Good morning. A lot has happened since Monday! I will start with an editorial on the Clin Infect Dis article on 3 feet vs 6 feet and opening schools.

Under COVID-19 News, Pfizer has reported initial data on preventing asymptomatic diseases in Israel. Next is the announcement of starting vaccine trials in children ages 6 months to 11 years. This followed by the updated IDSA/AMP statement on Ct thresholds for clinical decision making.

For journal reviews I have selected an article suggesting that B.1.1.7 is associated with higher mortality. The next article is the Clin Infect Dis article on 3 vs 6 feet, the focus of my editorial. The next article reviews the effectiveness of the AstraZeneca vaccine against the variant B.1.351. The last article is from CDC NHSN which confirms an earlier report from Ascension that there has been a marked increase in CLABSIs during the pandemic.

Have a wonderful day.

Ed

VII Editorial

In this issue of the COVID-19 Daily Briefing, colleagues in Massachusetts conducted a comparison of 3 feet vs 6 feet in schools by taking advantage of a natural experiment. (see below) Last year, the state's education department issued guidelines recommending three to six feet of distancing in schools that were planning to reopen in the fall. As a result, school policies varied: Some districts imposed strict, six-foot distancing, whereas others required just three. It should be emphasized that the state mandated all staff members, as well as students in second grade and above, to wear masks. The authors found no difference in COVID-19 comparing 3 feet versus 6 feet. The study also found that COVID-19 rates were lower in schools than in the surrounding communities supporting other studies. They conclude schools may be able to reduce their distancing requirements and still be safe, provided they are enforcing other mitigation strategies, especially universal masking. [I would add good ventilation] The authors acknowledged that they could not rule out the possibility that increased distancing provided a small benefit.

Where do we go from here? Some experts say that a small increase in risk is outweighed by the benefits of fully reopening schools. They say the six-foot guideline should not prevent us from getting kids back to school full time with masks, with at least three-foot distancing and I agree. In fact, the 6 feet recommendation is not universal. The American Academy of Pediatrics recommends three to six feet of social distancing in schools, and the World Health Organization recommends just one meter, or 3.3 feet. On the other hand, the more people there are in a room, the higher the odds that one of them will be infected with SARS-CoV-2. The 6-foot recommendation potentially does reduce the risk of overcrowding in classrooms. In addition, with aerosol/droplet transmission, the farther the aerosols travel, the more diluted they become and less likely to transmit infection as outlined by the article in JAMA Surg reviewed last Monday. However, masks and good ventilation can do a lot to reduce the risk. With these measures in place, the difference between three and six feet is likely to be relatively small. Some say we risk confusing the public health message if we establish different standards for schools than for other shared spaces. But I disagree since schools are unique since they are relatively controlled environments where we can enforce certain safety measures.

Ultimately, I think we should consider modifying guidance, but I am not sure this is the right time. Although rates of infection with COVID-19 have significantly fallen, the rate of decline may have leveled

off. There is also concern over the spread of variants which may be more contagious and severe, not to mention spring break, Passover, and Easter. Even proponents of changing the guideline say that any shift to reducing distancing must be done carefully, and in combination with other mitigation strategies such as proper ventilation and masks. However, on a positive note, vaccinations are accelerating and by the end of next month I think anyone who wants to be vaccinated should be able to get it. I also expect that before the fall, children ages 12-16 will be able to be vaccinated as well as teachers. Vaccines are amazingly effective in reducing infections and also transmission (see below on vaccine effectiveness against asymptomatic disease). Currently, the UK variant (B.1.1.7) appears to be the most fit in the US and current vaccines are amazingly effective against the UK variant. In conclusion, let me be clear, I believe schools should be open now for in person learning as long as current guidance is followed.

COVID-19 News

Vaccine Effectiveness against Asymptomatic Infection
Pfizer announced that real-world data from Israel suggests their COVID-19 vaccine is 94% effective in preventing asymptomatic infections, which in turn could significantly reduce transmission. The company also said the latest analysis of the Israeli data shows the vaccine was 97% effective in preventing symptomatic disease, severe disease, and death. That is in line with the 95% efficacy Pfizer reported from the vaccine's clinical trial in December submitted to the FDA.

The analysis also shows real-world evidence of the vaccine's effectiveness against a highly infectious variant of COVID-19 first discovered in the UK (B.1.1.7). More than 80% of the tested specimens when the analysis was conducted were variant B.1.1.7. There were only a limited number of infections in Israel caused by South African variant B.1.351 - so they were not able to evaluate effectiveness against this variant.

Comment: This is welcomed news. In the US B.1.1.7 accounts for 25-30% of cases. There are only ~100 cases of the South African and the Brazilian variants in the US to date according to the CDC.

COVID-19 Vaccinations in Children
Moderna has begun studying its Covid-19 vaccine in children aged 6 months to 11 years in the U.S. and Canada. Moderna is conducting the trial in collaboration with the NIAID and a division of the Department of Health and Human Services. Pfizer plans to conduct a trial of its vaccine in children ages 5 to 11 years old and will share more details when plans are completed.

Moderna and Pfizer started testing their vaccines late last year in adolescents aged 12 years and older. Both trials have fully enrolled subjects, and the results are pending. J&J is planning to start pediatric testing of its vaccine.

Comment: I expect the results of the adolescent trials by late spring. If safe and effective, we may be able to vaccinate children ages 12-18 before the fall.

IDSA and AMP (Association for Molecular Pathology) Joint Statement on the Use of SARS-CoV-2 PCR Cycle Threshold (Ct) Values for Clinical Decision-Making
March 12, 2021 Highlights provided by Cesar Arias

- There is an inverse relationship between Ct values and the amount of virus in the specimen. In general, low Ct values indicate a higher viral density (i.e., fewer amplification cycles are needed to detect a positive result) and high Ct values generally indicate a lower viral density.
- Qualitative real-time PCR tests, however, are not designed to provide a quantitative or semi-quantitative measurement of nucleic acid in a sample.
- Qualitative PCR assays do not reliably correspond to specific RNA concentrations and are not consistent across platforms.
- Recent reviews report an association between lower Ct values and worse clinical outcome.
- Multiple variables, other than the amount of nucleic acid present in the sample, may impact the determination of Ct values. (see below) Therefore, given the wide variability of Ct values both across and within PCR platforms, it is not possible to identify a universal threshold of prognostic value.

TABLE. Factors that impact Ct values

Patient factors	Specimen factors	Test factors
Presence or absence of symptoms	Adequacy of specimen collection	Volume of sample subjected to testing
Severity of symptoms	Reproducibility of the specimen collection method	Gene target
Time from symptom onset	Specimen type (e.g., nasal swab, saliva, BAL)	PCR primer and probe design, which may be variably affected by emerging viral variants
Immune status	Dilution of the sample in transport medium or other liquid	Nucleic acid extraction efficiency (note, not all tests include a nucleic acid purification and extraction step to remove potential PCR inhibitors in the specimen)
Age	Specimen transport and storage conditions	Gene target amplification efficiency
		PCR instrument parameters and settings

Comment: Although there is a relative relationship between Ct values and the amount of virus in a clinical specimen, Ct values generated by qualitative PCR tests should not be considered quantitative measures of viral load.

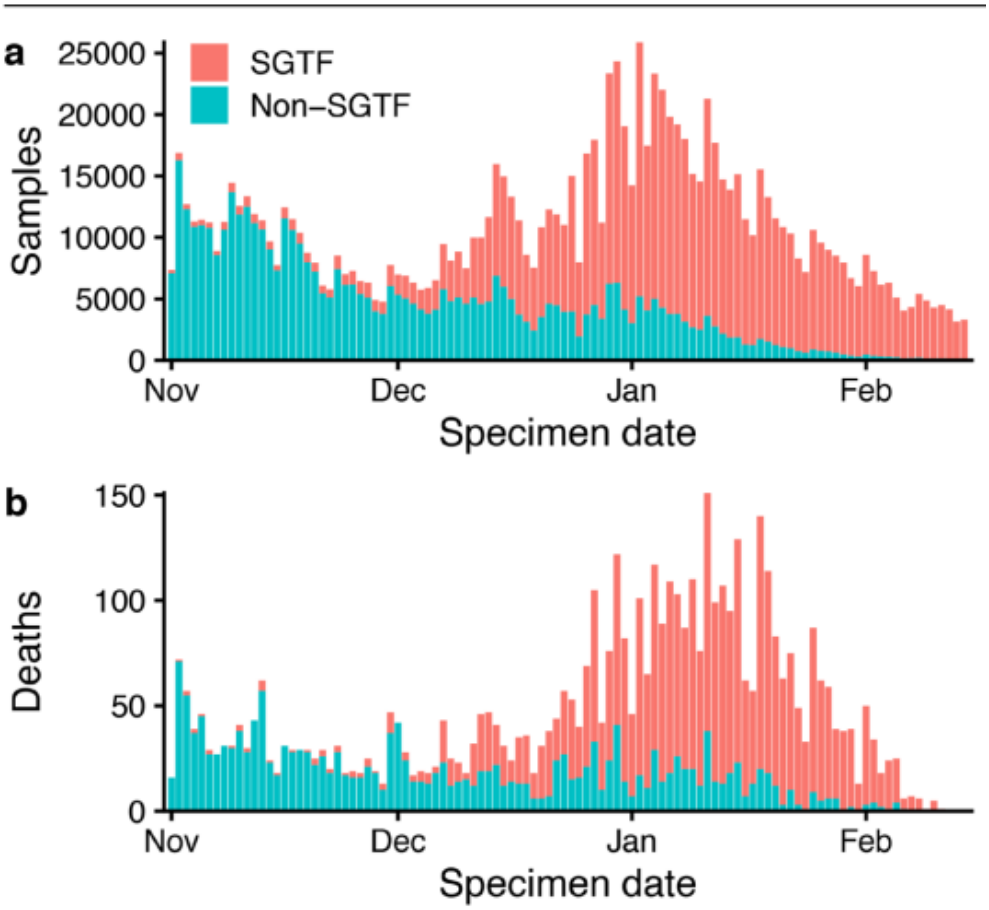
Journal Review

Increased Mortality in Community-Tested Cases of SARS-CoV-2 Lineage B.1.1.7
Nature published online March 15, 2021
doi.org/10.1038/s41586-021-03426-1
The investigators analyzed 2,245,263 positive COVID-19 community tests from all seven National Health Services regions in England from Sep 1, 2020, to Feb 14, 2021. About 0.8% (17,452) were fatal, and the researchers used Cox proportional hazard models to estimate increased 28-day risk of mortality.

Because only 51.1% of tests had conclusive S gene target failure (a mutation of B117, SGTF) status, the investigators estimated two risks: The first was solely for cases where SGTF status was known. The second was for all cases, and inverse probability weighting (IPW) helped compensate for missing data.

Almost 4,950 deaths in the study had known SGTF status, or 8.3% of the cohort's deaths and 9% of England's total COVID-19 deaths over the study period. After adjusting for factors such as demographics and testing date, the increased risk of 28-day mortality from B117 versus non-B117 COVID-19 strains was 55% (95% confidence interval [CI], 39% to 72%) among the verified status group and 61% (95% CI, 42% to 82%) for the whole cohort.

They do not identify any mechanism for increased mortality. [out of scope] However, B.1.1.7 infections are associated with higher viral concentrations on nasopharyngeal swabs, as measured by Ct values from PCR testing.

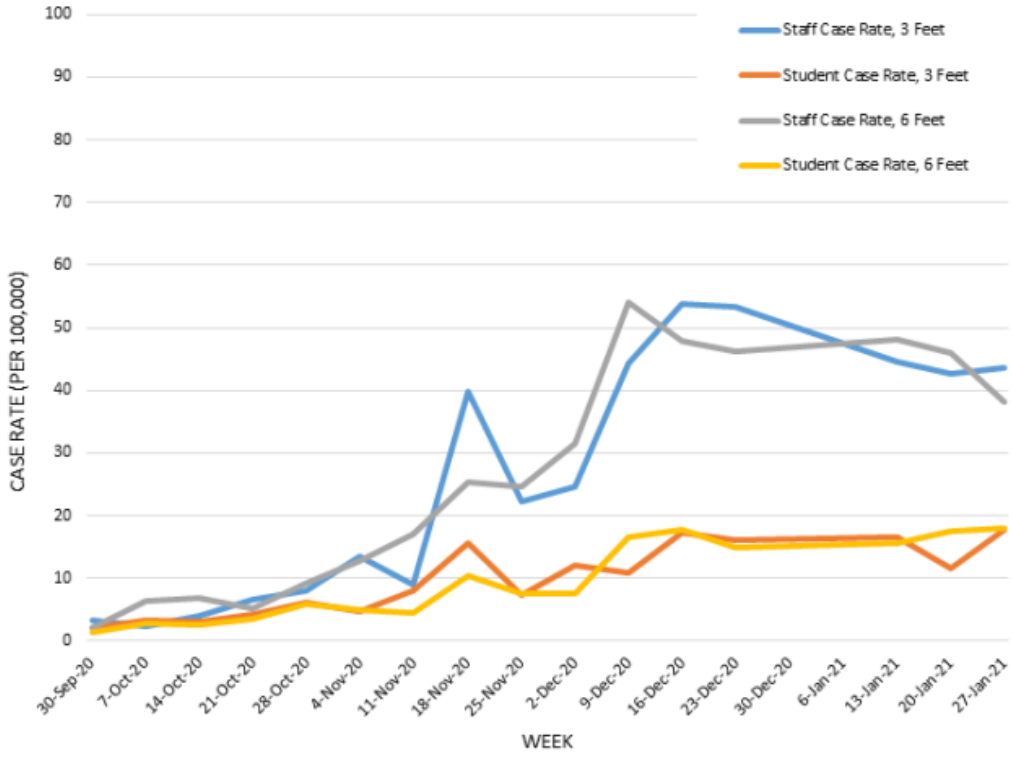


Comment: Their analysis suggests that B.1.1.7 is not only more transmissible than wild-type SARS-CoV-2 variants but may also cause more severe illness. This is consistent with analysis from last week in the Daily Briefing from BMJ.

Effectiveness of Three Versus Six Feet of Physical Distancing for Controlling Spread of COVID-19 Among Primary and Secondary Students and Staff: A Retrospective, State-Wide Cohort Study
Clin Infect Dis published online March 14, 2021
doi/10.1093/cid/ciab230/6167856

The purpose of this study was to compare incident cases of SARS-CoV-2 in students and staff in Massachusetts public schools among districts with different physical distancing requirements. In June 2020 Massachusetts released guidance to reopen schools. They recommended universal masking and ≥3-6 feet distancing between students. State guidance mandates masking for all school staff and for students in grades 2 and higher; the majority of districts required universal masking. Because the number of students varied over the study period, they defined high on-campus enrollment as districts with an average of 80% or more of their total enrolled students participating in on-campus instruction throughout the time period.

Among the 251 eligible school districts, 537,336 students and 99,390 staff attended in person classes during a 16-week period. Student and staff COVID-19 cases were similar in school districts with ≥3 feet versus ≥6 feet distancing between students. Results were similar adjusting for community rates.



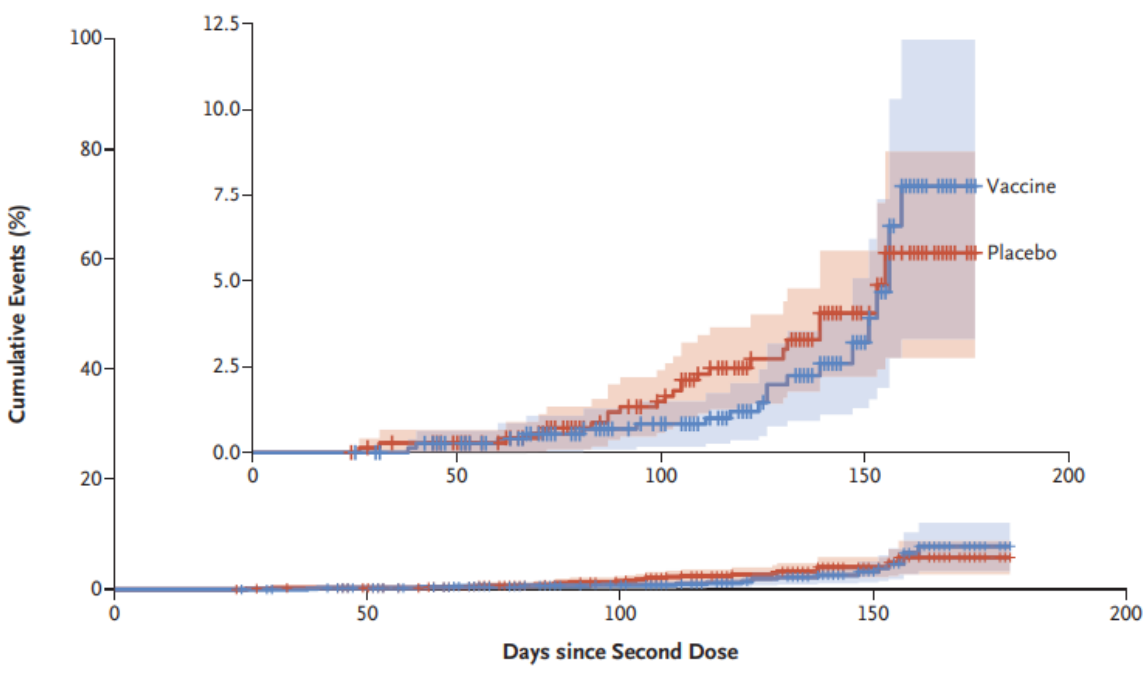
Comment: National and international guidance on distancing in schools varies. The WHO recommends 1 meter (3.3 feet) of distancing in school settings while conversely, CDC guidance recommends 6 feet of distance —to the greatest extent possible, and the American Academy of Pediatrics recommends 3-6 feet. This study was not able to measure the impact of physical distancing stratified by school type (elementary, middle, high) or age group. However, these findings may be used to update guidelines about SARS-CoV-2 mitigation measures in school and other settings. Compliance with universal masking was high which is an important point in interpreting the findings of this study. See editorial above.

Efficacy of the ChAdOx1 nCoV-19 Covid-19 Vaccine against the B.1.351 Variant

N Engl J Med published online March 16, 2021
DOI: 10.1056/NEJMoa2102214

The investigators conducted a multicenter, double-blind, randomized, controlled trial to assess the safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222-AstraZeneca) in people not infected with the human immunodeficiency virus (HIV) in South Africa. Participants 18 to less than 65 years of age were assigned in a 1:1 ratio to receive two doses of vaccine or placebo (0.9% sodium chloride solution) 21 to 35 days apart. Serum samples obtained from 25 participants after the second dose were tested by pseudovirus and live-virus neutralization assays against the original D614G virus and the B.1.351 variant. The primary end points were safety and efficacy of the vaccine against laboratory-confirmed symptomatic Covid-19 more than 14 days after the second dose.

Of the 750 participants vaccine recipients, 19 (2.5%) developed mild to moderate COVID-19 more than 14 days after the second dose, compared with 23 of 717 placebo recipients (3.2%). The incidence of COVID-19 among the vaccine group was 731 per 1,000 person-years, compared with 93.6 per 1,000 person-years among the placebo group, for an efficacy of 21.9% (95% confidence interval [CI], -49.9 to 59.8). Of the 42 total cases of COVID-19, 39 (92.9%) were caused by B1351, for a vaccine effectiveness against this variant of 10.4% (95% CI, -76.8 to 54.8). All 42 cases were mild to moderate, and no patients were hospitalized.



No. at Risk					
Vaccine	750	738	674	137	0
Placebo	717	707	632	124	0
Cumulative No. of Events					
Vaccine	0	2	6	14	19
Placebo	0	2	10	21	23

Figure 3. Kaplan–Meyer Plot of ChAdOx1 nCoV-19 Vaccine Efficacy against Symptomatic Covid-19 Illness of Mild or Moderate Severity after Two Doses, as Compared with Placebo.

Comment: A two-dose regimen of the AstraZeneca vaccine did not show protection against mild-to-moderate Covid-19 due to the B.1.351 variant. No patients were hospitalized, but the authors cautioned that the lack of severe COVID-19 cases in the study was likely a reflection of the relatively young mean age of participants (30 years) and thus that the trial could not determine whether the AstraZeneca vaccine is effective against severe infection with the B1351 variant. In early February, South African health officials paused the rollout of AstraZeneca-Oxford vaccine to investigate reports that it offered little protection against mild-to-moderate disease. It switched to using the Johnson & Johnson vaccine to immunize healthcare workers. Development of second-generation COVID-19 vaccines against strains such as B1351 and P1 has begun.

Impact of COVID-19 Pandemic on Central Line-Associated Bloodstream Infections During the Early Months of 2020, National Healthcare Safety Network

Infect Control Hosp Epidemiol published online March 15, 2021
DOI: 10.1017/ice.2021.108

A new study from the CDC shows a significant increase in central line-associated bloodstream infections (CLABSIs) in US acute care hospitals during the early months of the COVID-19 pandemic.

This study analyzed 13,136 inpatient units from 2,986 acute care hospitals and found that the standardized infection ratio (SIR) for CLABSI's in April, May, and June of 2020 climbed by 28% compared with the same months in 2019, from 0.68 to 0.87. Critical care units saw the greatest percentage increase (39%) in SIR, from 0.75 in 2019 to 1.04 in 2020, and ward locations experienced the second highest increase (13%). Critical care locations had the highest number of CLABSIs in the second quarter of 2020, with 1,911. Among ward types, significant increases in the SIR occurred in pediatric medical-surgical wards (118%), neurosurgical critical care (108%), medical critical care (60%), and medical-surgical critical care (59%). The highest regional SIR in the second quarter of 2020 (1.07) was in the Upper Northeast and represented a 45% increase compared with 2019. Hospitals of all bed sizes saw increases in SIR.

Comment: This study showed a significant increase in CLABSIs in US acute care hospitals during the early months of the COVID-19 pandemic. These findings are consistent with the review a few weeks from Ascension reviewed in the Daily Briefing. The authors suggest that changes in infection prevention practices that were made at acute care hospitals to accommodate increasing numbers of patients during the pandemic may have contributed to the increase in CLABSIs. Reducing the frequency of contacts with patients and of maintenance activities for central catheters (e.g., CHG bathing, scrubbing the hub, site examinations) as well as alterations to processes of care (such as risking disrupting catheter dressings when placing patients in a prone position) may have contributed to an increase in CLABSIs. I would add the stress on COVID units, staffing changes, use of traveling nurses, and compliance with the evidence-based strategies all may have led to increased CLABSIs. By contrast from 2015 through 2019, there was a 31% decline in the national SIR for CLABSIs. This report did not provide microbiology.