Good morning. This week the Daily Briefing will be published Monday and Wednesday only.

Today under COVID-19 news I review the CDC's new priority groups (1b and 1 c). Under Journal Reviews I review an article in MMWR, that among children and adolescents aged <18 years in Mississippi, close contact with persons with COVID-19 and gatherings with persons outside the household and lack of consistent mask use in school were associated with SARS-CoV-2 infection, whereas attending school or childcare was not associated with receiving positive SARS-CoV-2 test results. The next article is on tocilizumab which suggests that patients who are most likely to benefit from tocilizumab have moderate or severe disease (i.e., they have hypoxia but are not yet receiving mechanical ventilation) and that tocilizumab may add to the potential benefit of antiviral treatment and glucocorticoids. The next article is an interim report on the monoclonal from Regeneron. Bottom line, the REGN-COV2 antibody cocktail reduced viral load, with a greater effect in patients whose immune response had not yet been initiated or who had a high viral load at baseline. Evidence to date suggests monoclonals can stop disease from progressing and reduce need for hospitalization. I saved perhaps the most important on the new mutation reported from the UK. A few highlights -- Scientists have no reason to think the new variant would be resistant to the current vaccines being rolled out in the U.S., Canada, the U.K. and in my opinion to put into proper perspective -- human behavior is driving the pandemic not necessarily this new mutation. The first article in MMWR brings this out very nicely [look at slide below] and has been stressed in the last month in the Daily Briefing. I am providing you with a link to an excellent article in the New York Times from yesterday on when smallpox hit NYC in 1947. Remember mortality from smallpox was 30%!

How New York City Vaccinated 6 Million People in Less Than a Month - The New York Times (nytimes.com) (https://www.nytimes.com/2020/12/18/nyregion/nyc-smallpox-vaccine.html?searchResultPosition=1)

I hope this holiday season gives us time to reflect on the importance of family, health, and relationships and how we treat our fellow human beings.

Ed

COVID-19 News

First the CDC announced Saturday that it has accepted the recommendation of its vaccine panel for emergency use of Moderna's vaccine, clearing the way for immunization with the second vaccine to begin. (ages 18 and older) Shipments of the newly authorized Moderna COVID-19 vaccine make their way to states and amid federal projections that there will be enough vaccine to vaccinate 20 million people in December, 30 million in January, and 50 million in February.

Vaccine advisors for the CDC on Sunday recommended the next two priority groups—seniors, essential workers, and people with underlying health conditions—to receive the nation's growing supply of COVID-19 vaccine after healthcare workers and residents of long-term care facilities.

The priority group update vote passed with 13 yes votes and 1 no vote. The CDC typically accepts the recommendations of its Advisory Committee for Immunization Practices (ACIP). The interim recommendation, spelling out phase 1b and 1c of prioritization, serves as a guide for state and local health departments.

Phase 1b includes seniors ages 75 and older and frontline essential workers including, for example, those working as first responders, teachers, public transit employees, and grocery store staff. The list also includes people working in food and agriculture, manufacturing, corrections, and the US Postal Service.

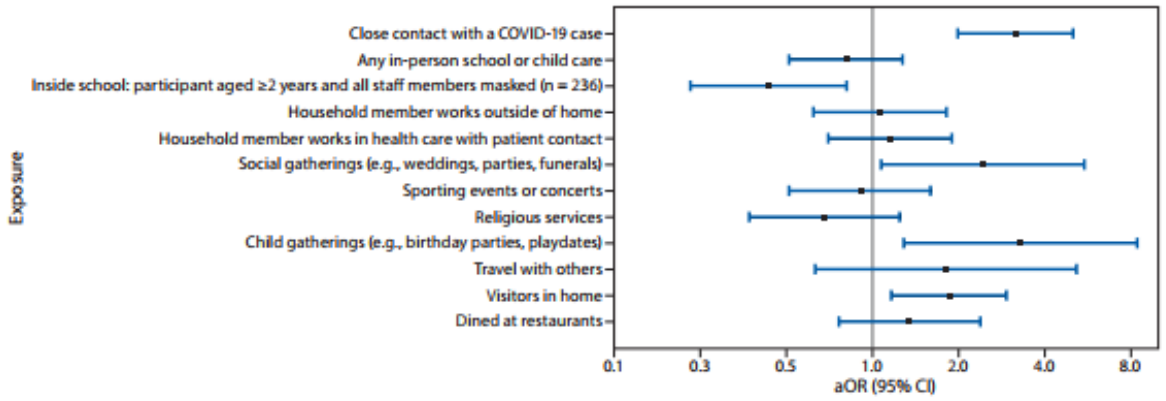
Phase 1c includes seniors aged 65 to 74 years old, people aged 16 to 64 with underlying health conditions, and other essential workers such as those working in transportation, food service, finance, and communications positions.

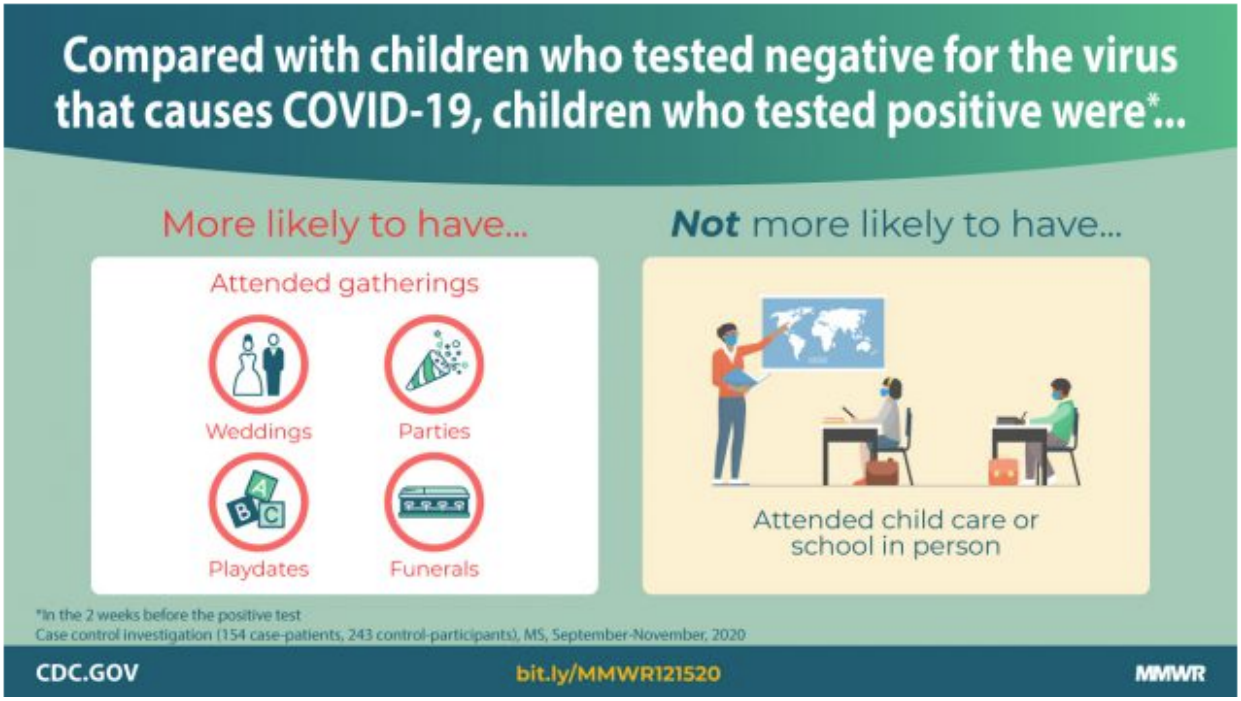
The CDC grappled with were whether to add people age 65 and older to the phase 1b group and what underlying health conditions should be prioritized. [I personally would have prioritized people age 65 and older with certain underlying medical problems (e.g., DM) to be in 1b]

Journal Reviews

Factors Associated with Positive SARS-CoV-2 Test Results in Outpatient Health Facilities and Emergency Departments Among Children and Adolescents Aged <18 Years — Mississippi, September–November 2020
MMWR 2020; 69: 1925-1929
To assess school, community, and close contact exposures associated with pediatric COVID-19, a case-control study was conducted to compare exposures reported by parents or guardians of children and adolescents, aged <18 years with SARS-CoV-2 infection confirmed by PCR testing (case-patients) with exposures reported among those who received negative SARS-CoV-2 PCR test results (control participants). Among 397 children and adolescents investigated, in-person school or childcare attendance ≤14 days before the SARS-CoV-2 test was reported for 62% of case patients and 68% of control participants and was not associated with a positive SARS-CoV-2 test result (adjusted odds ratio [aOR] = 0.8, 95% confidence interval [CI] = 0.5–1.3). Among 236 children aged ≥2 years who attended childcare or school during the 2 weeks before SARS-CoV-2 testing, parents of 64% of case-patients and 76% of control participants reported that their child and all staff members wore masks inside the facility (aOR = 0.4, 95% CI = 0.2–0.8). In the 2 weeks preceding SARS-CoV-2 testing, case-patients were more likely to have had close contact with a person with known COVID-19 (aOR = 3.2, 95% CI = 2.0–5.0), have attended gatherings with persons outside their household, including social functions (aOR = 2.4, 95% CI = 1.1–5.5) or activities with other children (aOR = 3.3, 95% CI = 1.3–8.4), or have had visitors in the home (aOR = 1.9, 95% CI = 1.2–2.9) than were control participants. Close contacts with persons with COVID-19 and gatherings contribute to SARS-CoV-2 infections in children and adolescents. Consistent use of masks, social distancing, isolation of infected persons, and quarantine of those who are exposed to the virus continue to be important to prevent COVID-19 spread.

FIGURE. Adjusted odds ratios (aORs)* and 95% confidence intervals (CIs) for close contact, school or child care, and community exposures† associated with confirmed COVID-19 among children and adolescents aged <18 years (N = 397) — Mississippi, September–November 2020





Comment: Among children and adolescents aged <18 years in Mississippi, close contact with persons with COVID-19 and gatherings with persons outside the household and lack of consistent mask use in school were associated with SARS-CoV-2 infection, whereas attending school or childcare was not associated with receiving positive SARS-CoV-2 test results. This report is c/w other publications: attending school where appropriate mitigation interventions are in place and enforced is not likely to spread SARS-CoV-2 infections; however, social gatherings, close contacts without masks, and visitors in the house at more likely to spread SARS-CoV-2 infection. The holiday season can create unsafe gatherings during a time of increased community spread.

Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia
N Engl J Med published online December 17, 2020
DOI: 10.1056/NEJMoa2030340

This is a RCT which randomly assigned (in a 2:1 ratio) patients hospitalized with Covid-19 pneumonia who were not receiving mechanical ventilation to receive standard care plus one or two doses of either tocilizumab (8 mg per kilogram of body weight intravenously) or placebo. The primary outcome was mechanical ventilation or death by day 28.

A total of 389 patients underwent randomization, and the modified intention-to-treat population included 249 patients in the tocilizumab group and 128 patients in the placebo group. The cumulative percentage of patients who had received mechanical ventilation or who had died by day 28 was 12.0% (95% confidence interval [CI], 8.5 to 16.9) in the tocilizumab group and 19.3% (95% CI, 13.3 to 27.4) in the placebo group (hazard ratio for mechanical ventilation or death, 0.56; 95% CI, 0.33 to 0.97; P=0.04 by the log-rank test). Clinical failure as assessed in a time-to-event analysis favored tocilizumab over placebo (hazard ratio, 0.55; 95% CI, 0.33 to 0.93). 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 (95% CI, –5.2 to 7.8). In the safety population, serious adverse events occurred in 38 of 250 patients (15.2%) in the tocilizumab group and 25 of 127 patients (19.7%) in the placebo group.

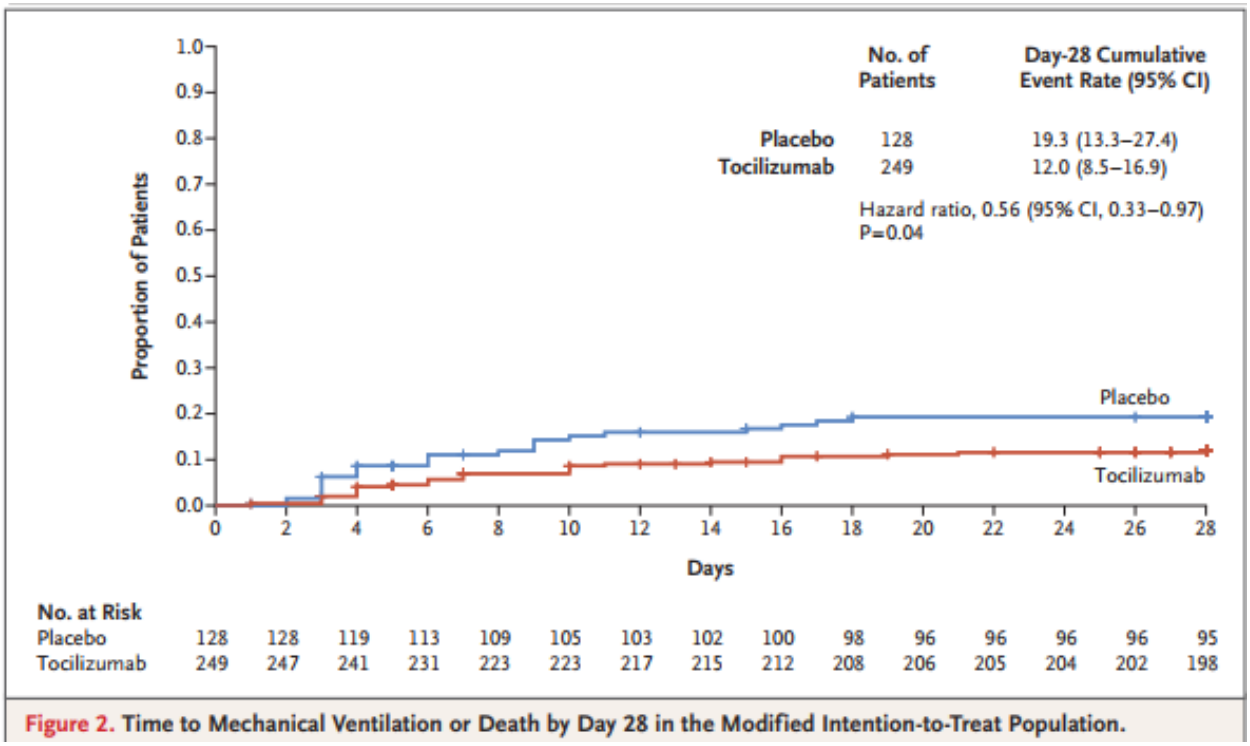


Figure 2. Time to Mechanical Ventilation or Death by Day 28 in the Modified Intention-to-Treat Population.

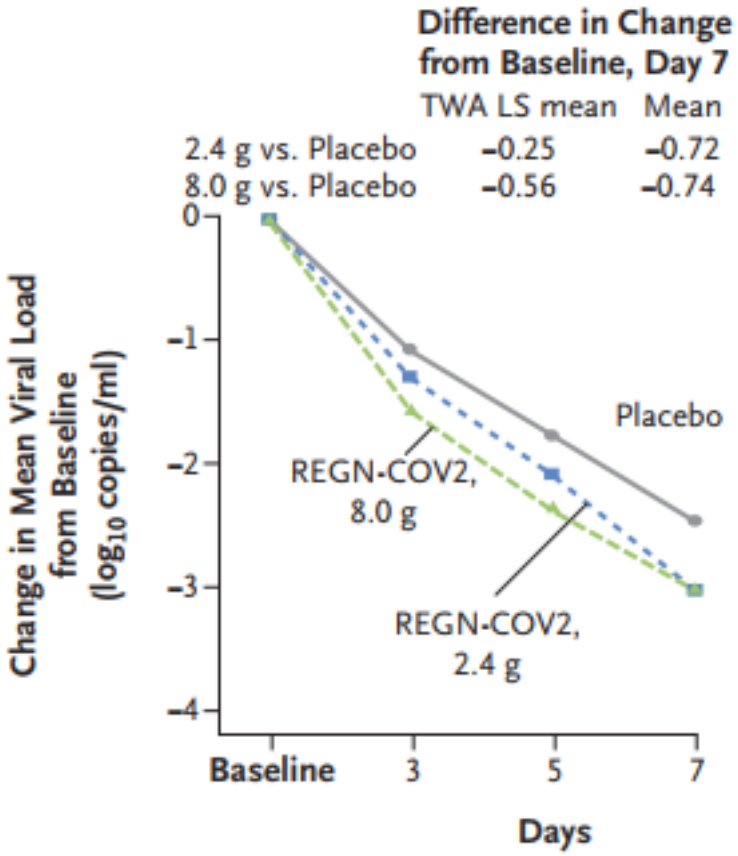
Comment: The results of our trial suggest that patients who are most likely to benefit from tocilizumab have moderate or severe disease (i.e., they have hypoxia but are not yet receiving mechanical ventilation) and that tocilizumab may add to the potential benefit of antiviral treatment and glucocorticoids. In this trial, 55.4% of the patients in the tocilizumab group and 67.2% of those in the placebo group received concomitant dexamethasone, and a greater benefit was observed with tocilizumab than with placebo with respect to the primary outcome. Ongoing trials are under way to provide clarity on the patient subgroups that are most likely to benefit from specific immunomodulatory therapies. One hypothesis is that patients who had progression to mechanical ventilation after receiving tocilizumab may compose a subgroup of patients with more severe disease and therefore a higher risk of death. In summary hospitalized patients with Covid-19 pneumonia who were not receiving

mechanical ventilation, tocilizumab reduced the likelihood of progression to the composite outcome of mechanical ventilation or death, but it did not improve survival at day 28. No new safety signals were identified.

REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19
New Engl J Med published online December 17, 2020
DOI: 10.1056/NEJMoa2035002
This is an ongoing, double-blind trial involving nonhospitalized patients with Covid-19, to evaluate two fully human, neutralizing monoclonal antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein, used in a combined cocktail (REGN-COV2) to reduce the risk of the emergence of treatment-resistant mutant virus. Patients were randomly assigned (1:1:1) to receive placebo, 2.4 g of REGN-COV2, or 8.0 g of REGN-COV2 and were prospectively characterized at baseline for endogenous immune response against SARS-CoV-2 (serum antibody–positive or serum antibody–negative). Primary endpoint was the time-weighted average change from baseline in viral load from day 1 through day 7 and the percentage of patients with at least one Covid-19–related medically attended visit through day 29. Safety was assessed in all patients.

At baseline, 123 patients (45%) were serum antibody-positive, 113 (41%) were serum antibody-negative, and 39 (14%) had an unknown antibody status. Participants who were serum antibody-negative at baseline had a larger reduction in viral load in the first 7 days than other participants. Among serum antibody-positive patients, those who received the high dose of REGN-COV2 had a larger reduction in viral load than those who received placebo or a low dose of REGN-COV2. Of all trial participants 6% in the placebo group and 3% in the combined REGN-COV2 dose groups had at least one medically attended visit. Of participants who were serum antibody-negative at baseline, 15% in the placebo group and 6% in the REGN-COV2 group had one or more medically attended visits (difference, 9 percentage points).

A Viral Load over Time in the Overall Population



No. at Risk				
Placebo	81	70	78	78
REGN-COV2, 2.4 g	73	66	69	70
REGN-COV2, 8.0 g	74	70	73	73

Comment: In this interim analysis, the REGN-COV2 antibody cocktail reduced viral load, with a greater effect in patients whose immune response had not yet been initiated or who had a high viral load at baseline. Higher viral loads have been correlated with an increased risk of death among hospitalized patients. High-titer convalescent-phase plasma has also been shown to lower the SARS-CoV-2 viral load and thereby reduce the risk of death from Covid-19 if given early before presence of antibodies. Likewise, in this trial, clearance of the virus was correlated with better clinical outcomes. The neutralizing titers achieved with REGN-COV2 were more than 1000 times the titers achievable with convalescent-phase plasma, and REGN-COV2 had a profound and rapid effect on viral load, with most reduction occurring within 48 hours. Their results also suggest that a shorter time to elimination of viral load would reduce the time of potential infectivity. This hypothesis is being studied in a separate REGN-COV2 trial. The time from the first Covid-19 symptom to randomization was similar in serum antibody–positive patients and serum antibody–negative patients. This observation suggests that symptom onset is not a good predictor of when an immune response is initiated in an individual patient. [this is a very

interesting finding] Currently monoclonals are being administered to outpatients who are at high risk for COVID-19 severe disease. The hope being to treat early before inflammatory stage and reduce progression and hospitalizations. The biggest difficulty is logistical. The infusions take several hours, and patients need to be referred soon after diagnosis. A specialized nurse with appropriate PPE in a special space separated from other patients are needed. Evidence to date suggests monoclonals can stop disease from progressing and reduce need for hospitalization. This could provide a reprieve to help hospitals from current surge. To remind everyone we now have two versions: Eli Lily and Regeneron.

Preliminary Genomic Characterisation of an Emergent SARS-CoV-2 Lineage in the UK Defined by a Novel Set of Spike Mutations

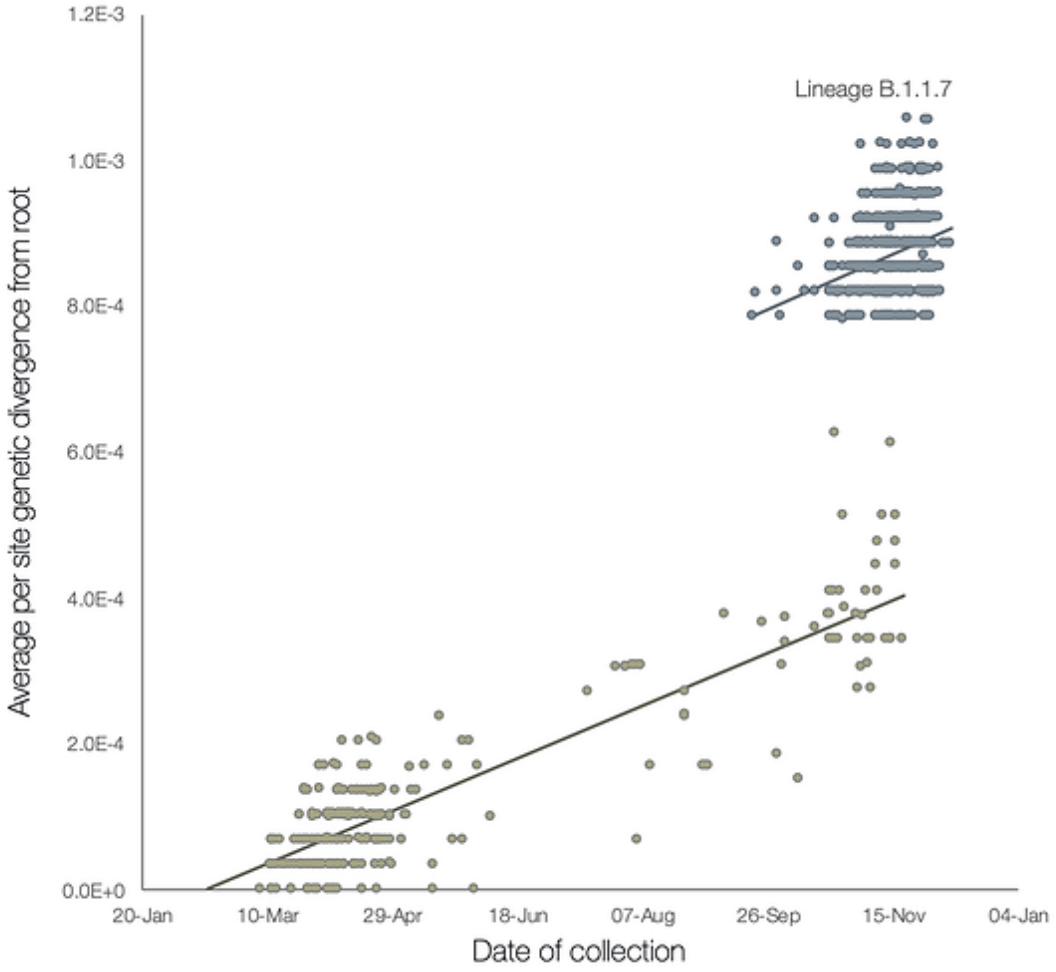
ARTIC Network published online December 18, 2020

Recently a distinct phylogenetic cluster (named lineage B.1.1.7) was detected within the UK surveillance dataset. This cluster has been growing rapidly over the past 4 weeks and since been observed in other UK locations, indicating further spread. Several aspects of this cluster are noteworthy for epidemiological and biological reasons and they report preliminary findings below. In summary:
The B.1.1.7 lineage accounts for an increasing proportion of cases in parts of England. The number of B.1.1.7 cases, and the number of regions reporting B.1.1.7 infections, are growing. B.1.1.7 has an unusually large number of genetic changes, particularly in the spike protein.

Three of these mutations have potential biological effects that have been described previously to varying extents:

- Mutation N501Y is one of six key contact residues within the receptor-binding domain (RBD) and has been identified as increasing binding affinity to human and murine ACE2.
- The spike deletion 69-70del has been described in the context of evasion to the human immune response but has also occurred a number of times in association with other RBD changes.
- Mutation P681H is immediately adjacent to the furin cleavage site, a known location of biological significance.

The rapid growth of this lineage indicates the need for enhanced genomic and epidemiological surveillance worldwide and laboratory investigations of antigenicity and infectivity.



Comment: Three main questions are now being investigated: Is the new variant more contagious, is it more likely to be fatal or cause serious illness, and is it more likely to defeat the body's immune responses, including those encouraged by vaccines? This variant is significantly more prone to be transmitted among people than earlier strains. The reproduction number for this variant is 3.4 from current estimates of around 2.5- 3 which would raise the basic estimate for the herd immunity threshold to over 70% from around 60-65%. There is no evidence yet that the new variant causes more serious infections or will neutralize the vaccines. Scientists have no reason to think the new variant would be resistant to the current vaccines being rolled out in the U.S., Canada, the U.K. and some other countries. [but we do not know for sure] The vaccines aim to trigger a broad immune response that teaches the body to recognize the virus's entire spike protein, so small mutations should not prevent that from happening. We will need to watch this carefully overtime as RNA do mutate. To put into proper perspective human behavior is driving the pandemic not necessarily this new mutation, but this is a real warning that we need to pay close attention.


CONTAGIOUSNESS
IS MORE A
FUNCTION OF
BEHAVIOR
Get Vaccinated!