Infectious Diseases Watch

April 18, 2022

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VII Comments: Boosters: To be or not to be?

I wanted to start ID Watch sharing a very thoughtful editorial by Paul Offit followed by some of my thoughts

Covid-19 Boosters — Where from Here N Engl J Med publisher online April 13, 2022

DOI: 10.1056/NEJMe2203329

Below are highlights I selected

1. Arguably, the most disappointing error surrounding the use of Covid-19 vaccines was the labeling of mild illnesses or asymptomatic infections after vaccination as “breakthroughs.” As is true for all mucosal vaccines, the goal is to protect against serious illness — to keep people out of the hospital, intensive care unit, and morgue. The term “breakthrough,” which implies failure, created unrealistic expectations, and led to the adoption of a zero-tolerance strategy for this virus. If we are to move from pandemic to endemic, at some point we are going to have to accept that vaccination or natural infection or a combination of the two will not offer long-term protection against mild illness.
2. A zero-tolerance strategy for mild or asymptomatic infection, which can be implemented only with frequent booster doses, will continue to mislead the public about what Covid-19 vaccines can and cannot do.
3. One year after the Pfizer vaccine became available, studies in the US, showed that a third dose of vaccine also enhanced protection against severe disease for people as young as 18 years of age. Unfortunately, these studies did not stratify patients according to whether they had coexisting conditions. Therefore, it was unclear who among these younger age groups most benefited from an additional dose. Nonetheless, the CDC later recommended that everyone 12 years of age or older should receive three doses of the Pfizer vaccine, regardless of whether risk factors were present. This universal booster recommendation led some summer camps, high schools, universities, hospitals, and businesses to require three doses of mRNA vaccine.
4. In February 2022, in a study that did not support the booster recommendation for children, CDC researchers found that two doses of Pfizer vaccine induced long-lived protection against serious illness in children 12 to 18 years of age. (N Engl J Med 2022; 386:713-723)
5. Boosters are not risk-free; we need to clarify which groups most benefit. For example, boys and men between 16 and 29 years of age are at increased risk for myocarditis caused by mRNA vaccines. And all age groups are at risk for the theoretical problem of an “original antigenic sin” — a decreased ability to respond to a new immunogen because the immune system has locked onto the original immunogen.

Comment: One big point of dispute concerns the purpose of boosters. As Dr. Offit points out the goal is to protect against serious illness — to keep people out of the hospital, intensive care unit, and morgue not to prevent mild illness.

Second how can respected scientists look at the same evidence and come to such different conclusions and recommendations? The lack of consensus is very confusing to the public who want forthright answers. And about that data, everyone wishes it were stronger. While some regard the research out of Israel as sufficient to back a second booster, there are methodological shortcomings that limit its usefulness in shaping public policy decisions. These population-wide observational studies aren't randomized, they're not taking place in a controlled environment, and there are many confounders. [see ID Watch April 11. 2022] Right now, Covid-19 infection rates in the US are near two-year lows, though some areas are seeing increases in cases. [see below] While there's concern about a coming wave of new cases spurred by the Omicron BA.2 subvariant, in most cases BA.2 seems to cause relatively mild illness especially for the vaccinated and hospitalizations do not seem to be increasing. Recent CDC numbers also suggest that most people who are vaccinated, and especially those who got the first booster, remain well protected against severe disease. Considering that second booster's impact appears to be short-lived, some US authorities say we should wait a bit longer before pushing out another shot. Will boosting people again and again reduce the efficacy of forthcoming vaccines? Some argue say that the second booster could offer protection against long Covid, other infection-related health risks or decrease transmission.

What about 12–18-year-olds? There is little science to support boosters in children ages 12-18, nonetheless as Dr Offit points out, the CDC still recommended that everyone 12 years of age or older should receive three doses. This has had significant impact on schools and summer camps who are reluctant to go against CDC guidance.

Despite all the opposing views, one area of consensus is that individuals with certain immune deficiencies [e.g., transplants, advanced untreated HIV, active treatment for solid and hematological malignancy, active treatment with other immunosuppressive or immune modulatory drugs, etc.] or multiple risk factors [diabetes, obesity, renal, cardiopulmonary disease etc.] should consider getting a second booster. As we look ahead, most say that boosters will probably be needed from time to time to protect us from new variants or waning vaccine protection. We still await CDC guidance on natural infection and hybrid immunity long overdue. The threat of Covid-19 is likely to be with us for years to come, which may necessitate periodic boosters [like influenza], but it is my sincere hope we can improve our message to gain back the trust of the American people.

General Infectious Disease

Effect of Gram Stain–Guided Initial Antibiotic Therapy on Clinical Response in Patients With Ventilator-Associated Pneumonia JAMA Netw Open 2022;5(4):e226136.

doi:10.1001/jamanetworkopen.2022.6136

For the GRACE-VAP (Gram Stain–Guided Antibiotic Choice for VAP) trial, a team of investigators recruited VAP patients from intensive care units (ICUs) at 12 Japanese hospitals from April 2018 through May 2020. Patients aged 15 years or older with a VAP diagnosis and a modified Clinical Pulmonary Infection Score of 5 or higher were included.

The patients were randomly assigned 1:1 to Gram stain–guided antibiotic therapy (using endotracheal aspirates) or guideline-based antibiotic therapy based on the 2016 Infectious Diseases Society of America and American Thoracic Society VAP clinical practical guidelines for VAP. Both of those guidelines recommend empirical coverage for both MRSA and *Pseudomonas aeruginosa*.

The primary outcome was the rate of clinical response, defined as completion of antibiotic therapy within 14 days, improvement, or lack of progression of baseline radiographic findings, resolution and signs and symptoms of pneumonia, and lack of antibiotic agent readministration. The non-inferiority margin was 20%. Secondary outcomes included the proportions of anti-MRSA or antipseudomonal agents used as initial therapy, 28-day mortality, intensive care unit (ICU)-free days, ventilator-free days, and adverse events.

A total of 206 patients (median age 69 years, 68.4% men) were included in the per-protocol analysis, with 103 in each group. The most frequently isolated bacteria from endotracheal aspirate were *S aureus* (50%), followed by *Klebsiella* spp (16.5%) and *Haemophilus influenzae* (9.7%). Clinical response occurred in 79 patients (76.7%) in the Gram stain–guided group and 74 patients (71.8%) in the guideline-based group, for a risk difference of 0.05 (95% confidence interval [CI], 0.07 to 0.17; $P < .001$). The 28-day cumulative incidence of mortality was 13.6% in the Gram stain–guided group versus 17.5% in the guideline-based group. There were no significant differences between the groups for ICU-free days, ventilator-free days, or adverse events.

Compared with the guideline-based treatment group, the use of anti-MRSA antibiotics was reduced by 38.8% (95% CI, 29.4% to 48.9%) in the Gram stain–guided group, and the use of antipseudomonal agents was reduced by 30.1% (95% CI, 21.5% to 39.9%). Escalation of antibiotics according to culture results was performed in 7 patients (6.8%) in the Gram stain–guided group, compared with 1 patient (1%) in the guideline-based group.

Comment: In this study gram stain–guided restrictive antibiotic therapy was noninferior to guideline-based broad-spectrum antibiotic therapy in patients with VAP in terms of the clinical response rate. They conclude that gram staining of endotracheal aspirates optimized the use of broad-spectrum antibiotic agents for VAP without detrimental effects on patient outcomes. They do not mention if specimens were purulent on gram stain or if patients met the definition of VAE. The investigators set the noninferiority margin at 20%, which was consistent with that in a

previous trial, but the magnitude of 20% may have been too large for clinicians and the sample size was not large enough to be conclusive Most noninferiority trials use a 10% margin. The frequency of MDR GNR was low (<10%) at all participating institutions, and nonfermenters, including *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, that were isolated from respiratory samples were lower than expected. Lastly, few of the trial participants had septic shock or an extremely low partial pressure of oxygen to fraction of inspired oxygen ratio. Despite the limitations, a gram stain is very inexpensive, readily available, and takes < 5 minutes to perform.

Antibiotic Prescriptions Associated With COVID-19 Outpatient Visits Among Medicare Beneficiaries, April 2020 to April 2021 JAMA published online April 8, 2022

doi:10.1001/jama.2022.5471

The analysis of Medicare carrier claims and data from the Medicare Part D prescription drug plan from April 2020 to April 2021 found that 29.6% of more than 1.1 million COVID-19 outpatient visits were associated with an antibiotic prescription. The rate of prescribing varied by month, with higher rates of prescribing occurring during a wave of COVID-19 cases in the winter of 2020-21 (range, 17.5% in May 2020 to 33.3% in October 2020). Prescribing was highest in the emergency department (33.9%), followed by telehealth (28.4%), urgent care (25.8%), and office visits (23.9%).

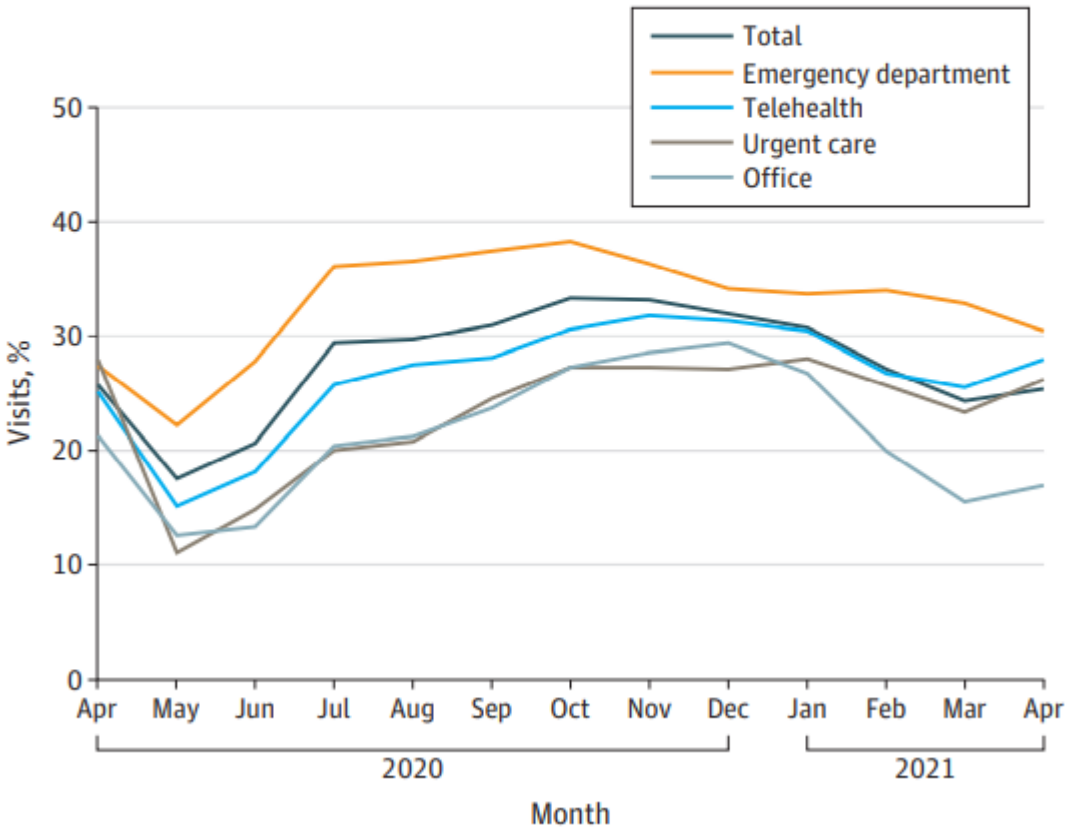
Azithromycin was the most frequently prescribed antibiotic (50.7% of cases), followed by doxycycline (13%), amoxicillin (9.4%), and levofloxacin (6.7%). Urgent care had the highest percentage of azithromycin prescriptions (60.1%), followed by telehealth (55.7%), office visits (55.1%), and ED (47.4%).

Differences were observed by age, sex, and location, with non-Hispanic White beneficiaries receiving antibiotics for COVID-19 more frequently (30.6%) than other racial and ethnic groups, including American Indian/Alaska Native (24.1%), Asian/Pacific Islander (26.5%), Black (23.2%), and Hispanic (28.8%) patients.

Despite some early studies that indicated azithromycin might benefit COVID-19 patients, subsequent randomized clinical trials demonstrated no benefit.

"These observations reinforce the importance of improving appropriate antibiotic prescribing in outpatient settings and avoiding unnecessary antibiotic use for viral infections such as COVID-19 in older adult populations," the CDC researchers wrote.

Figure. Outpatient Visits for COVID-19 and Associated Antibiotic Prescriptions Among Medicare Beneficiaries Aged 65 Years or Older, by Setting, US, April 2020 to April 2021



Comment: CDC authors found that during the first year of the COVID-19 pandemic (April 2020-April 2021), 30% of outpatient visits for COVID-19 among Medicare beneficiaries were associated with an antibiotic prescription. Azithromycin was the most frequently prescribed antibiotic (50.7). White beneficiaries were prescribed antibiotics at a higher rate than African American or Black beneficiaries.

Bottom line: Antibiotics, especially azithromycin, are not effective treatment for COVID-19 and should not be prescribed to outpatients with viral infections. Anytime antibiotics are prescribed, they can lead to adverse drug events and contribute to antibiotic resistance. Findings from this study reinforce the importance of improving appropriate antimicrobial prescribing in outpatient settings including the ED and avoiding unnecessary antibiotic use for viral infections, including COVID-19, in older adult populations.

Effect of Antimicrobial Prophylaxis Duration on Health Care–Associated Infections After Clean Orthopedic Surgery A Cluster Randomized Trial JAMA Netw Open 2022;5:e226095.

doi:10.1001/jamanetworkopen.2022.6095

In the multicenter, cluster randomized trial, 1,211 participants undergoing clean orthopedic surgery were divided into two groups: one had AP(antimicrobial prophylaxis) discontinued within 24 hours of wound closure (group 24), and the other had AP discontinued within 24 to 48 hours (group 48). Group allocation was switched every 2 to 4 months according to the facility-based cluster rule. The primary outcome was incidence of HAIs requiring antibiotic therapies within 30 days of surgery. The non-inferiority margin was 4%.

There were 633 participants (median age, 73; 60.5% women) in group 24 and 578 participants (median age, 74; 64.7% women) in group 48. HAIs occurred in 29 patients (4.6%) in group 24 and 38 patients (6.6%) in group 48. Intention-to-treat analyses showed a difference in the risk of HAIs of −1.99 percentage points (95% confidence interval [CI], −5.05 to 1.06 percentage points; $P < .001$ for non-inferiority) between groups, indicating non-inferiority. Results of adjusted intention-to-treat, per-protocol, and per designated procedure population analyses supported this result, without a risk of antibiotic resistance and prolonged hospitalization.

Comment: The findings are noteworthy because several studies have shown that AP is still routinely continued for several days after orthopedic and cardiovascular surgery, despite concerns that prolonged AP may increase the risk of antimicrobial resistance and *C difficile* infections. Both the WHO and the CDC state in clean and clean-contaminated procedures, do not administer additional AP after the surgical incision is closed in the operating room, even in the presence of a drain. (Lancet Infect Dis 2016; 16: e288–303; JAMA Surg. 2017;152(8):784-791). However, in the WHO document they state a meta-analysis of studies showed that AP continuation might be beneficial in reducing SSI compared with a single prophylactic dose in cardiac (OR 0·43; 0·25–0·76)232,233 and orthopedic (OR 0·30; 0·10–0·88) surgery. However, they rated the quality of the evidence to be low. In 2017 the American College of Surgeons and Surgical Infection Society published an update of their Surgical Site Infection Guidelines. (J Am Coll Surg 2017; 224:59-74). They state that there is no evidence for AP after the incision is closed. They go on to say there may be exceptions including implant-based breast reconstruction, joint arthroplasty and cardiac procedures where optimal duration of AP remains unknown.

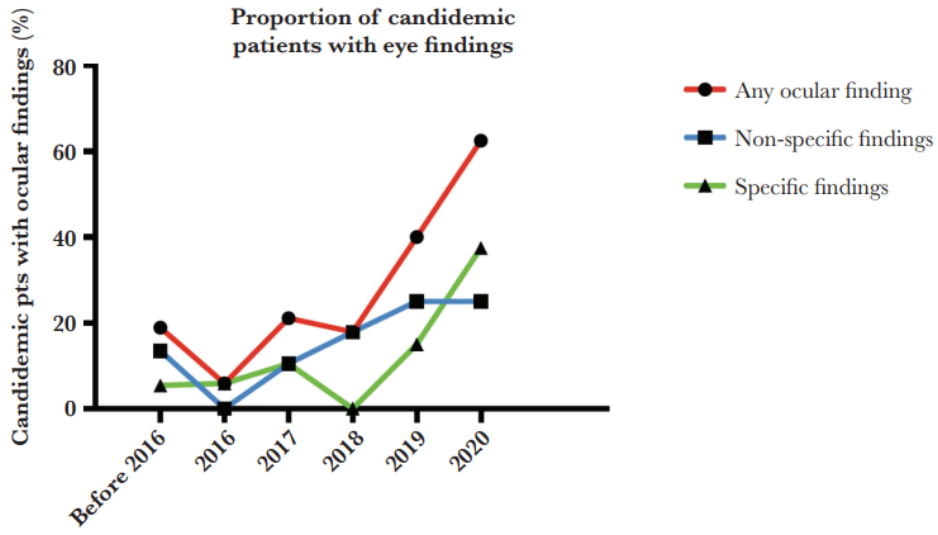
The Incidence of Ocular Complications in Candidemic Patients and Implications for the Practice of Routine Eye Exams published online OFID March 18, 2022

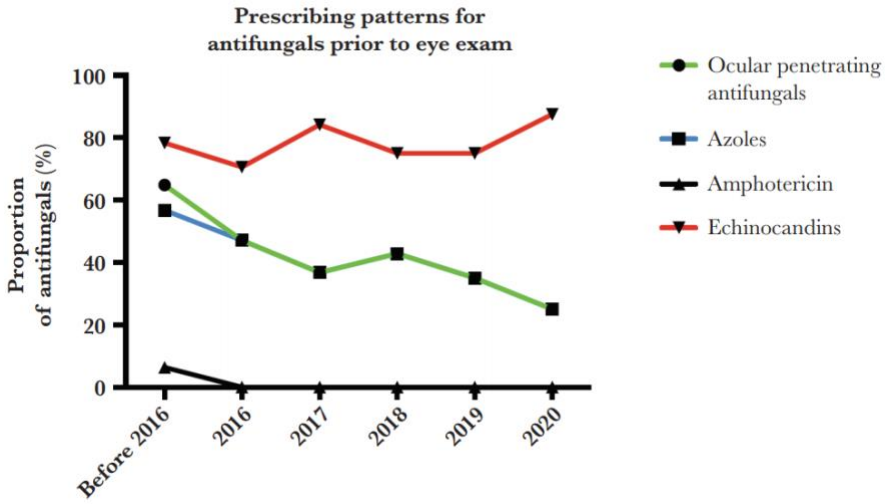
doi.org/10.1093/ofid/ofac045

Candidal chorioretinitis and endophthalmitis are well-recognized complications of candidemia, leading IDSA to recommend routine ophthalmologic examination of all candidemic patients. [Clin Infect Dis 2016;62:e1-e50] However, due to a decline in ocular candidiasis after the introduction of azole agents, other groups (including the American Academy of Ophthalmology) now recommend ophthalmologic screening only for symptomatic patients. Since 2016, candidemia has been increasingly managed with echinocandins (an antifungal class with poor intraocular penetration[not sure how this correlates with response]). To examine the potential

effect on risk for ocular complications, investigators undertook a retrospective review of patients with *Candida*-positive blood cultures between January 2014 and June 2020.

Among 226 candidemic patients, 129 (57%) underwent retinal examination and 30 had ocular findings, including 11 cases of chorioretinitis or endophthalmitis. Incidence of ocular findings increased from 7 in 37 candidemic cases diagnosed before 2016 to 5 in 8 cases in 2020 (*P*=0.008). Use of ocular-penetrating antifungal agents (azoles or amphotericin) decreased from 65% before 2016 to 40% after 2016 as the use of echinocandins increased. Echinocandin therapy was associated with higher risk for ocular findings (OR, 2.82; *P*=0.036).





Comment: The IDSA guidelines state that all nonneutropenic patients with candidemia should have a dilated ophthalmological examination, preferably performed by an ophthalmologist,

within the first week after diagnosis *(strong recommendation; low-quality evidence)*. The duration of treatment should be at least 4–6 weeks, with the final duration depending on resolution of the lesions as determined by repeated ophthalmological examinations *(strong recommendation; low-quality evidence)*. This article has several weaknesses. First it is retrospective and only 57% had an ophthalmologic exam. In addition, two thirds of ocular findings were considered nonspecific. Although most eye findings in this study were nonspecific (findings other than endophthalmitis and chorioretinitis), and the significance of these nonspecific eye findings remains unclear, it is notable that of the patients with nonspecific eye findings who underwent follow-up examination, 3 of 10 had worsening findings. In the real world, most hospitals may not have access to an ophthalmologist willing to see patients in the hospital. The finding that echinocandin use was associated with ocular complications suggests this is an issue that warrants further investigation and the true significance of some of these complications needs to be established. Despite these limitations, this study adds to the body of work evaluating the impact of the use of echinocandins on the development of ophthalmic complications after candidemia. So, the question now given the incidence of ocular findings over time [small #s] should we reemphasize regular ocular exams in patients with candidemia?

COVID-19

COVID-19 News

Sabizabulin Cuts COVID-19 Death

Positive results were announced from a phase 3 trial evaluating sabizabulin in hospitalized COVID-19 patients at high risk for acute respiratory distress syndrome (ARDS).

Sabizabulin is an oral cytoskeleton disruptor that blocks microtubule trafficking. The investigational treatment is expected to provide both antiviral and anti-inflammatory effects, thereby treating both the SARS-CoV-2 infection and the cytokine storm and septic shock that lead to ARDS.

The double-blind, randomized, placebo-controlled trial (ClinicalTrials.gov Identifier: NCT04842747) included approximately 210 patients hospitalized with moderate to severe COVID-19 (WHO Ordinal Scale for Clinical Improvement score of at least 4) who were at high risk for ARDS and death. Patients were randomly assigned 2:1 to receive sabizabulin orally once daily for up to 21 days or placebo. Both treatment arms were allowed to receive standard of care, which included remdesivir, dexamethasone, anti-interleukin 6 (IL6) receptor antibodies, and Janus kinase (JAK) inhibitors. The primary endpoint was the proportion of patients who died by day 60. The key secondary endpoint was the proportion of patients who were alive without respiratory failure at day 15, day 22, and day 29.

An interim analysis showed that treatment with sabizabulin resulted in a clinically and statistically meaningful 55% relative reduction in deaths in the intent to treat population (*P* =.0029). The mortality rates for the sabizabulin and placebo groups were reported to be 20% and 45%, respectively. As for safety, sabizabulin was well tolerated with no clinically relevant safety concerns compared with placebo. According to the Company, secondary efficacy endpoints are still being analyzed.

Based on these positive efficacy and safety results, the independent Data Safety Monitoring Committee has recommended that the trial be stopped early. The company intends to meet with FDA to discuss next steps including the submission of an emergency use authorization application.

Comment: The activity of sabizabulin appears independent of COVID-19 variant type. The addition of an effective agents in treating severe Covid-19 is welcomed

FDA Grants Emergency Use Authorization To COVID-19 Breathalyzer Test

"A Covid-19 breathalyzer test with the ability to provide diagnostic results in three minutes has won emergency-use authorization from the FDA, the agency announced Thursday." The test made by InspectIR Systems "is authorized for those 18 and older and in settings where samples are both collected and analyzed, such as doctor's offices, hospitals or mobile testing sites." The FDA "said the test was validated in a study of 2,409 people, where it correctly identified 91.2% of positive samples and 99.3% of negative samples."

Comment: If validated and cost effective this would be a welcome addition to diagnostic testing for Covid-19.

COVID-19 Vaccine Booster Increases Immune Defenses In School-Aged Children, Particularly Against Omicron Variant, Pfizer & BioNTech Say

Pfizer reported in a small study, 140 children aged five to 11 who'd already gotten two shots were given a booster six months later, and found the booster generally revved up their immune response. The data "has not been published or peer-reviewed." No safety data was reported.

Comment: Hard to know what to make of this announcement without seeing the paper and what the primary and secondary outcomes were other than increase "immune response."

COVID-19 By The Numbers

Another COVID surge might hit U.S.

Experts fear hospitalizations will increase in rising number of states in coming weeks

No one expects a peak nearly as high as the last one, when the contagious omicron version of

MORE INSIDE

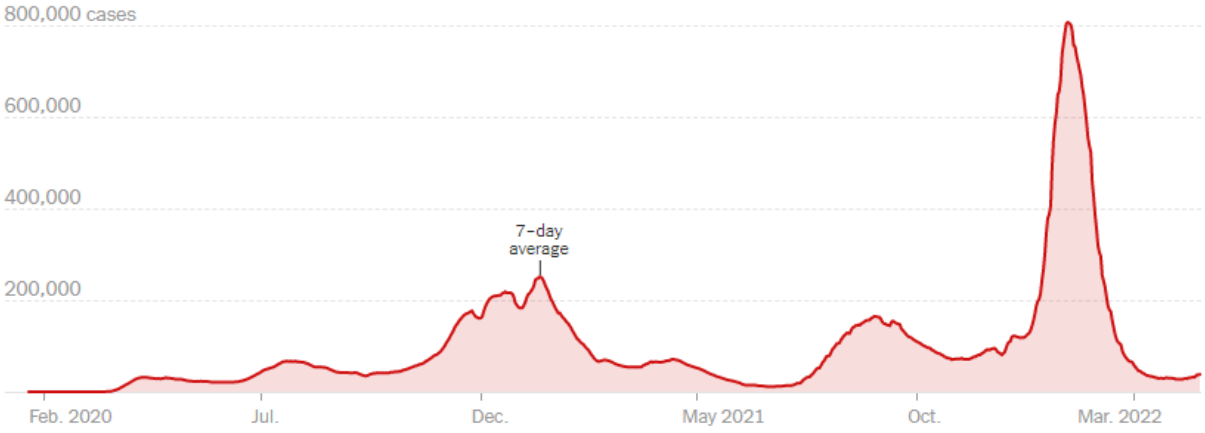
Two new omicron subvariants identified in Houston. **Page A9**

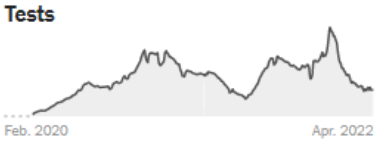
because reported numbers are vast undercounts as more people test at home without report-

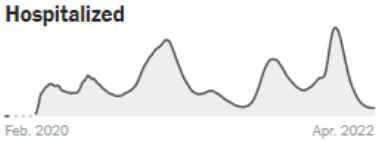
Comment: Once again, the media continues to alarm the public with headlines like above. Looking at the numbers reported below, one could have highlighted decreased hospitalization and deaths despite a small uptick in cases.

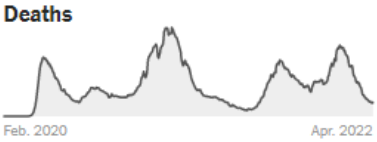
New reported cases

All time | Last 90 days









	DAILY AVG. ON APR. 16	14-DAY CHANGE	TOTAL REPORTED
Cases	37,810	+38%	80,524,337
Tests	765,515	+1%	—
Hospitalized	14,873	-8%	—
In I.C.U.s	1,999	-19%	—
Deaths	512	-22%	987,211

Comment: Rising cases on the East Coast have driven much of the country's increase, however, the number of new cases announced per day nationwide remains at its lowest level

since the summer of 2021. The seven-day average for percent positivity from tests is 4.1 percent, up 1.28 percentage points from the previous week. Hospitalizations, however, remain low. On average, fewer than 15,000 people are in American hospitals with the Covid-19 each day — a figure comparable only to the earliest weeks of the pandemic. The current seven-day death average is 409, down 15.7 percent from the previous week's average. This marks the ninth consecutive week deaths have fallen. CDC estimates the BA.2 omicron subvariant accounts for 85.9 percent of cases, while BA.1.1 accounts for 13.1 percent of COVID-19 cases in the US.

COVID-19 Journal Review

Infectious viral load in unvaccinated and vaccinated individuals infected with ancestral, Delta or Omicron SARS-CoV-2 Nat Med published online April 8, 2022

doi.org/10.1038/ s41591-022-01816-0

The effect of vaccination on infectious viral shedding and transmission from vaccinated individuals remains controversial. In this paper investigators compared RNA and infectious VL between pre-VOC strains, Delta and Omicron in unvaccinated individuals as well as in fully vaccinated (2 doses) or boosted (3 doses) subjects infected with Delta and Omicron using respiratory samples from mildly symptomatic patients of different age and sex, sampled in the first 5 days of symptoms. They quantified infectious VL in SARS-CoV-2 infected individuals by in vitro culturability assay in unvaccinated or vaccinated individuals infected with pre-variant of concern (pre-VOC) SARS-CoV-2, Delta, or Omicron. Only specimens with CT-values below 27 for the E-gene qRT-PCR diagnostic target (Cobas, Roche), as determined by the clinical laboratory at the time of diagnosis, were included in our study, as it has been shown previously that infectious virus cannot be reliably isolated from samples with higher CT values. In their laboratory no infectious virus was detected in pre-VOC and Delta samples with CT values ≥27. They also compared overall percentages of samples with a Ct ≥27 for time periods with almost exclusive circulation of pre-VOC, Delta and Omicron by analyzing the overall diagnostic data set from our outpatient testing center and separating patients by vaccination status and days of symptoms. The study quantified infectious VL in upper respiratory tract samples obtained from individuals infected with pre-VOC SARS-CoV-2 (n = 118), Delta variant (n = 293) or Omicron variant (n = 154) in the 5 days post onset of symptoms.

All vaccinated individuals included in this study were diagnosed positive at least 14 days after dose 2 or dose 3. Most of the individuals (274/287) were vaccinated with mRNA vaccines Pfizer or Moderna. All groups of individuals (pre-VOC, Delta-unvaccinated, Delta-vaccinated [2 doses], Omicron-unvaccinated, Omicron-vaccinated [2 or 3 doses]) had a similar age and sex distribution.

Of the Delta-infected individuals, 166 were fully vaccinated prior to infection and 127 were unvaccinated. Among Omicron-infected individuals, 91 were fully vaccinated prior to infection, 30 were boosted and 33 were unvaccinated. None of the individuals infected with pre-VOC

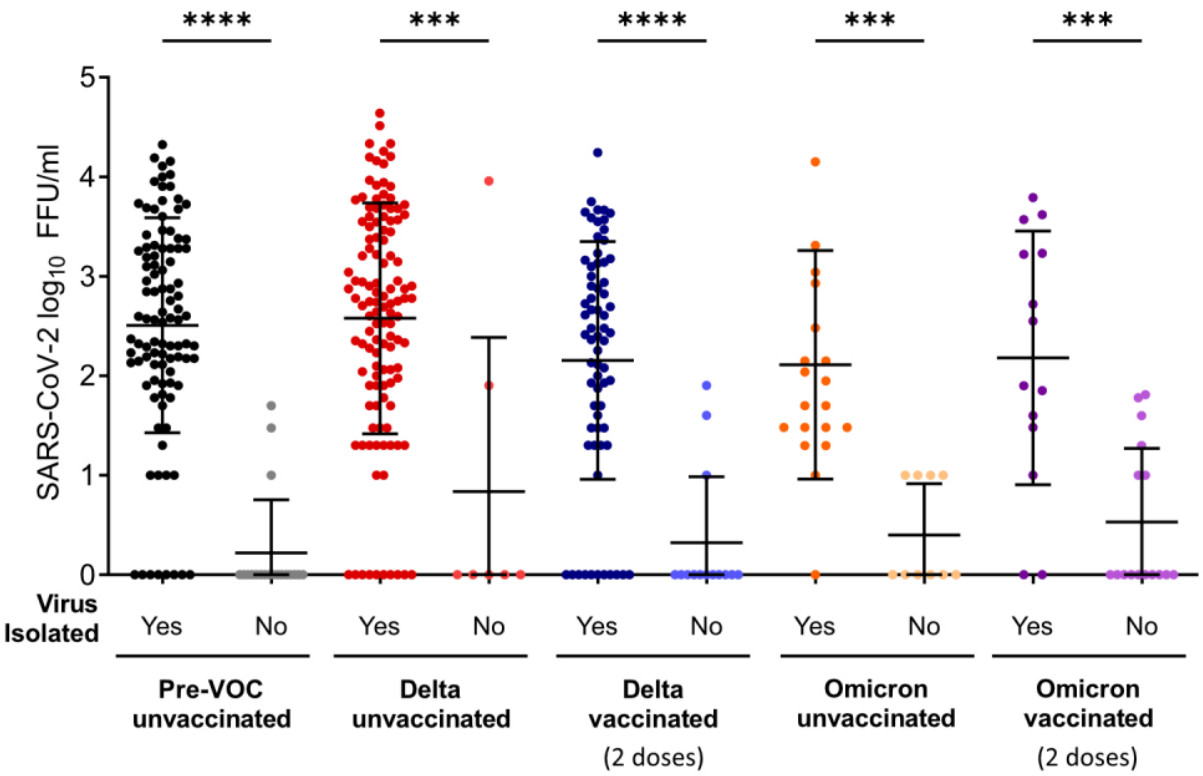
SARS-CoV-2 were vaccinated as vaccines were unavailable at the time of infection. All infected individuals had mild symptoms at the time of sampling.

Overall, pre-VOC samples had significantly more genome copies (2.98-fold, 0.4744 $\log_{10}$, P = 0.001) compared to Delta-infected unvaccinated samples, but infectious viral titers were significantly higher in Delta-infected unvaccinated individuals (2.2 fold, 0.343 $\log_{10}$, P = 0.0373). When the investigators compared genome copies and infectious VLs in unvaccinated and vaccinated individuals infected with Delta, they found that RNA genome copies were significantly lower in vaccinated individuals compared with those of unvaccinated individuals (2.8-fold, 0.44 $\log_{10}$, P = 0.0002) and the decrease in infectious VL was even more pronounced in vaccinated individuals (4.78-fold, 0.68 $\log_{10}$, P < 0.0001). The kinetics of RNA genome copies were observed to be largely similar between vaccinated and unvaccinated individuals until 3 days of symptoms with a faster decline for vaccinated individuals starting at 4 days of symptoms. In contrast, infectious VL were substantially lower in vaccinated individuals at all days of symptoms with the biggest effect at 3-5 days of symptoms. Nonetheless, at 5 days of symptoms infectious virus was detectable in 7/13 (53.8%) vaccinated and 11/13 (84.6%) unvaccinated individuals.

Further, when 79 Delta-infected unvaccinated individuals were matched with 188 Delta vaccine-breakthrough individuals in regard to age, sex and days of symptoms, infectious VLs were elevated in unvaccinated individuals in comparison to vaccine-breakthroughs (8.12-fold, 0.91 $\log_{10}$, P < 0.0001), confirming a significant reduction of infectious VLs among vaccinated individuals.

On the other hand, among fully vaccinated individuals, Omicron breakthrough infections resulted in similar genome copies but significantly lower infectious VLs (14-fold, 1.146 $\log_{10}$, P < 0.0001) in comparison with Delta breakthrough infections. A significant reduction of infectious VLs was also observed for Omicron samples when matching individuals for age, sex and days of symptoms (16.4-fold, 1.214 $\log_{10}$, P = 0.0003). Similar to Delta-infected fully vaccinated individuals, the RNA VLs only slightly decreased over 5 days of symptoms, while infectious VLs declined towards 5 days of symptoms.

Of interest, the investigators found no reduction of RNA or infectious VL in fully vaccinated Omicron-infected individuals compared with unvaccinated individuals. However, a significantly lower infectious VL, but not RNA VL, was observed for boosted individuals (5.3-fold, 0.7280 $\log_{10}$, P = 0.0004) in comparison with unvaccinated individuals.



Comment: RNA VL measured by qRT-PCR is only a weak proxy for infectiousness. On the other hand, higher culturable VL can serve as a proxy for greater risk of transmission. Studies on the kinetics of infectious VL are important to understand the mechanisms behind the different transmissibility of SARS-CoV-2 variants and the effect of vaccination on transmission, which can help guide public health policy. This study provides strong evidence for higher infectiousness of SARS-CoV-2 Delta as well as a significant impact of full vaccination on infectious VL and its speed of clearance. In addition, the investigators showed that Omicron has lower infectious VLs compared to Delta in fully vaccinated individual. However, after Omicron infection, lower infectious VL was only observed in boosted individuals. The investigators added that combined with other recent studies the results indicate that the observed high transmissibility of Omicron may not be caused by elevated VLs and the mechanism behind the higher transmissibility remains to be investigated.

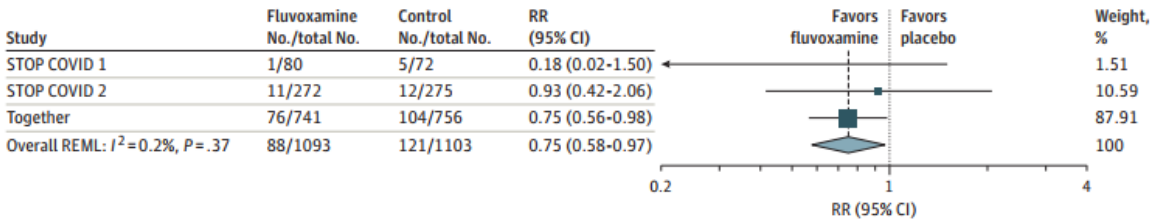
To my knowledge, this is the first study to quantify infectious VLs in individuals infected with different SARS-CoV-2 variants and in vaccination-breakthrough cases. They clearly demonstrated a higher infectious VL in unvaccinated Delta-infected compared to pre-VOC-infected individuals and showed a significant reduction of infectious VLs in fully vaccinated Delta-infected individuals. However, only booster vaccination significantly reduced infectious VL in Omicron-infected individuals. Furthermore, they found a lower infectious VL in Omicron compared to Delta breakthrough cases.

Fluvoxamine for Outpatient Management of COVID-19 to Prevent Hospitalization A Systematic Review and Meta-analysis JAMA Netw Open published online April 6, 2022

doi:10.1001/jamanetworkopen.2022.6269

The authors performed a meta-analysis of the available randomized clinical trial evidence for fluvoxamine in the outpatient management of COVID-19. They used the WHO International Clinical Trials Registry Platform and ClinicalTrials.gov. They followed the PRISMA 2020 guidelines and study details in terms of inclusion criteria, trial demographics, and the prespecified outcome of all-cause hospitalization were extracted. Risk of bias was assessed by the Cochrane Risk of Bias 2 tool and a Bayesian random effects meta-analysis with different estimates of prior probability was conducted: a weakly neutral prior (50% chance of efficacy with 95% CI for risk ratio [RR] between 0.5 and 2.0) and a moderately optimistic prior (85% chance of efficacy). A frequentist random-effects meta-analysis was conducted as a sensitivity analysis, and the results were contextualized by estimating the probability of any association (RR 1) and moderate association (RR 0.9) with reduced hospitalization.

This systematic review and meta-analysis of 3 randomized clinical trials and included 2196 participants. The RRs for hospitalization were 0.78 (95% CI, 0.58-1.08) for the Bayesian weakly neutral prior, 0.73 (95% CI, 0.53-1.01) for the Bayesian moderately optimistic prior, and 0.75 (95% CI, 0.58-0.97) for the frequentist analysis. Depending on the scenario, the probability of any association with reduced hospitalization ranged from 94.1% to 98.6%, and the probability of moderate association ranged from 81.6% to 91.8%.



Comment: These findings suggest that fluvoxamine, a widely available and inexpensive treatment for outpatients with COVID-19, was associated with a reduction in hospitalizations Ongoing randomized trials are important to evaluate alternative doses and duration, explore the effectiveness in vaccinated patients, and provide further refinement to these estimates. There are a few limitations to this analysis. First was including variability in health care practices, resource availability, and circulating variants between trials, leading to differences in the baseline event rates and the associated absolute risk reduction. They did attempt to correct for subjectivity by limiting this analysis to hospitalizations, but the decision to hospitalize may vary between geographic areas and even time points based on systemic burdens on the health care system. The investigators chose all-cause hospitalization as the most common important outcome of outpatient COVID-19 trials because ICU admission or death would require an enormously large study. Additionally, all 3 trials excluded fully vaccinated individuals, whose rates of hospitalization are greatly reduced, and therefore any estimates of absolute effect size would likely be an overestimate in vaccinated patient. Meanwhile, as I have expressed before I think fluvoxamine could be recommended as a therapeutic option, particularly in resource-

limited settings or for individuals without access to SARS-CoV-2 monoclonal antibody therapy or antivirals.

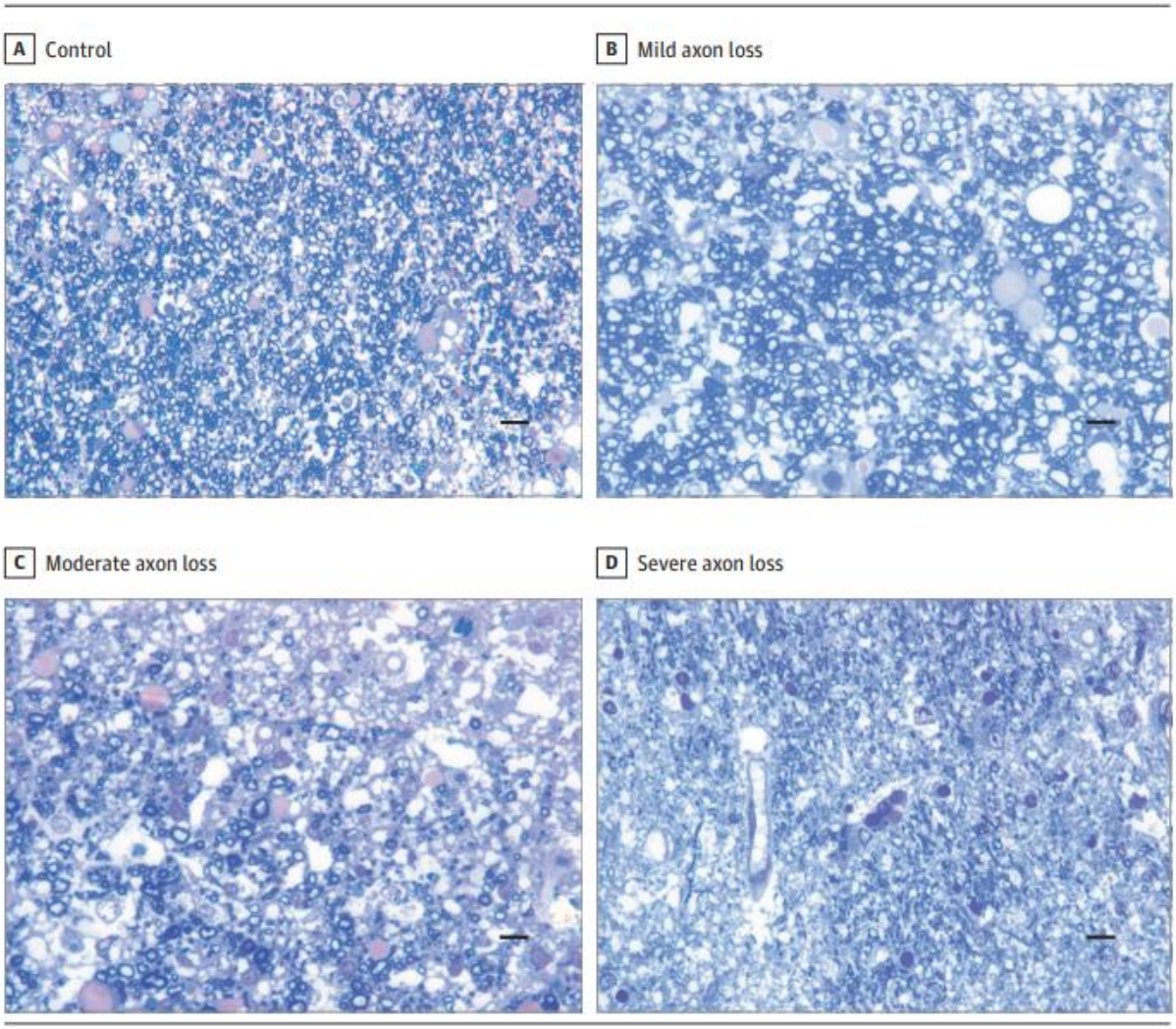
Postmortem Assessment of Olfactory Tissue Degeneration and Microvasculopathy in Patients With COVID-19 JAMA Neurol published online April 11, 2022

doi:10.1001/jamaneurol.2022.0154

This is a multicenter study, which involved examining the olfactory bulb at the base of the brain of 23 deceased COVID-19 patients and 14 matched controls who died of other causes from April 7, 2020, to September 11, 2021.

The investigators used light and electron microscopy to look for any SARS-CoV-2 genetic material and assess cell structures and characteristics and the blood vessels and neurons within them. They also measured the number of axons in the neurons, which inform sensory perception and movement. Information about sense of smell and taste was derived from the medical records of three patients and from family interviews for the remainder.

Three of the 23 COVID-19 patients lost their sense of smell, while 4 had an impaired ability to smell, and 2 lost both smell and taste. No controls lost either smell or taste. COVID-19 decedents had more severe vascular injury and far fewer axons in the olfactory bulb—particularly those with diminished or total loss of smell, strongly suggesting that these effects are not age related and therefore, probably linked to SARS-CoV-2 infection.



Comment: The investigators were surprised that despite nerve and vascular damage in COVID-19 decedents, most had no detectable SARS-CoV-2 virus particles in the olfactory bulb. This damage was initially thought to be caused by excessive cytokine release from immune cells, respiratory epithelial cells, and alveolar epithelial cells which has been shown to correlate with COVID-19 severity. However, this study did not find a strong association between olfactory endothelial injury and disease severity, suggesting that local inflammation in the upper respiratory tract may be sufficient to cause endothelial and axonal damage in the olfactory pathway. The findings suggest that SARS-CoV-2 infection of the olfactory epithelium leads to inflammation, which in turn, damages the neurons, reduces the numbers of axons available to send signals to the brain, and results in the olfactory bulb becoming dysfunctional. This study did not examine the pathologic association of COVID-19 with nasal mucosa, which contains primary olfactory neurons and their supporting cells. Therefore, how pathologic changes in nasal mucosa may contribute to smell alterations in COVID-19 infection could not be assessed in this cohort.

Myopericarditis following COVID-19 vaccination and non-COVID-19 vaccination: a systematic review and meta-analysis Lancet Respir Med published online April 11, 2022

doi.org/10.1016/ S2213-2600(22)00059-5

The authors analyzed more than 20 studies from international databases with reported incidences of myopericarditis following any type of vaccination between January 1947 and December 2021. Of these, 11 studies looked specifically at COVID-19 vaccinations, covering over 395 million COVID-19 vaccine doses -- nearly 300 million of which were mRNA vaccines. The rest of the studies covered other vaccinations such as smallpox (2.9 million doses), influenza (1.5 million doses), and others (5.5 million doses).

The rate of myopericarditis following COVID-19 vaccination was 18 cases per million doses. For all other viral vaccinations combined, the rate of myopericarditis was 56 cases per million doses.

Among COVID-19 vaccinations, the risk of myopericarditis was higher for those who received mRNA vaccines (22.6 cases per million doses) compared with non-mRNA vaccines (7.9 cases per million doses). Reported cases were also higher in people aged younger than 30 years (40.9 cases per million doses), males (23 cases per million doses), and following the second dose of COVID-19 vaccine (31.1 cases per million doses).

The authors also conducted a post-study analysis. Among 2.5 million patients who were hospitalized with COVID-19, many of whom had clinical or radiological suspicion for myopericarditis, 1.1% had myopericarditis. However, the authors noted that the results are not directly comparable with the number of cases of myopericarditis following COVID-19 vaccination due to different units of measurement.

The occurrence of myopericarditis following non-COVID-19 vaccination could suggest that myopericarditis is a side effect of the inflammatory processes induced by any vaccination and is not unique to the SARS-CoV-2 spike proteins in COVID-19 vaccines or infection.

Comment: The authors looked at more than 400 million vaccination doses, to compare the risk of myopericarditis following vaccination against COVID-19 and other diseases such as influenza and smallpox. They found no statistically significant difference between the incidence of myopericarditis following COVID-19 vaccination (18 cases per million doses) and other vaccinations (56 cases per million doses).

The study findings include only a small proportion of children aged younger than 12 years who have only recently been eligible for vaccination, and that results of this study cannot be generalized to this age group. In addition, comparisons have been made across different time

periods for different vaccines. Diagnostic tools might have differed or not been available leading to lower reporting of cases in earlier studies.

To put things into perspective, reports of unexpected adverse events -- albeit rare and limited to a select subset of vaccine recipients -- have the potential to damage vaccine confidence at a critical point in pandemic response. Most of us have emphasized that benefits of vaccination far outweigh the risk. Alternative vaccine platforms [protein based], vaccine doses, or vaccine schedules [changing primary series to be 2 months apart] may reduce the risk of rare adverse events following immunization. Overall, these findings should bolster public confidence in the safety of COVID-19 vaccinations.