First for those who have been hard or will be hit by this winter storm I hope you are safe and warm.

Today I have 5 interesting articles for your reading enjoyment. The first looks at the global emergence of spike protein variants. The next 2 articles examine the neutralizing activity first of the Moderna vaccine and next the Pfizer vaccine. The next article is a fascinating article assessing brain capillaries and the discovery in 5 cases of large cell nuclei morphologically consistent with megakaryocytes. The last article explores the association of VL and outcomes.

Monday we will review just published article on zinc, vitamin C and D.

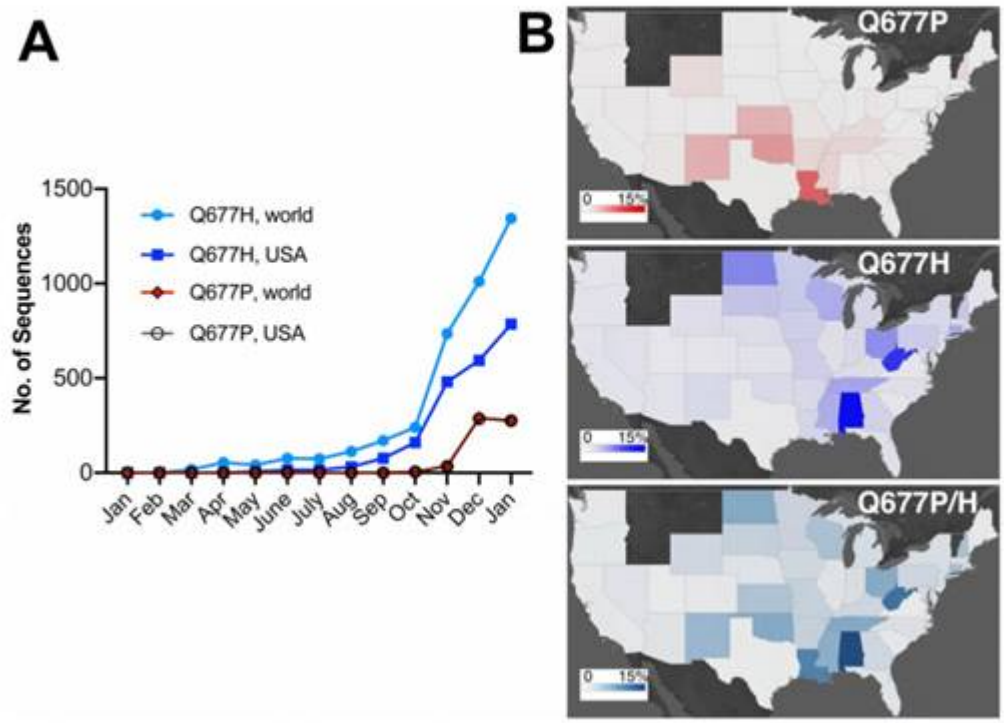
I hope everyone has a better weekend as weather and local conditions improve

Ed

Emergence in Late 2020 of Multiple Lineages of SARS-CoV-2 Spike Protein Variants Affecting Amino Acid Position 677

medRxiv published online February 12, 2021
doi.org/10.1101/2021.02.12.21251658

Non-synonymous substitutions affecting S are not uncommon and have become common in a number of SARS-CoV-2 lineages. A subset of such mutations enable escape from neutralizing antibodies or are thought to enhance transmission through mechanisms such as increased affinity for the cell entry receptor, ACE2. Independent genomic surveillance programs based in New Mexico and Louisiana contemporaneously detected the rapid rise of numerous clade 20G (lineage B.1.2) infections carrying a Q677P substitution in S. The variant was first detected in the US on October 23, yet between 01 Dec 2020 and 19 Jan 2021 it rose to represent 27.8% and 11.3% of all SARS-CoV-2 genomes sequenced from Louisiana and New Mexico, respectively. Q677P cases have been detected predominantly in the south central and southwest United States; as of 03 Feb 2021, GISAID data show 499 viral sequences of this variant from the USA. Phylogenetic analyses revealed the independent evolution and spread of at least six distinct Q677H sub-lineages, with first collection dates ranging from mid-August to late November 2020. Four 677H clades from clade 20G (B.1.2), 20A (B.1.234), and 20B (B.1.1.220, and B.1.1.222) each contain roughly 100 or fewer sequenced cases, while a distinct pair of clade 20G clusters are represented by 754 and 298 cases, respectively. Taken together, our findings demonstrate simultaneous convergent evolution, thus providing an impetus to further evaluate S:677 polymorphisms for effects on proteolytic processing, cell tropism, and transmissibility.

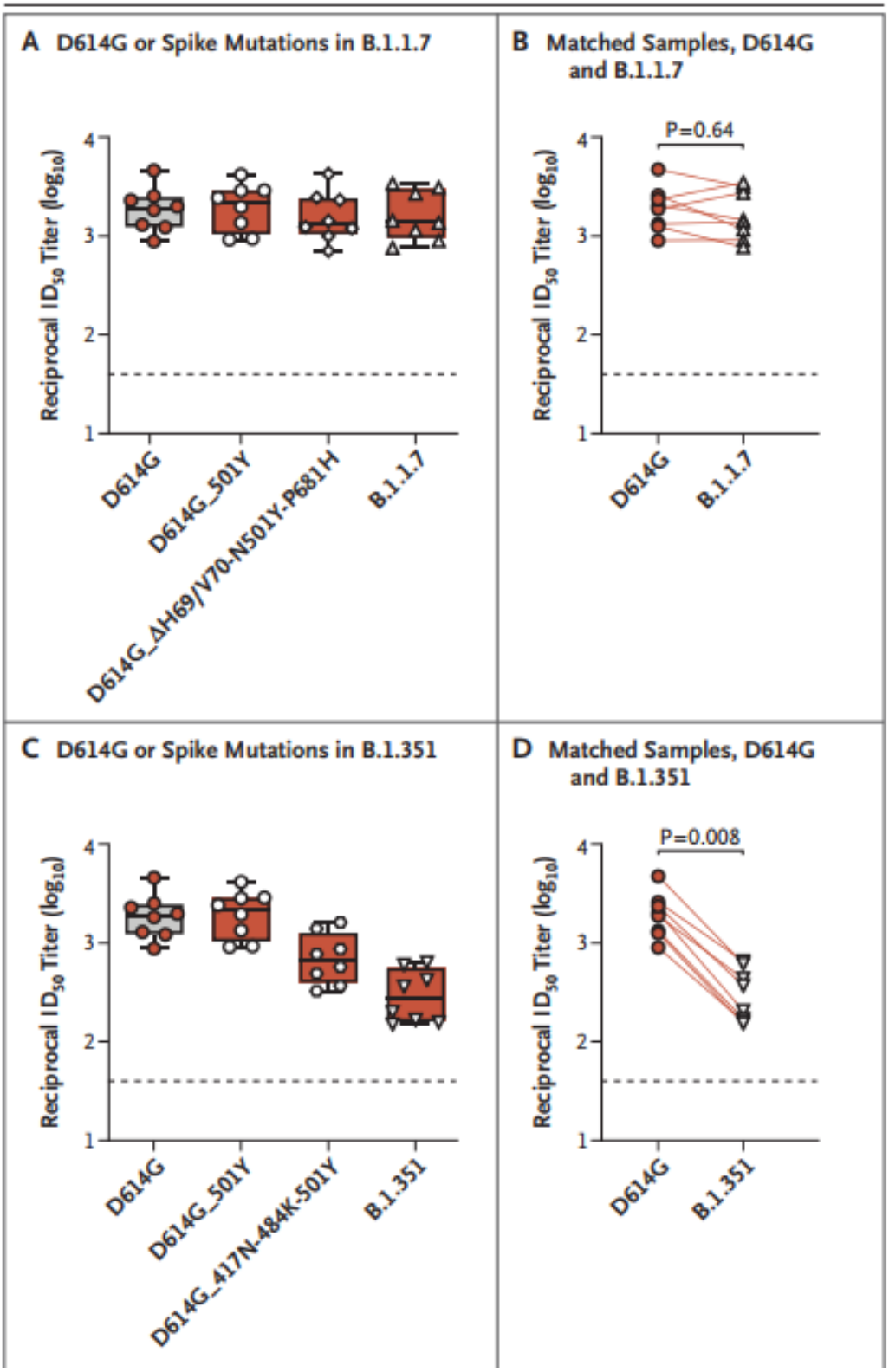


Comment: Other more contagious variants have been discovered elsewhere. A recent analysis found that a variant first discovered in the United Kingdom, known as B.1.1.7, is 35 to 45 percent more transmissible than other strains spreading in the US, while a new assessment by British government scientists found that the same variant could be 30 to 70 percent deadlier than the original coronavirus. (see Daily Briefing last Wednesday) Global surveillance of genomic changes in SARS-CoV-2 varies widely, with leading countries such as Australia, New Zealand, the United Kingdom, and Denmark sequencing viruses from 5-50% of all cases and lagging countries such as the United States, France, Spain, and Brazil sequencing less than 1% of all cases. Collectively, these findings demonstrate the value of greater genomic sequencing and the importance of tracking the emergence and spread of lineages that combine multiple mutations which could enhance transmissibility or evade immunity from prior infection or vaccines. I applaud this administration for additional funding to enhance our genomic surveillance.

Serum Neutralizing Activity Elicited by mRNA-1273 Vaccine [Moderna]—Preliminary Report
N Engl J Med published online February 18,2021
DOI: 10.1056/NEJMc2102179
Investigators from Moderna and the NIH, detailed the ability of sera from participants vaccinated in the phase 1 clinical trial of Moderna's mRNA-1273 vaccine trial to neutralize pseudovirus models. The different types of pseudoviruses featured the spike protein from the original isolate from Wuhan, China, along with the spike protein from variants such as B1351 and B117, and the variant first detected in the Danish mink farm cluster.

While the researchers found that the B117 variant had no significant effect on the vaccine's ability to kill the virus in serum samples obtained from participants who had received their second vaccine dose a

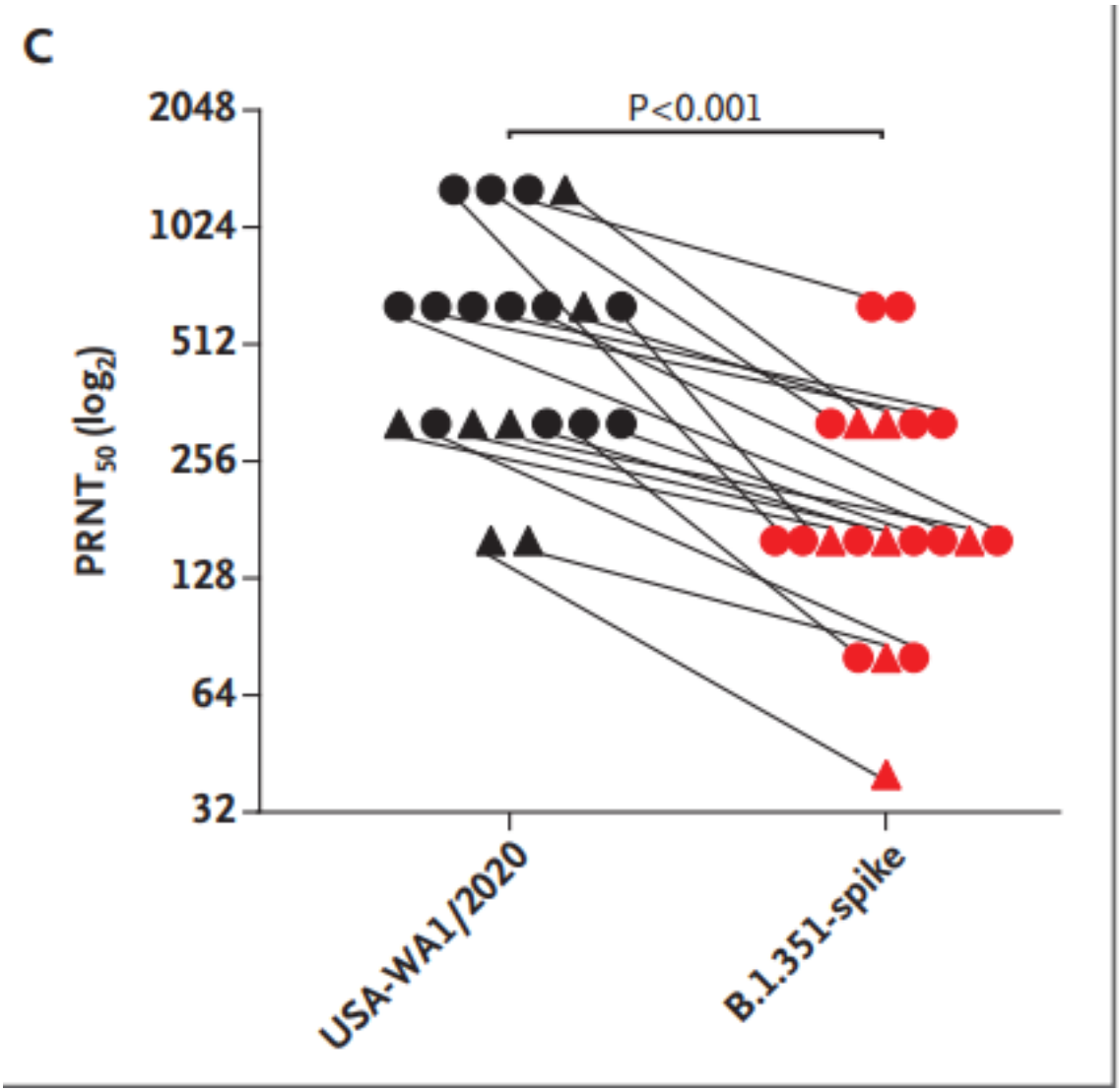
week before, they saw a 2.7-fold decrease in neutralizing antibodies against a partial panel of B1351 mutations and a 6.4-fold drop against the full set.



Comment: Level of protection against the B.1.351 variant conferred by the mRNA-1273 vaccine remains to be determined. Indirect evidence suggests the vaccine may not be as effective in preventing symptomatic disease, but it is hoped it will still prevent severe disease in persons infected with B1351.

Neutralizing Activity of BNT162b2-Elicited Serum — Preliminary Report
N Engl J Med published online February 17, 2021
DOI: 10.1056/NEJMc2102017
A team led by scientists made three recombinant viruses with different mutations using a SARS-CoV-2 isolate from January 2020. Using 20 serum samples collected from 15 participants in a 2020 trial of the vaccine 2 to 4 weeks after their second dose, they tested the samples' ability to neutralize the 2020 strain and all variants, including B1351 and B117. [Pfizer vaccine]

All serum samples were able to neutralize the viruses but were less effective against the B1351 spike protein.

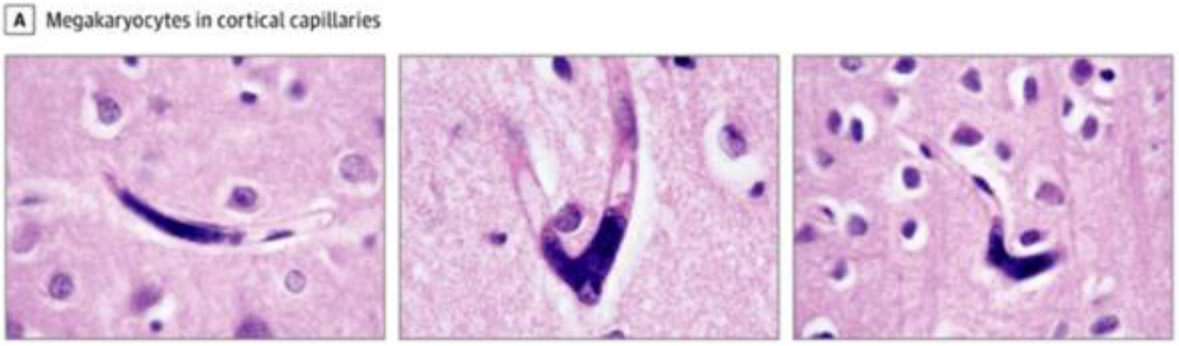


Comment: It is unclear what effect a reduction in neutralization would have on BNT162b2-elicited protection from Covid-19 caused by the B.1.351 lineage of SARS-CoV-2. However, the authors said that because the vaccines also produce other types of immune responses, such as from T cells, they may be more effective in real life than in the lab.

Assessing Brain Capillaries in Coronavirus Disease 2019
JAMA Neurol published online February 12, 2021
doi:10.1001/jamaneurol.2021.0225
Evidence suggests brain involvement in SARS-CoV-2 infection. Manifestations in acutely ill individuals often include confusion, alteration of consciousness, and even strokes. After recovery, many patients experience continued neurologic symptoms such as dysexecutive syndrome or "brain fog." However, in autopsies from patients with COVID-19 who had neurologic abnormalities, investigations have largely not identified the chronic inflammation or marked neural changes typically associated with viral infection, and viral genetic material has been minimal or absent. It has been difficult to reconcile the experience of patients and clinicians that COVID-19 is altering cognition with tissue studies that show no evidence of encephalitis.

Investigators evaluated brain tissue from autopsies of patients with nucleic acid–proven SARS-CoV-2 infection and confirmed pulmonary pathology. They assessed the brains from 15 cases free of infarcts. They included two control patients without COVID-19. COVID-19–negative cases were chosen because of comparable patient age and the presence of hypoxic-ischemic changes in brain.

In 5 cases in cortical capillaries, they identified large cell nuclei morphologically consistent with megakaryocytes. To further characterize these cells, they performed immunohistochemistry for CD61 and CD42b, markers of platelets and megakaryocytes. CD61 labels these cells, as does CD42b, confirming their megakaryocyte identity. The cells were distinct from platelet clusters, which were found in postmortem intravascular precipitates. Evaluation of the cortex of 2 patients who tested negative for COVID-19 who had hypoxic brain changes demonstrated no megakaryocytes on CD61.



Comment: Multiple studies have shown evidence of endothelial dysfunction may contribute to severe COVID-19 illness. Lung examination demonstrates megakaryocytes, and but not in other organs. One possibility is that altered endothelial or other signaling is recruiting megakaryocytes into the circulation and somehow permitting them to pass through the lungs. Although this study does not investigate mechanism, it is notable that they found megakaryocytes in cortical capillaries in 33% of cases examined. By occluding flow through individual capillaries, these large cells could cause ischemic alteration in a distinct pattern, potentially resulting in an atypical form of neurologic impairment.

Association Between Upper Respiratory Tract Viral Load, Comorbidities, Disease Severity, and Outcome of Patients With SARS-CoV-2 Infection

J Infect Dis published online January 3, 2021
DOI: 10.1093/infdis/jiaa804

The investigators studied 1122 patients (mean age, 46 years) diagnosed by PCR. Upper respiratory viral load, measured by PCR cycle threshold, which they categorized as high, moderate, or low.

There were 336 (29.9%) patients with comorbidities; 309 patients (27.5%) had high, 316 (28.2%) moderate, and 497 (44.3%) low viral load. In univariate analyses, compared to patients with moderate or low viral load, patients with high viral load were older, more often had comorbidities. Symptomatic disease was more likely to be intubated and died. Patients with high viral load had longer stay in intensive care unit and longer intubation compared to patients with low viral load (P values < .05 for all comparisons). Patients with chronic cardiovascular disease, hypertension, chronic pulmonary disease, immunosuppression, obesity, and chronic neurological disease more often had high viral load (P value < .05 for all comparisons). However, in the multivariate analysis high viral load was not associated with severe COVID-19. High viral load was detected in 29.3% of children <18.

Comment: In this study the significant association between a high viral load, clinical severity, and outcome was not found in the multivariate models which may surprise many of you. This may be partially attributed to the strong association between age, sex, and comorbidities on the one hand and disease severity and risk of a fatal outcome on the other, which in turn may reduce the impact of a high viral load. A limitation of this study is that the clinical samples were collected from different respiratory sites and from different days after onset of symptoms in each patient. Another limitation is that timing from symptom onset to hospitalization was not captured. Repeated sampling was not available; therefore, they could not study kinetics of SARS-CoV-2 and the temporal association of viral load with clinical course. The fact that Ct values concern viral nucleic acid and do not necessarily correspond to infectious virus is another consideration. Further studies are needed to explore the underlying pathogenetic mechanisms of disease severity and fatal outcome at the host level.