COVID–19
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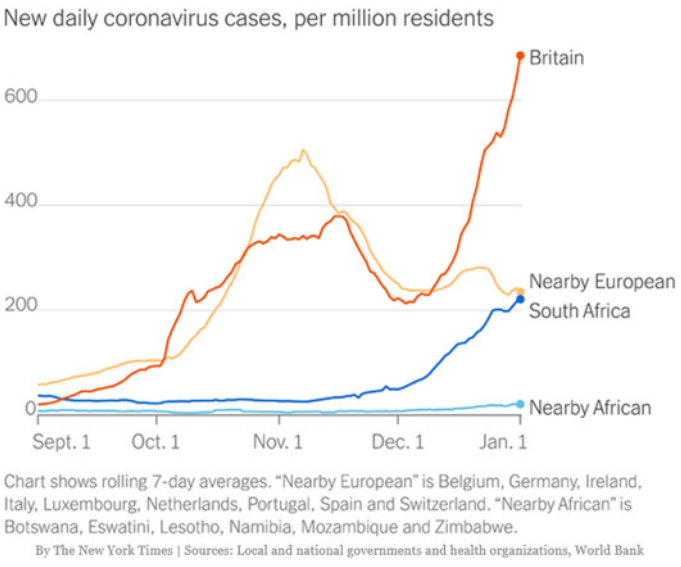
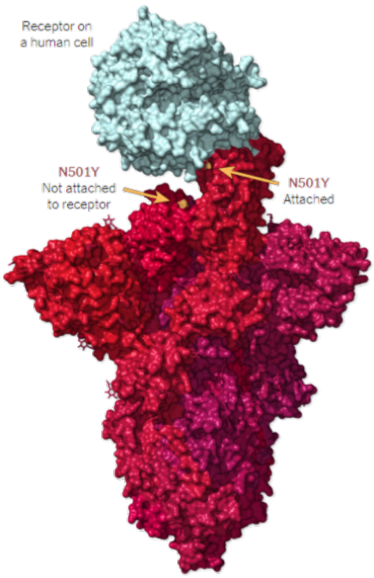
New SARS-CoV-2 variants

We understand that RNA viruses frequently mutate. Each patient infected with SARS-CoV-2 represents a crucible in which viral mutation may occur. With close to 100 million cases worldwide, the virus has almost limitless opportunity to mutate and therefore regularly evolving mutations are the norm. In most cases, the fate of a newly arising mutation is determined by natural selection. Those that confer a competitive advantage with respect to viral replication, transmission, or escape from immunity will increase in frequency, and those that reduce viral fitness tend to be culled from the population of circulating viruses. As disturbing as this may be, increased virulence in humans doesn't seem to be a driver in new strains becoming dominant since this offers no competitive advantage to the virus. As a grim reminder of how critical this point is, recall that the mortality rate of MERS was 35%. With this as a background, let's examine the most concerning of the new strains.

B.1.1.7. This variant of concern (VOC) was first detected near London in September and was formerly referred to as the UK variant. In December it rapidly spread throughout the southeastern part of the UK and was associated with local case rates increasing by 400% within one month (see graph below). It may be as much as ~50% more transmissible. This variant contains 17 mutations including 8 involving the spike protein domain changes. One particular spike protein gene mutation, called N501Y, may be critical in making B.1.1.7 coronaviruses more contagious. In a typical coronavirus, the tip of the spike protein is like an ill-fitting puzzle piece. It can latch onto human cells via the ACE-2 receptor, but the fit is so loose that the virus often fails to achieve cell entry. The N501Y mutation seems to refine the shape of the puzzle piece, allowing a tighter fit and increasing the chance of a successful infection.[1]





Images from *The New York Times*.

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Two other important mutations in the B.1.1.7 lineage may change the conformation of the spike protein in a way that makes it harder for antibodies to bind. One of these is a deletion (H69–V70) which also occurred in the Danish mink population. The remainder of the genetic mutations are of undetermined importance and still under study. Initially it was thought that the sum total of these mutations did not appear to increase the virulence of this strain, but there are now some early data from the UK equivalent of the CDC that suggest there may be a 10–20% increase in virulence. This strain is now present in over 50 countries. According to the CDC,[2] as of January 13, 2021, approximately 76 cases of B.1.1.7 have been detected in the U.S. in 12 states. The modeled trajectory of this variant in the U.S. exhibits rapid growth in early 2021, becoming the predominant variant in March. If the increased transmission mimics the UK experience, it might threaten strained health care resources, require extended and more rigorous implementation of public health strategies, and increase the percentage of population immunity required for pandemic control. Although our most recent severe surge appears to have peaked, cases thus could potentially dramatically increase over the next few months due to the B.1.1.7 strain.

B.1.351. This variant was originally described in South Africa and has eight mutations. This variant quickly spread to several other countries and also contains the N501Y mutation, believed to potentially confer increased transmissibility. To date, there is no compelling evidence suggesting increased virulence with this variant. However, this variant also contains the mutations E484K and K417N, which are thought to be associated with some degree of escape from the neutralizing antibodies produced by infection with the original SARS-CoV-2. How this strain will compete with the other new variants is unknown.

CAL.20C. This variant was first discovered in Denmark last spring and its prevalence is now increasing in California, currently accounting for over half of the cases in that state. We have only very preliminary information on this variant from a preprint of a paper submitted from Cedars-Sinai.[3] This variant contains five mutations including multiple mutations in the spike protein gene. One of the spike protein mutations of this strain is L452R. This might be important as mutations in this domain may create resistance to polyclonal sera as seen in convalescent patients or those post vaccination. The functional effect of this mutation in concert with other detected mutations in CAL.20C, both in terms of infectivity and antibody/vaccine resistance, is unknown currently.

B.1.1.28. This variant was first detected in Brazil and appears to have been transmitted to Japan in January 2021. It involves 17 unique amino acid changes and has several mutations that are known to be biologically important, including both the E484K and the N501Y mutations discussed above. This variant was discovered in Minnesota this week.

Vaccine efficacy, natural immunity, and pharmacologic monoclonal Ab efficacy against the new strains

Here once again we have only very preliminary information. A study in preprint looked at the sera of 16 participants in the phase I/II Pfizer-BNT vaccine trial to specifically examine whether the N501Y spike protein mutation, along with the other spike protein mutations in the B.1.1.7 strain could affect vaccine efficacy.[4] They studied the spike protein of the B.1.1.7 strain as well as the original Wuhan strain, and compared the ability of the participant's post-vaccination sera to neutralize both strains. The neutralizing potency of the sera was equal for both the B.1.1.7 strain and the original Wuhan strain, suggesting there should be no loss of vaccine efficacy against the B.1.1.7 strain solely as a result of the N501Y mutation. Early data consistent with these have also been obtained for the Moderna vaccine.

With respect to the E484K and K417N mutations present in the South Africa variant, there are three studies in preprint awaiting peer review.

- The first examined convalescent serum from patients in South Africa who were recovered from infection prior to the presence of the new variants. Patients with severe disease who typically have much higher levels of convalescent antibodies retained immunity to this new strain, however the larger majority of patients with mild to moderate disease did not have adequate antibody levels for viral neutralization in vitro, and therefore could theoretically be susceptible to reinfection with the newer strain.

- A second study looked at antibody and B cell responses in individuals who had recovered from infection, or had received either the Pfizer-BNT or the Moderna vaccines.[5] The types of antibodies produced, and the B cell responses were both quite similar in all three groups. The levels of antibody in the immunized subjects were similar to those with post-infection immunity at one month but significantly higher in the vaccinated group at six months. Looking at the N501Y, K417N, E484K mutations alone and in combination showed a decrease in antibody mediated viral neutralization that varied from one to three-fold less when compared to the pre mutation SARS-C0V-2. To what extent this decrease in viral neutralization would affect susceptibility to infection with these new variants is not yet known. A similar decreased response to neutralization is possible for the Brazil variant due to mutations common to both the South Africa and Brazil variants.[6] Further study is needed with respect to the California variant.

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- The third study was released from Moderna this week and available only in abstract form. Once again immunity was preserved to the B.1.1.7 variant. When testing vaccine efficacy against the B.1.351 South Africa variant, in the sera of immunized individuals, there was a decrease in viral neutralization that varied between 2.7 and 6.4-fold. Despite the observed decreases, the neutralization titers in human sera against the B.1.351 variant remained at ~1/300. Taken together these data demonstrate reduced but still significant neutralization against the full B.1.351 variant following the Moderna vaccination. Importantly, all of the tested sera were still able to fully neutralize the virus in this experimental assay used in the study.[7]

In summary, it appears that the N501Y mutation alone will not affect vaccine efficacy. Because the current vaccine platforms provide polyepitopic immune response with concurrent activation of neutralizing antibodies and T cells, and thus multiple potential mediators of protection, the hope is that vaccine efficacy will be preserved across the multiple new variants with their various mutations. Should these new mutations turn out to affect vaccine efficacy, it will not likely be an "all or none" phenomenon. Rather, they would cause a reduced efficacy in terms of immunity and disease severity from the current very high levels of protection seen with Pfizer-BNT and Moderna. The emergence of these new mutations also increases the likelihood that vaccines may need to be modified over time with periodic revaccination. In fact, Moderna is already working on modifying its vaccine to increase efficacy against the E484K and K417N mutations in the event that the efficacy of the original vaccine is substantially reduced against the variants discovered in South Africa and Brazil. It is not yet known to what extent these new mutations will affect the efficacy of the Lilly and Regeneron monoclonal Ab formulations, although early data suggests that the Regeneron product may be less effective against the B.1.351 variant from South Africa, which contains the E484K and K417N mutations.

COVID-19 mRNA severe allergic reactions

Even before the trials of the new mRNA vaccines began, concerns over adverse immune reactions to vaccines using this platform were present.[8] Advances in mRNA vaccine development have addressed many of these concerns. However, immediate vaccine reactions are known to occur with most available vaccines and specific recommendations are developed and well described.[9,10] It is not surprising that with a large number of persons receiving the COVID-19 vaccines, immediate allergic reactions of varying severity will be observed.

The CDC COVID-19 Response Team reported this month on the allergic reactions associated with the mRNA vaccine developed by Pfizer.[11] The first dose was given to 1,893,360 individuals. Adverse reactions to the vaccine were identified using the CDC Vaccine Adverse Event Reporting System (VAERS) in 4,393 patients (0.2% of vaccinated patients). Of these reactions, 175 cases of potentially serious reactions were identified with 21 cases of anaphylaxis (11.1 cases of anaphylaxis / million doses). Of the remaining 154 reactions 83 were non-anaphylaxis allergic reactions, 87% of which were determined to be not serious. The remaining 61 reactions were determined to be non-allergic in nature. The non-serious allergic reactions commonly reported included pruritus, rash and scratchy sensations in the throat, and mild respiratory symptoms. This is important as respiratory symptoms occurring more than 24 hours post vaccine receipt are not commonly associated with a vaccine reaction.

Of the 21 persons with anaphylaxis, 81% had a previous history of allergies or allergic reactions with 33% having a history of anaphylaxis. The median time to reaction was 13 minutes (range 2–150 minutes). Symptom onset began within 30 minutes in 86% of patients. While women received 64% of all vaccine doses, they accounted for 90% of anaphylactic reactions. Four of the patients were hospitalized and 17 were treated in the emergency room.

The Moderna mRNA vaccine adverse reactions reported to the CDC included 10 cases of anaphylaxis in the first 4,041,396 individuals immunized (rate 2.5 cases/million).[12] VAERS reported 1,266 adverse events associated with the vaccine (0.03% of vaccinated patients) with 108 identified as possible allergic reactions. The median time of symptom onset in the patients with anaphylaxis was 7.5 minutes (range 1–45 minutes). Like the Pfizer vaccine, while women made up 61% of the vaccine recipients, they accounted for 100% of the anaphylactic reactions (10 total). Ninety percent of the patients had a history of allergies or allergic reactions and 50% had a previous history of anaphylaxis. The 94 remaining cases were evenly divided between non-anaphylaxis allergic causes and non-allergic causes.

In summary, early vaccine data from almost 6 million recipients of the first dose of either the Moderna or Pfizer mRNA COVID-19 vaccine show a low risk of anaphylaxis (2.5–11 cases / million doses). The characteristics of the vaccine are typical of anaphylaxis in that most occur in under 30 minutes after vaccine receipt, require immediate intervention and emphasize the need for post-vaccination observation. Reactions occur more frequently in persons with a history of an allergic reaction, particularly previous anaphylaxis, and seem to have a female predominance.

The current published data on severe allergic responses to the mRNA vaccines references reactions to the first dose. We do not yet know if severe reactions to the second dose will be more frequent as a result of immune stimulation from the first dose or less frequent as those susceptible patients were removed from the vaccine pool after the first dose. Ongoing vigilance for reactions is warranted.

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Neutralizing monoclonal antibodies in patients with COVID-19

Severe disease from COVID-19 appears to be positively correlated with viral load. Several recent studies have demonstrated that neutralizing monoclonal antibodies can reduce viral load and, in some studies, improve clinical outcomes.

Bamlanivimab as monotherapy or in combination with etesevimab.[13] This phase 2/3 trial evaluated the effects of varying doses of bamlanivimab monotherapy and bamlanivimab plus etesevimab versus placebo among patients who tested positive for COVID-19 and had at least one mild or moderate symptom. The primary outcome was reduction in viral load on day 11 (±4 days). Secondary outcomes included hospitalization, ED visits, and death. A total of 533 patients were randomized. Only combination therapy led to statistically significant reduction in viral load compared to placebo. The proportion of patients who visited an ED or were hospitalized by day 29 was 1% in the 700 mg monotherapy group, 1.9% in the 2,800 mg monotherapy group, 2% in the 7,000 mg monotherapy group, 0.9% in the combination therapy group, and 5.8% in the group that received placebo. Although only combination therapy versus placebo was statistically significant, the outcome difference between the currently utilized 700 mg monotherapy dose and the combination therapy was only 0.1%, therefore the 700 mg dose barely missed statistical significance with this small sample size. There were no deaths in the study.

Neutralizing antibody LY-CoV555.[14] The published manuscript from this phase 2 trial provides an interim analysis of the viral load reduction on day 11 for three doses of LY-CoV555 (700 mg, 2,800 mg, 7,000 mg). Only the 2,800 mg dose led to a statistically different viral load reduction versus placebo (log viral load of -0.53; P=0.02). The other doses were associated with smaller (non-significant) differences in viral load.

Neutralizing antibody cocktail REGN-COV2.[15] The REGN-COV2 cocktail contains two fully human monoclonal antibodies against the SARS-CoV-2 spike protein. In this ongoing, double-blind, phase 1–3 trial, patients who tested positive for COVID-19 received 2.4 g or 8 g of REGN-CoV2, or placebo. Endpoints included the time-weighted average viral load from baseline (day 1) through day 7 and the percentage of patients with at least one medically attended visit. A total of 275 patients were randomized, and 269 received an infusion. The analyses were stratified according to the baseline presence of serum antibodies. In patients whose immune responses had not yet been initiated by the infection, the decrease in viral load was more significant. About 6% of patients in the placebo group and 3% of patients in the combined REGN-COV2 had at least one medical visit.

Press release for Eli Lilly, bamlanivimab.[16] Among nursing home residents and staff who had not been knowingly exposed, prophylactic infusion with monoclonal antibody, bamlanivimab, reduced the risk of getting COVID-19 by up to 57%. Analyzing only the nursing home residents, the risk was reduced by up to 80%. The study has not yet been published. Lilly will be supplying 300,000 vials to the U.S. government at a cost of $1,250 per vial.[17]

Overall, the several studies of monoclonal antibodies suggest promising results in terms of reducing viral load; however, clear benefits in clinical outcomes need further study. In the case of prophylactic use of the Eli Lilly drug, bamlanivimab in nursing home patients and staff, the results have not yet been published but the data above appears to be significant. Since the government has already pre-purchased over 2.5 million doses of monoclonal Ab therapy and there is no drug cost to the patients, utilization should be considered in high risk patients early in their disease course while more definitive data is accumulated. From a socioeconomic standpoint, broad vaccination should remain the primary goal, especially among higher-risk individuals.

Tocilizumab efficacy and safety

Patients with severe disease from COVID-19 can develop immune system dysregulation and hyperinflammation, which is thought to be triggered by a type of programmed cell death called pyroptosis. Pyroptosis induces several proinflammatory cytokines and chemokines and causes lymphopenia. The production of interleukins, including interleukin-6 (IL-6), leads to local recruitment of neutrophils and cytotoxic T cells which can contribute to acute lung injury. Higher levels of IL-6 have positively correlated with more severe disease from COVID-19.[18] Tocilizumab is an IL-6 antagonist that has been evaluated in several clinical trials treating patients with severe or critical COVID-19 disease.[19,20,21]

Among hospitalized patients with COVID-19, tocilizumab appears to reduce the risk of mechanical ventilation, although this finding has not been consistent in all studies. A meta-analysis of four randomized controlled trials with a total of 771 patients demonstrated a reduced risk of mechanical ventilation, with a pooled relative risk of 0.71 and corresponding number needed to treat of 17.[21] Three of the four trials favored tocilizumab, but the fourth trial[19] favored the control group. That fourth trial combined mechanical intubation and death as a single endpoint, with a hazard ratio of 1.11.[19] At 14 days, 18% of the patients in the tocilizumab group and 14.9% of the patients in the placebo had developed worsening disease.[19] Since publication of the meta-analysis, a fifth study showed that tocilizumab reduced the likelihood of progression to

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the composite outcome of mechanical intubation or death among a cohort of hospitalized patients, representing mostly underserved racial and ethnic minority populations.[22] However, death from any cause by day 28 occurred in 10.4% of the patients in the tocilizumab group and 8.6% of those in the placebo group.[22] Tocilizumab treatment does not appear to increase the risk of infections or other adverse events.[19, 21]

In conclusion, there is moderate-certainty evidence that tocilizumab reduces the risk of mechanical ventilation among patients hospitalized with severe or critical COVID-19. However, the drug did not improve short-term mortality in randomized controlled studies. Some studies showed higher mortality rates in the treated cohort. Accordingly, the overall potential benefit from tocilizumab treatment is questionable.

Interim analysis of AstraZeneca's viral vector COVID-19 vaccine

Researchers reported on an interim analysis of a non-replicating viral vector vaccine developed by AstraZeneca designed to confer immunity against infection with SARS-CoV-2.[23] The report combines the results of four trials conducted in the UK, South Africa and Brazil.

The vaccine trials studied patients 18 years of age and older. There were vaccinated with ChAdOx1, a viral vector vaccine designed to be delivered as a single dose, compared to a control group receiving meningococcal vaccine or saline. Subsequently, the single dose was modified to two-dose regimen 28 days apart. The primary end point was acquisition of symptomatic COVID-19 disease either 21 days after the first dose or 14 days after receipt of the second dose.

The trials encountered a number of challenges and results must be interpreted with caution. Manufacturing problems resulted in a delay in receipt of the second dose in over 50% of patients in the UK. Also, in some of the individuals the initial dose was roughly one-half of the intended dose, and this cohort was subsequently referred to as the low dose cohort as they received a half dose for the initial dose and a full dose for the booster dose. The total number of trial participants is small relative to the other vaccine phase III trials.

Despite these difficulties, critical early results of vaccine performance were determined. The combined trials involved 23,848 participants of which 11,636 were included in the interim analysis (7,548 UK; 4,088 Brazil). Vaccine efficacy in the cohort that received two full vaccine doses was 62%. COVID-19 occurred in 27 (0.6%) of 4,440 individuals in the vaccine group and in 71 (1.6%) of 4,455 individuals in the control group. Vaccine efficacy in the low dose cohort was 90%. COVID-19 occurred in 3 (0.2%) of 1,367 patients in the vaccine group and 30 (2.2%) of 1,374 persons in the control group. Overall vaccine efficacy was 70.4%, with 30 (0.5%) of 5,807 in the vaccine group acquiring COVID-19 vs 101 (1.7%) of 5,829 control patients acquiring COVID-19.

The vaccine seemed very effective in preventing hospitalization. Ten total hospitalizations occurred at least 21 days after the first dose all occurring in the control arm. These hospitalizations included two severe cases of COVID-19 and one death.

Safety data included 74,341 months of follow-up with a median follow-up of 3.4 months. Severe reactions were reported in 168 persons: 84 in the vaccine group and 91 in control group. Of these, three were felt related to vaccine, one in the vaccine group, one in the control group and one whose group assignment is still blinded.

Despite the obvious difficulties with the trials, this viral vector vaccine seems safe and efficacious in this interim analysis. We can expect future trial results to further inform these results. Importantly, this vaccine represents another vaccine platform and the vaccine can be distributed and stored at 2–8° C. These more favorable storage conditions may have advantages for vaccine delivery in many locations. The Johnson and Johnson vaccine also uses the viral vector platform and is being studied as a single dose regimen. The phase III trial has been fully enrolled with trial results expected soon. Lastly, the Novavax protein subunit vaccine has also fully enrolled its international phase III trial with results expected soon.

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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.

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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.

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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.

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