Good morning. A reminder the Daily Briefing will not be published this Friday.

Today I start with an editorial comment on the new variant and the lack of adequate genomic surveillance in the US. The next 2 reviews are different approaches in stretching the current number of available doses to increase vaccine coverage to more people. The next article is a nice review of multiple trials of ACEI and ARBs concluding with high certainty that use of these drugs is not associated with more severe disease. The next article builds on a theme about importance of glycemic control and clinical outcomes. Finally, a topic I have not covered adequately is the relationship of COVID-19 infections and cancer.

I hope you and your family has a safe and joyous holiday weekend.

Ed

VII Editorial Comment:

A new variant of the SARS-CoV-2 virus has been identified in the UK and elsewhere. The initial response has been the panic and fear so common during the course of this pandemic. Neither scientists nor policymakers have any idea how widespread the variant in question is. Did it originate in the UK or migrate there from somewhere else? How many other countries is it in? Could this strain already be in the United States? Let us explore what we know and what we do not know.

Public health officials advising the British government say initial evidence indicates the new strain is more contagious than older variants, but that so far there are no signs that it causes more severe disease. RNA viruses naturally mutate like the new coronavirus. Many variants of the new coronavirus have already surfaced since the beginning of the pandemic. This is not the first time a new variant crowded out others during the pandemic. Early in the pandemic we saw a mutation from the D614 strain to the G614. [reported in the Daily Briefing] Like the new strain, the G614 also appeared to be more contagious and was associated with lower RT-PCR cycle thresholds, [higher viral loads] but was not associated with increased severity.

UK scientists have investigated at what level this new variant is circulating, whether changes in its replication might make it more transmissible and whether this new strain correlates with increases in numbers and if increase in cases is the result of the new variant. Initial evidence points in the direction that this new variant may be slightly more transmissible than the previous strain. However, scientists admit more research is needed to figure out how much more transmissible it is and the biology behind it.

As the UK looked at the new variant, researchers found it had 23 mutations, 17 of which could influence the virus's behavior, including some on the spike protein that other research has found may help the virus to enter cells more effectively than earlier variants. Despite the findings, many researchers say more work needs to be done to figure whether the changes have a real-world impact. I do believe the new mutations are concerning, but there is still a lot we still do not know. I do not think we can make any conclusion about this mutation until we have had more time to study its impact. The molecular studies to accurately measure transmissibility have not been done yet.

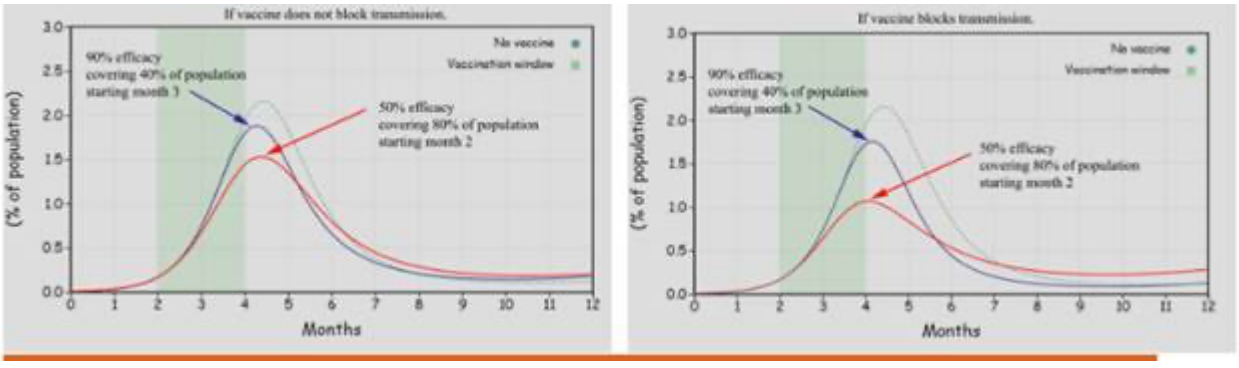
Scientists said they were not sure how these new mutations would affect the virus's ability to infect cells and to spread, but said they doubted the changes were enough to render current vaccines ineffective.

Pfizer and partner BioNTech SE have tested blood samples from people immunized with its vaccine for its ability to neutralize multiple mutant variants. To date, the companies have found consistent coverage of all the variants tested. The companies are now generating data on how well blood samples from people immunized with their vaccine may be able to neutralize the new variant from the UK.

This brings me to my last point. Genomic surveillance is one of the few ways we can determine whether, where, and how to put travel restrictions in place and make critical public health decisions. Without this data we are literally flying blind. The current situation reminds me of the pandemic's early days, when the virus was first detected in China and U.S. officials enacted a travel ban against visitors from China. At the time we did not realize that the virus was already spreading through Europe and would soon make its way to the United States from Europe not China. The UK has sequenced more than 3,700 SARS-CoV-2 cases, compared with fewer than 100 cases in the United States! Routine genetic sequencing of virus samples is critical to understanding how a virus is evolving: are mutations common, if new variants are emerging, how the virus is spreading, and whether cases in each cluster are linked to one another and how the virus is being spread in our community. In my opinion to solve this problem, we need to rapidly increase our ability to perform genomic surveillance now. Until we have this value tool, we will be stuck in the same place we have been for the better part of this year: making often severe sacrifices to try to slow the spread of the virus in the absence of science. There is no need for panic. Let us wait for the science!

Center for Disease Dynamics, Economics & Policy (CDDEP) Vaccination Scenarios:

CDDEP shows how different vaccine scenarios affect the transmission of SARS-CoV-2; modeling suggests that vaccinating more individuals with first shots and by delaying second shots, could save 20–30% more lives than administering two doses per individual this winter. The caveat of these simulations is that the closer one gets to the peak of the winter surge, the less a vaccine can flatten the curve. In other words, the earlier the vaccine is distributed in the epidemic, the greater its impact on flattening the curve. Across the US, the number of positive cases has increased from around 40,000 a day in August and September to almost 100,000 by the end of October and more than 200,000 a day in the first weeks of December. Yet, the next couple of months are likely to see even higher case numbers, unless we dramatically reduce the spread. While social distancing and face masks can slow transmission, they will not be enough. A COVID-19 vaccine distributed in the near term, even if only 50% effective, would be far more effective than the slower distribution of a 90% effective vaccine.



Comment: The suggestion of vaccinating more individuals with first shots by delaying second shots is an interesting proposal. See below for another suggestion on how to optimize vaccination against SARS-CoV-2.

Model-Informed COVID-19 Vaccine Prioritization Strategies by Age and Serostatus
medRxiv published online December 7, 2020
With limited supply of current SARS-CoV-2 vaccines, the question of how to prioritize available doses have arisen. The investigators used a mathematical model to compare five age-stratified prioritization strategies. A highly effective transmission-blocking vaccine prioritized to adults ages 20-49 years minimized cumulative incidence, but mortality and years of life lost were minimized in most scenarios when the vaccine was prioritized to adults over 60 years old. Use of individual-level serological tests to redirect doses to seronegative individuals improved the marginal impact of each dose while partially addressing existing inequities in COVID-19 impact. While maximum impact prioritization strategies were broadly consistent across countries, transmission rates, vaccination rollout speeds, and estimates of naturally acquired immunity, this framework was able to compare impacts of prioritization strategies across contexts.

Comment: Redirecting vaccines to people who do not have antibodies could allow health agencies to stretch vaccines further, especially in hard-hit areas. In one example, vaccinating one in five people in a hard-hit place like New York City, giving priority to people over 60, could bring death rates down by 73%. The study made the assumption that immunity lasts for one year, but it's unknown whether that is the case. The question is whether there would be any benefit to the larger population if previously infected people waited since Covid-19 reinfections have occurred but are rare, especially in the first 90 days after infection. This model suggests there would be a benefit in deferral of vaccination for person who have already had COVID-19 but note several drawbacks, the first of which is that no one knows how long natural immunity lasts. This article and the CDDEP proposal are worthy of discussion.

Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Blockers Use and COVID19 Infection Among 824,650 Patients with Hypertension from a US Integrated Healthcare System
Journal of the American Heart Association published online December 14, 2020
doi.org/10.1161/JAHA.120.019669
The investigators identified patients with hypertension as of March 1, 2020 (index date) from Kaiser Permanente Southern California. Patients who received ACEIs, ARBs, calcium channel blocks (CCB), beta-blockers (BB), thiazide diuretics (TD), or no therapy were identified using outpatient pharmacy data covering the index date. Outcome of interest was a positive PCR reaction test for Covid-19 between March 1-May 6, 2020. Patient sociodemographic and clinical characteristics were identified within 1-year pre-index date. Among 824,650 patients with hypertension, 16,898 (2.0%) were tested for Covid-19. Of those tested, 1,794 (10.6%) had a positive result.

Overall, exposure to ACEIs or ARBs was not statistically significantly associated with Covid-19 infection after propensity score adjustment (Odds ratio (OR)=1.06, 95%CI:0.90,1.25) for ACEIs vs CCB/BB/TD; OR=1.10, 95%CI:0.91,1.31 for ARBs vs CCB/BB/TD). The associations between ACEI use and Covid-19 infection varied in different age groups (*p*-interaction=0.03). ACEI use was associated with lower odds of Covid-19 among those aged ≥85 years (OR=0.30, 95%CI:0.12,0.77). Use of no antihypertensive medication was significantly associated with increased odds of Covid-19 infection compared with CCB/BB/TD (OR=1.32, 95%CI:1.11,1.56).

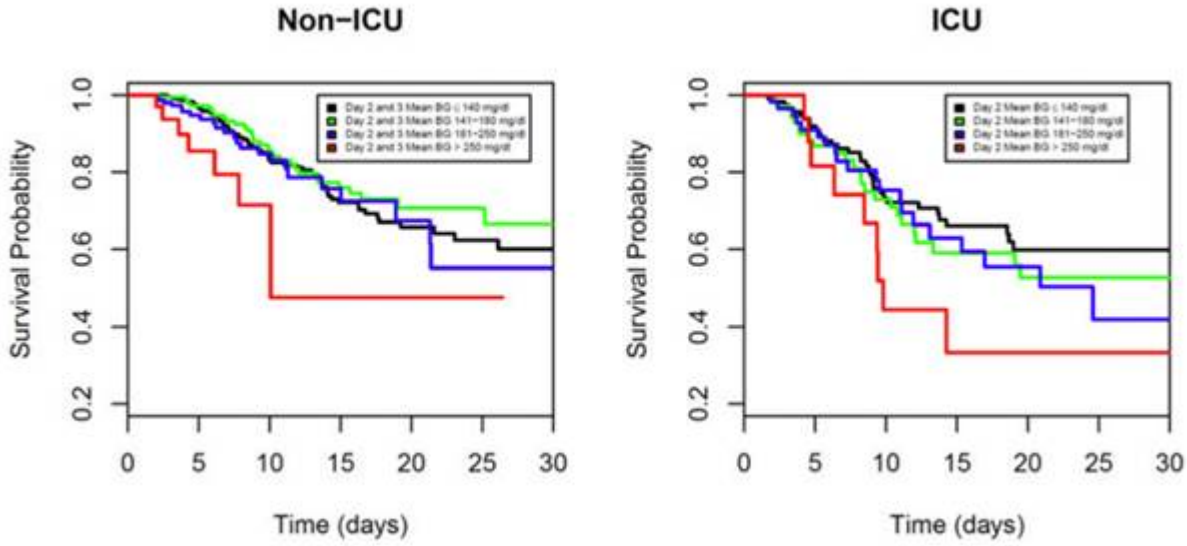
Comments: A review of multiple trials of ACEI and ARBs [reviewed over time in the Daily Briefings] have concluded with high certainty that use of these drugs is not associated with more severe disease. Decreased odds of Covid-19 infection among adults ≥85 years using ACEIs warrants further investigation.

Association Between Achieving Inpatient Glycemic Control and Clinical Outcomes in Hospitalized Patients With COVID-19: A Multicenter, Retrospective Hospital-Based Analysis

Diabetes Care published online December 15, 2020
doi.org/10.2337/dc20-1857

The investigators analyzed pooled data from the Glytec national database including 1,544 patients with COVID-19 from 91 hospitals in 12 states. Patients were stratified according to achieved mean glucose category in mg/dL (£7.77, 7.83–10, 10.1–13.88, and >13.88 mmol/L; £140, 141–180, 181–250, and >250 mg/dL) during days 2–3 in non-ICU patients or on day 2 in ICU patients. They conducted a survival analysis to determine the association between glucose category and hospital mortality.

Overall, 18.1% (279/1,544) of patients died in the hospital. In non-ICU patients, severe hyperglycemia (blood glucose [BG] >13.88 mmol/L [250 mg/dL]) on days 2–3 was independently associated with high mortality (adjusted hazard ratio [HR] 7.17; 95% CI 2.62–19.62) compared with patients with BG <7.77 mmol/L (140 mg/dL). This relationship was not significant for admission glucose (HR 1.465; 95% CI 0.683–3.143). In patients admitted directly to the ICU, severe hyperglycemia on admission was associated with increased mortality (adjusted HR 3.14; 95% CI 1.44–6.88). This relationship was not significant on day 2 (HR 1.40; 95% CI 0.53–3.69). Hypoglycemia (BG <70 mg/dL) was also associated with increased mortality (odds ratio 2.2; 95% CI 1.35–3.60).



Comment: Both hyperglycemia and hypoglycemia were associated with poor outcomes in patients with COVID-19. (independent of diabetes) Admission glucose was a strong predictor of death among patients directly admitted to the ICU. Severe hyperglycemia after admission was a strong predictor of death among non-ICU patients. Hyperglycemia is a well-known marker of disease severity, and its association with poor outcomes in patients with COVID-19 has been reported several times including publication reviewed in the Daily Briefing. However, most analyses have not accounted for disease severity on admission or temporality of glucose control, nor have they adjusted for confounders now known to be independent predictors of poor outcomes during COVID-19 (i.e., sex, age, and BMI) that are also associated with diabetes. Their analytic approach accounted for temporality (dysglycemia before outcomes), confounders, severity of disease on admission, and performance (achieving target within a window in which target can be met) and provides a rational approach to interpret glucose control

interventions. Given the retrospective nature of the analysis, selection bias and misclassification were possible. With increasing use of steroids, glycemic control should be part of the treatment protocol.

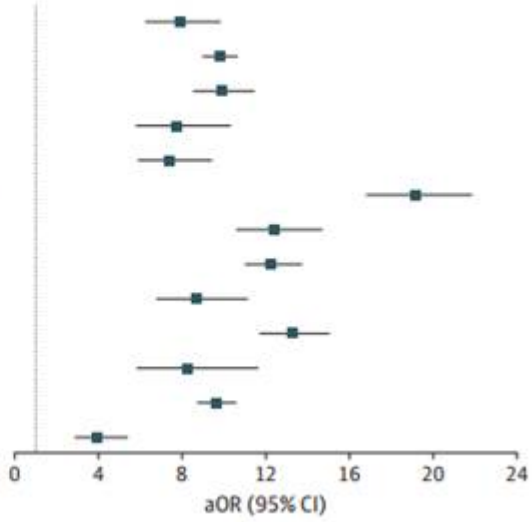
Analyses of Risk, Racial Disparity, and Outcomes Among US Patients with Cancer and COVID-19 Infection

JAMA Oncology published online December 10, 2020
doi:10.1001/jamaoncol.2020.6178

This is a retrospective case-control analysis of patient electronic health records included 73.4 million patients from 360 hospitals and 317,000 clinicians across 50 US states to August 14, 2020. [IBM Watson Health Explorys] The odds of COVID-19 infections for 13 common cancer types and adverse outcomes were assessed. Among the 73.4 million patients included in the analysis (53.6% female), 2,523,920 had at least 1 of the 13 common cancers diagnosed (all cancer diagnosed within or before the last year), and 273,140 had recent cancer (cancer diagnosed within the last year). Among 16,570 patients diagnosed with COVID-19, 1,200 had a cancer diagnosis and 690 had a recent cancer diagnosis of at least 1 of the 13 common cancers. Those with recent cancer diagnosis were at significantly increased risk for COVID-19 infection (aOR, 7.14 [95% CI, 6.91-7.39]; *P* < .001), with the strongest association for recently diagnosed leukemia (aOR, 12.16 [95% CI, 11.03-13.40]; *P* < .001), non–Hodgkin lymphoma (aOR, 8.54 [95% CI, 7.80-9.36]; *P* < .001), and lung cancer (aOR, 7.66 [95% CI, 7.07-8.29]; *P* < .001) and weakest for thyroid cancer (aOR, 3.10 [95% CI, 2.47-3.87]; *P* < .001). Among patients with recent cancer diagnosis, African Americans had a significantly higher risk for COVID-19 infection than White patients; this racial disparity was largest for breast cancer (aOR, 5.44 [95% CI, 4.69-6.31]; *P* < .001), followed by prostate cancer (aOR, 5.10 [95% CI, 4.34-5.98]; *P* < .001), colorectal cancer (aOR, 3.30 [95% CI, 2.55-4.26]; *P* < .001), and lung cancer (aOR, 2.53 [95% CI, 2.10-3.06]; *P* < .001). Patients with cancer and COVID-19 had significantly worse outcomes (hospitalization, 47.46%; death, 14.93%) than patients with COVID-19 without cancer (hospitalization, 24.26%; death, 5.26%) (*P* < .001) and patients with cancer without COVID-19 (hospitalization, 12.39%; death, 4.03%) (*P* < .001).

Figure 2. Association of Coronavirus Disease 2019 (COVID-19) Infection With Recent Cancer Diagnosis

Exposure	Outcome	aOR (95% CI)	P value
Bladder cancer	COVID-19	7.85 (6.26-9.83)	<.001
Breast cancer	COVID-19	9.78 (8.96-10.67)	<.001
Colorectal cancer	COVID-19	9.89 (8.54-11.45)	<.001
Endometrial cancer	COVID-19	7.73 (5.79-10.33)	<.001
Kidney cancer	COVID-19	7.46 (5.89-9.45)	<.001
Leukemia	COVID-19	19.18 (16.79-21.90)	<.001
Liver cancer	COVID-19	12.49 (10.59-14.72)	<.001
Lung cancer	COVID-19	12.30 (11.00-13.75)	<.001
Melanoma	COVID-19	8.70 (6.79-11.14)	<.001
Non-Hodgkin lymphoma	COVID-19	13.27 (11.70-15.06)	<.001
Pancreatic cancer	COVID-19	8.24 (5.82-11.66)	<.001
Prostate cancer	COVID-19	9.64 (8.76-10.61)	<.001
Thyroid cancer	COVID-19	3.94 (2.88-5.40)	<.001



Comment: In this case-control analysis of electronic medical records from 73.4 million unique patients, patients with a recent diagnosis of cancer were at significantly increased risk for COVID-19 infection and its adverse outcomes, especially in African Americans and particularly patients with leukemia, lung and liver cancer, and NHL. Patient EHR data have inherent limitations when used for research purposes: data are collected for billing purposes; often reflect underdiagnosis, overdiagnosis, or misdiagnosis; do not include all confounding factors; have limited time-series information for patients; have limited information on socioeconomic and lifestyle determinants.