Good morning.

The big news for COVID-19 is the CDC guidance for fully vaccinated people – see my comments. Under journal review, the first article suggests vaccination is not only important for an individual's protection but can reduce transmission. The second article confirms that the Pfizer vaccine can still neutralize B.1.351 and P.1 variants. The third article documents local reactions to mRNA vaccines which we have all seen. The next article used data from 555 US medical centers via the Vizient clinical database to look at outcomes and mortality in patients hospitalized with COVID-19. The last article confirms what many of us have experienced and prior articles suggested, morbid obesity increases severity and mortality in patients infected with COVID-19.

Have a wonderful day

Ed

COVID-19 News

CDC Interim Public Health Recommendations for Fully Vaccinated People
March 8, 2021
According to the new guidance, people who are at least 2 weeks out from their last dose can:

- Visit with other fully vaccinated people indoors without wearing masks or physical distancing.
- Visit with unvaccinated people from a single household who are at low risk for severe COVID-19 disease indoors without wearing masks or physical distancing.
- Avoid quarantine and testing following exposure to someone if they remain asymptomatic.

However, there are still restrictions that will remain until further data is collected. Those who are fully vaccinated must still:

- Wear masks and physically distance in public settings and around people at high risk for severe disease.
- Wear masks and physically distance when visiting unvaccinated people from more than one household.
- Avoid medium- and large-sized gatherings.
- Avoid unnecessary travel.
- Higher-risk situations include indoor dining, bars, gyms, and houses of worship, where people are singing and talking.

Comment: I think this is a good first step. The CDC guidelines note that evidence increasingly suggests that vaccinated people are potentially less likely to transmit the virus through asymptomatic infections, but there are also outstanding questions on the duration of the vaccines' protection and the effect of emerging variants. Recent studies found that vaccination reduced asymptomatic infection more than 80% when compared to unvaccinated individuals and nasal viral loads are lower and potentially less infectious. More conclusive data is needed. (See below) Some experts are saying there should be no limits on the size of gatherings for fully vaccinated individuals. There is currently no authorized vaccine for children and adolescents under 16 years old. This is going to be an issue family will have to consider. Dr. Sax at BWH commented that we know there is a significant difference between young children and adolescents or teens in terms of both transmission of the virus as well as getting the disease. Teenagers get and transmit Covid-19 similarly to young adults, while younger children do not get symptomatic

disease as often and do not appear to transmit as much. He says, “Every family and every group of friends is going to make decisions based on their own risk tolerance.” The travel comment is very conservative since some experts believe fully vaccinated people, including healthy grandparents, can travel safely if they take the appropriate precautions, such as wearing masks when in public.

This is not the time to run to a crowded bar where people are shouting at each other. We are not out of the woods yet!

Journal Review

Initial Real-World Evidence for Lower Viral Load of Individuals Who Have Been Vaccinated by BNT162b2
medRxiv published online February 8, 2021
doi.org/10.1101/2021.02.08.21251329
The vaccination rollout started on Dec 20, 2020, utilized mainly the Pfizer vaccine, and focused on individuals who are 60 years or older. More than 75% of the individuals of this age group have been at least 14 days after the first dose, compared to 25% of the individuals between ages 40-60 years old. The investigators traced the Ct value distribution of 16,297 positive qPCR tests in their lab between Dec 1st to Jan 31st that came from these two age groups. The hypothesis was that if vaccines reduce viral load, we should see a difference in the Ct values between these two age groups in late January but not before. Consistent with this hypothesis, until Jan 15th, they did not find any statistically significant differences in the average Ct value between the groups. In stark contrast, their results in the last two weeks of January show a significant weakening (higher Ct) in the average Ct value of 60+ individuals to the 40-60 group. To further corroborate these results, they also used a series nested linear models to explain the Ct values of the positive tests. This analysis favored a model that included an interaction between age and the late January time period consistent with the effect of vaccination. They then used demographic data and the daily vaccination rates to estimate the effect of vaccination on viral load reduction. Their estimate suggests that vaccination reduces the viral load by 1.6x to 20x in individuals who are positive for SARS-CoV-2. Results predict that positive vaccinated individuals are expected to have a lower viral load that is proportional to 0.72-4.29 cycles.

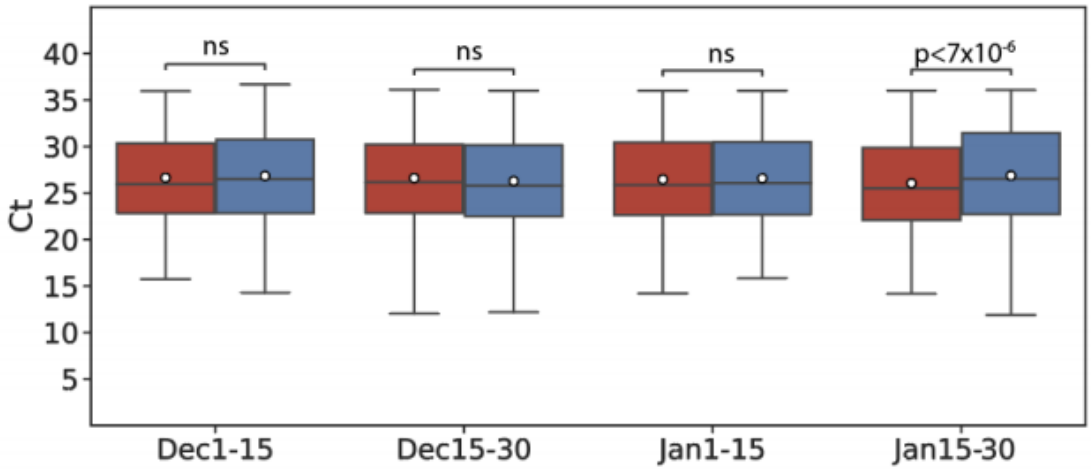


Figure 2: The Ct values for the two age groups as a function of time. Blue: 60+ individuals. Red: Individuals between age 40-60yrs. The first three time periods did not exhibit any statistically significant differences between the average Ct values. After Jan 15th, the individuals over age 60 showed a statistically significant weaker Ct value compared to individuals between age 40 to 60.

Comment: These estimates might improve after more individuals receive the second dose. Taken together, these findings suggest vaccination is not only important for the individual's protection but can also reduce transmission.

Neutralizing Activity of BNT162b2-Elicited Serum
N Engl J Med published online March 8, 2021
DOI: 10.1056/NEJMc2102017
New variants that were first detected in the United Kingdom (B.1.1.7 lineage), South Africa (B.1.351 lineage), and Brazil (P.1 lineage) with mutations in the *S* gene are spreading globally. To analyze effects on neutralization elicited by the Pfizer vaccine the investigators engineered *S* mutations from each of the three new lineages into USA-WA1/2020, a relatively early isolate of the virus from January 2020 thereby producing three recombinant viruses representing each of these lineages and two additional ones which they engineered from subsets of mutations of the B.1.351 lineage. The first recombinant virus had all the mutations found in the *S* gene in the B.1.1.7 lineage (B.1.1.7-spike), the second had all the mutations found in the *S* gene in the P.1 lineage (P.1-spike), the third had all the mutations found in the *S* gene in the B.1.351 lineage (B.1.351-spike), the fourth had an N-terminal domain deletion found in the B.1.351 lineage and the globally dominant D614G substitution (B.1.351-Δ242- 244+D614G), and the fifth had the three mutations from the B.1.351 lineage affecting amino acids in the receptor-binding site (K417N, E484K, and N501Y) and a D614G substitution (B.1.351- RBD+D614G).

They then performed 50% plaque reduction neutralization testing (PRNT50) using 20 serum samples that had been obtained from 15 participants in the pivotal trial 2 or 4 weeks after the administration of the second dose of 30 μg of BNT162b2 (which occurred 3 weeks after the first immunization). All the serum samples efficiently neutralized USA-WA1/2020 and all the viruses with variant spikes. Almost all of them did so at titers higher than 1:40. Geometric mean neutralizing titers against USA-WA1/2020, B.1.1.7-spike, P.1-spike, B.1.351-spike, B.1.351-Δ242-244+D614G, and B.1.351-RBD+D614G viruses were 532, 663, 437, 194, 485, and 331, respectively.

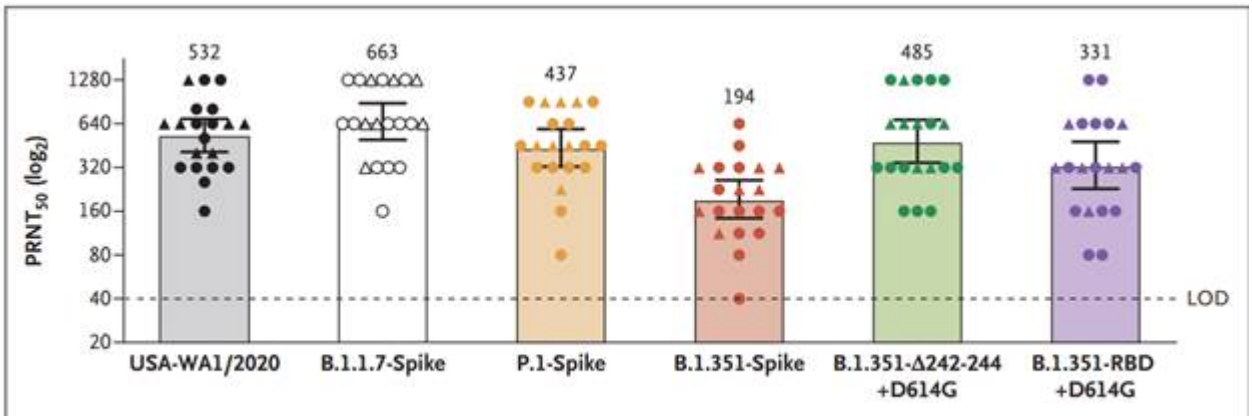


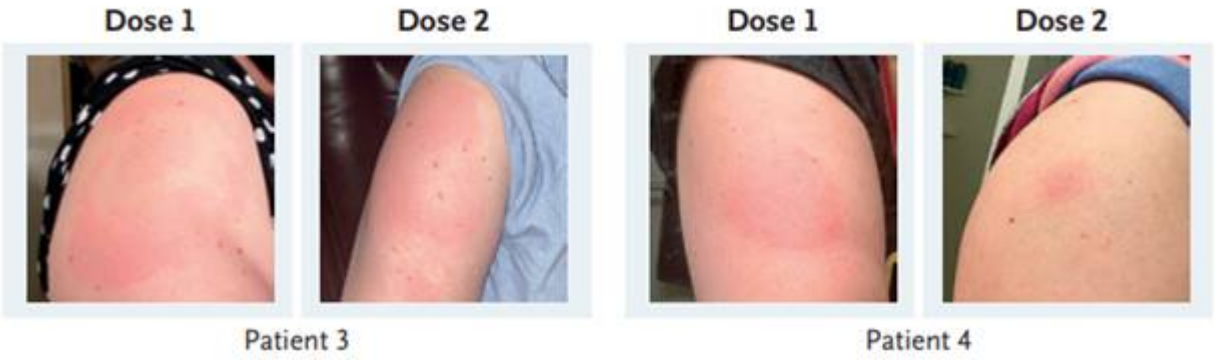
Figure 1. Serum Neutralization of Variant Strains of SARS-CoV-2 after the Second Dose of BNT162b2 Vaccine.

Comment: Compared with neutralization of USA-WA1/2020, neutralization of B.1.1.7-spike and P.1-spike viruses was roughly equivalent, and neutralization of B.1.351-spike virus was robust but lower. The data is also consistent with lower neutralization titers against the virus with the full set of B.1.351-spike mutations than against virus with either subset of mutations, however, I am encouraged that despite decreased neutralization against some variants, the serum still neutralized these variants. T-cell

immunity may also be involved in protection, and BNT162b2 immunization elicits CD8+ T-cell responses that recognize multiple variants.

Delayed Large Local Reactions to mRNA-1273 Vaccine against SARS-CoV-2
N Engl J Med published online March 4, 2021
DOI: 10.1056/NEJMc2102131
This report on a series of 12 patients with these reactions, all of which appeared near the injection site after complete resolution of the initial local and systemic symptoms associated with vaccination. Five of the reactions were grade 3 plaques (≥10 cm in diameter). Some patients had concurrent systemic adverse effects, and among these patients, 2 had additional skin findings. Most patients received treatment for their symptoms (e.g., with ice and antihistamines). Some patients received glucocorticoids (topical, oral, or both), and 1 patient received antibiotic therapy for presumptive cellulitis. The symptoms resolved a median of 6 days after onset (range, 2 to 11).

Given that neither local injection-site reactions nor delayed-type hypersensitivity reactions are contraindications to subsequent vaccination, all 12 patients were encouraged to receive the second dose and completed their vaccination course. Although half the patients did not have a recurrence of large local reactions, three patients had recurrent reactions that were similar to those after the initial dose, and three patients had recurrent reactions that were of a lower grade than those after the initial dose. The median onset of cutaneous symptoms after the second dose (day 2; range, 1 to 3) was earlier than that after the first dose.



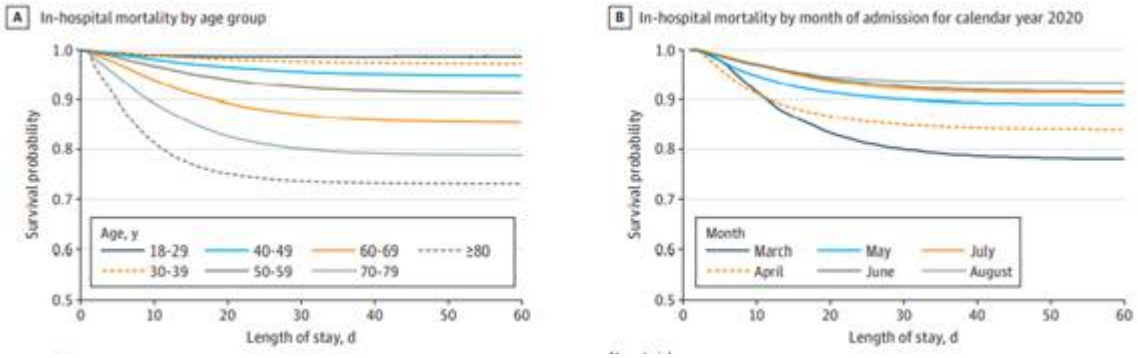
Comment: The current suspicion is this is a delayed-type or T-cell-mediated hypersensitivity. This is supported by skin-biopsy specimens obtained from a patient with a delayed large local reaction who was not among the 12 patients described here. Those specimens showed superficial perivascular and perifollicular lymphocytic infiltrates with rare eosinophils and scattered mast cells.

Outcomes and Mortality Among Adults Hospitalized With COVID-19 at US Medical Centers
JAMA Netw Open 2021;4(3):e210417
doi:10.1001/jamanetworkopen.2021.0417
The researchers used data from 555 US medical centers via the Vizient clinical database on 192,550 adults hospitalized with COVID-19 across 6 months. In-hospital mortality was 13.6%, which rose to 16.6% when the researchers included those discharged to hospice. In-hospital mortality (not including hospice), however, declined dramatically over the study period, from 22.1% in March to 6.5% in August. The biggest 1-month drop was from April to May, going from 18.1% to 12.0%.

The data also confirmed higher death rates with advancing age, with every 10-year age-group increasing in mortality rate, going from 1.4% in those 18 to 29 to 26.6% of those 80 years or older. (For reference, 6.6% of hospitalized adults in the study were in this youngest subgroup, compared with 16.2% of the oldest age-group.)

Almost 30% (28.9%) of the study cohort was admitted to the intensive care unit (ICU), which was associated with a median stay of 15 days (vs 6 days for those not in the ICU), as well as a median cost of $39,825 (vs $10,520).

Overall, 52.2% of Americans hospitalized with COVID-19 were men, 43.3% were White, and 65.2% were covered by Medicare or Medicaid. The most common comorbidities were high blood pressure (61.5%), diabetes (38.4%), and obesity (27.4%).



Comment: Limitations include: this was a retrospective study, including misclassification and accuracy of coding and missing data, management of COVID-19 was rapidly changing, and this study did not compare treatment modalities. Radiologic and laboratory clinical findings were not available. See next article.

Body Mass Index and Risk for COVID-19-Related Hospitalization, Intensive Care Unit Admission, Invasive Mechanical Ventilation, and Death — United States, March–December 2020
MMWR March 8, 2021
Data from nearly 150,000 US adults hospitalized with COVID-19 nationwide indicate that risk for more severe disease outcomes increases along with body mass index (BMI). The risk of COVID-19-related hospitalization and death associated with obesity was particularly high among people younger than 65. The risk of ICU admission was particularly associated with severe obesity. For example, those with a BMI in the 40 to 44.9 kg/m^2 category had a 6% increased risk, which jumped to 16% higher among those with a BMI of 45 or greater. Moreover, the risks for hospitalization and death increased in a dose-response relationship with obesity. For example, risks of being hospitalized were 7% greater for adults with a BMI between 30 to 34.9 and climbed to 33% greater for those with a BMI of 45. People with COVID-19 close to the border between a healthy and overweight BMI — from 23.7 kg/m^2 to 25.9 kg/m^2 — had the lowest risks for adverse outcomes. Interestingly, being underweight was associated with elevated risk for COVID-19 hospitalization as well. For example, people with a BMI of less than 18.5 had a 20% greater chance of admission vs people in the healthy BMI range.

Comment: The result in this report confirms what has been suggested early on, that morbid obesity especially in younger adults increases incidence of severe disease and death. Chronic inflammation or impaired lung function from excess weight are possible reasons that higher BMI imparts greater risk, the

researchers note. Because the study was limited to people hospitalized with COVID-19, the findings may not apply to all adults with COVID-19.