs include a phase of the Adult Respiratory Distress Syndrome (ARDS), Still's disease in the adult, hemophagocytic lymphohistiocytosis (HLH), and CAR-T therapy in the treatment of hematologic malignancies (cytokine release syndrome, CRS). Fundamental to understanding the role of CSS in Covid-19 are its frequency, its manifestations, what cytokines are involved, and whether anti-cytokine therapy might be effective. We review three recent articles reporting cytokine measurements and the frequency of CSS in Covid-19 that raise questions about the role of CSS in this disease.

A recent review article by Leisman et al.[3] reported the average levels of many cytokines and acute phase reactants in all 1,245 Covid-19 patients (25 studies) with cytokine measurements reported in the literature up to April 14, 2020, and compared them with those reported from 4 trials each of sepsis (n=5,320), CRS (n=72) and ARDS unrelated to Covid-19 (n=2,767). The results are illustrated using IL-6 (Figure 1).

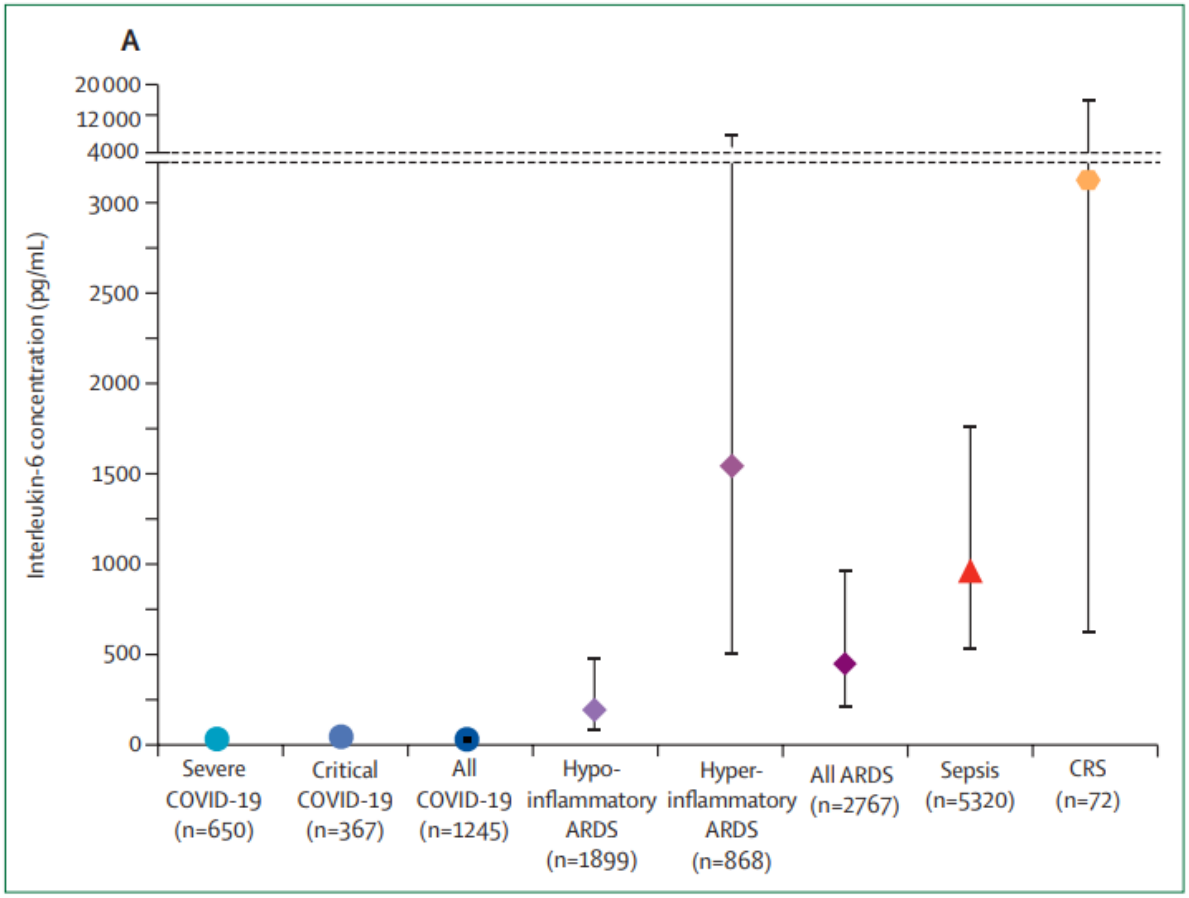


Fig. 1. IL-6 serum levels in Covid-19 compared with ARDS, sepsis and CRS (reproduced from [3]).

IL-6 is the major cytokine involved in juvenile rheumatoid arthritis. For IL-6, the values for any Covid-19 category are less than that seen with hyper-inflammatory ARDS, all ARDS, sepsis and CRS. The value of IL-6 for CRS was nearly 100 times higher than in patients with Covid-19. Other cytokines have been measured in Covid-19 and in the other comparator disease states (Figure 2, next page). IL-6, IL-8, tumor necrosis factor-alpha (TNFa), interferon-gamma (IFN-gamma, IFNg), soluble interleukin-2 receptor (sIL-2R) and IL-10 have been measured, and values of all, except TNFa and critical Covid-19, are greater than that seen with any category of Covid-19. Acute phase reactant measurements like CRP, ferritin, LDH, and procalcitonin (PCT) usually are less in Covid-19 patients than in the other disease compared, but the differences are less than those seen in the cytokine comparison. D-dimer values in sepsis are the same or less than Covid-19 values.

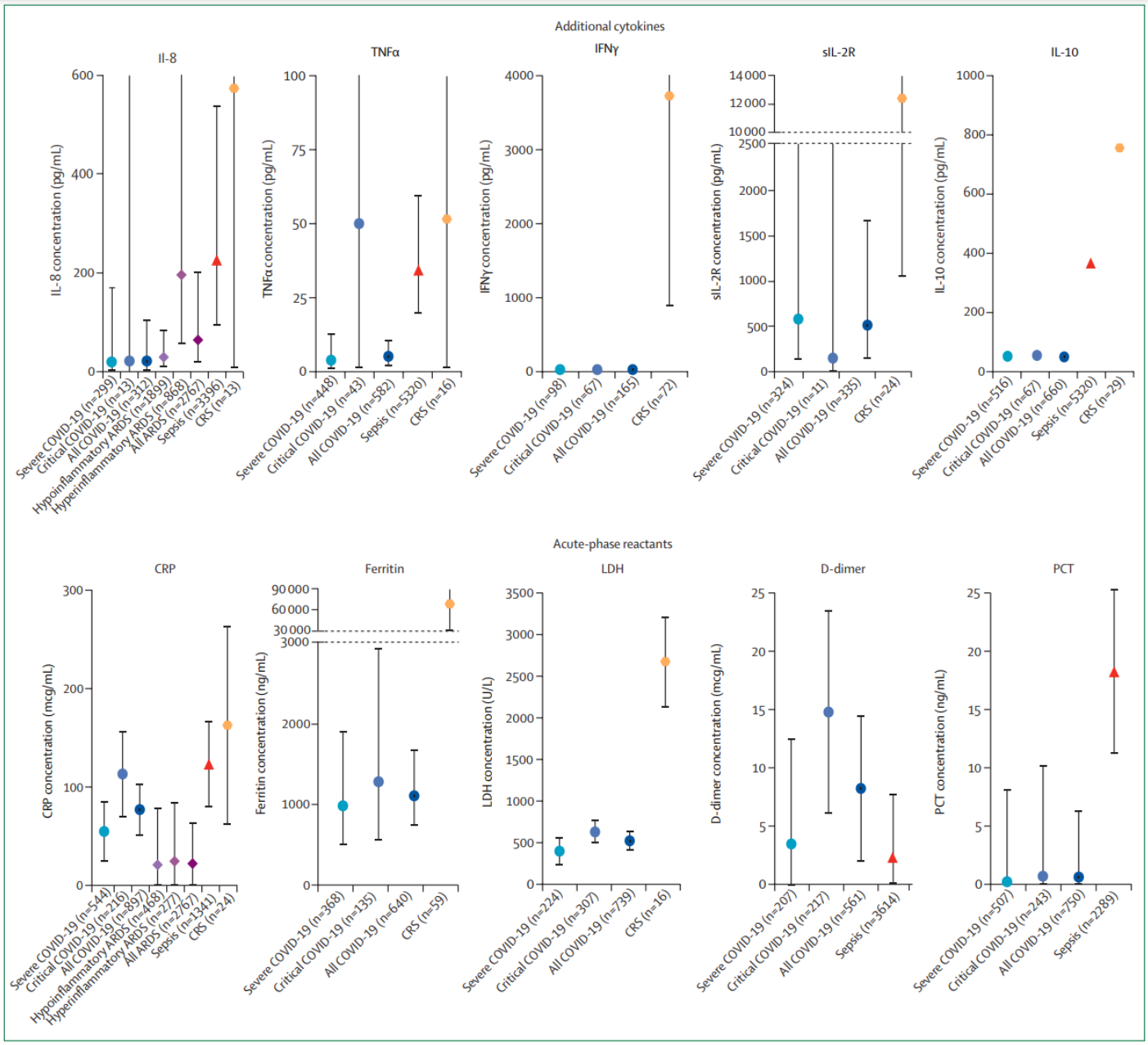


Fig. 2. Additional cytokines and biomarkers in patients with Covid-19 versus comparison disorders (from [3]).

The second study by Mudd et al.[4] at Washington University in St. Louis measured different cytokines in four groups of patients: Covid-19, primary group; Covid-19, validation cohort; normal controls; and a patient group with seasonal influenza, types A and B. Of the 168 patients in the two Covid-19 cohorts, seven (4.2%) had CSS characteristics with elevated levels of multiple cytokines. In this study, the in-hospital mortality was 24/79 (30.4%) in the primary cohort and 15/89 (16.9%) in the validation cohort, or 39/168 (23%) in all. Four of the 7 patients with CSS died, leaving 35 of the 39 (77%) deaths not having cytokine levels indicating CSS. Morevoer, 26 adults with seasonal influenza were studied, and the Covid-19 patients exhibited lower cytokine levels, including IL-6, than those with influenza. Single-cell transcription studies showed suppression of interferon signaling in Covid-19 patients. The authors concluded that Covid-19 patients "are less inflamed than influenza patients."

The third study, by Kox et al.,[5] consisted of the measurement of the levels of the cytokines TNF, IL-6 and IL-8 in patients with Covid-19 involving ARDS and compared them with patients with ARDS not related to Covid-19, sepsis with ARDS, sepsis without ARDS, out of the hospital cardiac arrest (OHCA), and trauma. Critically ill

patients with Covid-19 involving ARDS had circulating cytokine levels that were lower compared with patients with bacterial sepsis with and without ARDS and similar to other critically ill patients with OHCA and trauma. The authors suggest that Covid-19 "may not be characterized by cytokine storm."

Editorial Note: Critical to understanding Covid-19 is the assessment of the inflammatory response. The consensus of these 3 articles is that, although elevated pro-inflammatory cytokine values are seen in Covid-19, they are usually no higher, and often lower, than in other inflammatory states. Cytokine storm syndrome as strictly defined is uncommon (4.2%) in Covid-19. The studies discussed here usually have concentrated on single cytokine measurements, and other factors such as the duration of the cytokine elevation have not been considered. These findings may be useful in interpreting the effects of the anti-inflammatory drugs tocilizumab and dexamethasone in the therapy of Covid-19 as well as recent information on the beneficial effects of colchicine as seen in a recent trial with that drug in ambulatory patients.

References:

1. Fajgenbaum DC, June DL. Cytokine Storm. *N Engl J Med* 2020; 383:2255-2273 DOI: 10.1056/NEJMra2026131
2. Huang C, Wang Y, Li X et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395: 497-506.DOI.org/10.1016/S0140-6736(20)30183-5
3. Leisman DE, Ronner L, Pinotti R et al. Cytokine elevation in severe and critical COVID-19: a rapid systemic review, meta-analysis , and comparison with other inflammatory syndromes. *Lancet Respir Med* 2020; 8:1233-44. D0I.or/10.1016/S2213-2600(20)30404-5
4. Mudd PA, Crawford JC, Turner JS et al. Distinct inflammatory profiles distinguish COVID-19 from influenza with limited contributions from cytokine storm. *Sci Adv* 10.1126/sciadv.abe3024 (2020)
5. Kox M, Waalders NJ, Kooistra EJ et al. Cytokine Levels in Critically Ill Patients with COVID-19 and Other Conditions. *JAMA* October 20,2020; Vol 324, No. 15. DOI:10.1001/jama.2020.17052

Epi Corner

The Third Wave: Confluence of Four Sequential Surges

Like the rest of the country, Dallas County is presently deep into the Third Wave of the Covid-19 pandemic, the First Wave occurring in the spring of 2020 and the Second Wave last summer. The Third Wave has so far unfolded in 4 surges immediately following each other, but may now be declining (see the **figure**).

The first surge, beginning a few days after October 1, consisted of a relatively gradual rise that took a full 30 days to reach its peak on November 1.

The second surge took off explosively just after the confluence of Halloween weekend, October 31-November 2, and election day, November 3, reaching a plateau in 8-10 days; the plateau lasted about 2 weeks after which it began a definite downward plunge as if it was abating.

The third surge began with another explosive jump on December 1, the Tuesday after the Thanksgiving holiday, and reached a plateau within 7 days.

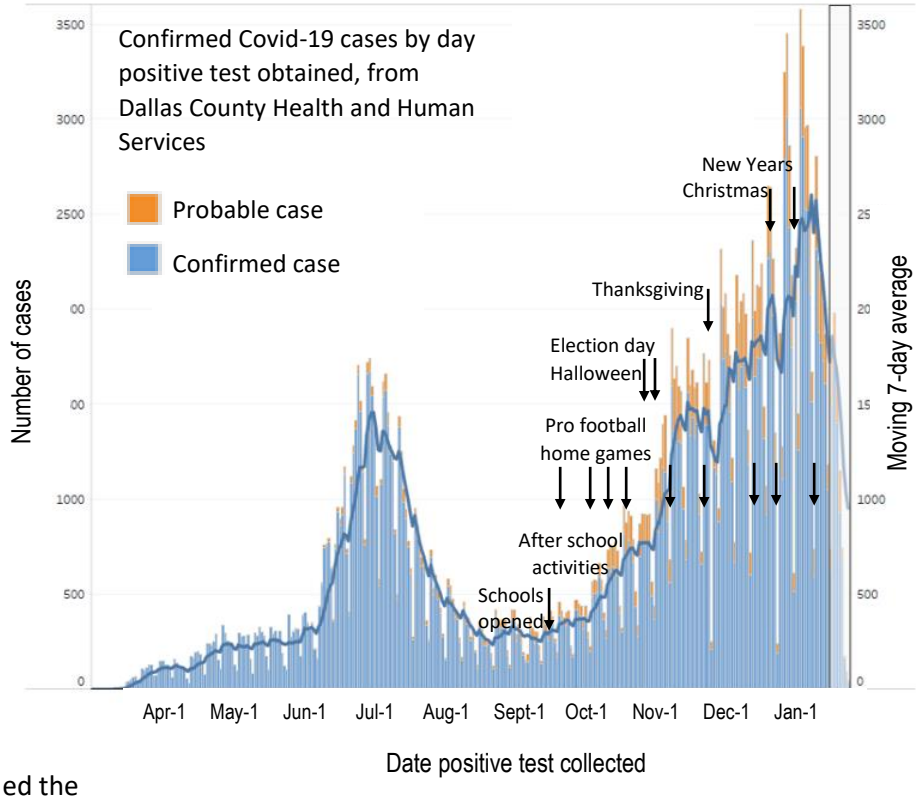
The fourth surge spiked upward approximately on Christmas Day, and after a brief falter, surged to its peak on about January 8, thereafter plunged downward, and remains in free fall in late January.

The pattern of the epidemic curve of the Third Wave is distinctive in its multiple-surge composition (**figure**). The second, third and fourth surges with their abrupt, explosive rises to a plateau followed by equally abrupt declines, each having the classic shape of a common-source infectious disease outbreak with limited secondary spread,[1] typified by the classic staphylococcal food poisoning outbreak from the potato salad at the Sunday church picnic. Starting just a couple of days after the Halloween, Thanksgiving, and Christmas-New Years holidays—population-wide super-spreader events that were expected to produce large surges—these clearly represent 3 post-holiday surges immediately following the other.

What of the first surge, which, unlike the other three, rose gradually to its peak over 30 days? Its epidemic curve is clearly different from the others and most resembles a continuing common-source epidemic[1] from the cumulative effect of a series of closely spaced super-spreader events, each smaller in scope than the three post-holiday surges. Of course, we cannot know with certainty the causes of this first surge, but to our

knowledge the only large-scale public events taking place close together in late September through October were the series of Dallas Cowboys professional football home games at AT&T Stadium in Arlington on September 20, October 4, 11, 19 and November 8 and 26 (**figure**). Although ticket sales had been capped at 28% of capacity, the attendance averaged approximately 28,000 fans[2] in an indoor stadium with little air movement and only spotty mask wearing. The team' average attendance was the highest of all the professional teams, almost twice that of the next highest.

Other possible repetitive super-spreader events that might have contributed to the first surge, and later ones as well, were the many high school football games played in the area. Although these almost entirely took place in outdoor stadiums in fall breezes, some were heavily attended, producing crowded, mostly unmasked seating conditions, with potential for localized super-spreading events. Indoor girls' volleyball games might also have contributed.



Another potential contributor to the first surge might have been increasing spread in after-school athletic and other programs for school children.

Fortunately, other potential fall super-spreading events were cancelled. These included the State Fair of Texas, the Dallas Opera, the Dallas Theater Center, and other arts events. The Dallas Symphony held several concerts, but orchestra size was reduced, masking and ventilation were enhanced, and attendance was held to 50-75. Six Flags Over Texas held nightly outdoor Halloween exhibits but limited attendance and enforced universal masking. SMU played a full schedule of football games in its outdoor stadium but limited attendance, enforced distancing with marked seating, and found no evidence of frequent Covid-19 transmission in careful post-game surveillance of players, coaches and student fans in attendance. Also notable is the absence of any immediate surge from in-school spread from the opening of K-12 schools in the county in mid-September, most of which encouraged in-person attendance, while offering limited virtual instruction. This would be expected in light of the recent CDC guidance recommending in-person schooling as safe.[3]

If the conclusions of this epidemiologic analysis are correct, it appears that the massive Third Wave in Dallas County, and probably across the country, resulted largely from widespread breakdown in personal protection from masking, social distancing and avoiding crowds in poorly ventilated spaces during holiday celebrations and attendance at crowded sporting events. Public health authorities predicted these risks and attempted to warn the public, but to no avail—reminiscent of the infamous war bond parade in Philadelphia at the height of the 1918 great influenza pandemic.[4]

Continuation of this pattern would predict further brisk drop in daily incidence possibly back to the September baseline until another surge following the next major holiday at spring break; however, rapid replacement of the original SARS-CoV-2 strain with the more contagious variants from England, South Africa and Brazil is likely to arrest the drop and possibly force the daily incidence back up sooner.

References:
1. Fontaine RE. Describing the findings. In: *The CDC Field Epidemiology Manual*. 3rd ed. Eds. Rasmussen SA, Goodman RA. Oxford University Press: New York. 2018.
2. 2020 NFL Football Attendance - National Football League - ESPN
3. Centers for Disease Control and Prevention. Operating schools during COVID-19:CDC's Considerations. https://www.cdc.gov/coronavirus/2019-ncov/community/schools-childcare/schools.html
4. Barry J. The Great Influenza: The Epic Story of the Deadliest Plague in History. Viking Penguin: New York. 2004.

From the Editors

The aim of this weekly newsletter is to serve as a source of information for the UT Southwestern community which can lead to better understanding and control of a new disease (COVID-19) caused by the pandemic spread of an emerging viral pathogen (SARS-CoV-2). We welcome questions, comments, and suggestions for topics and authors.