Good morning everyone

Under COVID-19 news I start with a review of the ACIP meeting last week on administering a third shot to certain immunocompromised individuals. I included a few slides from the meeting. Next a few graphs on COVID-19 activity and new COVID-19 hospitalized cases by age. Next is what I think is an important update on recommendations for fully immunized persons as it relates to people who are immunocompromised. Last is the announcement of COVID-19 vaccine mandates.

Under Journal Review I start with an article on administering a third dose of mRNA vaccine to kidney transplant patients. Next is using a large dataset to evaluate the role of statin and anti-hypertensive drugs and outcomes in patients hospitalized with SARS-CoV-2 infection. The last article looks at the safety of administering a second dose of a mRNA vaccine to individuals who had a reaction to the first dose.

Have a wonderful week and stay calm. It is only after the deepest darkness that the greatest joy can come. (Malcolm X)

Ed

COVID-19 Updates

Several members of the ACIP said immunocompromised people would benefit from a COVID-19 booster shot during the CDC panel's July 22 presentation.

ACIP does not have the regulatory authority to officially recommend a booster shot, but it presented data showing that a booster shot would help immunocompromised people prevent COVID-19.

Almost 3 percent of all U.S. adults are immunocompromised, including transplant recipients, some cancer survivors, and people with HIV, according to the CDC. Vaccines often are not as effective in immunocompromised people, as they require their immune system to be stimulated in order to protect them against disease.

The presenters discussed four small studies involving transplant and dialysis patients who did not develop antibodies after receiving their first two COVID-19 vaccine doses. After a third dose, 33 percent to 50 percent of them developed antibodies to fight COVID-19. See slides from ACIP below and new article under Journal Review.

mRNA vaccine effectiveness (VE) studies among immunocompromised populations

- VE: 7-27 days after 2nd dose of Pfizer-BioNTech vaccine[1]
  - **71%** (CI 37-87%) among immunosuppressed* people vs. **90%** (CI 83-96%) overall: **SARS-CoV-2 infection**
  - **75%** (CI 44-88%) among immunosuppressed people vs. **94%** (CI 87-97%) overall: **symptomatic COVID-19**

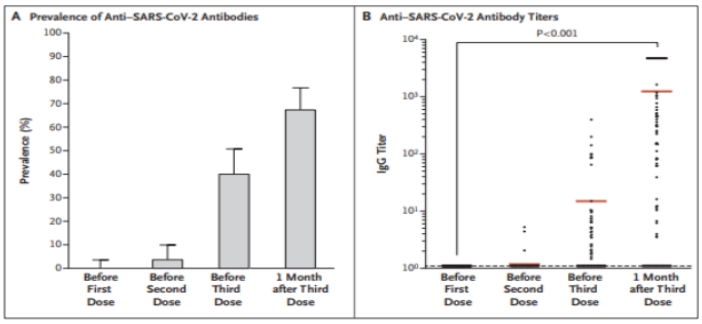
- VE: ≥7 days after 2nd dose of mRNA vaccine[2]
  - **80%** among people with inflammatory bowel disease on immunosuppressive meds: **SARS-CoV-2 infection**
  - VE of **25%** was noted after 1st dose of mRNA vaccine for **SARS-CoV-2 infection**

- VE: ≥14 days after 2nd dose of mRNA vaccine[3]
  - **59%** (CI 12-81%) among immunocompromised people vs. **91%** (CI 86-95%) without immunocompromise: **COVID-19 hospitalization**[3]

*Immunocompromised conditions (e.g., recipients of hematopoietic cell or solid organs transplant, patients under immunosuppressive therapy, asplenia, and chronic renal failure: advanced kidney disease, dialysis, or nephrotic syndrome)

1. Chodick et al. *Clinical Infectious Diseases*, ciab438, https://doi.org/10.1093/cid/ciab438; **2.** Khan et al. Gastroenterology (2021). https://www.gastrojournal.org/article/S0016-5085(21)03066-3/pdf; **3.** Tenforde et al. medRxiv preprint: https://doi.org/10.1101/2021.07.08.21259776

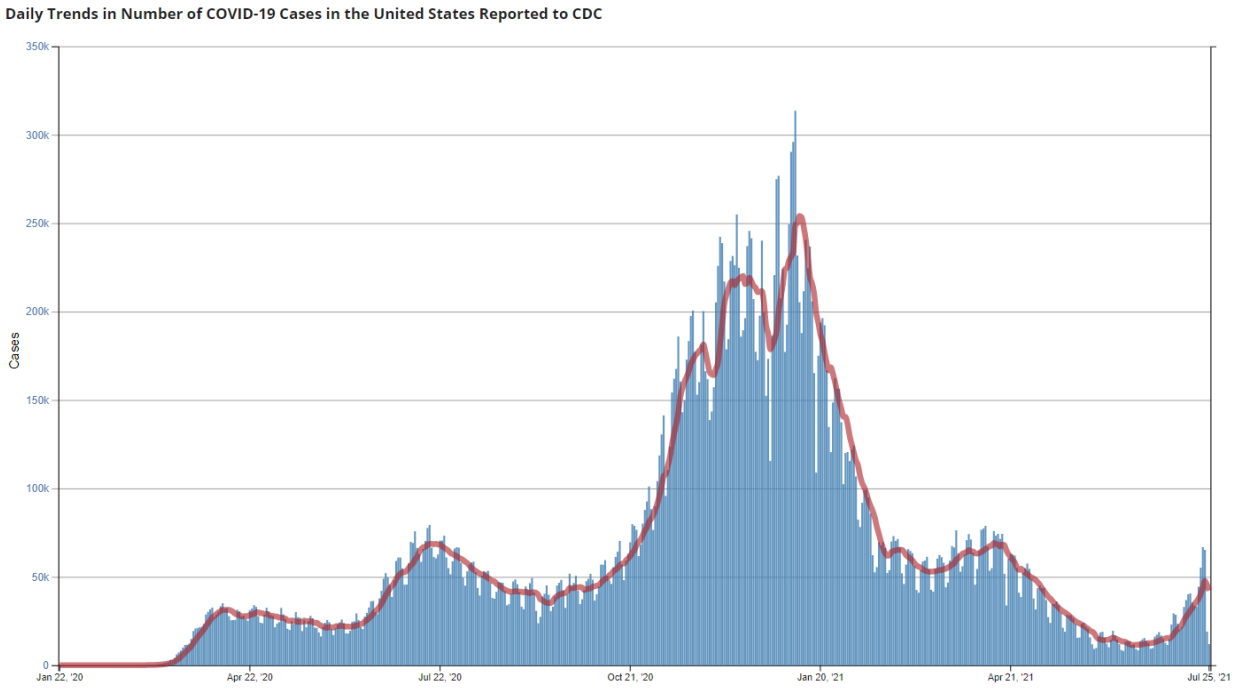
Three doses of an mRNA COVID-19 vaccine in solid-organ transplant recipients

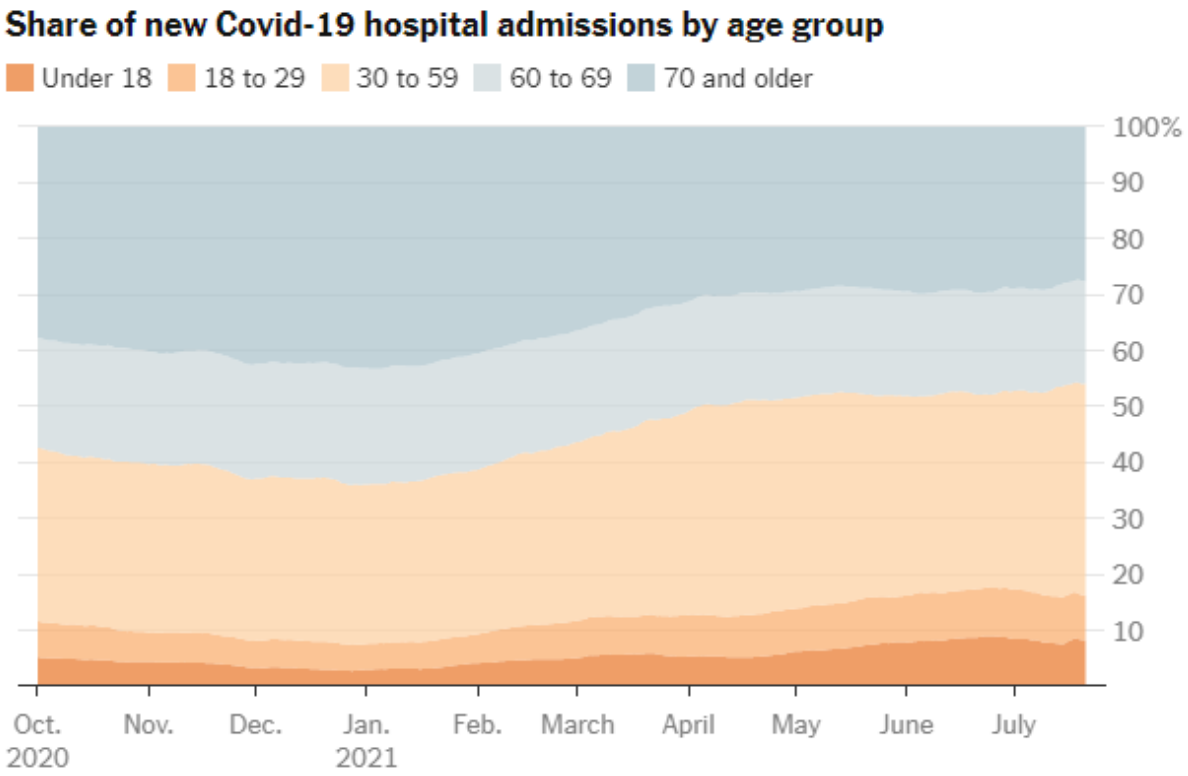


- No serious adverse events were reported after administration of the 3rd dose, and no acute rejection episodes occurred (n=99)

Kamar et al. (2021) NEJM Three Doses of an mRNA Covid-19 Vaccine in Solid-Organ Transplant Recipients (nejm.org)

COVID-19 Data Tracker





Comments: Almost every state is seeing an increase in COVID-19 hospitalizations, especially Nevada, Arkansas, Florida, Texas, and Missouri. The only states not seeing hospitalizations grow are Maryland,

North Dakota, Pennsylvania, Rhode Island, and Vermont. The majority are in ages 18-55 (see above). 97% of admissions are in unvaccinated individuals. The good news: vaccination rates are up 14% in the last week.

Interim Public Health Recommendations for Fully Vaccinated People
July 21, 2021
Update: People who are immunocompromised should be counseled about the potential for reduced immune responses to COVID-19 vaccines and to follow current prevention measures (including wearing a mask, staying 6 feet apart from others they don't live with, and avoiding crowds and poorly ventilated indoor spaces) to protect themselves against COVID-19 until advised otherwise by their healthcare provider.

Comment: This is welcomed addition. In my previous commentary last Friday:
If you are older, especially with underlying medical conditions or immune compromised, your response to the vaccine may not be as robust as the response in a younger person.

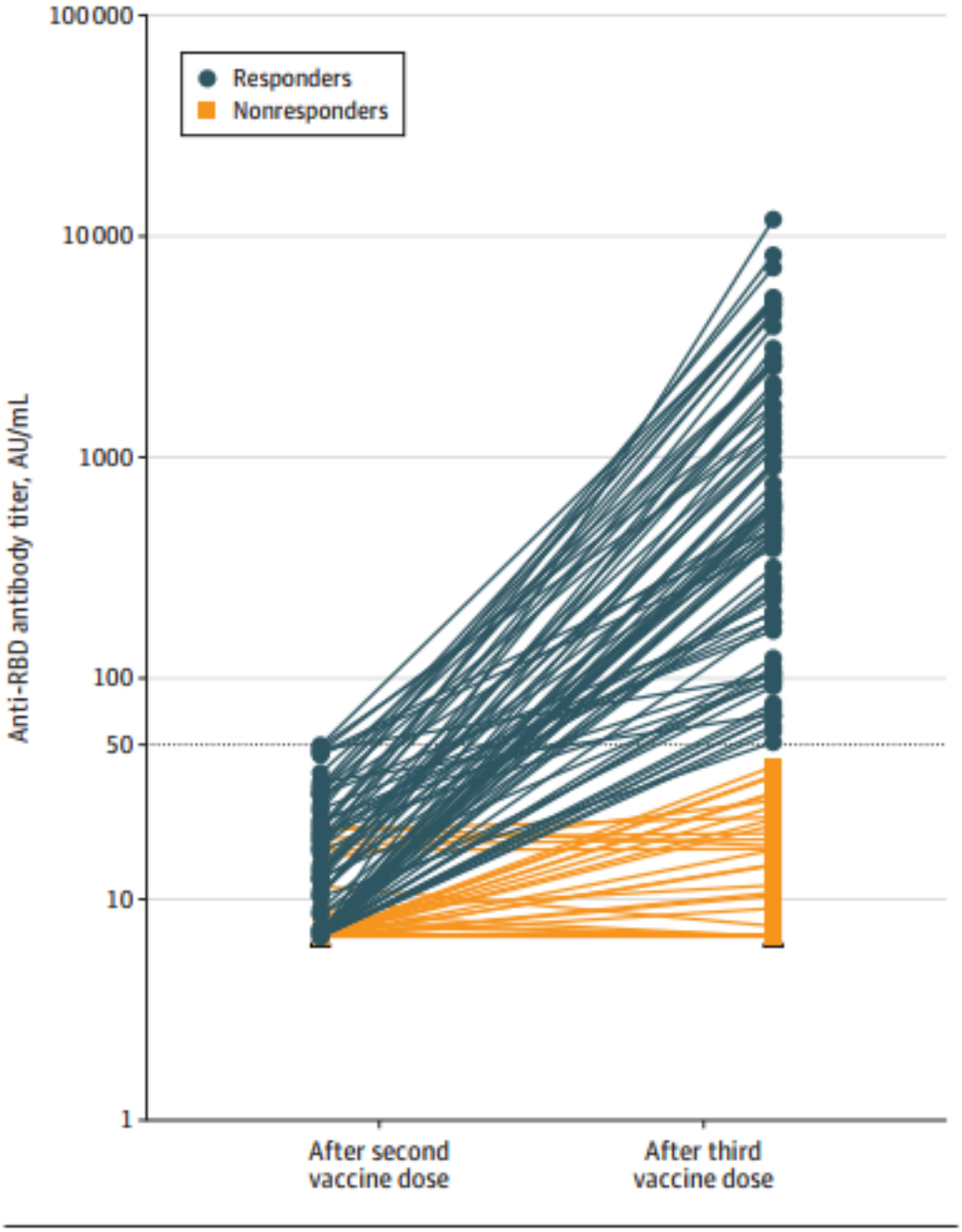
CDC now suggests this group should wear a mask and social distance when around others who you do not live with and avoid crowds.

Department of Veterans Affairs, California, and NYC Mandate Covid-19 Vaccine for Health Care Professionals
The Department of Veterans Affairs becomes first federal agency to mandate vaccination, California the first state, and NYC the first big city. I continue to be amazed at the low rate of vaccinations among certain HCWs.

Journal Review

Antibody Response After a Third Dose of the mRNA-1273 SARS-CoV-2 Vaccine in Kidney Transplant Recipients with Minimal Serologic Response to 2 Doses
JAMA published online July 23, 2021
doi:10.1001/jama.2021.12339
All kidney transplant recipients followed up in the outpatient between January 20, 2021, and June 3, 2021, with a negative history for COVID-19 and SARS-CoV-2 antispike IgG levels less than 50 arbitrary units (AU)/mL on the day of the first vaccine injection and 1 month after the second dose were included. All patients received a third vaccine dose between April 9, 2021, and May 12, 2021.

One month after the second dose, 159 kidney transplant recipients had IgG levels less than 50 AU/mL. The median age was 57.6 years, 61.6% were men, and the median time from transplantation was 5.3 years. Ninety-five patients (59.7%) had no antibody response after 2 doses (titers<6.8 AU/mL), and 64 patients (40.3%) showed a response below the positivity limit (titers, 6.8-49.9 AU/mL). The third dose was injected a median of 51 days after the second dose. The antibody response was measured a median of 28 days after the third vaccine injection, and 78 patients (49%) had antibody levels greater than 50 AU/mL (median antibody titers of responders, 586 AU/mL; IQR, 197.2-1920.1 AU/mL). Patients who had a weak response after the second dose were more likely to develop an antibody response after the third dose compared with those without an antibody response (81.3% vs 27.4%, respectively; *P* = .001). Patients taking tacrolimus, mycophenolate, and steroids were less likely to develop anti-SARS-CoV-2 antibodies than those treated with other regimens (35% vs 63%, respectively).



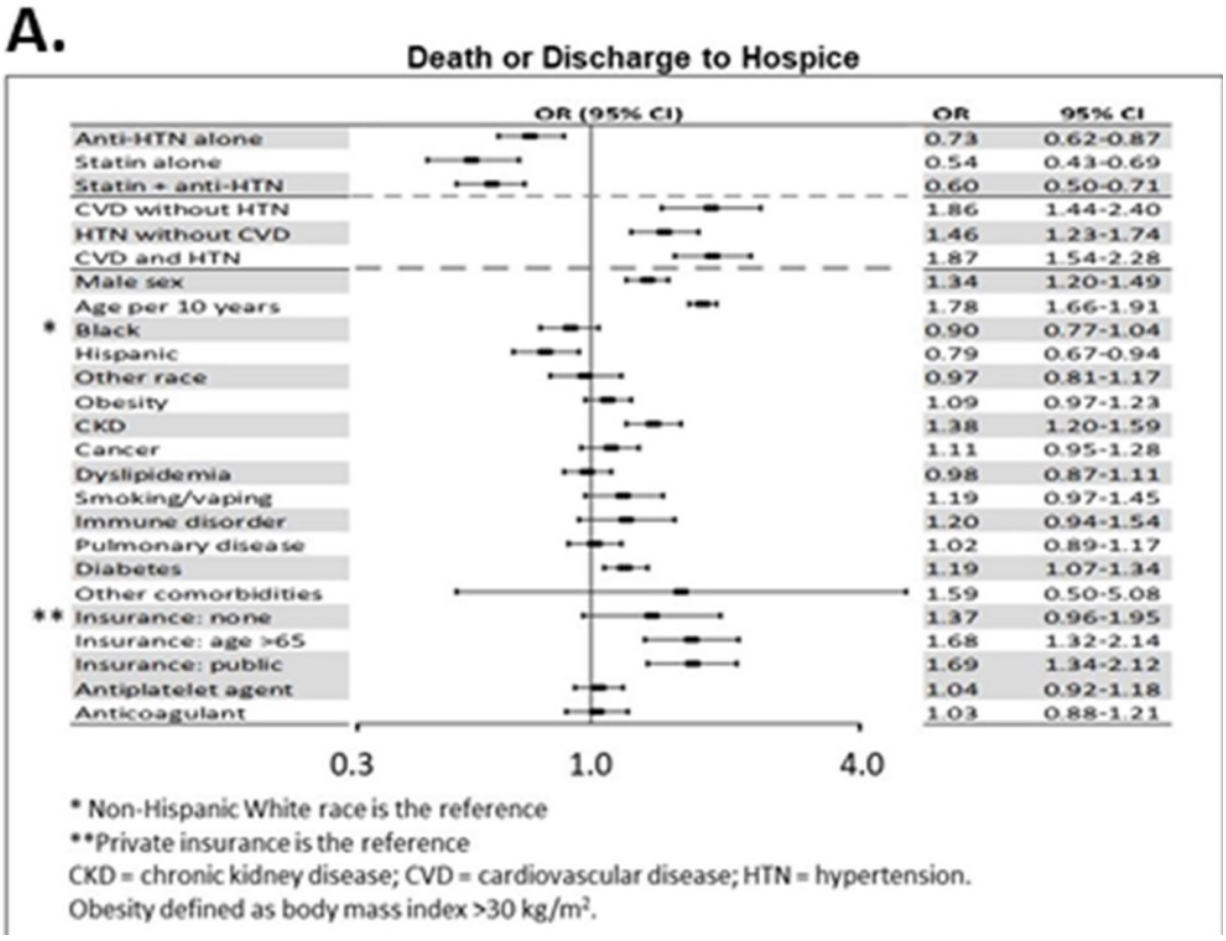
Comment: This study found that a third dose of Moderna vaccine induced a serologic response in 49% of kidney transplant recipients who did not respond after 2 doses. The findings in this large group of kidney transplant recipients are consistent with other studies of solid organ transplant recipients. However, 51% of the patients did not develop anti-SARS-CoV-2 antibodies after the third dose, especially those receiving triple immunosuppression. The major limitations of this study include that detailed B- and T-cell studies were not performed, and the antibody level that correlates with protection is unknown. The results suggest a third dose should be considered in organ transplant patients.

Relation of Prior Statin and Anti-Hypertensive Use to Severity of Disease Among Patients Hospitalized with COVID-19: Findings from the American Heart Association's COVID-19 Cardiovascular Disease Registry

PLOS ONE published online July 15, 2021
doi.org/10.1371/journal.pone.0254635

The investigators used data from 10,541 patients hospitalized with COVID-19 through September 2020 at 104 US hospitals enrolled in the AHA's COVID-19 cardiovascular disease (CVD) Registry to evaluate the associations between statin use and outcomes.

Prior to admission, 42% of subjects (n = 4,449) used statins (7% on statins alone, 35% on statins plus anti-hypertensives). Death (or discharge to hospice) occurred in 2,212 subjects (21%). Outpatient use of statins, either alone or with anti-hypertensives, was associated with a reduced risk of death (adjusted odds ratio [aOR] 0.59, 95% CI 0.50–0.69), adjusting for demographic characteristics, insurance status, hospital site, and concurrent medications by logistic regression. In propensity-matched analyses, use of statins and/or anti-hypertensives was associated with a reduced risk of death among those with a history of CVD and/or hypertension (aOR 0.68, 95% CI 0.58–0.81). An observed 16% reduction in odds of death among those without CVD and/or hypertension was not statistically significant. Comorbid conditions were generally associated with increased risk of death in adjusted analyses. See below.



Comment: Patients taking statins prior to hospitalization for COVID-19 had substantially lower odds of death, primarily among individuals with a history of CVD and/or hypertension. These results are consistent with most prior studies. As an observational study, this analysis is unable to prove causality. The investigators attempted to account for confounders with both multivariable models and with propensity-score matched analyses, but the possibility of residual confounding remains.

Safety Evaluation of the Second Dose of Messenger RNA COVID-19 Vaccines in Patients with Immediate Reactions to the First Dose

JAMA Intern Med published online July 26, 2021
doi:10.1001/jamainternmed.2021.3779

There is uncertainty as to whether to administer a second dose of mRNA COVID-19 vaccine after a first dose reaction. In this study, the investigators examined the safety of the second dose of Pfizer or Moderna vaccine in those with a history of immediate and potentially allergic reactions to the first dose. This is a multicenter, retrospective study conducted by Massachusetts General Hospital, Brigham and Women's Hospital, Vanderbilt University Medical Center, Yale School of Medicine, and University of Texas Southwestern Medical Center from January 1, 2021, to March 31, 2021, and included patients with an immediate allergic reaction to the Pfizer or Moderna vaccine, which was defined as: (1) symptom onset within 4 hours of dose 1, (2) at least 1 allergic symptom, and (3) referral for an allergy/immunology consultation with in-clinic or telehealth assessment. Anaphylaxis was scored using the Brighton and the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network criteria. The primary outcome was second dose tolerance, which was defined as either: (1) no immediate symptoms after second dose administration or (2) symptoms that were mild, self-limited, and/or resolved with antihistamines alone.

COVID-19 vaccine first-dose reactions were evaluated, 130 (69%) were to Moderna and 59 (31%) to Pfizer. The most frequently reported first-dose reactions were flushing or erythema (53 [28%]), dizziness or lightheadedness (49 [26%]), tingling (46 [24%]), throat tightness (41 [22%]), hives (39 [21%]), and wheezing or shortness of breath (39 [21%]). Thirty-two (17%) met anaphylaxis criteria. A total of 159 patients (84%) received a second dose. Antihistamine premedication before the second dose was given in 47 patients (30%). All 159 patients, including 19 individuals with first-dose anaphylaxis, tolerated the second dose. Thirty-two (20%) reported immediate and potentially allergic symptoms that were associated with the second dose that were self-limited, mild, and/or resolved with antihistamines alone.

Comment: Although mild symptoms were reported in 20% of patients with second dose administration, all patients who received a second dose safely completed their vaccination series and could potentially use mRNA COVID-19 vaccines in the future if indicated. Second dose tolerance following reactions to the first dose argues that either many of these initial reactions are not all truly allergic reactions, or supports an allergic, but non-immunoglobulin E-mediated mechanism in which symptoms can typically be abated with premedications. When the J&J vaccine received emergency use authorization, the CDC recommended that individuals with an immediate and potentially allergic reaction to the first dose of the Pfizer or Moderna mRNA COVID-19 vaccine could receive a J&J single as their second dose. With this publication it may not be necessary to use the J&J vaccine, but instead receive the second dose of an mRNA vaccine.