I am back! Just finished the 4th Annual Texas Medical Center AMR and Stewardship Meeting. Wonderful meeting!

On another note, my computer crashed, and I am trying to rebuild my distribution list, so I apologize for the delay. I hope you all get today's.

For today under COVID-19 News, see initial report on Novavax vaccine and first report of the of B1.351 (a variant of COVID-19 first discovered in South Africa).

Under Journal Review, a pre-publication the first reviews neutralization of SARS-CoV-2 spike 69/70 deletion, E484K, and N501Y variants by 2 BNT162b2 vaccine-elicited sera (Pfizer). The second article is an interesting article on use of colchicine as an outpatient treatment for high-risk patients with early symptoms. May be an oral alternative for parenteral therapeutics. The next article is the first randomized clinical trial to report the effects of anakinra in patients with mild-to-moderate COVID-19 pneumonia. The last 2 articles review the experience of K-12 this past fall. See my comments.

Have a wonderful weekend.

Ed

COVID-19 News

Novavax Vaccine Trials
Candidate NVX-CoV2373, from Novavax, has reported phase 3 findings showing 89.3% efficacy in prevention of COVID-19 in participants from the UK. NVX-CoV2373 is a vaccine comprised of a full-length, prefusion spike protein made of proprietary recombinant nanoparticle technology and the saponin-based Matrix-M adjuvant. Produced in insect cells, the purified protein is encoded by the SARS-CoV-2 spike protein genetic sequence.

Investigators enrolled 15,000-plus adult participants aged 18-84 years old, to assess the vaccine for a primary endpoint of occurrence of PCR-confirmed, symptomatic COVID-19 with onset at least 7 days following the booster vaccine dose in participants serologically negative for SARS-CoV-2 at baseline. More than one-fourth (27%) of trial participants were older than 65 years.

In the first interim analysis of 62 COVID-19 cases, 56 (89.2%) were observed in the placebo arm, versus just 6 in the vaccine group (95% CI, 75.2 – 95.4). Of the 62 cases, just 1 was severe—from a placebo patient. The UK variant strain was detected in more than half of all observed cases, investigators noted (n = 32). In a post hoc assessment, investigators reported that NVX-CoV2373 was 95.6% efficacious against the original COVID-19 strain, and 85.6% efficacious versus the UK variant strain.

In the phase 2b clinical trial in South Africa assessing the vaccine versus placebo in 4400-plus adult participants from August 2020 to mid-January 2021, investigators reported a 60% efficacy (95% CI, 19.9 – 80.1) in prevention of COVID-19 among participants. Most had the B1.351 variant, ~90%.

Comment: These results clearly show that the vaccine is less protective against the South African variant; however, the 60% reduced risk against COVID-19 illness in vaccinated individuals in South

Africans still underscores the value of this vaccine to prevent illness albeit less protective than against the UK variant. Pfizer lab found antibodies were slightly less effective against B1.351. See below.

South African COVID Variant Detected in South Carolina
CDC today confirmed the first US cases of B1.351 (a variant of COVID-19 first discovered in South Africa) in South Carolina. The variant was detected in two people with no known travel history and no contact with one another. Preliminary data suggests this variant may spread more easily and quickly than other variants.

Comment: More than 26 states have reported more than 300 cases of B117, a variant to date. Earlier this week, Minnesota reported the first US case of variant P.1 (known as the Brazilian variant) in someone who had recently traveled to that country**.**

Journal Review

Neutralization of SARS-CoV-2 Spike 69/70 Deletion, E484K, and N501Y Variants by 2 BNT162b2 Vaccine-Elicited Sera
bioRxiv published online January 27, 2021
The investigators at Pfizer engineered three SARS-CoV-2 viruses containing key spike mutations from the 22 newly emerged United Kingdom (UK) and South African (SA) variants: N501Y from UK and SA; 23 69/70-deletion+N501Y+D614G from UK; and E484K+N501Y+D614G from SA. Neutralization 24 geometric mean titers (GMTs) of twenty BTN162b2 vaccine-elicited human sera against the 25 three mutant viruses were 0.81- to 1.46-fold of the GMTs against parental virus, indicating small 26 effects of these mutations on neutralization by sera elicited by two BNT162b2 doses. The magnitude of the differences in neutralization GMTs against any of the mutant viruses in this study was small (0.81- to 1.41-fold), as compared to the 4-fold differences in hemagglutination inhibition titers that have been used to signal potential need for a strain change in influenza vaccines. Researchers didn't assess whether their results were statistically significant.

Comment: A recent preliminary study by Moderna, in collaboration with scientists at the NIH showed antibodies generated by its vaccine were less effective at binding the mutated spike proteins of the South African variant. [bioRxiv published online January 25, 2021] The researchers did not find a difference for the UK variant's spike proteins. As a precaution, the company said it was developing a booster shot for the South Africa variant. Bottom line seems to be, we are OK for now against B.1.1.7, but the vaccine may be less effective against B1.351.

Efficacy of Colchicine in Non-Hospitalized Patients with COVID-19: COLCORONA Trial Treating Non-Hospitalized Patients
medRxiv published online January 26, 2021
COLCORONA is a randomized, double-blind, placebo-controlled trial comparing colchicine (0.5 mg twice daily for the first 3 days and then once daily for 27 days thereafter) with placebo in a 1:1 ratio. The clinical trial took place in non-hospitalized patients. It has been conducted in Canada, the United States, Europe, South America and South Africa. It was designed to determine whether colchicine could reduce the risk of severe complications associated with COVID-19. COLCORONA was conducted among approximately 4,500 COVID-19 patients not hospitalized at the time of enrollment, with at least one risk factor for COVID-19 complications. This is the world's largest study testing an orally administered drug in non-hospitalized patients with COVID-19.

The analysis of the 4159 patients in whom the diagnosis of COVID-19 was proven by a NP PCR test showed that the use of colchicine was associated with statistically significant reductions in the risk of death or hospitalization compared to placebo. In these patients with a proven diagnosis of COVID-19, colchicine reduced hospitalizations by 25%, the need for mechanical ventilation by 50%, and deaths by 44%.

Comment: This is the world's largest study testing an orally administered drug in non-hospitalized patients with COVID-19. The study makes colchicine the world's first oral drug that could be used to treat non-hospitalized patients with COVID-19. Currently, the list of outpatient therapies that work for COVID-19 includes convalescent plasma and monoclonal antibodies, which require infusions, must be started very early after symptom onset. We await peer review of this online publication.

Effect of Anakinra Versus Usual Care in Adults in Hospital with COVID-19 and Mild-to-Moderate Pneumonia (CORIMUNO-ANA-1): A Randomised Controlled Trial
Lancet Resp Med published online January 22, 2021
doi.org/10.1016/ S2213-2600(20)30556-7
This multicenter trial included patients with mild-to-moderate COVID-19 pneumonia requiring at least 3 L/min of oxygen by mask or nasal cannula but without ventilation assistance, a score of 5 on the WHO Clinical Progression Scale (WHO-CPS), and a C-reactive protein serum concentration of more than 25 mg/L not requiring admission to the intensive care unit at admission to hospital. Patients were randomly assigned to receive either usual care plus anakinra (200 mg twice a day on days 1–3, 100 mg twice on day 4, 100 mg once on day 5) or usual care alone. The two coprimary outcomes were the proportion of patients who had died or needed non-invasive or mechanical ventilation by day 4 (i.e., a score of >5 on the WHO-CPS) and survival without need for mechanical or non-invasive ventilation (including high-flow oxygen) at day 14. A total of 114 patients with a median age of 66 years, comprising 70% men, were included in the final analysis.

On day 4, 21 (36%) of 59 patients in the anakinra group had a WHO-CPS score of more than 5 compared to 21 (38%) of 55 in the usual care group (median posterior absolute risk difference [ARD], −2.5%; 90% credible interval [CrI], −17.1 to 12.0). The posterior probability of any efficacy of anakinra (i.e., ARD of less than 0) was 61.2%, while the median posterior adjusted odds ratio was 0.90 (90% CrI, 0.47 to 1.73).

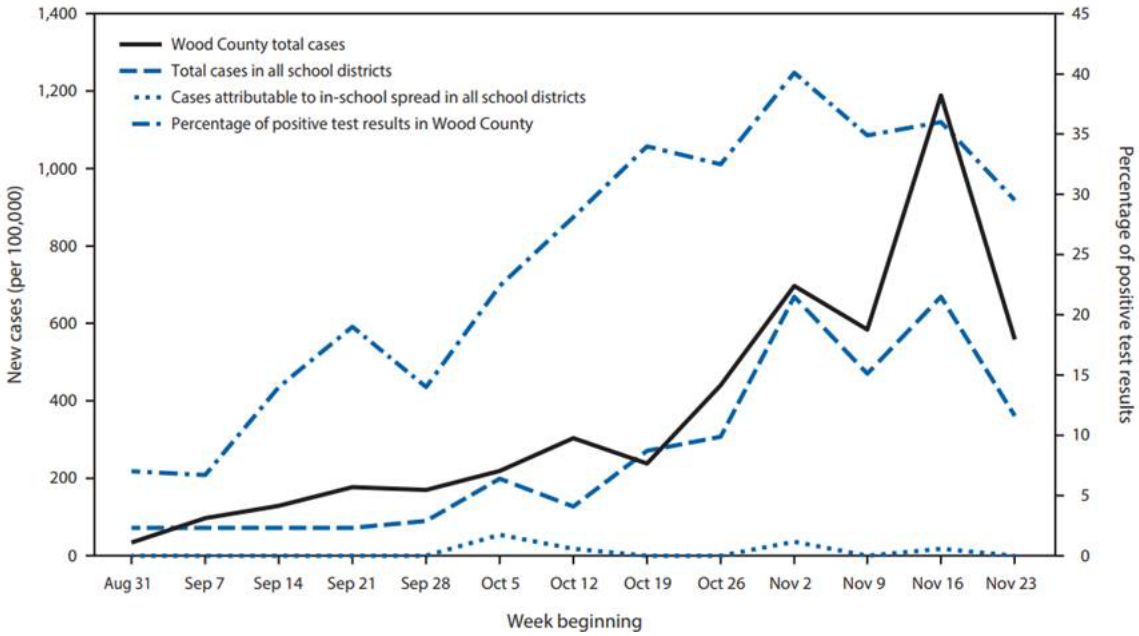
Meanwhile, at day 14, 28 (47%; 95% confidence interval [CI], 33 to 59) patients in the anakinra group and 28 (51%; 95% CI, 36 to 62) patients in the usual care group needed ventilation or died, with a posterior probability of any efficacy of anakinra (hazard ratio [HR] being less than 1) of 54.5% (median posterior HR 0.97; 90% CrI 0.62 to 1.52). The study was stopped early following the recommendation of the data and safety monitoring board.

Comment: Anakinra is a recombinant human IL-1 receptor antagonist. This is the first randomized clinical trial to report the effects of anakinra in patients with mild-to-moderate COVID-19 pneumonia requiring at least 3 L/min of oxygen but not receiving non-invasive or invasive mechanical ventilation at randomization. Dexamethasone is now SOC in the treatment of mild-to-moderate, severe, or critical COVID-19. The trial was not blinded, and a potential significant limitation is that usual care differed among centers and over time, especially regarding corticosteroid use. Lastly the sample size was small, restricting the power of the study, and the CrIs and CIs were wide. The findings here do not preclude the possible efficacy of anakinra in more severe cases of COVID-19 as we have seen in the recent IL-6 antagonist results.

COVID-19 Cases and Transmission in 17 K-12 Schools —Wood County, Wisconsin, August 31–November 29, 2020

MMWR published online January 26, 2021

Current evidence suggests that transmission of SARS-CoV-2 in kindergarten through grade 12 (K-12) schools might not significantly contribute to COVID-19 spread nationwide. During August 31-November 29, 2020, COVID-19 cases, spread, and compliance with mask use were investigated among 4,876 students and 654 staff members who participated in in-person learning in 17 K-12 schools in Wisconsin. School-attributable COVID-19 case rates were compared with rates in the surrounding community. School administration and public health officials provided information on COVID-19 cases within schools. During the study period, widespread community transmission was observed, with 7%-40% of COVID-19 tests having positive results. Masking was required for all students and staff members at all schools, and rate of reported student mask-wearing was high (>92%). COVID-19 case rates among students and staff members were lower (191 cases among 5,530 persons, or 3,453 cases per 100,000) than were those in the county overall (5,466 per 100,000). Among the 191 cases identified in students and staff members, one in 20 cases among students was linked to in-school transmission; no infections among staff members were found to have been acquired at school.



Neutralization of SARS-CoV-2 spike 69/70 deletion, E484K, and N501Y variants by 2 BNT162b2 vaccine-elicited sera

Comment: With masking requirements and student cohorting, transmission risk within schools appeared to be very low, suggesting that schools can safely open with appropriate mitigation efforts in place. This is one of several publications with the same result. The key is to open with the appropriate safety/mitigation interventions in place.

Data and Policy to Guide Opening Schools Safely to Limit the Spread of SARS-CoV-2 Infection

JAMA published online January 26, 2021

doi:10.1001/jama.2021.0374

Planning for the 2020/2021 school year included much uncertainty about the risk of transmission in school settings. While the benefits of in person school attendance are well understood, the appropriate evaluation of its risks vs benefits was hampered initially by limited information about transmission risk in classroom settings. Closing schools has been shown to adversely affect students' academic progress, mental health, and access to essential services; however, if SARS-CoV-2 rapidly spread in classrooms, opening schools might accelerate community transmission of the virus. In the beginning there were no simple decisions for parents, teachers, administrators, or public officials.

As many schools have reopened for in-person instruction in some parts of the US as well as internationally, school-related cases of COVID-19 have been reported, but there has been little evidence that schools have contributed to increased community transmission. A case-control study of exposures among children aged 0 through 18 years with (n = 154) and without (n = 243) SARS-CoV-2 infection in Mississippi found that having attended gatherings and social functions outside the home as well as having had visitors in the home was associated with increased risk of infection; however, in-person school attendance during the 14 days prior to diagnosis was not. [Mississippi, September-November 2020. MMWR 2020;69(50):1925-1929. Reviewed in the Daily Briefing several months ago]

In the fall of 2020, 11 school districts in North Carolina with more than 90,000 students and staff were open for in person education for 9 weeks. [Pediatrics. 2021-just review 2 weeks ago in the Daily Briefing]. During this time, within school transmissions were very rare (32 infections acquired in schools; 773 community-acquired infections) and there were no cases of student-to-staff transmission. Similarly, in a report released by CDC on January 26, 2021, with data from 17 K-12 schools in rural Wisconsin with high mask adherence (4876 students and 654 staff), COVID-19 incidence was lower in schools than in the community. [see above] During 13 weeks in the fall of 2020, there were 191 COVID-19 cases in staff and students, with only 7 of these cases determined to result from in-school transmission.

Comment: The available evidence from the fall school semester has been reassuring. Preventing transmission in school settings will require addressing and reducing levels of transmission in the surrounding communities as well through policies to interrupt transmission (e.g., restrictions on indoor dining at restaurants and gatherings). In addition, all recommended mitigation measures in schools must continue: requiring universal face mask use, increasing physical distance by dedensifying classrooms and common areas, using hybrid attendance models when needed to limit the total number of contacts and prevent crowding, increasing room air ventilation, and expanding screening testing to rapidly identify and isolate asymptomatic infected individuals. Staff and students should continue to have options for online education, particularly those at increased risk of severe illness or death if infected with SARS-CoV-2.

However, some school-related activities have increased the risk of SARS-CoV-2 transmission among students and staff. Numerous media reports of COVID-19 outbreaks among US high school athletic teams suggest that contact during both practices and competition, and at social gatherings associated with team sports, increase risk.

I want to leave everyone with some last thoughts: The first fact is that remote learning is not optimal, especially for disadvantaged students. Reports have surfaced where online classes in which almost no students show up (or not really listening), schedules rearranged at the last minute, zoom links that are inaccessible and poor access to high-speed internet. The broader data on school closure is sobering.

Second, mental health problems have increased. [recent report of increase in suicides in Las Vegas] Third the children who are attending are not learning as much. A Stanford study suggested that the average student has lost at least a third of a year's worth of learning in reading and three quarters of a year's worth of learning in math. The effects could be long term. Finally, the fact is that this situation is especially devastating to disadvantaged and minority students. Many affluent kids have fled the public school for private schools. More importantly we now know in-person learning can be done safely with the right precautions.