COVID–19
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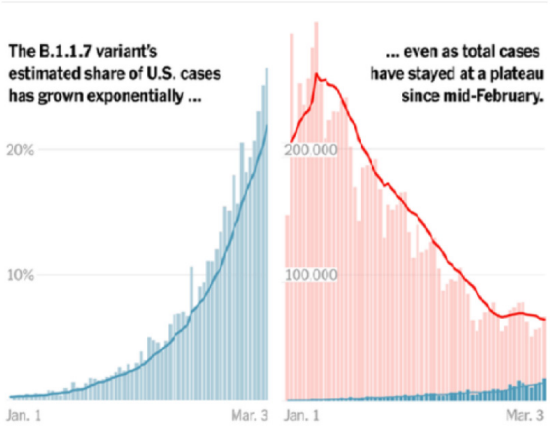
The new variants, vaccination status, and herd immunity

We understand herd immunity to be the goal, but this is not a binary endpoint. It will be achieved gradually, and perhaps not completely. Factors responsible for driving down the Ro are masking and social distancing, increasing seroprevalence in the population from prior infection, and increasing vaccination rates. These factors are counterbalanced by the increased Ro of the B.1.1.7 variant, and perhaps other variants in circulation, including the variant first discovered in California, CAL.20C, about which we still know very little. Estimates as of today suggest that about 30% of Americans have been infected and about 18% have received at least one vaccine dose as of mid-March. We may be starting to see the effects of herd immunity, although current estimates are that we need to reach the 70% range for a significant impact. Our daily case counts have continued to drop but not at the rate they had been over the prior two months. We are still averaging about 56,000 daily cases and over 1,700 daily deaths, emphasizing that we still have a long way to go. As noted in ***The New York Times*** graph below, about 20% of cases in the U.S. are now due to the B.1.1.7 UK variant. It appears that the rise in B.1.1.7 cases may account for the leveling off of the case rate curve.[1]

A more contagious coronavirus variant



2. A more contagious coronavirus variant first discovered in the U.K. is spreading fast in the U.S., even as the overall number of cases is leveling off there.

The New York Times , March 6, 2021.

CAL.20C/L452R (B.1.427/B.1.429) variant (awaiting peer review, "preprint" study)

The study sequenced samples from over 2,100 patients in 44 California counties to examine this new variant of concern. The variant consists of two closely related lineages with their prevalence increasing in parallel (and hence the two names). It emerged around May 2020, diverged into the two lineages on July 27, and now accounts for over 50% of cases in California, with a doubling time of 18 days. It is believed to be 18-24% more transmissible relative to wild-type circulating strains. It does appear to be however, somewhat less infectious than the other three variants of concern, including the B.1.1.7 UK variant which all contain the N501Y mutation. This variant also carries an L452R mutation which is in the RBD region and confers some degree of resistance to convalescent and vaccine induced antibodies. Again, this degree of antibody resistance is less than that observed in the B.1.351 and P1 strains from S. Africa and Brazil. Notably, because these findings reveal that the infectivity of this variant is slightly reduced compared to that of N501Y mutation containing variants including the B.1.1.7 UK variant (which now accounts for about 22% of US cases), it might not remain the predominant circulating strain in California, and may eventually be replaced by the N501Y-carrying B.1.1.7 variant.[2]

EDUCATIONAL FORUM

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B.1.1.7. A study published in the *British Medical Journal* in mid-March looked at the case rate fatality of the B.1.17 variant.[3] The study examined 55,000 matched pairs of patients who had been infected with SARS-CoV-2. One group was infected in October, prior to the discovery of the variant, and the other in late December when it had already become the predominant circulating strain, with 75% of new cases attributed to the variant. Early on, it was known that due to the N501Y mutation in the spike protein region, the variant had a higher Ro with estimates of 20–30% increased transmissibility. It was not yet known if the virulence of the variant was also increased. Overall, the population studied tended to be young and healthy. That being said, the mortality associated with the B.1.1.7 variant was about 64% higher (HR 1.64). As in other studies, older patients and males had the highest mortality rate.

The other three most actively watched variants include the CAL.20C as noted above, the S. African variant B.1.351 first detected in early August, and the Brazil variant P.1 which first appeared in December. Both B.1.351 and P.1 contain the N501Y mutation conferring increased transmissibility and the E484K mutation conferring increased antibody resistance. Peer reviewed studies on the transmissibility and virulence of all three of these are due out soon, but not currently available in the preprint version. All three of these variants are currently circulating in the U.S. with varying prevalence.

B.1.351. The findings on B.1.351 are worrisome in that this variant is partially refractory to neutralization by multiple individual antibodies to the receptor-binding domain (RBD) largely owing to the effect of the E484K mutation. Moreover, B.1.351 is markedly more resistant to neutralization by convalescent plasma (9.4 fold) and vaccinee sera (~11 fold).[4] Supporting these lab data, information presented this week on the performance of the Novavax protein subunit vaccine showed a 96% efficacy in the UK but only a 55% efficacy when studied in S. Africa. Additionally, a study just published looked at over 2,000 individuals in S. Africa who were immunized with the Oxford–AstraZeneca viral vector DNA vaccine or placebo. Ninety-three percent of the cases in this study were of the B.1.351 variant. The vaccine showed only a 22% efficacy compared to placebo against mild to moderate COVID-19. Fifteen of the vaccine recipients who became infected had mild disease and four had moderate disease. There were no hospitalizations or deaths in either group. Fortunately, despite the lower efficacy against the B.1.351 variant, the vaccine does seem to protect against severe disease and mortality, although the specifics around these data are not yet published. Moreover, possibly due to increasing herd immunity in S. Africa, the infection rate of this variant is in steep decline.

P.1. Manaus, Brazil is a city of over two million on the banks of the Amazon and is serving as a learning lab for the rest of the world. Related to, among other factors, a national strategy of minimizing the importance of the pandemic including no mandate around masking and distancing, it had a severe outbreak over the spring with an estimated attack rate of 76% based on seroprevalence studies. This should have resulted in effective herd immunity, however, with the emergence of the P.1 strain, Manaus is now in the midst of a second surge which has exceeded the spring surge with daily hospitalization rates six-fold higher.[5] This is not altogether surprising for two reasons. We now know that milder infections are associated with lower levels and shorter duration of convalescent antibodies and these individuals are now eight months or so out from their initial infection, and this variant is resistant to antibody neutralization.

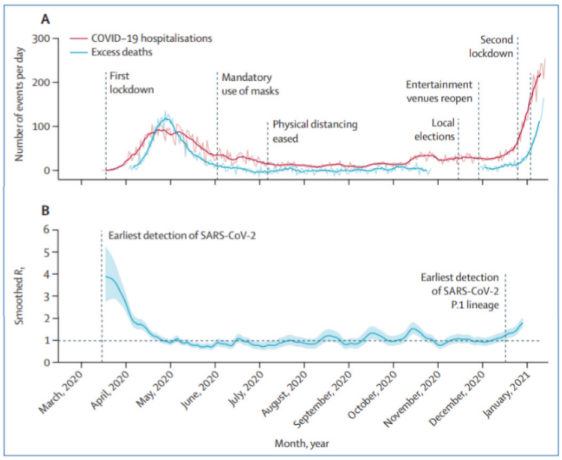

Figure: **COVID-19 hospitalisations, excess deaths, and R_t in Manaus, Brazil, 2020–21**

In summary, the race to attain herd immunity is accelerating, and our vaccination rates are climbing. Fortunately, vaccination is associated with antibody titers which are several multiples higher than those associated with mild to moderate infection, which likely accounts for the vaccine's protective effect against severe illness and death even in regions with a high prevalence of the new variants. With increasing availability of the current EUA (Emergency Use Authorization) vaccines, and the likely EUA of the Novavax protein subunit vaccine in the near future, vaccine hesitancy will soon be the major barrier. This will be fueled by any perceived complications of vaccination. This was highlighted this week when nine European countries paused the use of the AstraZeneca vaccine due to concerns that it increased thrombosis risk. It does not appear that the rate of thrombosis is higher in the vaccinated compared to unvaccinated portions of the population in these countries.[6] Lastly, given the continued emergence of newer variants, it is likely that periodic booster immunizations to cover new viral variants will be needed

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mRNA COVID-19 vaccine protection against emerging viral variants

In two separate studies researchers evaluated immune response after vaccination with one of the mRNA vaccines. They specifically evaluated immunity directed toward the emerging viral strains of SARS-CoV-2. Sera from eight participants in the phase 1 trial of the mRNA-Moderna vaccine were analyzed for neutralizing antibody against SARS-CoV-2 strain D614G, the most common strain in mid-2020, and emerging variants B.1.351 (first identified in South Africa) and B.1.1.7 (first identified in the UK).[7] Sera was obtained seven days after the second dose of the vaccine. The 50 percent inhibitory dilution (ID50) of the sera was not significantly decreased against the B.1.1.7 strain but was reduced by a factor of 6.4 against the B.1.351 strain. Despite this reduction, the mean neutralizing titer was still 1:290 and effectively neutralized the pseudovirus in the laboratory studies.

In the second study, sera from 15 participants from the Pfizer/BioNtech vaccine trial were analyzed in a viral neutralization assay. Testing used engineered virus to replicate SARS-CoV-2 strain USA-WA1/2020 (early lineage from Seattle, WA.), D614G, and variants B.1.351, B.1.1.7, and P1 (first identified in Brazil).[8] Sera samples were obtained two or four weeks after receipt of the second dose of the vaccine. All serum samples effectively neutralized all strains. The mean neutralization titers were also lowest against B.1.351 with BNT162b2.

In both trials very few individuals were studied. The sera from the Moderna vaccine recipients was obtained only one week after the second vaccine dose, earlier than peak antibody response. In both trials it is not known how well these neutralization trials will translate into real world protection. There is concern that lower neutralizing titers against emerging strains may induce selection for additional variants.[9] Ongoing analysis of how the current vaccines are performing against the new viral variants is essential, and will help inform the decisions around the necessity and timing of subsequent booster vaccinations.

Immunity to SARS-CoV-2: Vaccine generated and naturally acquired

Health care workers (n= 3816) from Maryland Medical Center were involved in a sero-survey in July and August of 2020. A randomly selected subset of those workers (n= 59) were recruited to analyze their immune responses around vaccination in December 2020 and January of 2021.[10] They had sera collected at the time of vaccination and 7– and 14–days post vaccine receipt. The workers were divided into three groups:

1. Antibody positive for COVID-19 with no history of symptoms.
2. Antibody positive for COVID-19 and history of symptomatic disease.
3. COVID-19 antibody negative. Subjects IgG titers and viral neutralization titers were examined (Table 1).

Table 1

Patient group	Patient number	IgG binding titer to spike protein (ELISA) Days after vaccination⁺			Viral neutralizing titers days after vaccination⁺	
		0	7	14	0	14
COVID antibody positive and asymptomatic	16	208	29,364	34,033	80	40,960
COVID antibody positive and symptomatic	26	302	32,301	35,460	320	40,960
COVID antibody negative	17	<50	<50	924	<20	80

⁺p<0.001 antibody for all antibody positive vs antibody negative data and time points.

The response to a single dose of mRNA vaccine was significantly higher in persons with antibody evidence of prior COVID-19 infection whether disease was symptomatic or asymptomatic. This heightened immune response was distant from the original PCR positive testing by six to nine months following IgG positivity. This data is in a small set of relatively young health care workers (average age 38-40). We also do not know how accurately antibody levels and in-vitro viral neutralization titers correlate with protection post vaccination or natural infection, but the correlation should be strong. This data is therefore encouraging that amnestic immune responsiveness to previous COVID-19 infections may last at least six to nine months and result in significantly heightened immune responses post vaccination.

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In an interesting and related study, Lumley and colleagues studied a group of 12,541 health care workers in the United Kingdom.[11] They looked at the protective immunity following natural infection with SARS-CoV-2. Workers were tested at baseline for anti-spike IgG antibody, and 1265 were initially positive. The full cohort was then followed for PCR evidence of infection with SARS-CoV-2 either as a serial screening test (asymptomatic infections) or in response to symptomatic disease. Workers were followed for an average of 200 days after a negative antibody test and for an average of 139 days following a positive antibody test. Antibody evidence of previous infection afforded protection against subsequent PCR confirmed infection, with an 88% lower rate of infection in those previously infected (Table 2).

Table 2

Baseline IgG antibody status (% symptomatic)	PCR confirmed SARS-CoV-2 infection (% symptomatic)	Positive PCR test (rate/10,000 days at risk)
11,364 IgG negative	223 (55)	1.09
1265 IgG positive (68)	2 (0)	0.13

This study therefore also suggests that immune protection by natural infection is enduring for at least six months. This is consistent with studies of other coronavirus infections where the average time to reinfection with the same coronavirus was 12 months.[12] This is also consistent with early health care worker cohort studies showing the persistence of antibodies to SARS-CoV-2.[13] Importantly, we know that natural immunity and vaccine induced immunity also induce a T-cell immune response and therefore immunity is not limited to antibody production.[14,15] We also know that vaccine induced immunity is associated with much higher antibody levels than natural immunity and therefore will likely provide more prolonged immunity. Further study and longer-term studies of more aspects of the immune response to SARS-CoV-2 infection are needed to fully understand the duration of the immune amnestic response.

COVID-19 can lead to long-term losses of smell and taste

Based on a preliminary submission to the American Academy of Neurology, people with COVID-19 who develop anosmia and/or dysgeusia may have persistent symptoms. A press release summarized the findings.[16]

Among 813 health care workers who tested positive for COVID-19, 580 (71%) lost their sense of smell at the time of presentation. Of these 297 (51%) denied having regained smell five months later, on an online questionnaire. Similarly, 512 participants reported losing their sense of taste at symptom onset, and 200 (38%) had not regained taste at five months. Home tests for smell and taste were abnormal in 17% and 9%, respectively, but the specific test results were not addressed by the press release. It appears that altered taste and smell related to COVID-19 may have a protracted course.

Although this information is preliminary, we thought to share it to best counsel our patients who continue to be challenged by these persistent and annoying symptoms.

Inhaled glucocorticoid, budesonide, reduces need for urgent medical care and improves COVID-19 recovery (non-peer reviewed "preprint" study)

A randomized, phase II, open label study of inhaled budesonide demonstrated a reduced need for urgent medical care and improved recovery times compared to usual care among patients with mild COVID-19 symptoms.[17] Study enrollment occurred within seven days of symptom onset. A total of 146 adult patients were enrolled and randomized, and 139 were analyzed. The primary endpoint was urgent medical intervention: urgent care visit, emergency department assessment, or hospitalization. An interim statistical analysis demonstrated study success without potential benefit from further enrollment, so the study was discontinued early.

The primary outcome was seen among 10 patients in the usual care arm and one patient in the treatment arm (difference in proportion of 0.131, p=0.004). The number needed to treat to reduce urgent medical intervention was eight. Recovery with budesonide occurred at a median of seven days versus a median of eight days with usual care, p=0.007. Additionally, fewer patients in the treatment group had persistent symptoms at days 14 and 28. Assuming this study passes peer review, inhaled budesonide should be considered as an early treatment for symptomatic patients with COVID-19.

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Ivermectin not better than placebo for mild disease from COVID-19

Ivermectin is thought to act at different SARS-CoV-2 protein binding sites to reduce viral replication. In vitro and animal studies support its potential role as a therapeutic for COVID-19, however concentrations of drug necessary for antiviral effects are higher than those achieved with standard oral dosing. Researchers explored whether ivermectin would accelerate recovery when given to patients early in the course of their disease.[18] In a double-blind clinical trial based in Cali, Columbia, patients (n=200) were randomized to receive ivermectin (300 µg/kg/day) or placebo (n=200) over five days. The primary outcome was time to symptom resolution over a 21-day follow-up period.

By study day 21, symptoms had resolved in 82% of patients given ivermectin and 79% of patients given placebo. The median time to resolution of symptoms in the ivermectin group was 10 days and in the placebo group 12 days, for a difference of -2 days (interquartile range, -4 to 2; hazard ratio for symptom resolution, 1.07, p = 0.53). Thus, a 5-day course of ivermectin did not improve the time to symptom resolution when compared to placebo.

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Kenneth Roy Cohen, MD, FACP

Dr. Kenneth Cohen is an experienced physician leader, practicing internist, and researcher who has attained national recognition for health care quality improvement. He was one of the founding physicians of New West Physicians, which is the largest primary care group practice in Colorado and now part of OptumCare. He served as Chief Medical Officer from 1995 to 2020. He now serves as the Executive Director of Clinical Research for UHG R&D and Senior National Medical Director for OptumCare. Dr. Cohen has received awards of recognition and distinction for teaching, including the Lutheran Medical Center Physician of the Year award in 2011. Under his stewardship New West Physicians was awarded the AMGA Acclaim award in 2015 and the Million Hearts Hypertension Champion Award in 2017. He is a Clinical Associate Professor of Medicine and Pharmacy at the University of Colorado School of Medicine. Dr. Cohen holds degrees from Dickinson College and Hahnemann University. He is a Fellow of the American College of Physicians and a member of the Phi Beta Kappa and Alpha Omega Alpha honor societies.

John Hitt, MD, MBA

Dr. Hitt has been a physician executive for more than 25 years. Most recently he was the CMO of Ativa Medical a medical device startup company and an independent health care consultant. Previously, he was CMO at Maricopa Integrated Health System (MIHS) and a key member of the senior leadership team having responsibility for Medical Staff Services, Grants and Research, Academic Affairs, Risk Management, physician contracted services and the activity of Residency Program Directors, Clinical Department Chairs, and Medical Staff.

Dr. Hitt has over 25 years of experience in quality and performance improvement, clinical integration, academic and medical staff affairs. He served as the Chief Medical Quality Officer for Hennepin Health System, a premier Level 1 Adult and Pediatric Trauma Center. He was a physician leader for VHA (now Vizient). He was the national Medical Director for Disease Management at Caremark International and the VP of Medical Affairs at the University of Minnesota Hospital.

Dr. Hitt is a graduate of the University of Virginia where he played Division 1 soccer. He received his Medical Doctorate from the Medical College of Georgia in 1984 (AOA honors) and completed his Internal Medicine and Infectious Disease Fellowship training at the University of Minnesota Hospital and Clinics. Dr. Hitt completed his MBA at the Carlson School of Management at the University of Minnesota in 2003. He is the proud father of seven children.

Geoffrey Heyer, MD

Dr. Heyer is board certified in neurology with special certification in child neurology and in headache medicine. Prior to joining our team, Dr. Heyer was an associate professor of neurology and pediatrics at The Ohio State University and Columbia University Medical Center, specializing in autonomic disorders, headache, and pain management. He has published over 50 peer-reviewed research papers and numerous editorials, clinical reviews, and textbook chapters. He also co-authored a textbook on childhood stroke and cerebrovascular disorders.

Dr. Heyer received his medical degree from Columbia University, College of Physicians and Surgeons. He completed his neurology and child neurology residencies at Columbia-Presbyterian Medical Center. He has additional research training from the Mailman School of Public Health, Columbia University.