I hope everyone had a great weekend. Help is on the way. Under COVID-19 News I review current statistics and projections ending with the great news that vaccinations start this week. The other item is the CDC Advisory Committee report on the vaccine. For literature review I have chosen 3 interesting topics. The first is the ACTT-2 Trial evaluating baricitinib plus remdesivir in hospitalized adults with Covid-19. The next article reviewed positive blood cultures during the pandemic, and the last paper is a fascinating genomic study that sheds light on superspreader events, especially a biotech conference in Boston.

Have a great week and get vaccinated!

Ed

COVID News

COVID Facts

- More Americans have died from Covid-19 in nine months than in combat over four years in World War II. The virus death toll exceeds 292,000, compared with 291,557 American World War II battle deaths.
- We are now losing more Americans from the virus in a single day than perished in the Pearl Harbor attacks or 9/11.
- The Institute for Health Metrics and Evaluation projects that 500,000 Americans will have died of the coronavirus by the end of March. It expects that vaccines will have saved 25,000 lives by then — but that broader mask usage in this period could save even more lives, 56,000.
- **Despite the current situation we should be celebrating. We have new Pfizer and Moderna vaccines that are 95 percent effective! These vaccines are amazing, far better than I could have imagined. The challenge now is to assure the public that these vaccines are safe and effective and will save lives.**

CDC Advisory Committee MMWR
published early release December 13, 2020
http://dx.doi.org/10.15585/mmwr.mm6950e2 icon
On Saturday, the CDC advisory committee recommended the recently authorized Pfizer-BioNTech COVID-19 vaccine for people age 16 and over in the United States, stating they found it was safe and effective. The agency said it will quickly issue guidance to clinicians so they can determine when and when not to give the vaccine, and to help them communicate the risks and benefits to patients.
CDC staff gave a preview of those clinical considerations at the agency's Advisory Committee on Immunization Practices (ACIP) meeting on December 12 and said it would be holding calls with clinicians on December 13 and 14. The CDC will also issue guidance December 13 on how organizations can handle the workforce problems that might arise as health care workers experience side effects from vaccination. ACIP voted 11-0, with three recusals, to recommend use of the Pfizer-BioNTech mRNA vaccine in individuals 16 years or older according to the guidelines of the Food and Drug Administration's (FDA's) emergency use authorization issued on Friday.

The panel also voted unanimously to include the vaccine in 2021 immunization schedules. All panel members said the recommendation should go hand-in-hand with ACIP's previous recommendation on December 1 that allocation of the vaccine be phased-in, with health care workers and residents and staff of long-term care facilities in phase 1a. ACIP panelists said clinicians need more guidance on whether to

use the vaccine in pregnant or breastfeeding women, the immunocompromised, or those who have a history of allergies. The FDA health care provider information sheet said there is not enough data to recommend vaccinating those women or the immunocompromised, and also advises against giving the vaccine to individuals who have a history of serious allergic reaction to any component of the vaccine. CDC says for any woman considering vaccination, she should consider the level of COVID-19 in the community, her personal risk of contracting the virus, the risks to her or her fetus of developing the disease, and the vaccine's known side effects. The American College of Obstetricians and Gynecologists (ACOG) will also soon release guidance for vaccinating pregnant and breastfeeding women. ACOG and the CDC met the morning of December 12 to discuss risks and benefits with experts in immunology, placental pathology, and vaccine kinetics. The overall complete consensus was that they don't see biological plausibility currently for placental transfer of the mRNA and that we see that direct fetal exposure, or the possibility of fetal inflammatory response is extremely unlikely. A Pfizer official told the ACIP panel that preliminary data show no indication of either developmental or reproductive toxicity, and that the company plans to send the final data to the FDA at the end of December.

On the potential for allergic reactions, the CDC concurred with the FDA that the vaccine should not be given to people with a history of serious reactions. Adverse events that occur in a recipient after receipt of COVID-19 vaccine should be reported to the Vaccine Adverse Events Reporting System (VAERS).

Literature Review

Baricitinib Plus Remdesivir for Hospitalized Adults with Covid-19
N Engl J Med published online December 11, 2020
DOI: 10.1056/NEJMoa203199
This was a double-blind, randomized, placebo-controlled trial evaluating baricitinib plus remdesivir in hospitalized adults with Covid-19. All the patients received remdesivir (≤10 days) and either baricitinib (≤14 days) or placebo (control). The primary outcome was the time to recovery. The key secondary outcome was clinical status at day 15. Baricitinib inhibits Janus kinase (JAK) enzymes, which mediate signaling of proinflammatory cytokines including IL-6, IL-2, IL-10, and interferon-γ known to be elevated in severe Covid-19. Baricitinib is FDA-approved for the treatment of RA.

A total of 1033 patients underwent randomization (with 515 assigned to combination treatment and 518 to control). Patients receiving baricitinib had a median time to recovery of 7 days (95% confidence interval [CI], 6 to 8), as compared with 8 days (95% CI, 7 to 9) with control (rate ratio for recovery, 1.16; 95% CI, 1.01 to 1.32; P=0.03), and 30% higher odds of improvement in clinical status at day 15 (odds ratio, 1.3; 95% CI, 1.0 to 1.6). Patients receiving high-flow oxygen or noninvasive ventilation at enrollment had a time to recovery of 10 days with combination treatment and 18 days with control (rate ratio for recovery, 1.51; 95% CI, 1.10 to 2.08). [observed benefit was most evident in patients on high-flow oxygen or noninvasive ventilation-see curves below] The 28-day mortality was 5.1% in the combination group and 7.8% in the control group (hazard ratio for death, 0.65; 95% CI, 0.39 to 1.09). [The ACTT-2 trial was not powered to detect differences in mortality] Serious adverse events were less frequent in the combination group than in the control group (16.0% vs. 21.0%; difference, -5.0 percentage points; 95% CI, -9.8 to -0.3; P=0.03), as were new infections (5.9% vs. 11.2%; difference, -5.3 percentage points; 95% CI, -8.7 to -1.9; P=0.003).

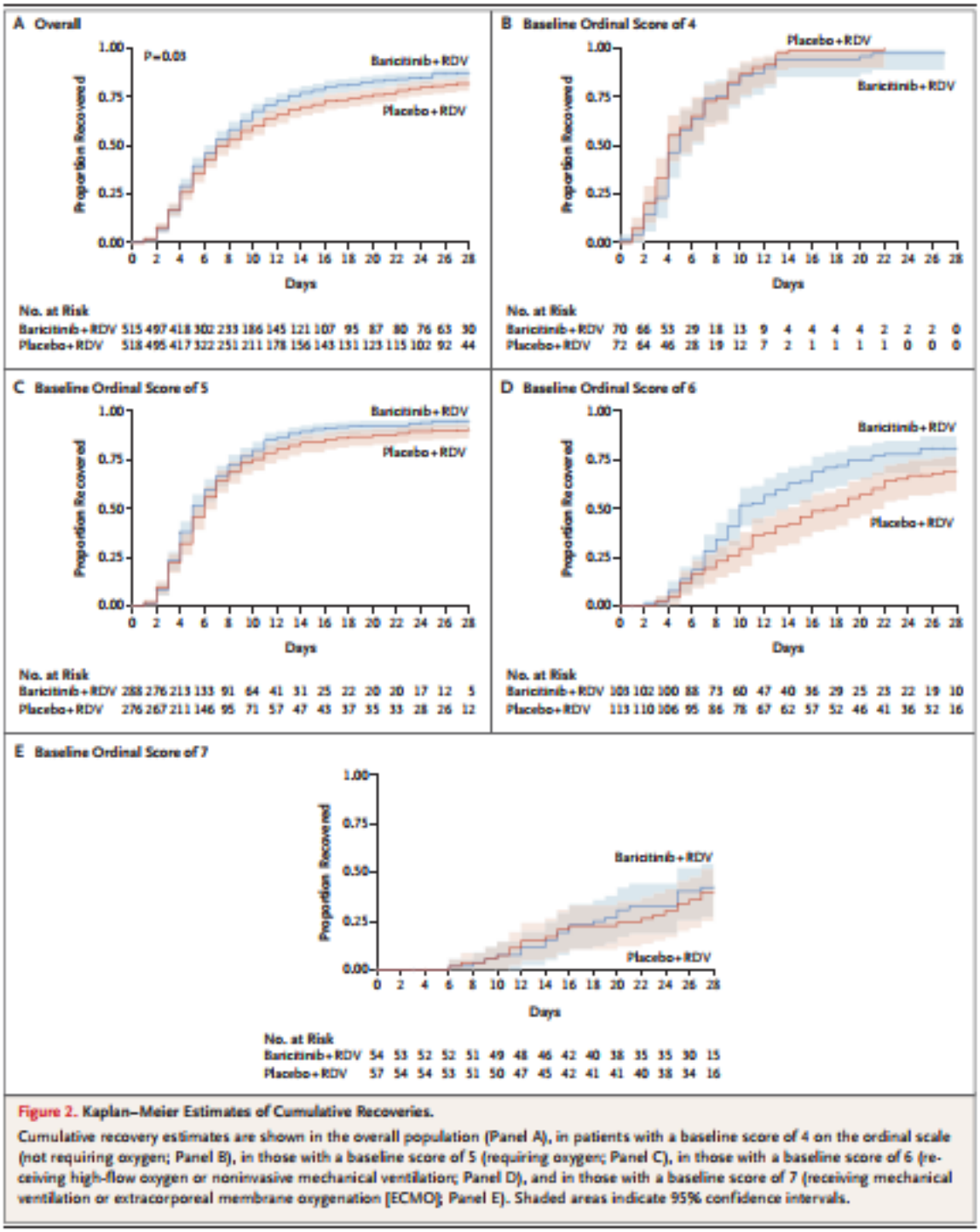


Figure 2. Kaplan–Meier Estimates of Cumulative Recoveries.

Cumulative recovery estimates are shown in the overall population (Panel A), in patients with a baseline score of 4 on the ordinal scale (not requiring oxygen; Panel B), in those with a baseline score of 5 (requiring oxygen; Panel C), in those with a baseline score of 6 (receiving high-flow oxygen or noninvasive mechanical ventilation; Panel D), and in those with a baseline score of 7 (receiving mechanical ventilation or extracorporeal membrane oxygenation [ECMO]; Panel E). Shaded areas indicate 95% confidence intervals.

Comment: Baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time and accelerating improvement in clinical status among patients with Covid-19, notably among those receiving high-flow oxygen or noninvasive ventilation. There is another ongoing trial with just baricitinib. There are no head-to-head trials comparing dexamethasone versus baricitinib. The authors point out Baricitinib and dexamethasone have important biologic differences, and ACTT-2 and the RECOVERY trial have design differences. Dexamethasone has a long half-life, acts on glucocorticoid receptors, and

reduces inflammation through a broad-pathway approach that can be associated with immunosuppression, hospital-acquired infections, gastrointestinal bleeding, hyperglycemia, and neuromuscular weakness, even with short courses. [this may be a little overstated since current duration for COVID-19 is 10 days] Baricitinib has a short half-life, acts on targeted critical pathways to reduce inflammation while minimizing biologic redundancy with less immunosuppression, and may have antiviral activity. Prior to this trial the NIH recommended against use of JAK inhibitors except in the context of a clinical trial because of concerns about immunosuppressive effects which were not noted in the ACTT-2 trial. FDA has granted EUA for the combination RDV+baricitinib. We are still awaiting RCT trials on tocilizumab both alone and in combination.

Risk Factors and Outcomes of Hospitalized Patients with Severe COVID-19 and Secondary Bloodstream Infections: A Multicenter, Case-Control Study
Clin Infect Dis published online November 20, 2020
doi.org/10.1093/cid/ciaa1748
The investigators performed a multicenter, case control study including all hospitalized patients with severe COVID-19 with blood cultures drawn. Data collection included demographics, clinical and microbiologic variables, and patient outcomes. Risk factors and outcomes were compared between cases with BSI versus cases without BSI.

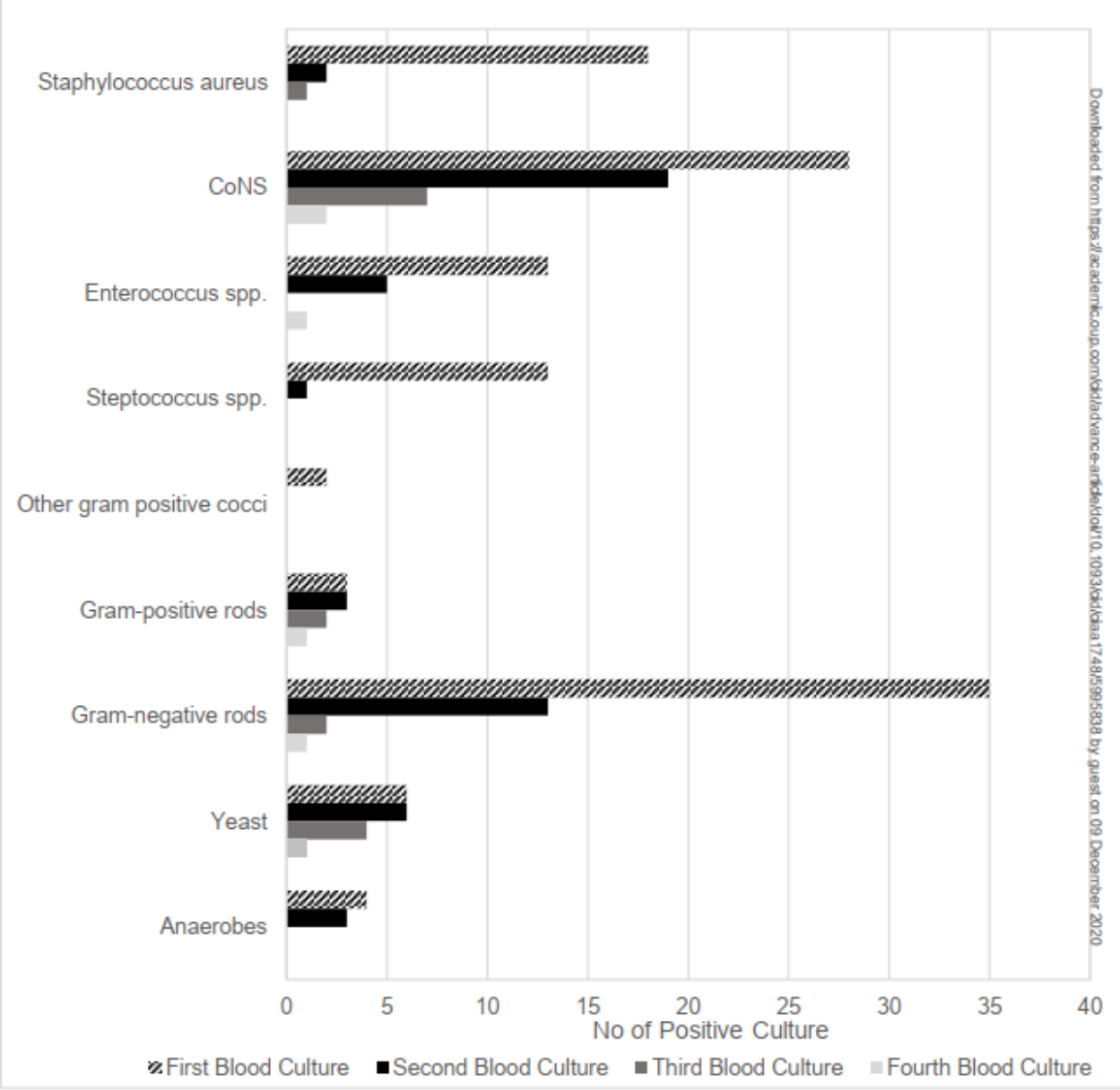
There were 128 BSIs during hospitalization. For the first set of +blood cultures, 91% were bacterial and 5.5% were fungal. Those with BSIs were more likely to have altered mental status, lower mean percent oxygen saturation on room air, have septic shock and be admitted to the intensive care unit compared to the controls. In-hospital mortality was higher in those with BSIs versus controls (53.1% vs 32.8%, p=0.0001).

CLABSI was found to be the most common presumed source of BSIs. Prior studies report bacterial pneumonia as the primary source of bacteremia in those with influenza or other coronaviruses. This has infection prevention barriers as the presence of airborne/contact precautions and fear of prolonged patient contact and aerosolization could be a barrier to good catheter care and maintenance, increasing the risk of CLABSI. Alternatively, patients with BSIs were more likely to require longer hospitalization or ICU stay thus predisposing them to a prolonged indwelling line and developing CLABSI. They found that the most common cause of bacteremia was due to *S. aureus*, *Enterococcus faecalis* and *Escherichia coli*. They observed numerous cases of fungemia caused by *Candida* species which is in contrast to previous reports. (J Infect 2020). One notable finding was a positive blood culture for *Cryptococcus neoformans.* Invasive fungal infections in COVID-19 patients, such as *Aspergillus spp* have been reported but they are usually not fungemic. A recent study assessing blood culture utilization in New York City observed a significant proportion of contaminant blood cultures. In this study they noted a large number of blood cultures deemed to be a contaminant before or after the first positive blood culture with true pathogen. At the time of this study, New Jersey was experiencing a surge in cases along with New York City. They claim this may cause a strain on the health care system causing a lack of PPE and affecting how some of the blood cultures may have been drawn.

Presenting symptoms such as fever, cough and dyspnea have been widely reported in severe COVID-19. However, the findings here indicated that AMS was a more common presenting symptom in patients with BSIs while fever and cough were less common. Additionally, the higher prevalence of leukocytosis [for typical COVID-19 WBC usually normal with lymphopenia] and acute kidney injury in the BSIs cohort represent classical markers of immune response to systemic infection and organ dysfunction secondary to impending onset of septic shock. Lastly, they observed that patients with BSIs present to

the hospital in more severe respiratory distress as noted by lower oxygen saturation and need for advanced oxygen supplementation. These presenting symptoms may reflect a superimposed effect of bacterial or fungal sepsis with severe COVID-19 or a marker of critical illness due to COVID-19 itself. They hypothesized that the presence of abdominal pain or diarrhea on admission may be a risk factor for developing BSIs due to an enteric organism.

80% of patients received antimicrobials at some point during hospitalization. More importantly, most patients received antimicrobials despite having negative blood cultures. [in most instances without evidence of bacterial infection elsewhere] This finding supports the role of a robust antimicrobial stewardship program.



Comment: Not surprisingly this study observed hospitalized adult patients with severe COVID-19 and BSIs had a more severe initial presentation, prolonged hospital course, and worse clinical outcomes.

This, however, was a retrospective, observational trial and many patients were missing key variables. The investigators did not collect data such as cultures of other types of infection. Other studies have found a low rate of coinfections on presentation with patients infected with SARS-CoV-2. Studies are ongoing nationwide to determine impact of SARS-CoV-2 infections and HAIs. In addition, other publications have also highlighted increase antibiotic use and challenges in maintaining the usual stewardship resources in the face of the pandemic.

Phylogenetic Analysis of SARS-CoV-2 in Boston Highlights the Impact of Superspreading Events
Science published online December 10, 2020
DOI: 10.1126/science.abe3261
This is a wonderful genomic study that sheds light on superspreader events. The investigators analyzed over 770 SARS-CoV-2 genomes in Boston. The first known COVID-19 case in the Boston area was confirmed on February 1, 2020 and cases rapidly increased in March and April. Their analysis revealed two superspreader events. One in an SNF which led to rapid transmission, but little broader spread. The second was an international business conference in which sustained community transmission was exported resulting in regional, national, and international spread. The meeting brought in 175 executives, including officials from Italy, Switzerland and Germany, for its leadership meeting. I will concentrate this review on the international meeting.

This new analysis of the event at a Boston hotel has concluded that the coronavirus strains at the meeting have since migrated worldwide, infecting about 245,000 Americans — and potentially as many as 300,000 — by the end of October. The virus strains spread to at least 29 states. They were found in Australia, Sweden and Slovakia. The virus spread from a room packed with biotechnology executives where they also spread widely among occupants. The conclusion is based on genetic analyses of the coronavirus taken from 28 people who attended an annual leadership conference, at a Marriott hotel on the Boston waterfront, on Feb. 26 and 27. At the time, only 30 SARS-CoV-2 infections had been confirmed in the United States.

The analysis of the 28 cases determined that each person had been infected with a strain of the coronavirus, named C2416T, that had not previously been seen in the United States. The only known instances of the strain that preceded the conference involved two French patients, ages 87 and 88. The investigators believe this was a single importation into Boston, and that single importation was tightly linked to the spread that occurred at the conference. This finding and a second marker, a mutation of C2416T(G26233T) that appears linked solely to some infections at the conference, enabled researchers to track this strain across the nation and the world, and make broad estimates that excluded cases unconnected to the meeting. The investigators estimated that the Boston strain of the virus was responsible for only 1.9 percent of all known SARS-CoV-2 cases in the United States through October.

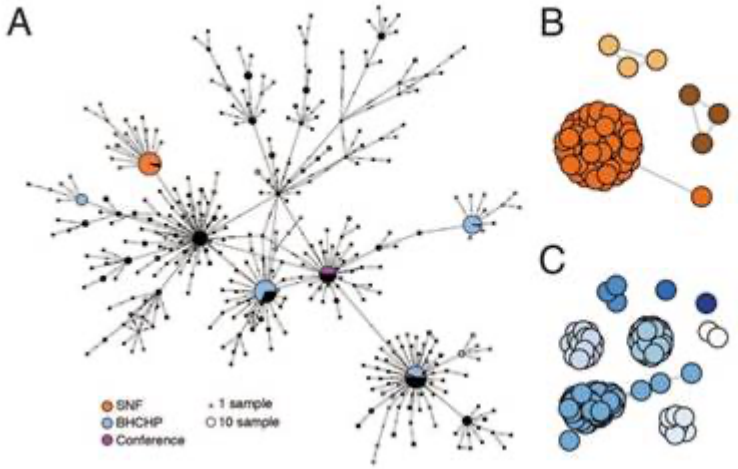


Fig. 4. SARS-CoV-2 superspreading events. (A) Minimal spanning network showing genetic similarity of SARS-CoV-2 genomes in the MA dataset, with genomes from major known superspreading events highlighted. (B and C) Gene graphs showing clusters of highly similar sequences among viral genomes from the SNF (B) and BHCHP (C) cohorts. Sequences are clustered when they are separated by < 4 SNPs, and the lengths of lines between points reflect genetic distance.

Comment: This phylogenetic analysis of the early infections in the Boston area provides powerful evidence of the nature and importance of superspreader events. In their dataset, a small minority of importations accounted for most observed cases. Because the strains circulating at the international business conference had distinct genomic signatures, the investigators were able to track its downstream impact far beyond the event itself. This study provides clear evidence of the importance of superspreader events and the importance of prevention.