TGIF 😊 Lots to share today especially with the FDA meeting scheduled for today.

Under Covid-19 News, the UK approves a third shot for persons >age 50. Under comments I have tried to put all this into perspective based of the current science.

Under Journal Review the first two articles are studies demonstrating the potential benefit of booster doses in persons who received the Pfizer vaccine. Next is an article on the effect of vaccination on household transmission of SARS-CoV-2. Next is an article showing the potential value of wastewater surveillance in public health. In the last article Investigators enrolled COVID-19 case-patients who provide paired breath samples at two visits 2 days apart, first while wearing a mask (surgical and cloth) and then without to determine the efficacy of masks.

Have a marvelous weekend. In many areas the surge has peeked and slowly improving.

Ed

COVID-19 News

Third Shot: UK to Offer COVID Booster Dose to Over 50s
September 14, 2021
The UK announced Tuesday it will offer a third dose of coronavirus vaccine to everyone over 50 and other vulnerable people to help the country ride out the pandemic through the winter months. The booster shots, which will be rolled out beginning next week, were approved a day after the government also backed plans to offer one vaccine dose to children 12 to 15 years old.

The Joint Committee on Vaccination and Immunization (JCVI), which advises the government, recommended that booster shots be offered to everyone over 50, health care workers, people with underlying health conditions and those who live with people whose immune systems are compromised. They will be given no earlier than six months after a person received their second dose of vaccine. The JCVI said the Pfizer vaccine should be the primary choice for booster shots, with a half-dose of Moderna as an alternative. It said these messenger RNA vaccines are more effective as booster shots. The AstraZeneca vaccine shot, which is based on a different technology, will be offered to anyone who can't receive an mRNA vaccine for clinical reasons.

The other interesting UK decision is only offering one dose to children 12-15. There is information that this age group responds very well to just one dose. If verified this may cut down on side effects such as myocarditis which generally occurs after the second dose.

VII Comment: The decision to offer booster shots is not one that's being recommended by the WHO, which has asked wealthy nations to delay giving them out until every country has vaccinated at least 40% of their people. To date Israel and the UK have announced offering booster doses. In the US, the FDA is publicly debating booster shots and will meet today and the CDC next week. [only for Pfizer vaccine for now – the FDA will hear presentations from Pfizer, which has asked regulators to clear booster shots for people 16 years and older] In a new review, published in The Lancet [reviewed in the Briefing September 14, 2021], experts said that whatever advantage boosters provide would not outweigh the benefit of using those doses to protect the billions of people who remain unvaccinated worldwide. They also concluded that boosters may be useful in some people who are

immunocompromised but are not yet needed for the general population. Several studies published by the CDC last Friday [also reviewed in the Briefing September 14, 2021] suggest that VE against infection with the Delta variant seems to wane slightly over time, but the vaccines hold up well against severe illness in all age groups. Only in older adults over 75 do the vaccines show some decrease in protection against hospitalization. To complicate the discussion two studies published online Wednesday in The N Engl J Med [see Review below] appears to support the case made by the White House and its senior health advisers, stating that those who received a third shot of the Pfizer vaccine in Israel were far less likely to develop severe Covid than those who received two injections. [Over age 60] A review by regulators at the FDA, also made public on Wednesday, looked at broader evidence on third doses of the Pfizer vaccine and raised some concerns. Some experts caution that promoting boosters before they are needed, as well as any reports of side effects from booster shots such as myocarditis/pericarditis or Guillain-Barre syndrome, may undermine confidence in primary vaccination although data to date show side effects from a third dose are similar to the second dose. It is clear once again that the administration and some leaders of the scientific agencies who signed on got out in front of any public discussion and before a thorough review of the data. That puts the FDA and the CDC and their respective advisory committees in a bind. Whatever the FDA and CDC decides, it should clearly and publicly explain its reasoning and speak with one voice. Be transparent. In layman's terms state how you looked at the data, here are the conclusions we made from the data, and here's is why we're recommending _____. The agencies also need to advise persons who received the one dose J&J vaccine regarding a second dose. I continue to say, the messaging has been disappointing and undermines our efforts to control the pandemic, this includes the news and social media. If I were a betting person, which I am not, I believe the FDA will approve boosters for persons >65, HCWs, and perhaps persons with certain underlying diseases who were vaccinated at least 6 months earlier. See a few cartoons below.

PHOTO: MARTIN KOZLOWSKI

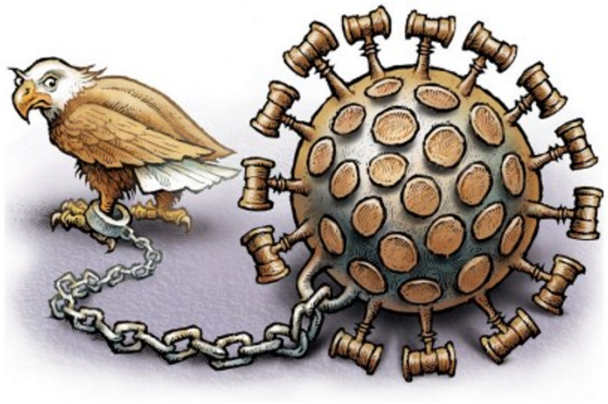
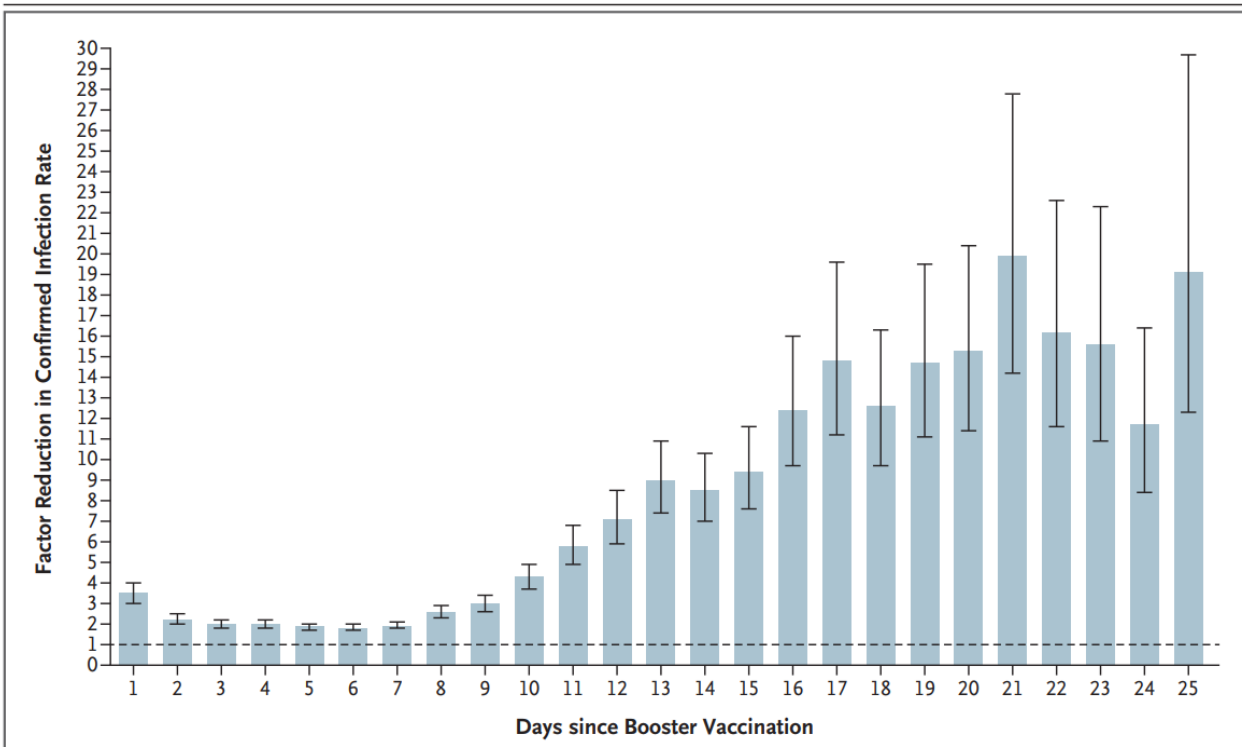


PHOTO: PHIL FOSTER

Journal Review

Protection of BNT162b2 Vaccine Booster Against Covid-19 in Israel
N Engl J Med published online September 15, 2021
DOI: 10.1056/NEJMoa2114255
Investigators extracted data for the period from July 30 through August 31, 2021, from the Israeli Ministry of Health database regarding 1,137,804 persons who were 60 years of age or older and had been fully vaccinated (i.e., had received two doses of Pfizer vaccine) at least 5 months earlier. In the primary analysis, they compared the rate of confirmed Covid-19 and the rate of severe illness between those who had received a booster injection at least 12 days earlier and those who had not received a booster dose (control). They performed Poisson regression to estimate the rate of a specific outcome, using the function for fitting generalized linear models (glm) in R statistical software. These analyses were adjusted for the following covariates: age (60 to 69 years, 70 to 79 years, and ≥80 years), sex, demographic group (general Jewish, Arab, or ultra-Orthodox Jewish population), and the date of the second vaccine dose (in half-month intervals). They included the date of the second dose as a covariate to account for the waning effect of the earlier vaccination and for the likely early administration of vaccine in high-risk groups.

At least 12 days after the booster dose, the rate of confirmed infection was lower in the booster group than in the control group by a factor of 11.3 (95% confidence interval [CI], 10.4 to 12.3); the rate of severe illness was lower by a factor of 19.5 (95% CI, 12.9 to 29.5). In a secondary analysis, the rate of confirmed infection at least 12 days after vaccination was lower than the rate after 4 to 6 days after the booster dose by a factor of 5.4.



Comment: In this study, the investigators found that a booster dose of the Pfizer vaccine reduced the rates of both confirmed infection and severe Covid-19 illness in a large population of participants who were 60 years of age or older. This study was conducted during the increased prevalence of the Delta variant. One of the weaknesses of this study is the possible biases in the source data, such as the effects of confounders and behavioral changes after vaccination, some sources of bias may not have been measured or corrected adequately. These biases include differences between the booster recipients and those who did not receive the booster with respect to care-seeking behaviors and cautiousness, along with differences in coexisting illnesses that are not recorded in the national database. As one example, the group of people who are first in line to get boosted may be more cautious with other virus-prevention methods, like masking or social distancing. Additionally, the study has a very limited follow-up time, and doesn't show how long protection from boosters may last which hopefully will be investigated moving forward. The real challenge is that there's an absence of high-quality data that provides better answers to these questions. The leading vaccine developers are not running RCTs testing booster doses against a placebo and seeing which group fares better in the long term. Lastly, there is no mention of T and B-cell immunity.

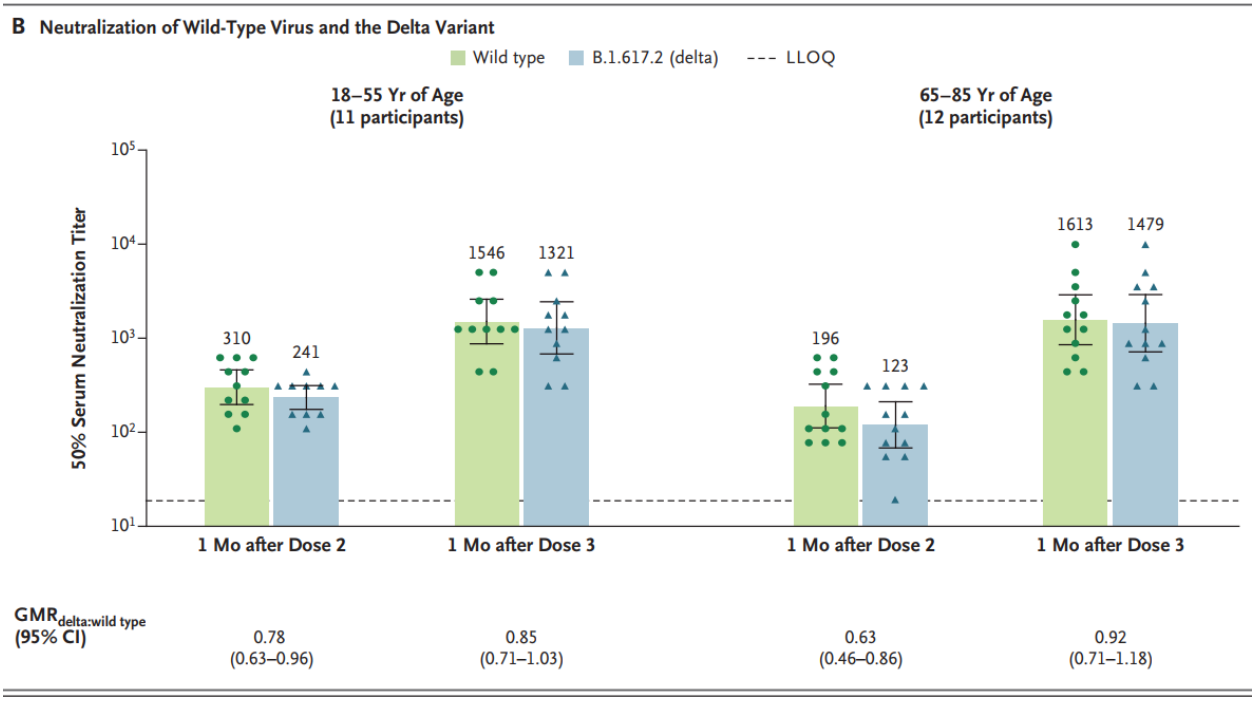
SARS-CoV-2 Neutralization with BNT162b2 Vaccine Dose 3

N Engl J Med published online September 15, 2021
DOI: 10.1056/NEJMc2113468

The investigators conducted a global, randomized, placebo-controlled, phase 1-2-3 pivotal trial in which two 30-µg doses of Pfizer were administered 21 days apart (ClinicalTrials.gov number, NCT04368728). These doses of vaccine provided 95% efficacy against Covid-19 from 7 days to approximately 2 months after dose. Efficacy waned to 84% between 4 and approximately 6 months after dose 2. Since vaccine authorization, viral variants have replaced the original strain, with the highly transmissible Delta variant. The investigators admit the effectiveness of the vaccine against severe disease, hospitalization, and death remains high, but they were concerned about waning immunity and viral diversification

creating a possible need for a third vaccine dose. Therefore, they administered a third 30-µg dose 7.9 to 8.8 months after dose 2 to 11 participants 18 to 55 years of age and to 12 participants 65 to 85 years of age from U.S. sites in the phase 1 part of the trial. They determined 50% serum neutralization titers against wild-type (USA-WA1/2020) SARS-CoV-2 and a recombinant beta variant strain determined 50% serum neutralization titers against wild-type (USA-WA1/2020) SARS-CoV-2 and recombinant variant strains. Serum specimens were obtained before dose 1, at 7 days and 1 month after dose 2, and before and 7 days and 1 month after dose 3.

Results demonstrated that during the approximately 8 months from 7 days after dose 2 to before dose 3, SARS-CoV-2 neutralization geometric mean titers (GMTs) in this subgroup of participants from phase 1 of the trial declined far more rapidly than vaccine efficacy declined in participants in the phase 2-3 pivotal trial. Second, by 1 month after dose 3, neutralization GMTs against wild-type virus increased to more than 5 times as high (in 18-to- 55-year-olds) and to more than 7 times as high (in 65-to-85-year-olds) as the GMTs 1 month after dose 2. Neutralization GMTs against the delta variant increased more after dose 3 in all age groups.



Comment: The immunogenicity of a booster dose of Pfizer vaccine administered 7 to 9 months after the primary two-dose series suggest that a third dose could prolong protection and further increase the breadth of protection. The number of participants is low. We still do not know what level of neutralization is associated with protection. See comments in article above.

Effect of Vaccination on Transmission of SARS-CoV-2
N Engl J Med published online September 8, 2021
DOI: 10.1056/NEJMc2106757
The investigators evaluated data from 194,362 household members (which represented 92,470 households of 2 to 14 persons per household) of 144,525 health care workers who had been employed during the period from March 2020 through November 2020. The mean ages of the household members

and the health care workers were 31 and 44 years, respectively; a majority (>96%) were White. A total of 113,253 health care workers (78.4%) had received at least one dose of either the Pfizer vaccine or the AstraZeneca) vaccine. The primary outcome was any confirmed case of Covid-19 that occurred between December 8, 2020, and March 3, 2021. They also report results for Covid-19-associated hospitalization. The primary time periods they compared were the unvaccinated period before the first dose and the period beginning 14 days after the health care worker received the first dose.

Cases of Covid-19 were less common among household members of vaccinated health care workers during the period beginning 14 days after the first dose than during the unvaccinated period before the first dose (event rate per 100 person-years, 9.40 before the first dose and 5.93 beginning 14 days after the first dose). After the health care worker's second dose, the rate in household members was lower still (2.98 cases per 100 person-years). Relative to the period before each health care worker was vaccinated, the hazard ratio for a household member to become infected was 0.70 (95% confidence interval [CI], 0.63 to 0.78) for the period beginning 14 days after the first dose and 0.46 (95% CI, 0.30 to 0.70) for the period beginning 14 days after the second dose. Not all the cases of Covid-19 in the household members were transmitted from the health care worker; therefore, the effect of vaccination may be larger.

Comment: Given that vaccination reduces asymptomatic infection with SARS-CoV-2, it is logical that vaccination should reduce transmission. [asymptomatic infection much less likely to transmit infection] This study provides empirical evidence suggesting that vaccination probably reduces transmission by showing that vaccination of health care workers is associated with a decrease in documented cases in household contacts. The article ends by saying: "This finding is reassuring for health care workers and their families."

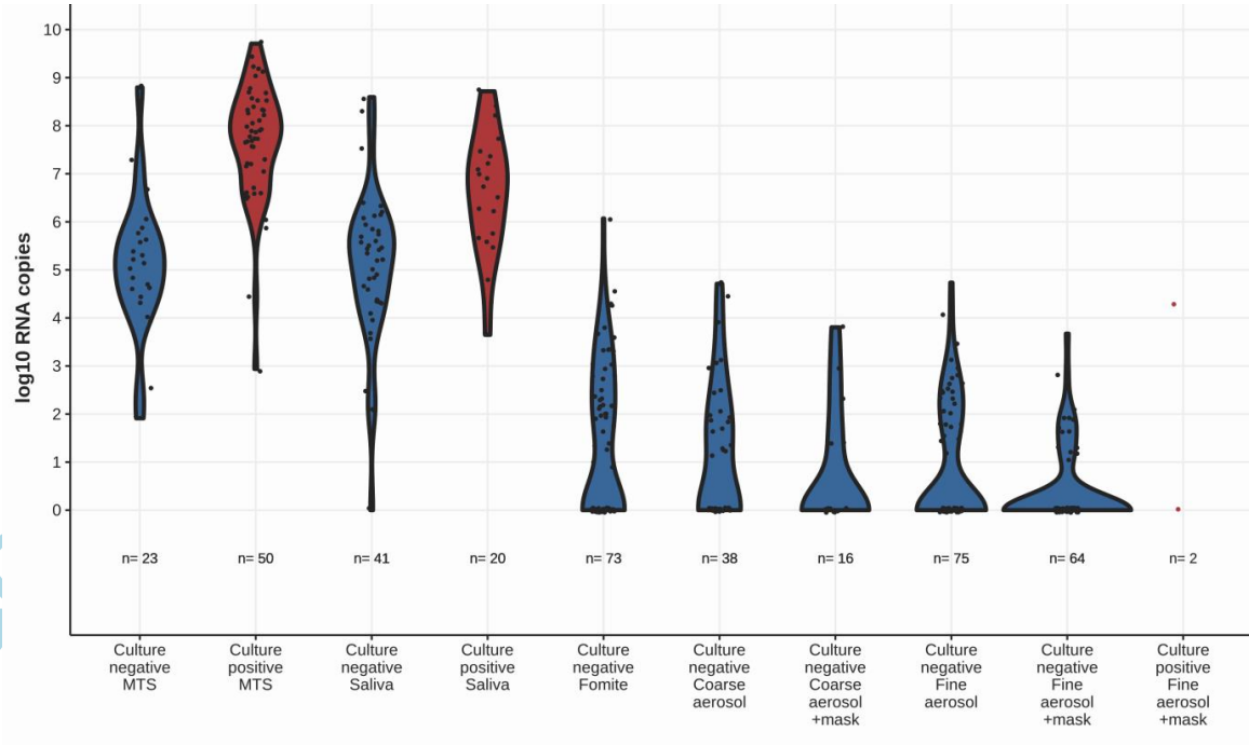
Using Wastewater Surveillance Data to Support the COVID-19 Response — United States, 2020-2021
MMWR 2021; 70: 1242-1244 article provided by Robert Atmar
Wastewater surveillance, the measurement of pathogen levels in wastewater, is used to evaluate community-level infection trends, augment traditional surveillance that leverages clinical tests and services (e.g., case reporting), and monitor public health interventions. Approximately 40% of persons infected with SARS-CoV-2, the virus that causes COVID-19, shed virus RNA in their stool; therefore, community-level trends in SARS-CoV-2 infections, both symptomatic and asymptomatic can be tracked through wastewater testing. CDC launched the National Wastewater Surveillance System (NWSS) in September 2020 to coordinate wastewater surveillance programs implemented by state, tribal, local, and territorial health departments to support the COVID-19 pandemic response. In nearly 80% of U.S. households, fecal waste is transported from homes to wastewater treatment plants within hours. Wastewater represents a pooled community stool sample that can provide information on infection trends in the community served by the sewer network. The wastewater surveillance is designed to provide early warning of increasing SARS-CoV-2 infection in communities and continues to support and guide local and state public health actions to mitigate COVID-19.

Comment: The accuracy of this surveillance approach is independent of health care-seeking behavior, health care access, or testing capacity. The NWSS is a 43-jurisdiction, CDC-coordinated system for SARS-CoV-2 wastewater surveillance. The local wastewater surveillance has been shown to predict rates 1-2 weeks before clinical cases; therefore, wastewater surveillance can provide community-level surveillance data that complement traditional surveillance and facilitate earlier, focused health department intervention and support in communities experiencing increasing trends in wastewater SARS-CoV-2 concentrations. Wastewater surveillance cannot provide data in communities and facilities

that are not served by municipal sewer systems. In addition, the limit of detection for wastewater surveillance (e.g., the fewest infections in a community that can be reliably detected in wastewater) is not well established. Nonetheless this type of surveillance can be used for rapid assessment of emerging threats and preparedness for future pandemics.

Infectious SARS-CoV-2 in Exhaled Aerosols and Efficacy of Masks During Early Mild Infection
Clin Infect Dis published online September 14, 2021, article provided by Suzanne Tomlinson
doi/10.1093/cid/ciab797/6370149
Investigators enrolled 49 COVID-19 case-patients who provided paired breath samples at two visits 2 days apart, first while wearing a mask and then without. The study used breath samples collected using a Gesundheit II machine. At one visit, a surgical mask was provided; at the other visit, the participants wore their own masks. Participants recited the alphabet, sang, and yelled during their visit. All cases were asymptomatic or mild at the time of study, and no one was taking antiviral medications. Viral infectivity was measured by first propagating virus on Vero E6 cells stably expressing TMPRSS2 then transferring the media to A549 cells stably expressing human ACE2. Infected A549-ACE2 cells were quantified using immunofluorescence staining with anti-SARS-CoV-2 nucleocapsid antibody. The types of face masks brought by participants varied and progressed from single-layer homemade cloth masks to more substantial double-layer cloth masks, surgical masks, double masks, and a KN95 over the course of the year.

Alpha variant infection was associated with a 100-fold and a 73-fold increase in coarse- (>5µm) and fine-aerosol (≤5µm) RNA shedding, respectively (95% confidence intervals [CIs], 16- to 650-fold and 15- to 350-fold). Surgical masks did not outperform cloth masks [a surprise], and there was an overall reduction of 77% (95% CI, 51% to 89%) coarse and 48% (95% CI, 3% to 72%) fine aerosols. Alpha variant infection yielded one to two orders of magnitude more viral RNA in exhaled breath when compared with earlier strains and variants not associated with increased transmissibility. The team was only able to culture live SARS-CoV-2 from 2 of 66 fine-aerosol samples, 1 of which was the Alpha variant, in 50 (68%) of 73 MTS (mid turbinate swabs), and 20 (32%) of 62 saliva samples. The RNA concentration associated with a 50% probability of a positive culture was 7.8×10^5 for MTS and 5.2×10^6 for saliva.



Comment: Cloth or surgical facial masks reduced SARS-CoV-2 RNA 77% in exhaled coarse aerosol particles and 48% in exhaled fine aerosol particles, offering "modest" source control. The study also found that the Alpha (B117) COVID-19 variant contained 43-fold more fine-aerosol viral RNA compared with earlier virus strains. Consistent with previous studies of influenza, SARS-CoV-2 viral RNA was shed more abundantly in fine than coarse aerosol and masks were more effective at blocking release of coarse aerosol. The type of mask purchased changed over the course of the trial and they did not control for type of cloth mask. They conclude that “loose-fitting” masks provide only modest source control. Therefore, they suggest continued layered controls and tight-fitting masks and/or respirators will be necessary. This study was done before delta.