Good morning and TGIF

Under COVID-19 News the ACIP meeting on myocarditis in adolescence has been postponed until next week. Next is the CDC announcement last Tuesday to make delta a VOC and that the US death toll has now exceeded 600,000. CDC has also put out interim guidance on evaluating patients with post-COVID-19.

For Journal Review I have chosen a systematic review on persistent symptoms following COVID-19 infection. Next is a pre-publication from another RECOVERY Trial showing that administering REGEN-COV on top of usual care reduced the risk of dying by 20% among hospitalized COVID-19 patients who had not produced antibodies to the virus yet. The last two papers look at vaccine response in patients with AIIRD [autoimmune inflammatory rheumatic diseases] and SOT. The last article is a real-world experience on the influence of two vaccines on delta variant infection and admissions.

Have a safe and relaxing weekend – next week review of the OHSA guidance and a study on the efficacy and safety of tofacitinib, a Janus kinase inhibitor to name a few.

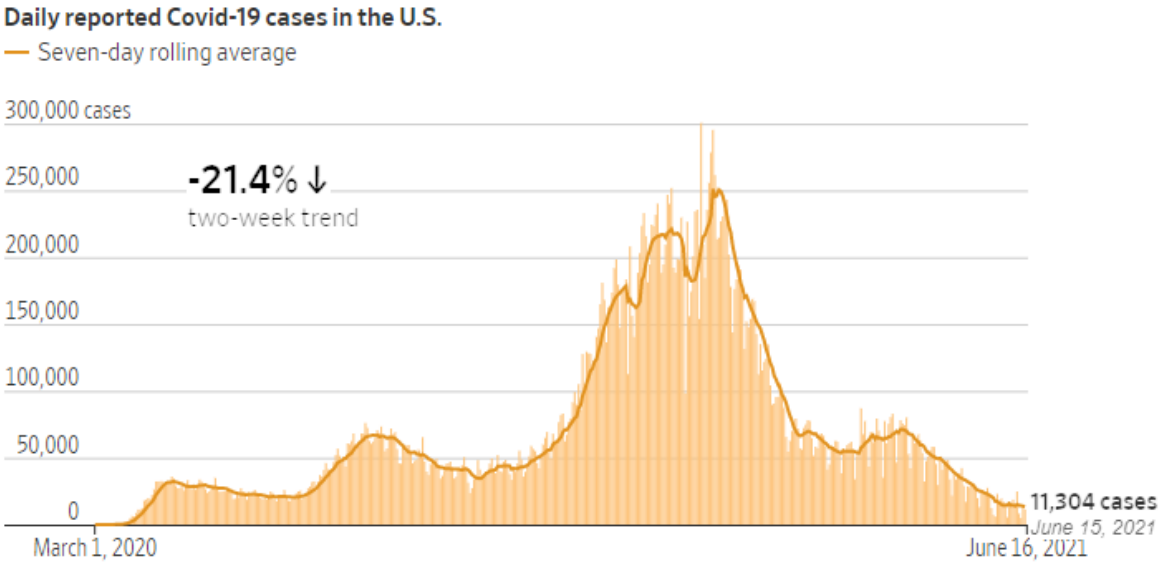
Ed

COVID-19 News

ACIP Meeting
June 18, 2021
The June 18, 2021, COVID-19 meeting is being rescheduled due to the observation of the Juneteenth National Independence Day holiday. The discussion will be rescheduled to be included as part of the June 23-25 ACIP meeting.

CDC Updates COVID-19 Delta Variant to One "Of Concern"
June 15, 2021
The US Centers for Disease Control and Prevention (CDC) has now upgraded the (B.1.617.2) Delta mutation to a classification of "variant of concern." It had previously been a "variant of interest."
The CDC defines a "variant of concern," as "a variant for which there is evidence of an increase in transmissibility, more severe disease (e.g., increased hospitalizations or deaths), significant reduction in neutralization by antibodies generated during previous infection or vaccination, reduced effectiveness of treatments or vaccines, or diagnostic detection failures." CDC said Tuesday that Delta, a highly transmissible COVID-19 variant currently sweeping through the United Kingdom, now makes up at least 10% of all US cases. On May 22, the variant had made up only 2.7% of cases. See below.

U.S. COVID-19 Deaths Top 600,000
June 15, 2021
The number of confirmed U.S. deaths from Covid-19 surpassed 600,000 on Tuesday. The good news is since the rollout of highly effective vaccines, deaths have plummeted, reaching their lowest point since March 2020. Over 43% of the U.S. population is now fully vaccinated, according to the CDC.



John Hopkins June 16, 2021

Comment: As these Briefings have said many times, vaccinations are our way back to "normal". We have more to do especially if the Delta variant takes hold in the US as many predict.

CDC: Evaluating and Caring for Patients with Post-COVID Conditions: Interim Guidance
June 14, 2021

- The term "Post-COVID Conditions" is an umbrella term for the wide range of physical and mental health consequences experienced by some patients that are present four or more weeks after SARS-CoV-2 infection, including by patients who had initial mild or asymptomatic acute infection.
- Based on current information, many post-COVID conditions can be managed by primary care providers, with the incorporation of patient-centered approaches to optimize the quality of life and function in affected patients.
- Objective laboratory or imaging findings should not be used as the only measure or assessment of a patient's well-being; lack of laboratory or imaging abnormalities does not invalidate the existence, severity, or importance of a patient's symptoms or conditions.
- Healthcare professionals and patients are encouraged to set achievable goals through shared decision-making and to approach treatment by focusing on specific symptoms (e.g., headache) or conditions (e.g., dysautonomia); a comprehensive management plan focusing on improving physical, mental, and social wellbeing may be helpful for some patients.
- Understanding of post-COVID conditions remains incomplete and guidance for healthcare professionals will likely change over time as the evidence evolves.

Comment: This is a very general and vague document in part based on limited understanding of post-Covid syndromes. More research is desperately needed. See study below.

Journal Review

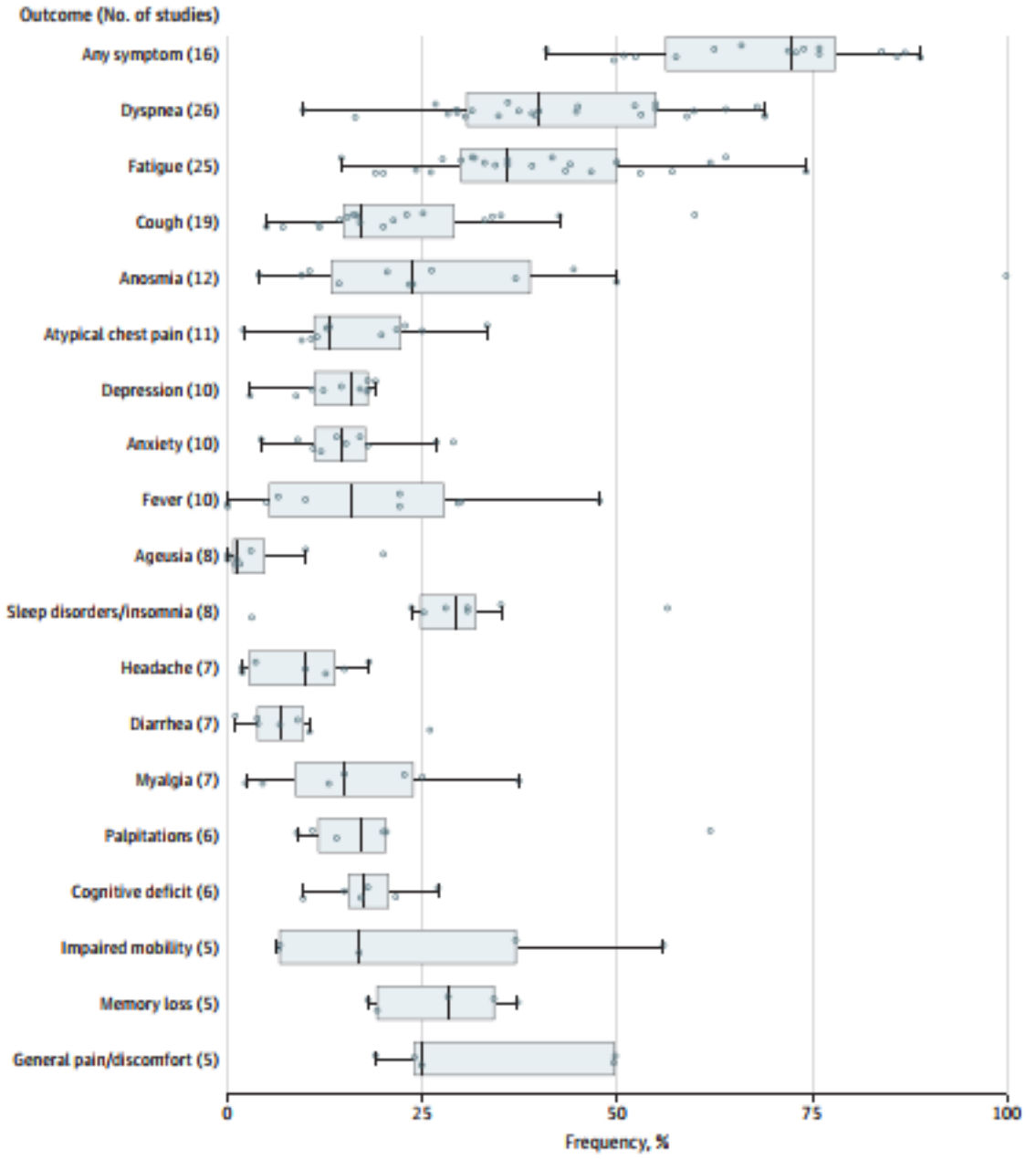
Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19: A Systematic Review

JAMA Netw Open published online May 26, 2021
doi:10.1001/jamanetworkopen.2021.11417

A search of PubMed and Web of Science was conducted to identify studies published from January 1, 2020, to March 11, 2021, that examined persistent symptoms after COVID-19 infection. Persistent symptoms were defined as those persisting for at least 60 days after diagnosis, symptom onset, or hospitalization or at least 30 days after recovery from the acute illness or hospital discharge. Search terms included COVID-19, SARS-CoV-2, coronavirus, 2019-nCoV, long-term, after recovery, long-haul, persistent, outcome, symptom, follow-up, and longitudinal.

A total of 1974 records were identified; of those, 1247 article titles and abstracts were screened. After removal of duplicates and exclusions, 92 full-text articles were assessed for eligibility; 47 studies were deemed eligible, and 45 studies reporting 84 clinical signs or symptoms were included in the systematic review. Of 9751 total participants, 5266 (54.0%) were male; 30 of 45 studies reported mean or median ages younger than 60 years. Among 16 studies, most of which comprised participants who were previously hospitalized, the median proportion of individuals experiencing at least 1 persistent symptom was 72.5% (interquartile range [IQR], 55.0%-80.0%). Individual symptoms occurring most frequently included shortness of breath or dyspnea (26 studies; median frequency, 36.0%; IQR, 27.6%-50.0%), fatigue or exhaustion (25 studies; median frequency, 40.0%; IQR, 31.0%-57.0%), and sleep disorders or insomnia (8 studies; median 29.4%, IQR, 24.4%-33.0%). There were wide variations in the design and quality of the studies, which had implications for interpretation and often limited direct comparability and combinability. Major design differences included patient populations, definitions of time zero (ie, the beginning of the follow-up interval), follow-up lengths, and outcome definitions, including definitions of illness severity.

Figure 1. Reported Frequencies of Symptoms Examined by 5 or More Studies

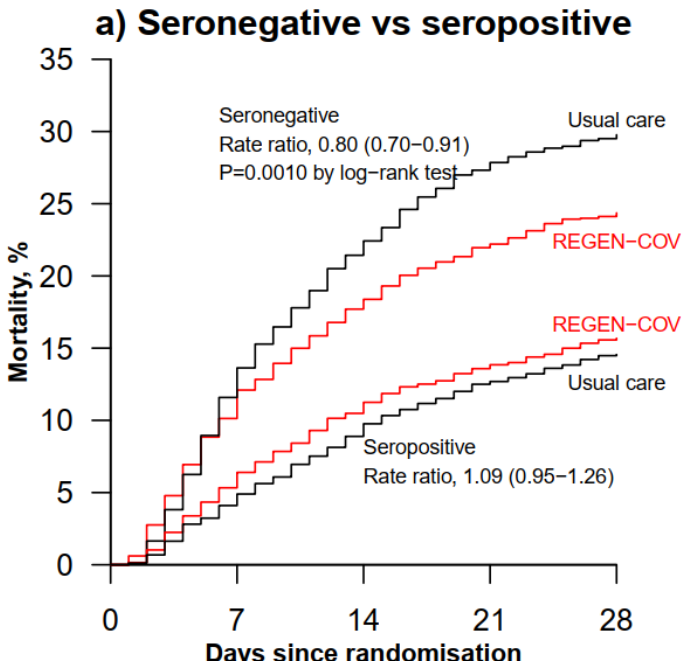


Comment: This systematic review found that COVID-19 symptoms commonly persisted beyond the acute phase of infection, with implications for health-associated functioning and quality of life. Current studies of symptom persistence are highly heterogeneous, and future studies need longer follow-up, improved quality, and more standardized designs to reliably quantify risks. See CDC above.

Casirivimab and Imdevimab in Patients Admitted to Hospital with COVID-19 (RECOVERY): A Randomised, Controlled, Open-Label, Platform Trial
RECOVERY Collaborative Group medRxiv published online June 15, 2021

doi.org/10.1101/2021.06.15.21258542
This is a randomized, controlled, open-label platform trial, where several possible treatments were compared with usual care in patients hospitalized with COVID-19. [RECOVERY format] Eligible and consenting patients were randomly allocated (1:1) to either usual standard of care alone (usual care group-90+% received steroids) or usual care plus a single dose of REGEN-COV 8g (casirivimab 4g and imdevimab 4g) by intravenous infusion (REGEN-COV group). The primary outcome was 28-day mortality assessed first among patients without detectable antibodies to SARS-CoV-2 at randomization (seronegative) and then in the overall population. Most patients enrolled were on supplemental oxygen (60+%). ~20% were on non-invasive ventilation.

9785 patients were randomly allocated to receive usual care plus REGEN-COV or usual care alone, including 315 (32%) seronegative patients, 5272 (54%) seropositive patients and 1360 (14%) patients with unknown baseline antibody status. In the primary efficacy population of seronegative patients, 396 (24%) of 1633 patients allocated to REGEN-COV and 451 (30%) of 1520 patients allocated to usual care died within 28 days (rate ratio 0·80; 95% CI 0·70-0·91; 43 p=0·0010). [20% reduction] In an analysis involving all randomized patients (regardless of baseline antibody status), 944 (20%) of 4839 patients allocated to REGEN-COV and 1026 (21%) of 4946 patients allocated to usual care died within 28 days (rate ratio 0·94; 95% CI 0·86 1·03; p=0·17). The proportional effect of REGEN-COV on mortality differed significantly between seropositive and seronegative patients (p value for heterogeneity = 0·001).



Comment: In this large UK trial involving nearly 10,000 patients showed that administering REGEN-COV on top of usual care reduced the risk of dying by 20% among hospitalized COVID-19 patients who had not produced antibodies to the virus yet. The drug had no effect among patients who had already produced antibodies. In the trial, REGEN-COV was used on top of dexamethasone, which has been associated with a 17% decrease in mortality. [N Engl J Med 2021; 384:693-704] What they observed was a layering effect on top of steroids in antibody negative patients. [see Kaplan Meier curve above] The RECOVERY Trial recently published their study using CP which showed no benefit. Given this new

information, should we now test admitted Covid-19 patients on supplemental oxygen for antibodies? If negative, should we now use REGEN-COV instead of RDV in combination with dexamethasone? Therapeutic use of REGEN-COV in the hospital setting should be restricted to seronegative patients. The dose of REGEN-COV used in this study was higher compared to those used in the outpatient setting. They did not study the emergence of resistance variants in this trial, the major variants circulating in the UK throughout the trial, including the B.1.1.7 (alpha) variant which was the dominant variant in the UK from December 2020 to April 2021, remained sensitive to REGEN-COV. Although spike glycoprotein mutations in some variants (e.g. B.1.351 [beta] and B.1.617 [delta]) have been associated with a reduction of neutralization activity of casivirimab, the combination of casirivimab with imdevimab retains potency against these variants due to the inhibitory activity of imdevimab. Currently in US delta variant is increasing. (See above)

Immunogenicity and Safety of the BNT162b2 mRNA COVID-19 Vaccine in Adult Patients with Autoimmune Inflammatory Rheumatic Diseases and in the General Population: A Multicentre Study
Ann Rheum Dis published online June 2021
doi:10.1136/ annrheumdis-2021-220647
This is a complicated multicenter observational study, to compare the immunogenicity and safety of the two-dose Pfizer vaccine between adult patients with AIIRD [autoimmune inflammatory rheumatic diseases] (n=686) and the general population (n = 121) by measuring serum immunoglobulin (Ig)G antibody levels against SARS-CoV-2 spike S1/S2 proteins 2-6 weeks after the second vaccine dose. Seropositivity was defined as IgG ≥15 binding antibody units (BAU)/mL. Patients with AIIRD were significantly older than controls (mean age, 56.76 vs 50.76 years; $P < 0.0001$). Rheumatoid arthritis (RA) was the most common disease (n = 263) among the patients with AIIRD, followed by psoriatic arthritis (PsA; n = 165), systemic lupus erythematosus (SLE; n = 101), systemic vasculitis (n = 70), axial spondyloarthritis (axSpA; n = 68) and idiopathic inflammatory myositis (IIM; n = 19).

The vaccine was immunogenic in most patients with AIIRD, with an acceptable safety profile. However, the study also found that treatment with glucocorticoids (GC), rituximab, mycophenolate mofetil (MMF), and abatacept was associated with a significantly reduced vaccine-induced immunogenicity. Following vaccination, the researchers found that the seropositivity rate (86% vs 100%, $P < 0.0001$) and S1/S2 IgG levels (mean, 132.9±91.7 vs 218.6±82.06 BAU/mL, $P < 0.0001$) were significantly lower among patients with AIIRD compared with controls. Study data showed that more than 97% of patients treated with anticytokine therapies, including tumor necrosis factor inhibitors, interleukin 17 inhibitors and interleukin 6 inhibitors, had an appropriate immunogenic response when used as monotherapy, while anti-CD20 therapies were found to significantly impair vaccine's immunogenicity, with the lowest seropositivity rate of 39%. The researchers also observed that the time interval between the prevaccination administration of rituximab and the vaccination had a significant impact on the vaccine's immunogenicity, with the seropositivity rate in patients vaccinated within 6 months after rituximab treatment being below 20%, compared to about 50% in patients who were vaccinated 1 year after rituximab treatment. Similarly, the use of GC (66%), MMF (64%), and abatacept (62%) was found to be significantly associated with reduced seropositivity rate. Multivariate regression analysis showed that age >65 years (adjusted odds ratio [OR] 0.43, [CI] 0.25-0.75, $P = 0.002$), treatment with GC (adjusted OR 0.48, 95% CI 0.26-0.87, $P = 0.02$), rituximab (adjusted OR 0.13, 95% CI 0.07-0.24, $P< 0.001$), MMF (adjusted OR 0.1, 95% CI 0.03-0.34, $P = 0.0013$), and abatacept (adjusted OR 0.14, 95% CI 0.04-0.43, $P<0.001$) were associated with reduced immunogenicity.

Comment: Most disease-modifying antirheumatic drugs, including methotrexate, anticytokine biologics, and Janus kinase inhibitors, can be continued with relation to the administration of the Pfizer

mRNA vaccine. Postponing treatment with rituximab, when feasible, should be considered to improve immunogenicity. Holding treatment with mycophenolate mofetil and abatacept, especially when combined with methotrexate, should be considered on an individual basis. This is to my knowledge the largest observational prospective study to examine the immunogenicity of the Pfizer mRNA vaccine in patients with AIIRD compared with controls. Bottom line, patients with impaired immunity due to drugs and/or disease even if fully vaccinated may still be at risk for contracting Covid-19. Further studies are needed to assess the durability of the humoral vaccination response, T-cell-mediated immunity in patients with a poor humoral response and long-term efficacy and safety of vaccination in patients with AIIRD. See next article.

Safety and Immunogenicity of a Third Dose of SARS-CoV-2 Vaccine in Solid Organ Transplant Recipients: A Case Series

Ann Intern Med published online June 15, 2021

doi:10.7326/L21-0282

This study included 30 solid organ transplant (SOT) recipients who had a suboptimal response to standard 2-dose Pfizer vaccine or Moderna vaccine and subsequently received a third dose of vaccine between March 20 and May 10, 2021. In 25 patients, maintenance immunosuppression included tacrolimus or cyclosporine plus mycophenolate. In addition, corticosteroids were used for 24 patients, sirolimus for 1 patient, and belatacept for 1 patient. The median time between transplantation and initial vaccination was 4.5 years (interquartile range [IQR], 2.3-10.5). Patients received the third dose of vaccine a median of 67 days (IQR, 54-81) after the second dose of their initial vaccine series. Of the patients, 15 received the J&J, 9 received the Moderna vaccine, and 6 received the Pfizer vaccine. Among SOT recipients, receiving a third dose of coronavirus disease 2019 (COVID-2019) vaccine increased antibody titers in one third of patients who had negative antibody titers, and in all patients who had low-positive antibody titers.

Comment: Limitations of this study include that this was a small and heterogeneous sample and the absence of assays for neutralizing antibody, B-cell memory, and T-cell responses. This study supports the use of clinical trials to determine whether booster doses to prevent COVID-19 in transplant and other immunosuppressed patients can be incorporated into clinical practice, as well as mixing different vaccines.

SARS-CoV-2 Delta VOC in Scotland: Demographics, Risk of Hospital Admission, and Vaccine Effectiveness

Lancet published online June 14, 2021

doi.org/10.1016/ S0140-6736(21)01358-1

On May 19, 2021, the Delta Variant of Concern (VOC), formerly known as B 1.617.2, became the dominant strain of SARS-CoV-2 in Scotland. The Alpha VOC (formerly known as B.1.1.7, or *S* gene negative) had been the dominant strain previously, but it has rapidly been replaced.

This analysis covered the period from April 1 to June 6, 2021, for the demographic distribution of cases. By April 1, 2021, 44·7% of the population in Scotland had received one dose of the COVID-19 vaccine, and 7·6% had received two doses. Among people aged 65 years or older, the percentages were 91·2% and 15·9%, respectively. By the end of the study period (i.e., June 6, 2021), 59·4% had received one dose and 39·4% two doses; the corresponding proportions were 91·7% and 88·8%, respectively for those aged 65 years or older. There were 19,543 confirmed SARS-CoV-2 infections over the period of interest, of whom 377 were admitted to hospital for COVID-19; 7723 (39·5%) of these cases and 134 (35·5%) hospital admissions were in those who were infected with the Delta variant. Most cases (70%) had no

underlying relevant comorbidities. 70% of Delta cases had not had any COVID-19 vaccination doses, compared to 75% of Alpha cases. The Cox regression analysis for time to hospital admission found that Delta cases were associated with an increased risk of COVID-19 hospital admission: hazard ratio (HR) 1·85 (95% CI 1·39–2·47) when compared to cases, after adjusting for age, sex, deprivation, temporal trend, and comorbidities. Considering the whole population cohort (rather than just hospital cases), the test-negative analysis to estimate vaccine effectiveness in preventing PCR-confirmed SARS-CoV-2 infection showed that, compared to those unvaccinated, at least 14 days after the second dose, Pfizer offered very good protection: 92% (95% CI 90-93) Alpha, 79% Delta. Protection associated with AstraZeneca vaccine was, however, substantial but reduced: 73% (95% CI 66-78) for Alpha cases versus 60% (53-66) for Delta.

Comment: In summary, this study showed that the Delta VOC in Scotland was found mainly in younger, more affluent groups. Risk of COVID-19 hospital admission was approximately doubled in those with the Delta VOC when compared to the Alpha VOC, with risk of admission particularly increased in those with five or more relevant comorbidities. Both the AstraZeneca and Pfizer COVID-19 vaccines were effective in reducing the risk of SARS-CoV-2 infection and COVID-19 hospitalization in people with the Delta VOC, but these effects on infection appeared to be diminished when compared to those with the Alpha VOC. [but still rather good ~80% for Pfizer] The AstraZeneca vaccine appeared less effective than the Pfizer vaccine in preventing SARS-CoV-2 infection in those with the Delta VOC. This may be a preview of what to expect in the US by this fall as Delta VOC increases. See above.