Good morning

Today under COVID-19 News I review hospital and vaccine trends.

Under Journal Review I start with the RECOVERY Trial results on convalescent plasma from the RCT in the UK. I would be curious how many of you are still including CP as a therapeutic given recent RCTs's results. The next article is a look at variant escape neutralization by vaccine-induced humoral immunity. This article was suggested by Sanjat Kanjilal. The last article looks at convalescent plasma IgG response to SARS-CoV-2. These last two articles provide further insights into the immune response to SARS-CoV-2. I must say I may not totally understand all of it, but I'm amazed at how we can use new tools to study this amazing virus. I hope you enjoy these selections.

Have a great day

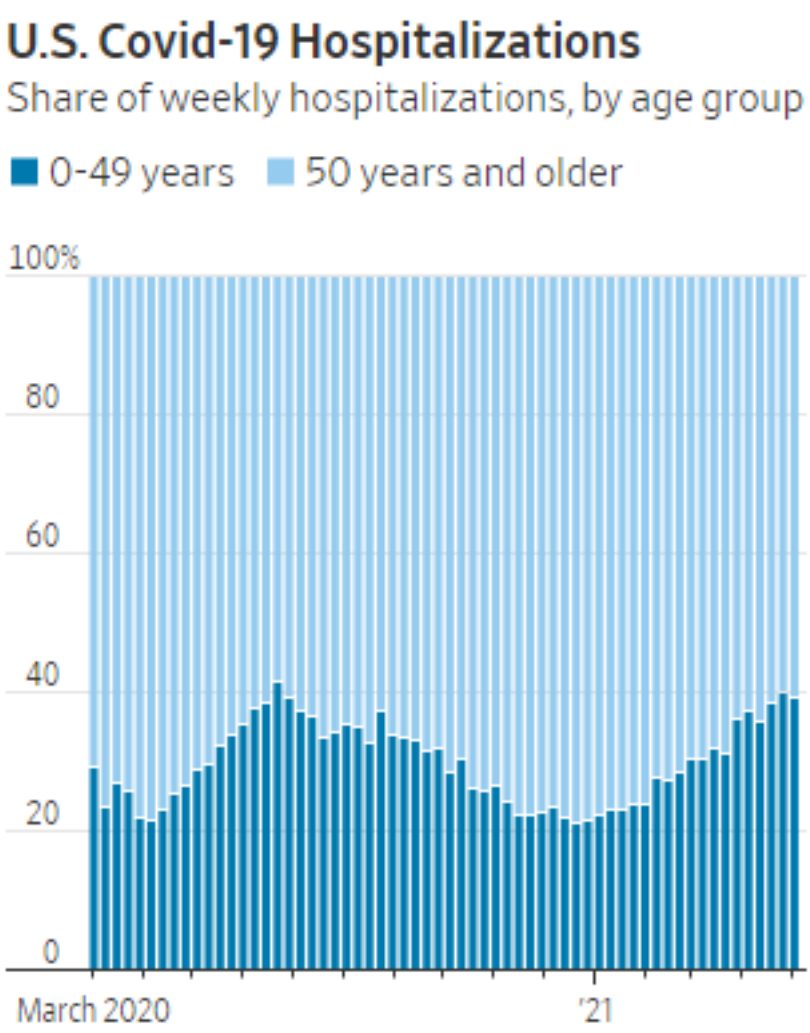
Ed

COVID-19 News

Covid-19 Hospital Trends
At the start of this year, people aged 65 and older made up 53% of Covid-19 related hospitalizations, according to data from the CDC. Those between the ages of 18 and 49 made up 20.5%, while patients in the 50-to-64 age group were 25.3% of hospitalizations. Americans aged 65 and older now make up 28.5% of hospitalizations—a 24.5 percentage point decrease from early January. The proportion of Covid-19 patients between the ages of 18 to 49, meanwhile, shot up. That age group now accounts for 36% of hospitalizations—a 15.5 percentage-point increase. Patients 50 to 64 years old have also gone up, to 32.4%, a 7.1 percentage-point increase. The virus is now infecting younger, unvaccinated people. We are now starting to notice a disproportionate rise in younger people with Covid-19 needing to be hospitalized in March.

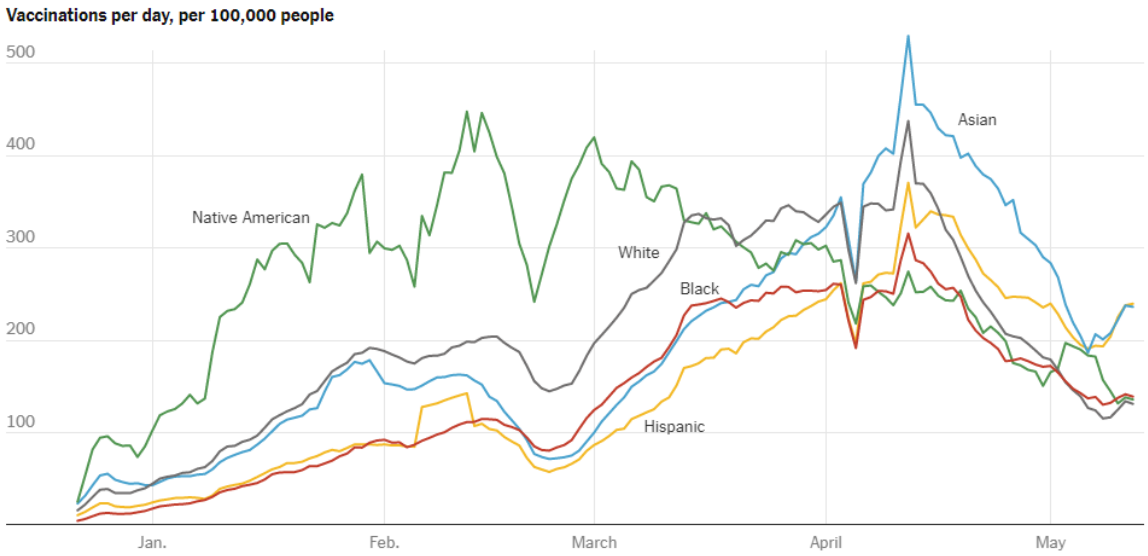
Vaccination rates differ among age groups, according to the CDC. Only 27% of those between the ages of 18 and 29 are fully vaccinated, and 36% of those 30 to 39 are fully vaccinated. Almost 44% of 40- to 49-year-olds are fully vaccinated, and that percentage jumps for those between the ages of 50 and 64, to 53.7%. For those 65 and older, it climbs higher, to 71.7%.

CDC



Comment: Bottom line, vaccines work! We are seeing fewer hospitalizations in the older age groups, and the only patients we are seeing in the ICU now are those who are not vaccinated. If you are not vaccinated, you are not safe.

Vaccinations and Racial Gaps
NY Times May 19, 2021
Black and Hispanic people across the United States have received a disproportionately smaller share of vaccinations to date, according to a New York Times analysis of state-reported race and ethnicity information. And vaccine disparities have grown in some of the most socially vulnerable parts of the nation, leaving many low-income communities of color with vaccination rates well below the national average. However, state and federal data reveal that the country has made some progress toward vaccine parity.



Source: Centers for Disease Control and Prevention | Note: Race and ethnicity were unknown for 40 percent of those vaccinated. Excludes all data from Texas. Figures show the date people received their first doses. The last five days of data are excluded because not all vaccinations on these dates have been reported yet. Lines show the seven-day moving average of people newly vaccinated.

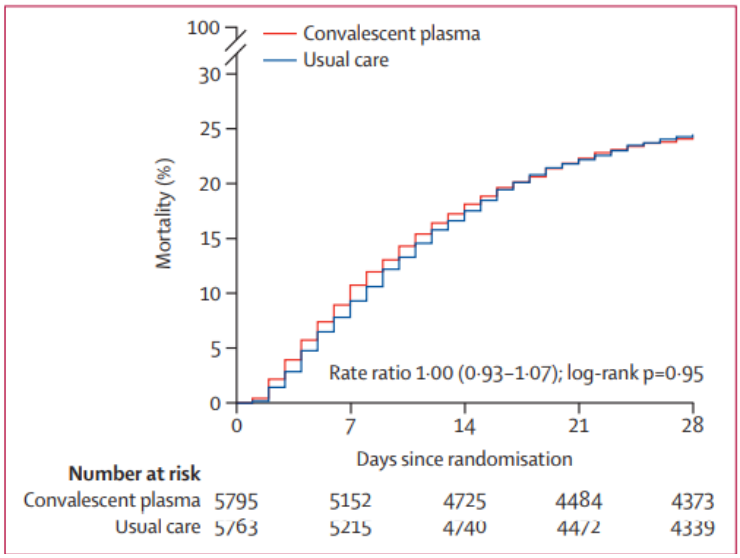
Comment: This is good news. However, despite recent equity gains, there is still work ahead to ensure that everyone gets equal access to the vaccine.

Journal Review

Convalescent Plasma in Patients Admitted to Hospital with COVID-19 (RECOVERY): A Randomised Controlled, Open-Label, Platform Trial
Lancet published online May 14, 2021
doi.org/10.1016/ S0140-6736(21)00897-7
This is a randomized, controlled, open-label, platform trial (Randomised Evaluation of COVID-19 Therapy [RECOVERY]) which has been assessing several possible treatments in patients hospitalized with COVID-19 in the UK. This trial was conducted at 177 NHS hospitals from across the UK. Eligible and consenting patients were randomly assigned (1:1) to receive either usual care alone (usual care group) or usual care plus high-titer convalescent plasma (convalescent plasma group). The primary outcome was 28-day mortality, analyzed on an intention-to-treat basis.

Between May 28, 2020, and Jan 15, 2021, 11,558 (71%) of 16,287 patients enrolled in RECOVERY were eligible to receive convalescent plasma and were assigned to either the convalescent plasma group or the usual care group. At randomization, 617 (5%) of 11,558 patients were receiving invasive mechanical ventilation, 10,044 (87%) were receiving oxygen only (with or without non-invasive respiratory support), and 897 (8%) were receiving no oxygen therapy. 10,681 (92%) of 11,558 patients were receiving corticosteroids at time of randomization. There was no significant difference in 28-day mortality between the two groups: 1,399 (24%) of 5,795 patients in the convalescent plasma group and 1,408 (24%) of 5,763 patients in the usual care group died within 28 days (rate ratio 1·00, 95% CI 0·93–1·07; p=0·95). The 28-day mortality rate ratio was similar in all prespecified subgroups of patients, including in those patients without detectable SARS-CoV-2 antibodies at randomization. Allocation to convalescent plasma had no significant effect on the proportion of patients discharged from hospital within 28 days

(3832 [66%] patients in the convalescent plasma group vs 3822 [66%] patients in the usual care group; rate ratio 0·99, 95% CI 0·94–1·03; p=0·57). Among those not on invasive mechanical ventilation at randomization, there was no significant difference in the proportion of patients meeting the composite endpoint of progression to invasive mechanical ventilation or death (1,568 [29%] of 5,493 patients in the convalescent plasma group vs 1,568 [29%] of 5,448 patients in the usual care group; rate ratio 0·99, 95% CI 0·93–1·05; p=0·79).



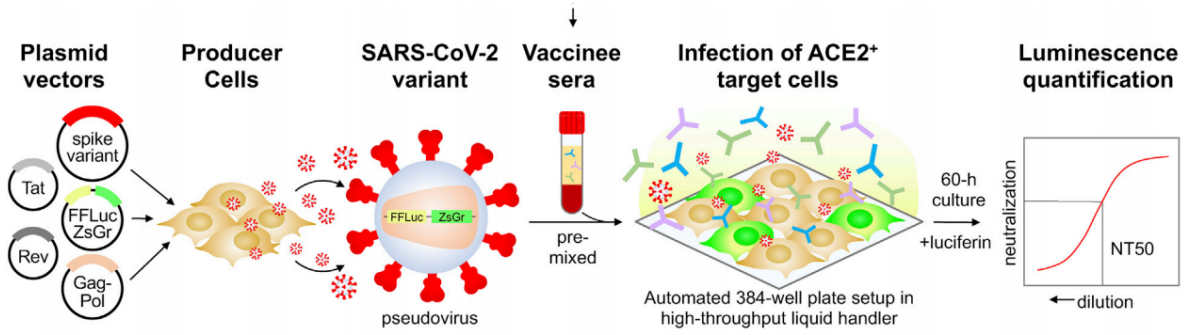
	Convalescent plasma group (n=5795)	Usual care group (n=5763)
(Continued from previous column)		
SARS-CoV-2 PCR test result		
Positive	5593 (97%)	5566 (97%)
Negative	126 (2%)	116 (2%)
Unknown	76 (1%)	81 (1%)
Patient SARS-CoV-2 antibody test result		
Positive	3078 (53%)	2810 (49%)
Negative	2016 (35%)	1660 (29%)
Missing	701 (12%)	1293 (22%)
Corticosteroids received		
Yes	5370 (93%)	5311 (92%)
No	391 (7%)	413 (7%)
Not recorded	34 (1%)	39 (1%)
Other randomised treatments		
Lopinavir–ritonavir	5 (<1%)	14 (<1%)
Dexamethasone	3 (<1%)	3 (<1%)
Hydroxychloroquine	1 (<1%)	0
Azithromycin	587 (10%)	585 (10%)
Colchicine	792 (14%)	791 (14%)
Aspirin	1266 (22%)	1207 (21%)

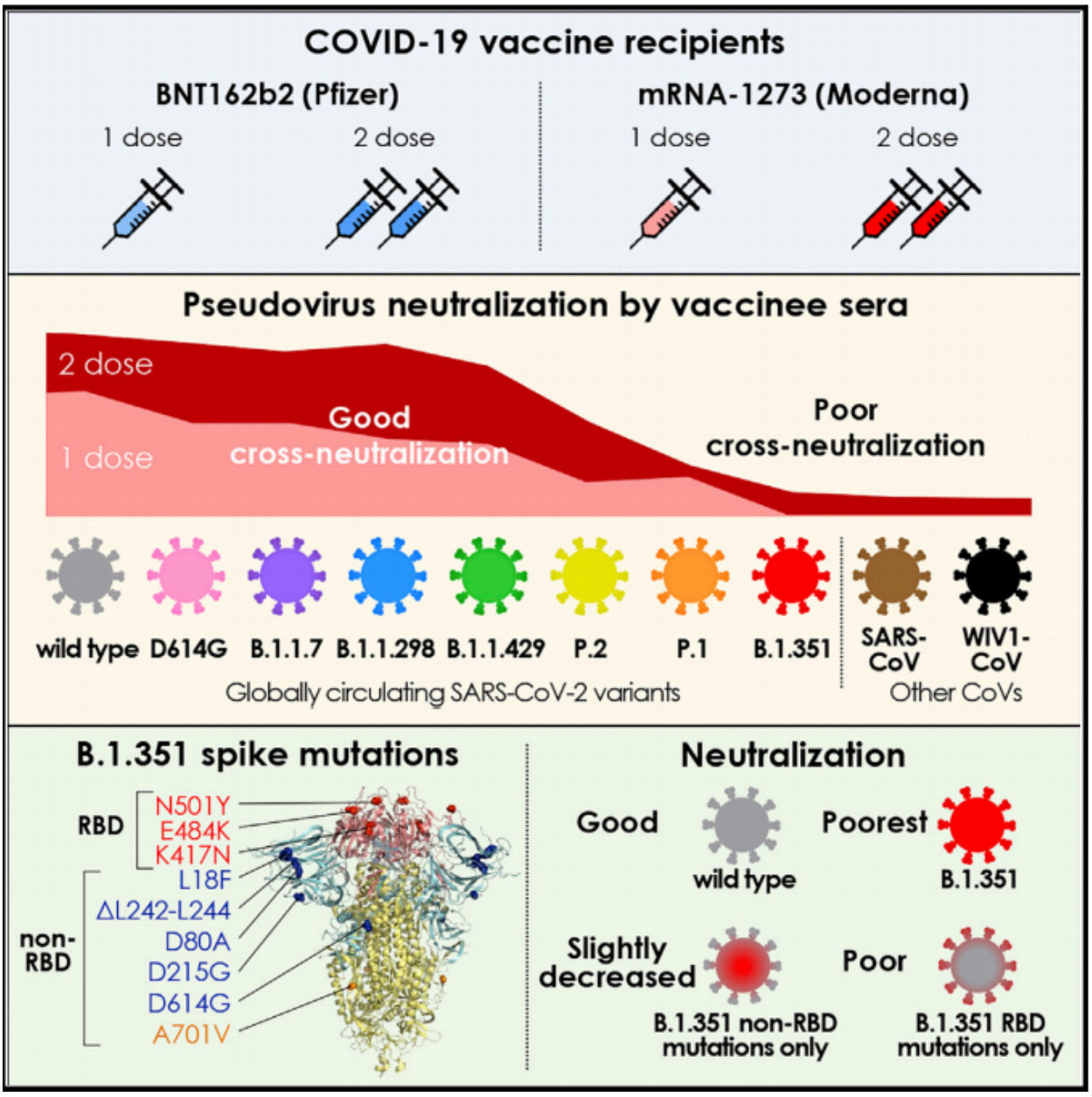
ata are mean (SD), n (%), or median (IQR). *Includes 26 children (<18 years). Includes 28 pregnant women. ‡Includes non-invasive ventilation. §Defined as equiring ongoing specialist care. ¶Defined as estimated glomerular filtration rate 30 mL/min per 1·73 m².

able 1: **Baseline characteristics**

Comment: The results of this large, randomized trial [the largest by far] show that high-tittered convalescent plasma did not improve survival or other clinical outcomes in patients hospitalized with COVID-19. The results were consistent across subgroups of age, sex, ethnicity, duration of symptoms before randomization, level of respiratory support received at randomization, and use of corticosteroids. The results are consistent with the evidence from previously reported RCTs of convalescent plasma for patients hospitalized with COVID-19. Although B.1.1.7 has changes in the spike glycoprotein that could theoretically modify antigenicity, only modest reductions in neutralization by convalescent plasma have been reported. Is it time we remove CP from potential therapeutics?

Multiple SARS-CoV-2 Variants Escape Neutralization by Vaccine-Induced Humoral Immunity
Cell published April 29, 2021 article provided by Sanjat Kanjilal
doi.org/10.1016/j.cell.2021.03.013
The investigators evaluated the neutralization potency of 99 people that received one or two doses of either The Pfizer or Moderna vaccines against pseudoviruses representing 10 globally circulating strains of SARS-CoV-2. Five of the 10 pseudoviruses, harboring receptor binding domain mutations, including K417N/T, E484K, and N501Y, were highly resistant to neutralization. Cross-neutralization of B.1.351 variants was comparable to SARS-CoV and bat-derived WIV1-CoV, suggesting that a relatively small number of mutations can mediate potent escape from vaccine response. When comparing pseudovirus neutralization titer as a function of time post-vaccination, they observed an expected increase in titer after the second dose.



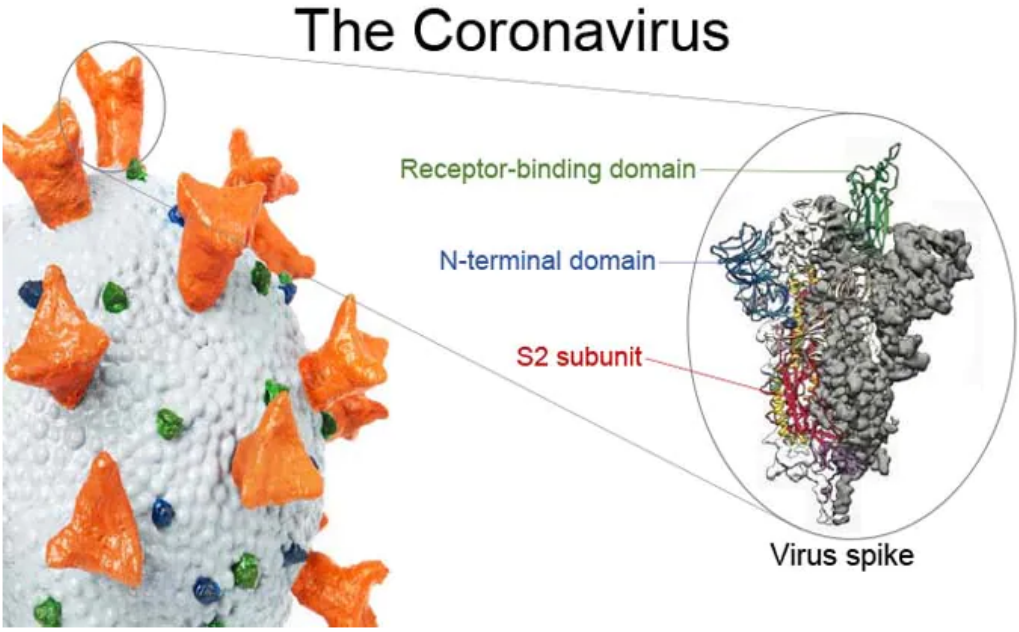


Comment: There are over 107 million confirmed infections documented (coronavirus.jhu.edu), which has enabled viral diversification and the emergence of six distinct major lineages with numerous variants. A subset of these variants has been denoted as variants of concern by the WHO given the presence of mutations with potential to increase transmissibility, virulence, or evade immune response. The investigators focused on variants of concern first described in the United Kingdom (B.1.1.7), Denmark (B.1.1.298), United States (B.1.429), Brazil and Japan (P.2 and P.1), and South Africa (B.1.351). The recent variant from India (B.1.617.1) was not included. Most studies have shown a polyclonal immune response that arise in the context of infection and vaccination which target multiple antigenic sites. Most prior publications have shown reduced neutralization of variant. However, the investigators here found that while many strains, such as B.1.1.7, B.1.1.298, or B.1.429, continue to be potently neutralized despite the presence of individual RBD mutations, other circulating SARS-CoV-2 variants escape vaccine-induced humoral immunity. The P.2. variant, which contains an E484K mutation within

the RBD region, was capable of significantly reducing neutralization potency of fully vaccinated individuals. Similarly, the P.1 strain, which has three RBD mutations, more effectively escaped neutralization, possibly explaining recently reported cases of reinfection with this variant. Finally, they found that B.1.351 variants exhibited remarkable resistance to neutralization, largely due to three mutations in RBD but with measurable contribution from non-RBD mutations. [see figure below] They did not assess other antibody-mediated functions such as complement deposition, antibody-dependent cellular cytotoxicity, or antibody-dependent cellular phagocytosis, which may contribute to protection even in the absence of neutralizing antibodies. This paper highlights the challenges facing all vaccines.

Prevalent, Protective, and Convergent IgG Recognition of SARS-CoV-2 Non-RBD Spike Epitopes
Science published online May 4, 2021.
doi:10.1126/science.abg5268
Using proteomic deconvolution of the IgG repertoire to the spike glycoprotein in convalescent subjects, the investigators demonstrated that the response is directed predominantly (>80%) against epitopes residing outside the receptor-binding domain (RBD). In one subject, just four IgG lineages accounted for 93.5% of the response, including an N-terminal domain (NTD)-directed antibody that was protective against lethal viral challenge. Genetic, structural, and functional characterization of a multi-donor class of "public" antibodies revealed it is an NTD epitope that is recurrently mutated among emerging SARS-CoV-2 variants of concern. These data show that "public" NTD-directed and other non-RBD plasma antibodies are prevalent and have implications for SARS-CoV-2 protection and antibody escape.

In summary, the authors found that the convalescent plasma IgG response to SARS-CoV-2 is oligoclonal and directed overwhelmingly toward non-RBD epitopes in the S-ECD. This includes public, near-germline, and potently neutralizing antibodies against the NTD. The degree to which public anti-NTD antibodies contribute to protection is likely related to their relative levels in plasma, which can be dominant in some individuals. The role of S2-binding antibodies needs further study.



Coronavirus spikes protrude to infect cells (adapted from an illustration by the University of Texas at Austin)

Comment: So far, investigators have focused on one part of the coronavirus spike — the receptor-binding domain (RBD) — which the virus uses to attach and gain access to human cells. This part of the virus attaches directly to a person's cells to infect them and is the part that researchers have made their top priority for vaccine and drug development. The monoclonal antibody therapies use this same target. In this manuscript, immunologists from the University of Texas at Austin have taken a closer look at blood samples from four people who recovered from COVID-19 and found that most of the antibodies made in response to infection targeted other parts of the coronavirus spike. In fact, up to 80% of their antibodies targeted other parts of the spike protein. Antibodies were aiming at another area called the N-terminal domain. As luck would have it, the N-terminal domain mutates most frequently. Changes in this region are responsible for many of the variants of concern. However, another large group of antibodies targets the stalk of the spike, called the S2 subunit. That is reassuring, because this is a region that does not mutate as often, so if the antibodies that recognize the virus are able to neutralize it, they should offer a layer of protection against any variant. However, no S2-binding antibodies have been found to be strongly protective yet, but they could play a role in the next generation of vaccines and booster shots developed to deal with the variants.