Woo a lot has happened in just a few days since the last COVID-19 Briefing.

Under COVID-19 News I start with some updated numbers from the CDC which will not surprise this audience. Next, I attempt to delve into the recent FDA/CDC/ACIP recommendation of administering a third vaccine dose for the immunosuppressed. I end with the recent announcement that Pfizer has already filed for clearance for a third dose of vaccine for the general population.

Under Journal Review I start with the Moderna results of vaccinating adolescents. Next is the largest report on the impact of COVID-19 on HAIs and MDROs. Next is a report on vaccinating HD patients and if they develop adequate neutralizing antibodies to the Pfizer vaccine. I end with an very interesting study suggesting that younger children may be as likely to transmit SARS-CoV-2 infection compared with older children.

I hope everyone has a good day and good week ahead.

Ed

COVID-19 News

Latest CDC Numbers

- The nation's current seven-day case average is 114,190, an 18.4 percent increase from the previous week's average of 96,454. The U.S. confirmed more than 900,000 cases in one week, reported Aug. 15. This tally marks the highest total seen in the U.S. since the seven-day period ending Feb. 4.
- The U.S. had administered more than 353.9 million total vaccine doses as of Aug. 12.
- About 196.5 million people have received at least one dose — representing 59.2 percent of the total U.S. population — and more than 167.4 million people have gotten both doses, about 50.4 percent of the population.
- The United States has confirmed 36,781,481 cases, including 622,058 deaths.
- The seven-day average number of vaccines administered daily was 699,068 as of Aug. 12, a 0.03 percent decrease from the previous week, but up overall in the last month.
- The number of children hospitalized in this country is now also at a new pandemic high, with confirmed and suspected pediatric hospitalizations at 1,902 on Aug 14, according to HHS. Though children currently make up about 2.4% of hospitalizations, that percent is expected to climb as people 12 years and older are increasingly vaccinated, leaving younger children vulnerable to Delta.
- Based on an analysis of specimens collected in the two weeks ending Aug. 7, the CDC estimates the delta variant accounts for 97.4 percent of all U.S. COVID-19 cases.
- The alpha variant, also known as B.1.1.7, is estimated to account for 0.9 percent of all cases, and the gamma variant, also known as P.1, comprises about 0.5 percent of all cases.

Third COVID-19 Vaccine for the Immunocompromised

This past Saturday I sent out these questions for about a dozen well-respected colleagues across the country. Below represents the consensus in red

1. The CDC recommends giving an additional dose of a Covid-19 vaccine from Pfizer in moderately or severely immunocompromised people who are 12 years and older, or the vaccine from Moderna in the immunocompromised 18 years and older. All agree
2. The CDC states people who have moderately or severely weakened immune systems due to the drugs they are taking for organ transplants, certain cancers, autoimmune diseases, or because they have HIV or other conditions that diminish their immune defenses may be eligible. Concern is how one defined immunosuppression – below is current statement on CDC website from August 13, 2021

For public health purposes, immunocompromised people who have completed a primary vaccine series (i.e., 2-dose mRNA vaccine series [Pfizer-BioNTech and Moderna] or single dose of the Janssen vaccine) are considered fully vaccinated ≥2 weeks after completion of the series. However, an additional dose of an mRNA COVID-19 vaccine after an initial 2-dose primary mRNA COVID-19 vaccine series should be considered for people with moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments. These conditions and treatments include <u>but are not limited to</u>: [key phrase – some expressed that the definition of immunosuppressed will become very broad] See #3

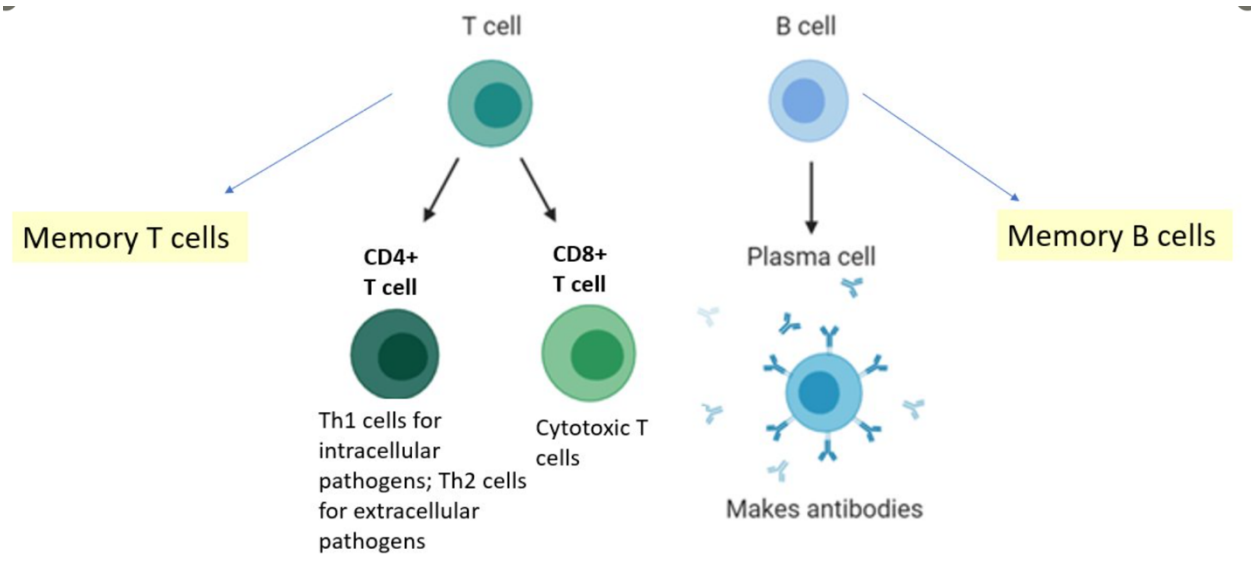
- Active treatment for solid tumor and hematologic malignancies
- Receipt of solid-organ transplant and taking immunosuppressive therapy
- Receipt of CAR-T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy)
- Moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome)
- Advanced or untreated HIV infection
- Active treatment with high-dose corticosteroids (i.e., ≥20mg prednisone or equivalent per day), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor-necrosis (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory.

3. The eligible people wouldn't require any documentation or prescriptions for a third shot and would be able to declare their eligibility at any site where vaccines are administered. [The honor system – one system will provide a 3rd dose but only by appointment and patients are to sign an attestation they have a condition listed on their website. They list all of the above conditions plus a few other like active treatment for solid tumor and hematologic malignancies]
4. CDC recommends that people receiving a third dose try to get the same vaccine as their first two shots, at least 28 days after receiving the first two doses. If someone who is immunocompromised is unable to obtain the same shot as their first two, they can mix and match messenger RNA vaccines.
5. Immunocompromised people who received a J&J vaccine aren't currently eligible for an additional mRNA dose because there isn't enough data to support such a recommendation. J&J said it is working on studies investigating the impact of an extra dose of its vaccine among immunocompromised people. [Most were critical of FDA for not addressing the J&J issue. Most felt they would offer a second dose preferably with a mRNA vaccine.]
6. Per CDC data, third doses are only "moderately effective" at increasing antibody levels in immunocompromised people and therefore they should maintain physical precautions such as mask wearing, social distancing, and avoiding crowds to help prevent Covid-19. [This is an important statement – not recommended should this population have post vaccine AB even

though we do not know what level of neutralizing AB is protective? Some did consider doing AB study to see if there were any detectible AB after the 3rd dose]

7. The FDA said other fully vaccinated individuals are sufficiently protected and don't need an additional dose of a Covid-19 vaccine currently, however, the ACIP panel is also weighing whether to support booster shots for the wider public.

Additional Comments: Of interest no one is discussing memory T and B cells. (See below) In addition, in the UK, AZ is not recommending a third shot currently. See next COVID-19 Briefing News.



Your comments are always welcomed. I think everyone would be interested on how to operationalize this new recommendation.

Pfizer and BioNTech Seek FDA Clearance for Covid-19 Booster

Pfizer said yesterday they sent to the FDA results from a small, early-stage study showing a third dose of their vaccine generated higher levels of neutralizing antibodies against the original virus and against the Beta and Delta variants than the standard two-dose regimen. The addition of the third dose also appeared safe in the trial, the companies said. Pfizer and BioNTech are also conducting a larger late-stage study evaluating whether a third dose safely provides more protection. The companies said they expect those results shortly and will then submit the data to the FDA.

Comment: Physicians and scientists in the US are still evaluating whether boosters are needed for the general population, partly because the evidence continues to show vaccines continue to be highly effective at preventing severe disease. As mentioned above UK is taking a different path at present, but Israel is now giving a third dose to immunosuppressed and anyone now over age 50.

Journal Review

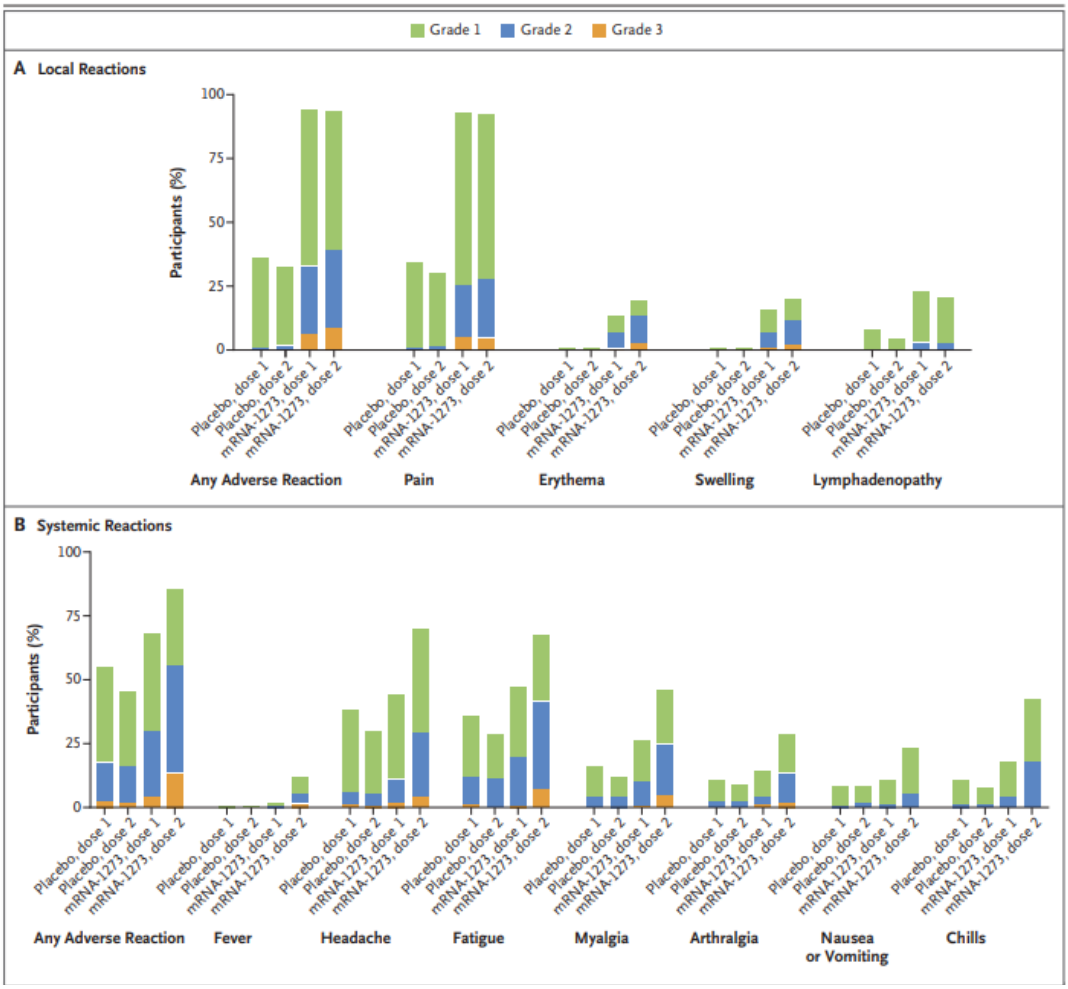
Evaluation of mRNA-1273 SARS-CoV-2 Vaccine in Adolescents

N Engl J Med published online August 11, 2021

DOI: 10.1056/NEJMoa2109522

Between December 9, 2020, and February 28, 2021, the investigators randomly assigned healthy adolescents (12 to 17 years of age) in a 2:1 ratio to receive two injections of the mRNA-1273(Moderna) vaccine (100 µg in each) or placebo, administered 28 days apart. The primary objectives were evaluation of the safety of Moderna in adolescents and the noninferiority of the immune response in adolescents as compared with that in young adults (18 to 25 years of age) in a phase 3 trial. Secondary objectives included the efficacy of Moderna vaccine in preventing Covid-19 or asymptomatic SARS-CoV-2 infection.

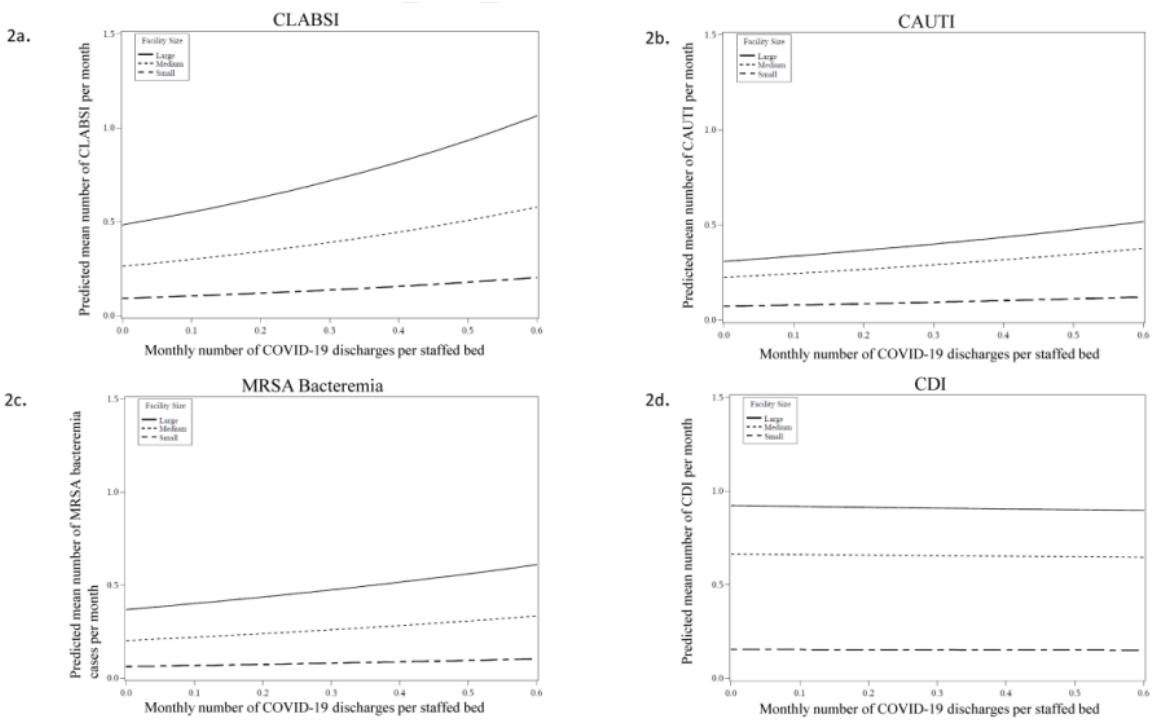
A total of 3732 participants were randomly assigned to receive Moderna (2489 participants) or placebo (1243 participants). In the Moderna group, the most common solicited adverse reactions after the first or second injections were injection-site pain (in 93.1% and 92.4%, respectively), headache (in 44.6% and 70.2%, respectively), and fatigue (in 47.9% and 67.8%, respectively); in the placebo group, the most common solicited adverse reactions after the first or second injections were injection-site pain (in 34.8% or 30.3%, respectively), headache (in 38.5% and 30.2%, respectively), and fatigue (in 36.6% and 28.9%, respectively). No serious adverse events related to Moderna vaccine or placebo were noted. The geometric mean titer ratio of neutralizing antibody titers in adolescents relative to young adults was 1.08 (95% confidence interval [CI], 0.94 to 1.24), and the absolute difference in serologic response was 0.2 percentage points (95% CI, −1.8 to 2.4), which met the noninferiority criterion. No cases of Covid-19 with an onset of 14 days after the second injection were reported in the mRNA-1273 group, and four cases occurred in the placebo group.



Comment: The Moderna vaccine had an acceptable safety profile in adolescents. The immune response was similar to that in young adults, and the vaccine was efficacious in preventing Covid-19. No cases of myocarditis or pericarditis in this trial were reported. However, the reported incidence of myocarditis and pericarditis associated with mRNA vaccination against SARS-CoV-2 in young men has been estimated to be in the range of 13 cases per million doses of vaccine; thus, it was unlikely that these events would not be detected in this trial. In addition, this trial was conducted before Alpha and Delta variants. Nonetheless as expected Moderna performed well in adolescents similar to the Pfizer vaccine. I hope Moderna will complete their application for EUA so Moderna can be authorized as well as Pfizer in this age group.

The Impact of COVID-19 on Healthcare-Associated Infections
Clin Infect Dis published online August 9, 2021
doi/10.1093/cid/ciab688/6346721
This study included 148 HCA Healthcare-affiliated hospitals from 3/1/2020-9/30/2020, and a subset of hospitals with microbiology and cluster data through 12/31/2020. The investigators evaluated the association between COVID-19 surges and HAIs, hospital-onset pathogens, and cluster rates using negative binomial mixed models. To account for local variation in COVID-19 pandemic surge timing, they included the number of discharges with a COVID-19 laboratory-confirmed diagnosis per staffed bed per month at each hospital.

CLABSI, CAUTI, and MRSA increased as COVID-19 burden increased ($P \leq 0.001$ for all), with 165 (95% CI 82 to 228) more CLABSI (60% increase), 85 (95% CI, 20 to 133) more CAUTI (43% increase), and 91 (95% CI 26 to 139) more cases of MRSA bacteremia (44% increase) than expected over 7 months based on predicted HAIs had there not been COVID-19 cases. *C. difficile* infection (CDI) was not significantly associated with COVID-19 burden. Microbiology data from 81 of the hospitals corroborated the findings. Notably, rates of hospital-onset bloodstream infections and multidrug resistant organisms, including MRSA, VRE, and Gram-negative organisms were each significantly associated with COVID-19 surges ($P<0.05$ for all). Finally, clusters of hospital-onset pathogens increased as the COVID-19 burden increased ($p=0.02$).



Comment: This study is one of several recent publications confirming increased HAIs during Covid-19. Almost all have shown increased CLABSIs and BSI, some but not all showed increased CAUTIs. Most have also shown increased MDROs as well. Of interest most have not shown an increase in CDIs. Studies have postulated HCW turnover, burnout, use of traveling nurses, increase device utilization, potential challenges in performing line and catheter maintenance for patients who are proned, immunosuppression (most are now getting steroids which also increase glucose levels), and use of PPE. Bottom line, COVID-19 surges can adversely impact HAI rates and clusters of infections within hospitals, emphasizing the need for increased investment in hospital infection prevention and antimicrobial stewardship during the pandemic.

Neutralising Antibodies After COVID-19 Vaccination in UK Haemodialysis Patients
Lancet published online August 12, 2021
doi.org/10.1016/ S0140-6736(21)01854-7
Of the 178 patients, 108 were COVID-19 infection-naive. When the researchers assessed nAb responses in these 108 patients 33 days after receiving two vaccine doses of either AZD1222 (n = 53) or BNT162b2 (n = 55), they observed that the BNT162b2 vaccine induced nAb titers across all five variants, whereby the median nAb titer concentration needed to achieve 50% inhibition (IC50) was 582 against the wild type, 327 against D614G, 174 against alpha, 136 against beta, and 267 against delta variants. In contrast, the response to AZD1222 was observed to be markedly reduced compared to BNT162b2 and might fall below the likely correlate of protection from severe disease against alpha (>4 fold reduction, falling below the limit of detection of IC50>40), beta (>3 fold reduction, falling below the limit of detection), or delta (>6 fold reduction, falling below the quantitative range) variants.

On the other hand, the corresponding analysis for infection-experienced patients revealed smaller differences between AZD1222 and BNT162b2, with AZD1222 achieving median nAb titers IC50>150 for all variants.

In comparison with infection-naive healthy controls, infection-naive patients were observed to have similar responses to the mRNA vaccine, despite the age difference between the cohorts.

Comment: Findings from a study suggest Pfizer vaccine induced comparable neutralizing antibodies (nAb) titers in hemodialysis patients and healthy controls. Further, study data also showed AstraZeneca vaccine induced suboptimal nAb titers against all variants of concern (VOCs), including the delta variant.

Association of Age and Pediatric Household Transmission of SARS-CoV-2 Infection
JAMA Pediatr published online August 16, 2021
doi:10.1001/jamapediatrics.2021.2770
This is a population-based cohort study which took place between June 1 and December 31, 2020. Private households in which the index case individual of laboratory-confirmed SARS-CoV-2 infection was younger than 18 years were included. Age group of pediatric index cases categorized as 0 to 3, 4 to 8, 9 to 13, and 14 to 17 years. Household transmission, defined as households where at least 1 secondary case occurred 1 to 14 days after the pediatric index case.

A total of 6280 households had pediatric index cases, and 1717 households (27.3%) experienced secondary transmission. The mean (SD) age of pediatric index case individuals was 10.7 (5.1) years and 2863 (45.6%) were female individuals. Children aged 0 to 3 years had the highest odds of transmitting SARS-CoV-2 to household contacts compared with children aged 14 to 17 years (odds ratio, 1.43; 95% CI, 1.17-1.75). This association was similarly observed in sensitivity analyses defining secondary cases as 2 to 14 days or 4 to 14 days after the index case and stratified analyses by presence of symptoms, association with a school/childcare outbreak, or school/childcare reopening. Children aged 4 to 8 years and 9 to 13 years also had increased odds of transmission (aged 4-8 years: odds ratio, 1.40; 95% CI, 1.18-1.67; aged 9-13 years: odds ratio, 1.13; 95% CI, 0.97-1.32).

Comment: This study suggests that younger children may be more likely to transmit SARS-CoV-2 infection compared with older children, and the highest odds of transmission was observed for children aged 0 to 3 years. In other words, unlike prior studies younger children may have greater risk of transmitting SARS-CoV-2 to caregivers and siblings in the household than older children. We also learned that young children (those younger than 4 years) were less likely to be a child primary case. How do we explain this finding? In an excellent editorial by Susan Coffin and David Rubin they recalled the Hall and Douglas study that examined the likelihood of transmission from an infant infected with RSV to an adult who either sat with the infant on their lap, touched the infant while they laid in their crib, or sat next to the crib. They found cuddlers were the most likely to get infected. [J Pediatr. 1981;99(1): 100-103] They point out that many respiratory viruses rely on time, proximity, and contact to spread. They wrote "behavior matters! Infants and young children demand attention when sick. The youngest toddlers are unreliable maskers and do not always understand the messaging of a 6-ft distancing rule—nor should they. Cuddling and touching are part and parcel of taking care of a sick young child and that will obviously come with an increased risk of transmission to parents as well as to older siblings who may be helping to care for their sick brother or sister." The real challenge is what do we advise families with young children with COVID. It is unrealistic to imagine a household wearing masks. As a parent and grandparent, we will always hold our young, sick children to provide comfort. With school starting especially in pre-K this report does partially speak against the prior science that young children are less likely to get infected and less likely to spread SARS-CoV-2. The contact in school may not be quite the same as cuddling a sick child, but I think you get the concern as schools reopen during this delta surge.