Good morning and TGIF

Under COVID-19 News I review the concern of the global spread of the delta variant (B.1.617.2-India). The good news is the remarkable efficacy of mRNA vaccines against this variant. Next is a heads up that ACIP next Friday will review the possible link of mRNA vaccination and myocarditis in young males. The third item is the report of the growing number of healthcare systems moving to mandatory Covid-19 vaccinations for HCWs. Last is the follow-up report of the incidence of RSV in the southern half of the US.

Under Journal Review the first article is an important report from Germany. The authors concluded that children were unlikely to be the driving transmission during the pandemic. Next is a pre-publication study from Cleveland Clinic which demonstrated that immunity acquired by natural infection provides effective robust protection against future infection with SARS-CoV-2 up to at least 5 months. The next paper shows that infections occurring 12 days or longer after vaccination have significantly reduced viral loads [by PCR] at the time of testing, potentially affecting viral shedding and contagiousness as well as the severity of the disease. I finish with two very nice papers on the risk of CVST and ITP after vaccination.

Have a marvelous weekend

Ed

COVID-19 News

Global Spread of Covid-19 Delta Variant
The B.1.617.2 variant, now renamed the Delta variant, is in at least 60 countries, including the U.S. and the U.K., and British scientists recently estimated that it might be 40% to 50% more transmissible than the B.1.1.7 variant, or Alpha, which in turn is more transmissible than the original virus and quickly spread across the globe. Previously, around 98% of cases in the U.K. were due to the Alpha variant, but the Delta variant has started to take over after being introduced into the country in March and now constitutes about 75% of cases! CDC reports the Delta variant currently accounts for more than 6% of sequenced Covid-19 cases in the U.S. The Alpha variant is still dominant in the US.

Comment: The currently available vaccines do work against the Delta variant, but they seem to be somewhat less effective, especially after just one dose. According to data from Public Health England, both the AstraZeneca and Pfizer vaccines were about 33% effective against symptomatic Covid-19 caused by the Delta variant after one dose, compared with being about 50% effective against the Alpha variant. After two doses, however, the Pfizer vaccine efficacy against the Delta variant increased to 88%, and the AstraZeneca vaccine was about 60% effective. Bottom line we need everyone who is eligible to be vaccinated.

CDC Advisory Committee Investigating Report of Myocarditis and mRNA Vaccines
CDC announced it is investigating the reports of myocarditis in male adolescents and young adults after the second dose of Pfizer or Moderna vaccines. As of the end of May, there have been 275 reports of myocarditis in 16-24-year-olds. This is out of over 12 million second dose administrations of the vaccines. These cases have been mild and most have fully recovered. [see prior Daily Briefing last

Monday: Pediatrics published online May 4, 2021] The ACIP will meet on June 18th to further evaluate the possible risk.

2 Baltimore Health Systems to Mandate COVID-19 Vaccines for Workers

The University of Maryland Medical System and Johns Hopkins Medicine, both based in Baltimore, will require employees to be vaccinated for COVID-19, making them the latest health systems to do so. The University of Maryland Medical System will require COVID-19 vaccination for those at the manager level and above by Aug. 1, and current and new employees beginning Sept. 1. The medical system operates 13 hospitals and a network of urgent care centers in Maryland and has more than 29,000 employees. The medical system will provide exceptions for medical conditions, religious beliefs, and pregnancy. Weekly COVID-19 testing will be required for team members and partners, including contractors, volunteers, and students who remain unvaccinated. COVID-19 vaccination will become a requirement for all team members and partners once the vaccine is granted full FDA approval.

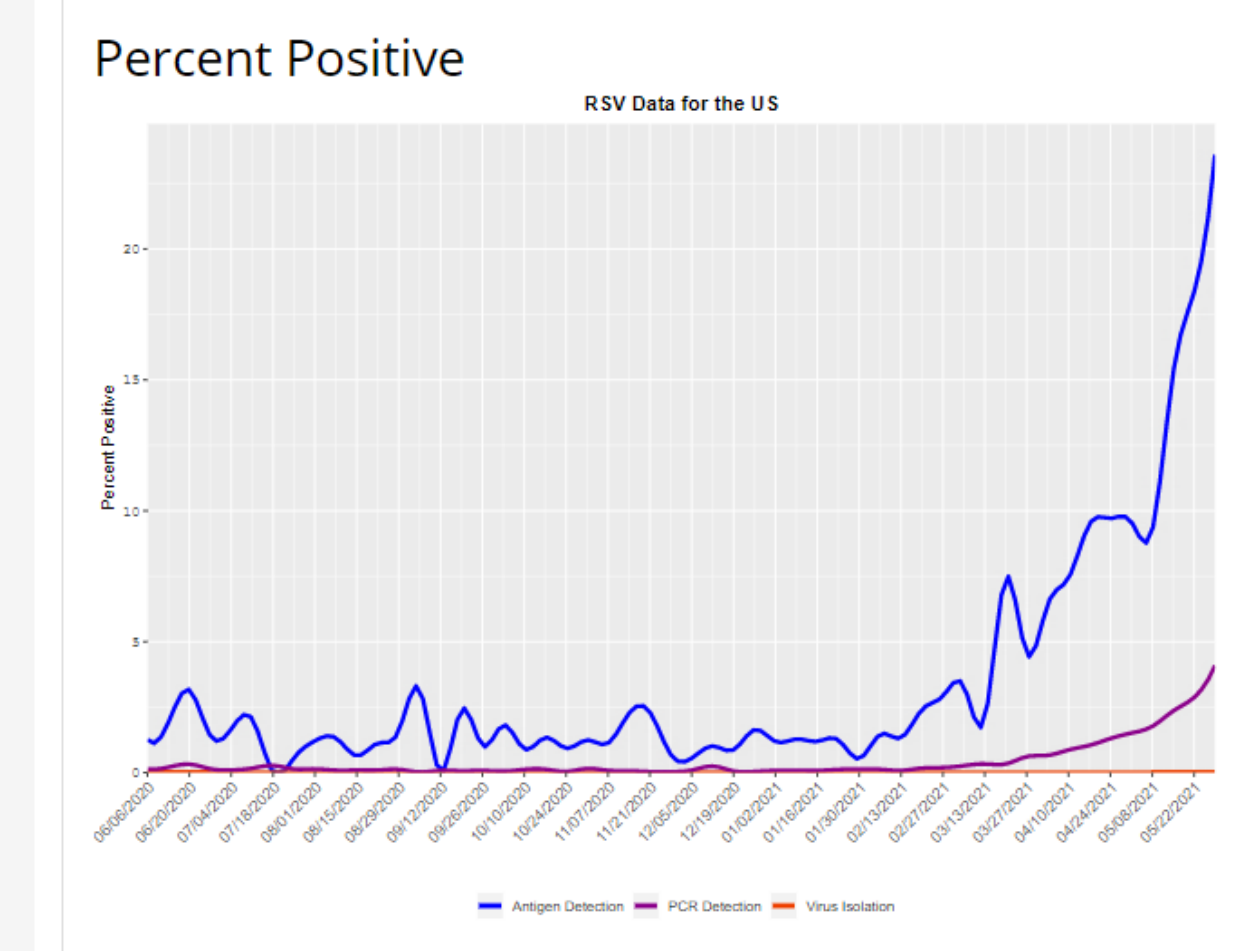
Johns Hopkins Medicine is taking a similar approach, requiring its clinical and nonclinical personnel to be fully vaccinated by Sept. 1. Johns Hopkins Medicine first offered the COVID-19 vaccine to their personnel in December 2020, however, only three-quarters of their workforce has been vaccinated. Johns Hopkins Medicine's policy applies to faculty, staff, temporary staff, students, postdoctoral fellows, house staff, providers, volunteers, and vendors.

Comment: Momentum is growing to strongly encourage HCWs to be vaccinated. Houston Methodist has been sued but is standing by its decision. I commend Houston Methodist for its leadership and decisive action and the message it sends in assuring patients and other HCWs that we have a moral obligation in protecting our patients and other HCWs from vaccine-preventable diseases.

Increased Interseasonal Respiratory Syncytial Virus (RSV) Activity in Parts of the Southern United States

CDC June 10, 2021

The CDC has issued a health advisory to notify clinicians and caregivers about increased interseasonal RSV activity across parts of the Southern US. Due to this increased activity, CDC encourages broader testing for RSV among patients presenting with acute respiratory illness who test negative for SARS-CoV-2.



Comment: This is a follow-up report from CDC last month. This has been a strange year.

Journal Review

Prevalence of SARS-CoV-2 Infection in Children and Their Parents in Southwest Germany
JAMA Pediatrics 2021; 175:586-593.
doi:10.1001/jamapediatrics.2021.0001
This is a large-scale, multicenter, cross-sectional investigation which enrolled children aged 1 to 10 years and a corresponding parent between April 22 and May 15, 2020, in southwest Germany. The main outcomes were infection and seroprevalence of SARS-CoV-2. Participants were tested for SARS-CoV-2 RNA from nasopharyngeal swabs by RT-PCR and SARS-CoV-2 specific IgG antibodies in serum by enzyme-linked immunosorbent assays and immunofluorescence tests.

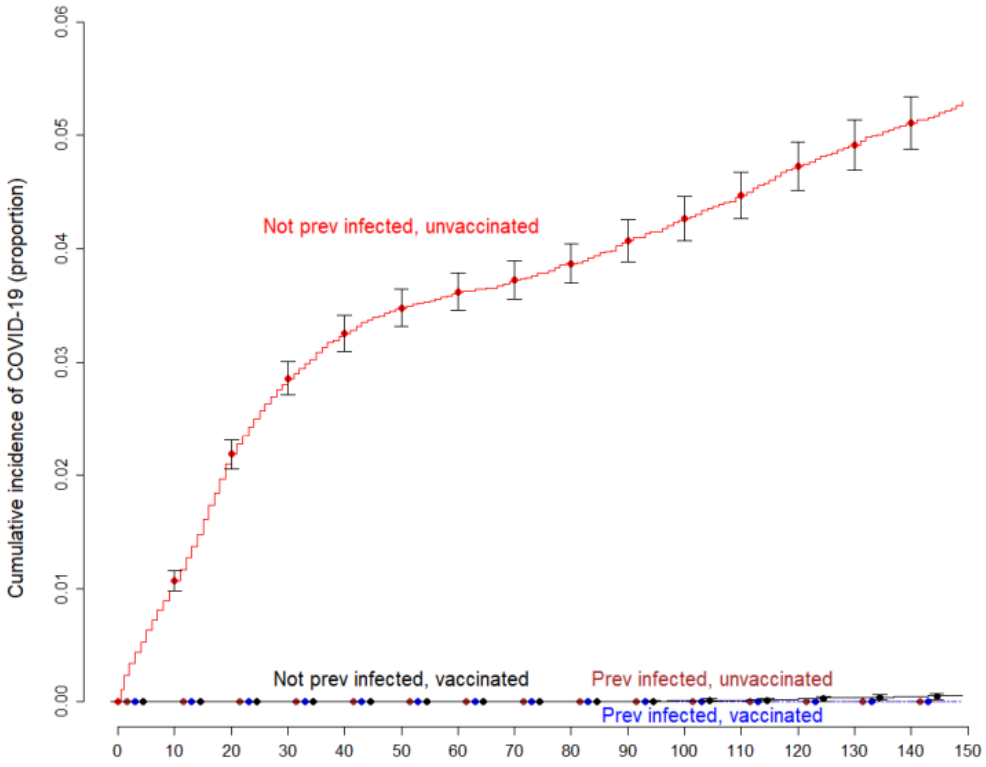
This study included 4964 participants: 2482 children (median age, 6 [range, 1-10] years; 1265 boys [51.0%]) and 2482 parents (median age, 40 [range, 23-66] years; 615 men [24.8%]). Two participants (0.04%) tested positive for SARS-CoV-2 RNA. The estimated SARS-CoV-2 seroprevalence was low in parents (1.8% [95% CI, 1.2–2.4%]) and 3-fold lower in children (0.6% [95% CI, 0.3-1.0%]). Among 56 families with at least 1 child or parent with seropositivity, the combination of a parent with seropositivity and a corresponding child with seronegativity was 4.3 (95% CI, 1.19-15.52) times higher

than the combination of a parent who was seronegative and a corresponding child with seropositivity. We observed virus-neutralizing activity for 66 of 70 IgG-positive serum samples (94.3%).

Comment: The investigators attempted to answer certain other questions, such as whether there were differences by age (child aged 1 to 5 years vs 6 to 10 years): there was no significant differences. They also tried to see whether childcare attendance influenced seropositivity. Although numbers were fairly small for the childcare attendance outcome, children who attended childcare actually had lower seroprevalence than those who did not (0.5% for children in childcare vs 1.0% for children not in childcare). The authors concluded that children were unlikely to be driving transmission during the pandemic. This is the largest seroprevalence study among children to date that I am aware of. By examining parent child dyads within the same household, this study suggests that children were both less likely to acquire infection when it was in the household and less likely to spread it in the household when they were infected. The investigators acknowledge that this study was performed during a period of lockdown, and children may have been less likely to be exposed than their parents, thus partially explaining the findings. However, the lack of increased prevalence in children in childcare somewhat addresses this limitation and is consistent with other studies showing relatively low transmission in childcare settings. Another potential limitation is the voluntary study participation. However, the authors feel the inclusion of 4 geographically separated towns and their adjacent regions, and the high number of study participants at least partially compensates for this shortcoming and allows for drawing general conclusions on the role of children in the pandemic. The answer to this question could not be clearer: we must prioritize the reopening of childcare facilities and elementary schools to full time, in-person learning.

Necessity of COVID-19 Vaccination in Previously Infected Individuals
medRxiv published June 5, 2021
doi.org/10.1101/2021.06.01.21258176.
The purpose of this study was to evaluate the necessity of COVID-19 vaccination in persons previously infected with SARS-CoV-2. Employees of the Cleveland Clinic Health System working in Ohio on Dec 16, 2020, the day COVID-19 vaccination was started, were included. Any subject who tested positive for SARS-CoV-2 at least 42 days earlier was considered previously infected. One was considered vaccinated 14 days after receipt of the second dose of a SARS-CoV-2 mRNA vaccine. The cumulative incidence of SARS-CoV-2 infection over the next five months, among previously infected subjects who received the vaccine, was compared with those of previously infected subjects who remained unvaccinated, previously uninfected subjects who received the vaccine, and previously uninfected subjects who remained unvaccinated.

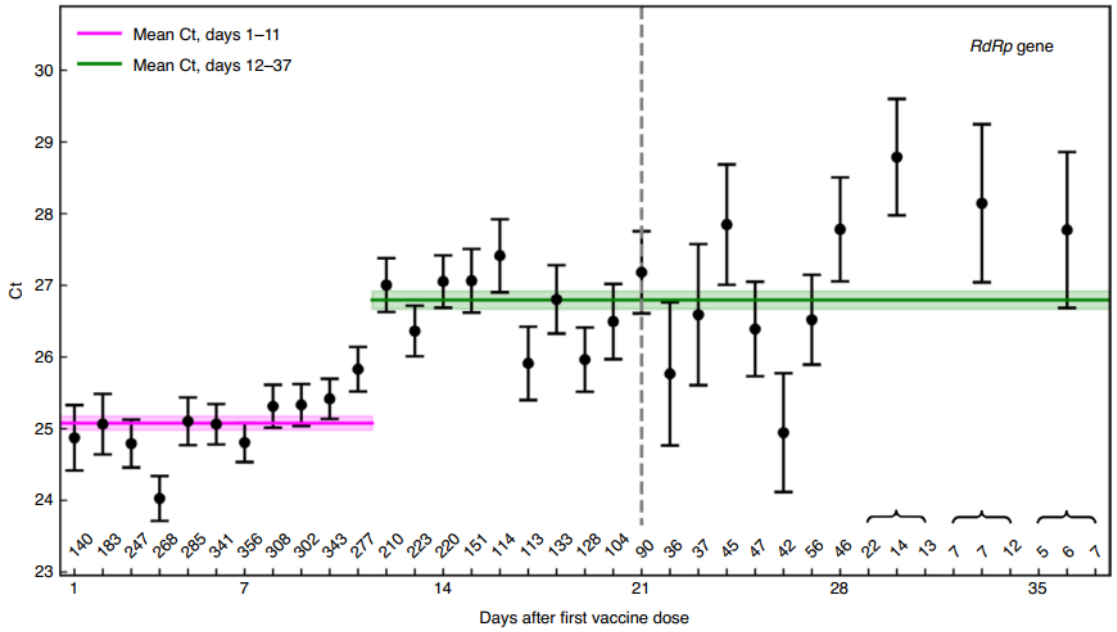
Among the 52,238 included employees, 1,359 (53%) of 2,579 previously infected subjects remained unvaccinated, compared with 22,777 (41%) of 49,659 not previously infected. The cumulative incidence of SARS-CoV-2 infection remained almost zero among previously infected unvaccinated subjects, previously infected subjects who were vaccinated, and previously uninfected subjects who were vaccinated, compared with a steady increase in cumulative incidence among previously uninfected subjects who remained unvaccinated. Not one of the 1,359 previously infected subjects who remained unvaccinated had a SARS-CoV-2 infection over the duration of the study. In a Cox proportional hazards regression model, after adjusting for the phase of the epidemic, vaccination was associated with a significantly lower risk of SARS-CoV-2 infection among those not previously infected (HR 0.031, 95% CI 0.015 to 0.061) but not among those previously infected (HR 0.313, 95% CI 0 to Infinity).



Comment: This study was not specifically designed to determine the duration of protection in persons with natural infection, but for the previously infected subjects the median duration since prior infection was 143 days (IQR 76 - 179 days), and no one had SARS-CoV-2 infection over the following five months, suggesting that SARS-CoV-2 infection may provide protection against reinfection for 10 months or longer. [great news] This study demonstrated that immunity acquired by natural infection provides effective protection against future infection with SARS-CoV-2. Observational studies have indeed found very low rates of reinfection over the following months among survivors of COVID-19 [Clin Infect Dis 2021 https://doi.org/10.1093/cid/ciab234; N Engl J Med 2021; 384:533–40]. Reports of true reinfections are extremely rare in the absence of emergence of new variants. Because they did not have a policy of asymptomatic employee screening, previously infected subjects who remained asymptomatic might have been misclassified as previously uninfected. The study follow-up duration was short, being only five months. Given the short supply of vaccines worldwide, and the knowledge that vaccination does not provide significant additional protection to those previously infected, it would make most sense to initially limit vaccine administration to those who have not been previously infected. This is a pre-publication article and has not been peer reviewed yet.

Initial Report of Decreased SARS-CoV-2 Viral Load After Inoculation with the BNT162b2 Vaccine
Nature Med 2021 27:790-792
doi.org/10.1038/s41591-021-01316-7
This is an analysis of a real-world dataset of positive SARS-CoV-2 test results after inoculation with the Pfizer vaccine. They found that the viral load was substantially reduced for infections occurring 12-37d after the first dose of vaccine. These reduced viral loads hint at a potentially lower infectiousness,

further contributing to vaccine effect on virus spread. Viral loads are even lower after the second dose as seen after 28 days.



Comment: The results show that infections occurring 12d or longer after vaccination have significantly reduced viral loads at the time of testing, [higher Ct values] potentially affecting viral shedding and contagiousness as well as the severity of the disease [Lancet Respir. Med. 8, e70 (2020)]. This report is based on an observational study. Different viral variants, which could be associated with different viral loads, might affect different parts of the population. This suggests that fully vaccinated patients that experience breakthrough infection [very rare] are less likely to spread infections compared to natural infection in non-immune patients.

First-Dose ChAdOx1 and BNT162b2 COVID-19 Vaccines and Thrombocytopenic, Thromboembolic and Hemorrhagic Events in Scotland

Nat Med published online June 9, 2021

doi.org/10.1038/ s41591-021-01408-4

The investigators estimated associations between exposure to first dose ChAdOx1 (AZ) or BNT162b2 (Pfizer) vaccination and hematological and vascular adverse events using a nested incident-matched case-control study and a confirmatory self-controlled case series (SCCS) analysis. An association was found between AZ vaccination and idiopathic thrombocytopenic purpura (ITP) (0-27d after vaccination; adjusted rate ratio (aRR) = 5.77, 95% confidence interval (CI), 2.41-13.83), with an estimated incidence of 1.13 (0.62-1.63) cases per 100,000 doses. An SCCS analysis confirmed that this was unlikely due to bias (RR = 1.98 (1.29-3.02)). There was also an increased risk for arterial thromboembolic events (aRR = 1.22, 1.12-1.34) 0-27d after vaccination, with an SCCS RR of 0.97 (0.93-1.02). For hemorrhagic events 0-27d after vaccination, the aRR was 1.48 (1.12-1.96), with an SCCS RR of 0.95 (0.82-1.11). A first dose of AZ was found to be associated with small increased risks of ITP, with suggestive evidence of an increased risk of arterial thromboembolic and hemorrhagic events. No positive associations were seen between Pfizer and thrombocytopenic, thromboembolic, and hemorrhagic events. They found no association between prior AZ vaccination and venous thromboembolic events (including CVST-cerebral venous sinus

thrombosis) at 0-27d after vaccination (aRR = 1.03, 95% CI, 0.89-1.21) or for the Pfizer vaccination 0-27d after vaccination (aRR = 0.50, 95% CI, 0.40-0.62).

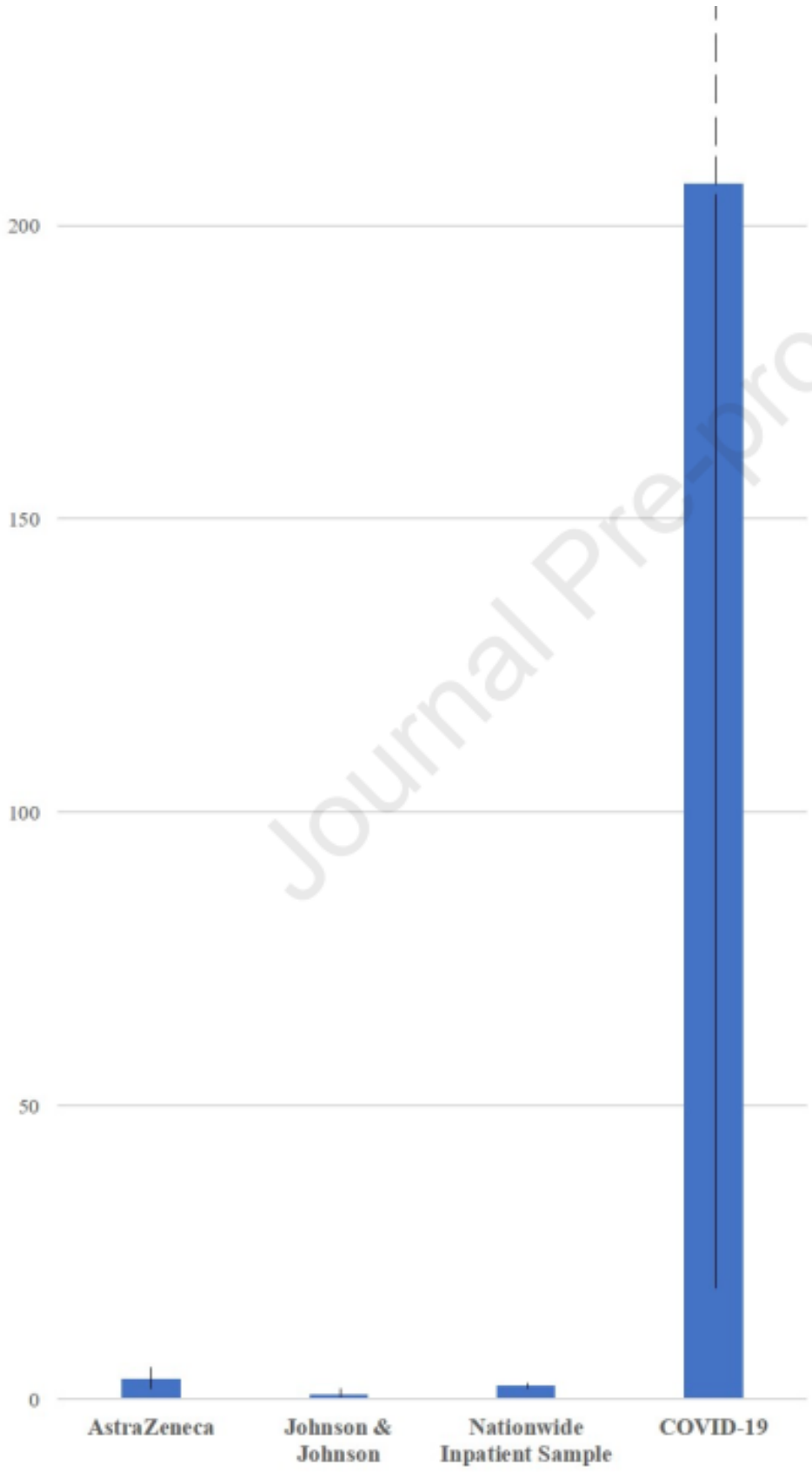
Comment: This new study found that the AZ vaccine was linked to a slight increase in the risk of an I.T.P. The risk was estimated at 1.13 cases per 100,000 people receiving their first dose, up to 27 days after vaccination. The condition is treatable, and none of the cases in vaccine recipients were fatal. The study also found very small increased risks of arterial blood clots and bleeding possibly associated with the AZ vaccine. But the investigators said there was not enough data to conclude that the vaccine was linked to CVST. Earlier this year, reports of CVST led some countries to suspend or limit AZ vaccine use. Similar concerns have been raised about CVST, primarily in younger women, linked to the J&J vaccine, which is authorized in the United States and other countries. Bottom line: the benefits of the vaccine far outweighed the small risk and noted that Covid itself is far more likely than the vaccine to cause I.T.P or CVST.

Cerebral Venous Sinus Thrombosis in the US Population, after Adenovirus-Based SARS-CoV-2 Vaccination, and After COVID-19

J Am Coll Cardiol published June 5, 2021
doi.org/10.1016/j.jacc.2021.06.001

The investigators used the data from The Medicines and Healthcare products Regulatory Agency (from the United Kingdom), and the US CDC to report the number of events per vaccinated people with AstraZeneca and J&J vaccines respectively. They used the data from a multinational study of cerebrovascular events to report CVST rates in hospitalized patients with COVID-19. Data from the Nationwide Inpatient Sample database (an all-payer database including an approximate 20% sample of inpatient hospitalizations in the US) from March and April 2018, the latest year with available information, were used to report the weighted monthly incidence of CVST using principal discharge diagnostic codes 437.6 and 325 (with positive predictive value of 92% for CVST divided by the US population as reported by the US census bureau. They estimated 99% confidence intervals around the proportions.

As of April 14, 2021, there were 77 CVST cases out of 21,200,000 AstraZeneca vaccine recipients reported by the Medicines and Healthcare products Regulatory Agency (3.6 per million, 99% CI: 2.7 to 4.8 per million). As of April 13, 2021, the CDC reported 6 cases of CVST out of 6.85 million vaccinated people (0.9 per million, 99% CI: 0.2 to 2.3 per million). In the SVIN COVID-19 registry, 3 out of 14,483 patients hospitalized with COVID-19 had CVST (207.1 per million, 99% CI: 23.3 per million to 757.7 per million). In the Nationwide Inpatient Sample, the weighted average rate of CVST in the US population for the months of March and April 2018 was 2.4 per million (99% CI: 2.1 to 2.6 per million).



Comment: The estimated relative frequency and 99% confidence interval estimates for CVST for AstraZeneca and J&J vaccines based on the available reported events are markedly lower than those for patients hospitalized with COVID-19 infection. The estimates in this report are consistent with previous reports: there is a very low absolute risk of CVST after adenovirus-based vaccination. A unique feature of CVST after vaccination for SARS-CoV2 is the phenomenon of vaccine-induced thrombotic thrombocytopenia. This condition has features resembling heparin induced thrombocytopenia, despite the absence of heparin exposure. The recommendation is to avoid heparin in these patients. Some experts recommend the administration of IVIG or steroids. The data from the Nationwide Inpatient Sample indicates the hospitalization rates, rather than incidence, however, most patients with CVST will require hospitalization. They were unable to report event rates per specific age groups, since the numerators and denominators for such analyses are not publicly available. Bottom line: CVST is rare in the general population and after adenovirus-based SARS-CoV-2 vaccination but appears to be several-fold more common in hospitalized patients with COVID-19 infection.