I hope everyone had a wonderful weekend

Today under COVID-19 News I review the initial results of using SQ Regeneron in exposed household contacts, followed by Revised NIH Guidance on Monoclonals, ending with the announcement that Pfizer is seeking EUA authorization for children 12-15.

Under literature review the first article demonstrated anticoagulants at discharge, mostly in prophylactic doses, were associated with a 46% decrease in the composite endpoint of major thromboembolic events. The second article showed that a considerable portion of low-risk HCP with mild COVID-19 reported several long-term symptoms, and that these symptoms disrupted work, social, and home life. The last 3 articles look at different aspects of vaccines and plasma in neutralizing activity against wild types and variants.

Have a great week

Ed

COVID-19 News

Regeneron
The newest prevention study enrolled about 1,500 people living with someone recently diagnosed with Covid-19. They were randomly assigned to receive Regeneron monoclonal or a placebo. After one month, 1.5% of volunteers receiving REGEN-COV had symptomatic Covid-19 infections, compared with 7.8% of those who received a placebo, amounting to an 81% risk reduction. There were no hospitalizations or emergency-room visits stemming from Covid-19 among volunteers taking Regeneron's drug, compared with four volunteers in the placebo group, according to the company. In Regeneron's prevention study, volunteers were given the drug with simpler-to-use subcutaneous injections.

Comments: This is great news on 2 fronts**:** First, it prevented symptomatic infection in household contacts and second, the convenient subcutaneous administration of REGEN-COV could help control outbreaks in high-risk settings where individuals have not yet been vaccinated, including individual households and group living settings. In addition, could avoid sending patients for infusions. See below.

NIH Monoclonal Antibodies Guidance Update
The National Institutes of Health COVID-19 Treatment Guidelines Panel now recommends that outpatients with mild-to-moderate COVID-19 at high risk for clinical progression be given either of these monoclonal antibody combinations:

- Bamlanivimab (700 mg) plus etesevimab (1400 mg)

- Casirivimab (1200 mg) plus imdevimab (1200 mg)

The panel notes that some SARS-CoV-2 variants have shown to be less susceptible to monoclonal antibodies, particularly bamlanivimab, *in vitro*, but it is not known what the clinical implications might be. Because of these concerns, the panel recommends against bamlanivimab monotherapy. Some panel

members said that in areas where variants with reduced *in vitro* susceptibility to bamlanivimab and etesevimab are common, it would be reasonable to choose casirivimab plus imdevimab.

Pfizer Children 12-15
Pfizer has requested EUA from FDA For Their Coronavirus Vaccine for Children Between 12 And 15 based on phase 3 studies showing high efficacy and safety in this age group.

Comment: This is very encouraging. I believe the FDA will hear request in ~3 weeks. Moderna I am sure will not be far behind and Novavax also is conducting trials in children. If approved before the summer, I hope all children in middle school and high school can be vaccinated before the start of the fall semester.

Journal Review

Post-Discharge Thromboembolic Outcomes and Mortality of Hospitalized COVID-19 Patients: The CORE-19 Registry
Blood published online April 6, 2021
doi.org/10.1182/blood.2020010529
The investigators developed a prospective registry which included consecutive COVID-19 patients hospitalized a multihospital system from March 1- May 31, 2020. They recorded demographics, comorbidities, laboratory parameters, medications, post-discharge thromboprophylaxis, and 90-day outcomes. Data from electronic health records, health informatics exchange, a radiology database, and telephonic follow-up were merged. The primary outcome was a composite of adjudicated VTE, ATE, and all-cause mortality (ACM). The principal safety outcome was major bleeding (MB). Among 4,906 patients (53.7% male) mean age was 61.7 years. Comorbidities included hypertension (38.6%), diabetes (25.1%), obesity (18.9%), and cancer history (13.1%). Post-discharge thromboprophylaxis was prescribed in 13.2%. VTE rate was 1.55%, ATE 1.71%, ACM 4.83%, and MB 1.73%. The composite primary outcome rate was 7.13% and was significantly associated with advanced age (OR: 3.66, 95%CI: 2.84-4.71), prior VTE (OR: 2.99, 95%CI: 2.00-4.47), ICU stay (OR: 2.22, 95%CI: 1.78-2.93), chronic kidney disease (CKD) (OR: 2.10, 95%CI: 1.47- 3.0), peripheral arterial disease (OR: 2.04, 95%CI: 1.10-3.80), carotid occlusive disease (OR: 2.02, 95%CI: 1.30-3.14), IMPROVE-DD VTE score ≥4 (OR: 1.51, 95%CI: 1.06-2.14), and coronary artery disease (OR: 1.50, 95%CI: 1.04-2.17). Post-discharge anticoagulation was significantly associated with reducing the primary outcome (OR: 0.54, 95%CI: 0.47-0.81).

Comment: Based on their registry, the 90-day post-discharge venous and arterial thromboembolism and all-cause mortality rates were 1.55%, 1.71%, and 4.83%. Anticoagulants at discharge, mostly in prophylactic doses, were associated with a 46% decrease in the composite endpoint of major TE or ACM. This is an important consideration in discharge planning for recovering hospitalized COVID-19 patients

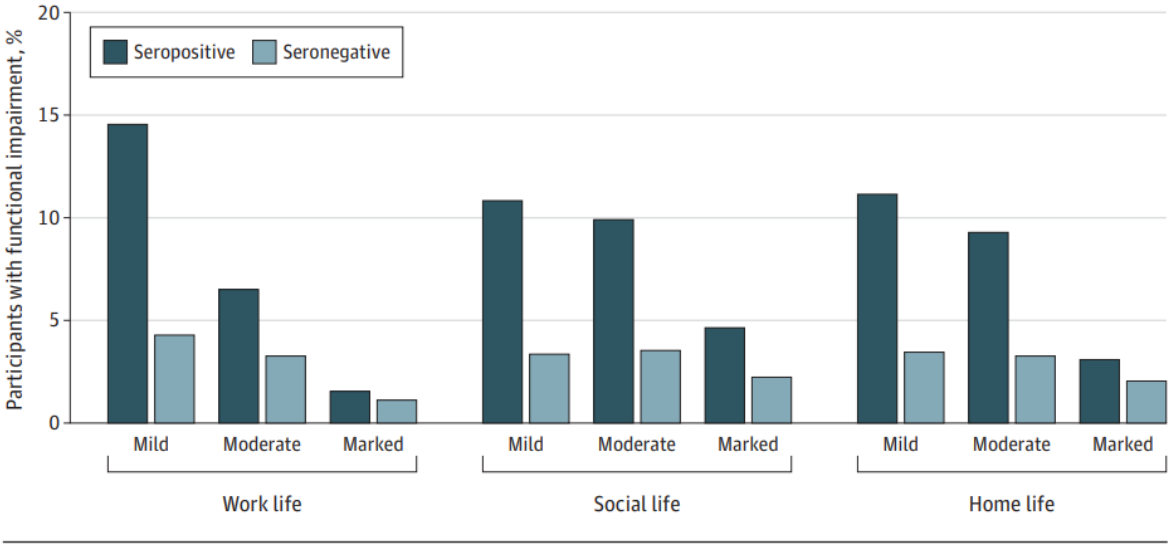
Symptoms and Functional Impairment Assessed 8 Months After Mild COVID-19 Among Health Care Workers
JAMA published online April 7, 2021.
doi:10.1001/jama.2021.5612
Between April 15, 2020, and May 8, 2020, HCP in Sweden, were invited to participate. Participants had blood sampling performed every 4 months. Demographics, symptoms and severity (mild or severe), and chronic diseases were obtained through questionnaires at baseline. Participants who were seropositive

for SARS-CoV-2 anti-spike IgG at baseline and who reported severe symptoms were excluded, as were initially seronegative participants who seroconverted during follow-up.

At the 8-month follow-up (January 11-29, 2021), participants reported via smartphone app the presence, duration (<2months, ≥2 months, ≥4 months, ≥8 months), and severity (mild, moderate, or severe) of 23 predefined symptoms. For participants reporting at least 1 symptom persistent for at least 2 months, the Sheehan Disability Scale was used to score functional impairment from present or prior long-term symptoms (0, not at all; 1-3, mild; 4-6, moderate; and 7-10, marked) in 3 interrelated domains (work, social, and home life). Participant enrollment was closed after 2149 of 4375 HCP (49%) enrolled; 393 were seropositive. Fifty seropositive participants with severe symptoms and 404 seronegative participants who seroconverted were excluded.

Comparing seropositive vs seronegative participants, 26% vs 9% reported at least 1 moderate to severe symptom lasting for at least 2 months (RR, 2.9 [95% CI, 2.2-3.8]) and 15% vs 3% reported at least 1 moderate to severe symptom lasting for at least 8 months (RR, 4.4 [95% CI, 2.9-6.7]. The most common moderate to severe symptoms lasting for at least 2 months in the seropositive group were anosmia, fatigue, ageusia, and dyspnea.

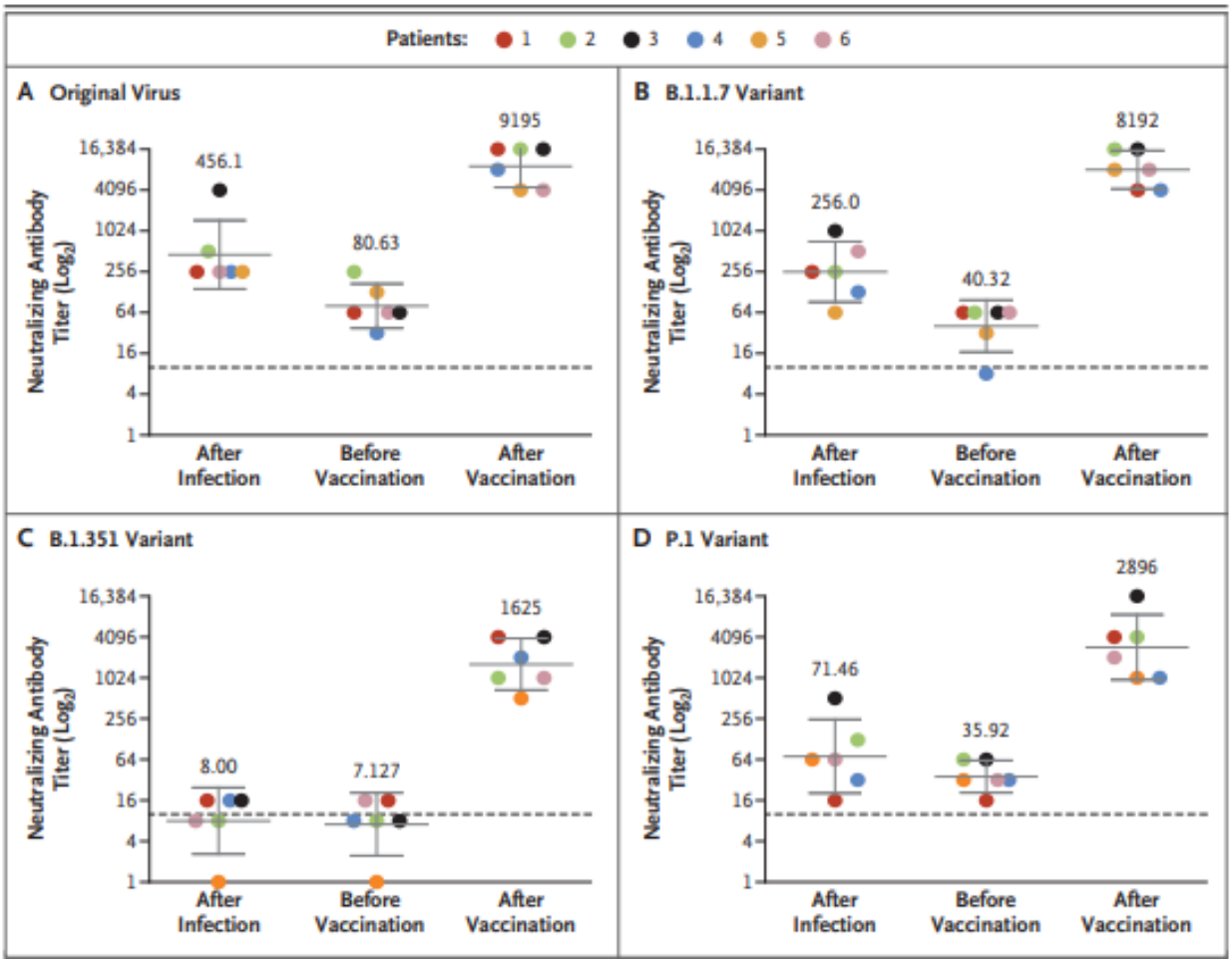
Figure. COVID-19–Related Long-term Functional Impairment



Comment: The results of this study showed that a considerable portion of low-risk individuals with mild COVID-19 reported several long-term symptoms, and that these symptoms disrupted work, social, and home life. Major limitations of the study include the possibility of recall bias and the subjective rating of symptoms. Nonetheless this study adds to the mounting evidence of prolonged symptom duration in people recovering from COVID-19.

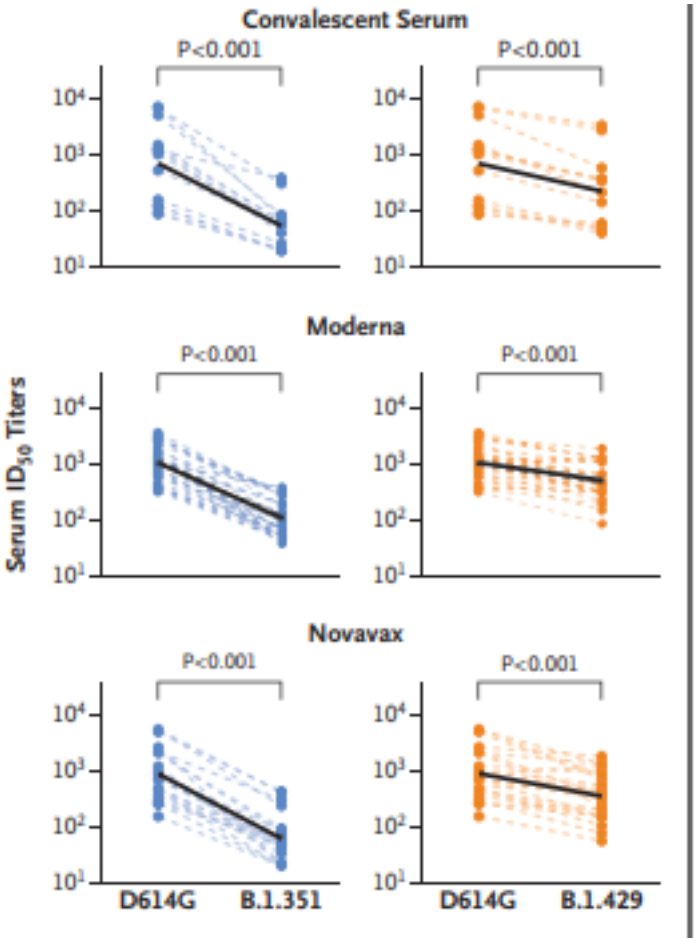
Neutralizing Response against Variants after SARS-CoV-2 Infection and One Dose of BNT162b2
N Engl J Med published online April 7, 2021
DOI: 10.1056/NEJMc2104036
In those who have already had COVID-19, a single dose of the Pfizer vaccine had substantially increased neutralizing activity against several circulating variants. Investigators used 18 serum samples from six healthcare workers previously infected with the original wild type virus. In the weeks after infection and

again right before vaccination, neutralizing activity was shown against the original virus and the B.1.1.7 (U.K. variant) and P.1 (first seen in Brazil) variants, but not the B.1.351 (South Africa variant). Within weeks of vaccination, neutralizing antibody titers were 81-228 times as high as before vaccination, with significant improvement in all strains.



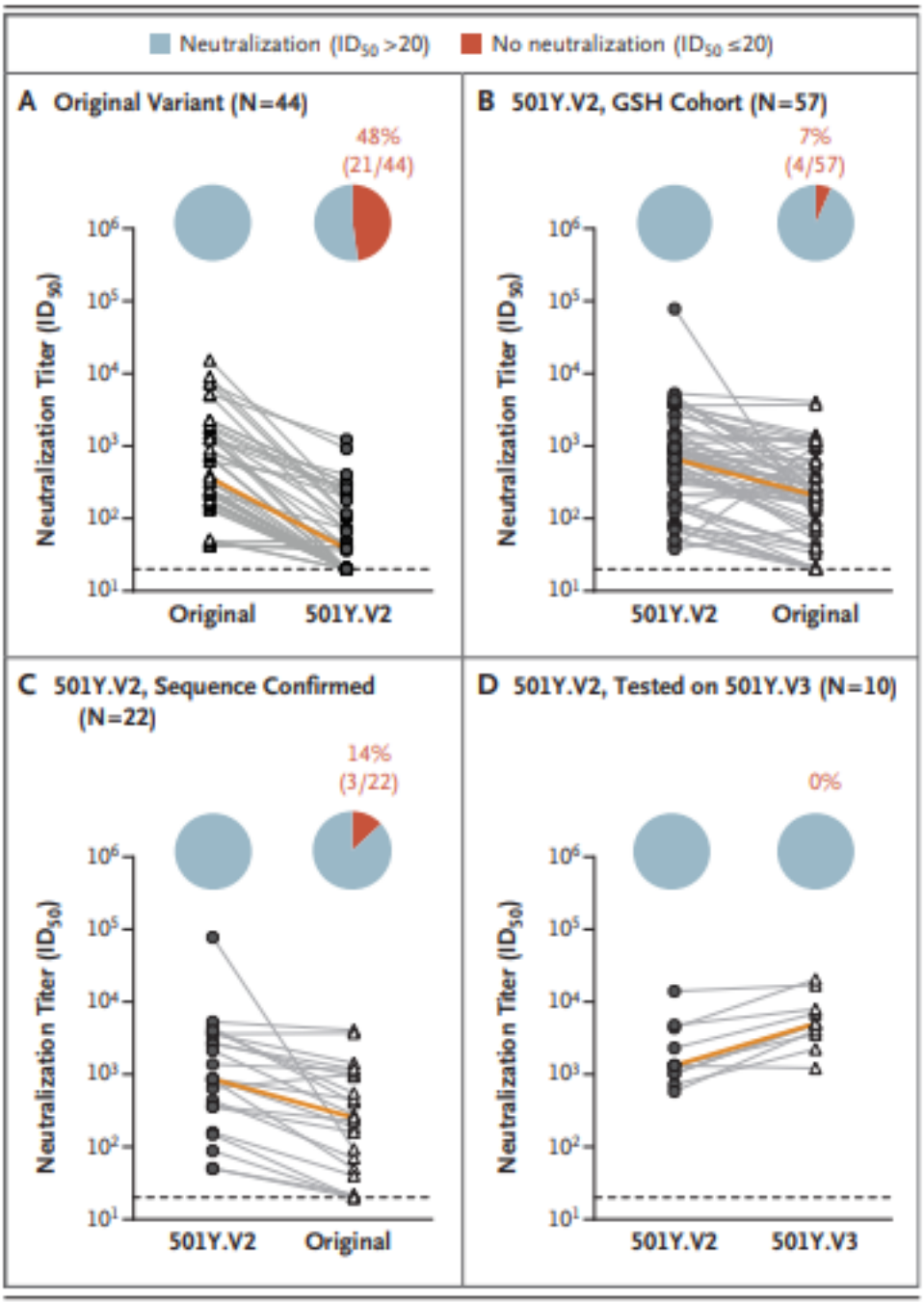
Comment: This highlights the importance of vaccination even in previously infected patients, given the added benefit of an increased antibody response to the variants tested. This is a small cohort, but these results are very encouraging. See next article.

Neutralization of SARS-CoV-2 Variants B.1.429 and B.1.351
N Engl J Med published online April 7, 2021
DOI: 10.1056/NEJMc2103740
Researchers studied serum from 49 Novavax and Moderna vaccine recipients. Relative to the original strain, B.1.429 (first identified in California) was 2-3 times less sensitive to neutralization by convalescent serum and by serum samples from vaccinated people, while B.1.35 (South African) was 9-14 times less sensitive. The investigators say vaccine-elicited neutralizing antibodies are likely to remain effective against the B.1.429 variant.



Comment: The modestly lower value in neutralization titers against the B.1.429 variant seen in this study is similar to that we saw previously when neutralization of the B.1.1.7 variant (UK) was tested with the same assay using serum samples obtained from recipients of the Moderna and Novavax vaccines. [Cell Host Microbe 2021 published March 5, 2021] However, magnitude of resistance seen with the B.1.351 variant is of greater concern with respect to current vaccines. Studies still suggest that even with lower vaccine neutralization against B.1.351-elicited neutralizing antibodies, vaccines still may impact severity and deaths. See article above and next article.

Cross-Reactive Neutralizing Antibody Responses Elicited by SARS-CoV-2 501Y.V2 (B.1.351)
N Engl J Med published online April 7, 2021
DOI: 10.1056/NEJMc2104192
Researchers studied roughly 90 hospitalized COVID-19 patients in South Africa. All were infected with the B.1.351 strain. Plasma from these patients-maintained neutralization against both the original virus and against the P.1 variant (Brazil). The investigators suggest that vaccines built on the spike protein of 501Y.V2 [B.1.351] may be promising candidates for the elicitation of cross-reactive neutralizing antibody responses to SARS-CoV-2 to multiple variants.



Comment: The investigators found that 501Y.V2 elicits robust neutralizing antibody responses against both the original variant and 501Y.V3 (P.1), which indicates high levels of cross-reactivity. This data indicate that vaccines built on the spike protein of 501Y.V2 may be promising candidates for the next generation of vaccines.