Good morning.

First, I wanted to give everyone a heads up. I am finally able to take a vacation starting November 15th and back December 3rd. I will publish the regular edition on Friday and will probably send 1-2 Briefings between the 15thand the 3rd depending on internet access bandwidth.

I am thinking that starting in 2022, I will publish a weekly Infectious Diseases Newsletter to contain not just Covid-19 but other significant non-Covid-19 publications. Your thoughts are appreciated.

Today under COVID-19 News the press release on the Pfizer Covid-19 oral antiviral. A second item from skimming through the Pfizer application (page 80) for children 5-11 which says no cases of COVID-19 were observed in either the vaccine group or the placebo group in participants with evidence of prior SARS-CoV-2 infection. I just mention it in follow-up to the discussion on natural immunity.

Under Journal Review, I focus on new publications on the J&J vaccine. The first is a population-based cohort study, on the CVST incidence rate after J&J vaccination. The second article looks at VE efficacy in US Veterans for all 3 vaccines over time. The last article is an analysis of the J&J vaccine.

Have a great day.

Ed

## COVID-19 News

**Pfizer Paxlovbid Antiviral**
In a randomized clinical trial that included more than 1,900 patients who tested positive for COVID-19 and were at risk for having severe complications for their infections, those who received Paxlovid within 3 days of the start of their symptoms were 89% less likely to be hospitalized than those who got a placebo pill — three patients out of 389 who got the drug were hospitalized, compared with 27 out of 385 who got the placebo. Among patients who got the drug within 5 days of the start of their symptoms, six out of 607 were hospitalized within 28 days, compared to 41 out of 612 who got the placebo.

There were no deaths over the course of a month in patients who took Paxlovbid, but 10 deaths in the group that got the placebo. The DMC in consultation with the FDA stopped trial based on interim results.

Paxlovbid is an investigational protease inhibitor designed to be administered orally. Low dose ritonavir was co-administered to slow metabolisms of Paxlovbid to prolong action and increase concentration. This is a 5-day course like molnupiravir.

**Comment:** This news could be a real game-changer in the global efforts to control the pandemic and reduce severe disease. The U.K. became the first country to authorize the use of molnupiravir another oral antiviral which in trials reduced progression by about 50% (see last week's Briefing).

## Journal Review

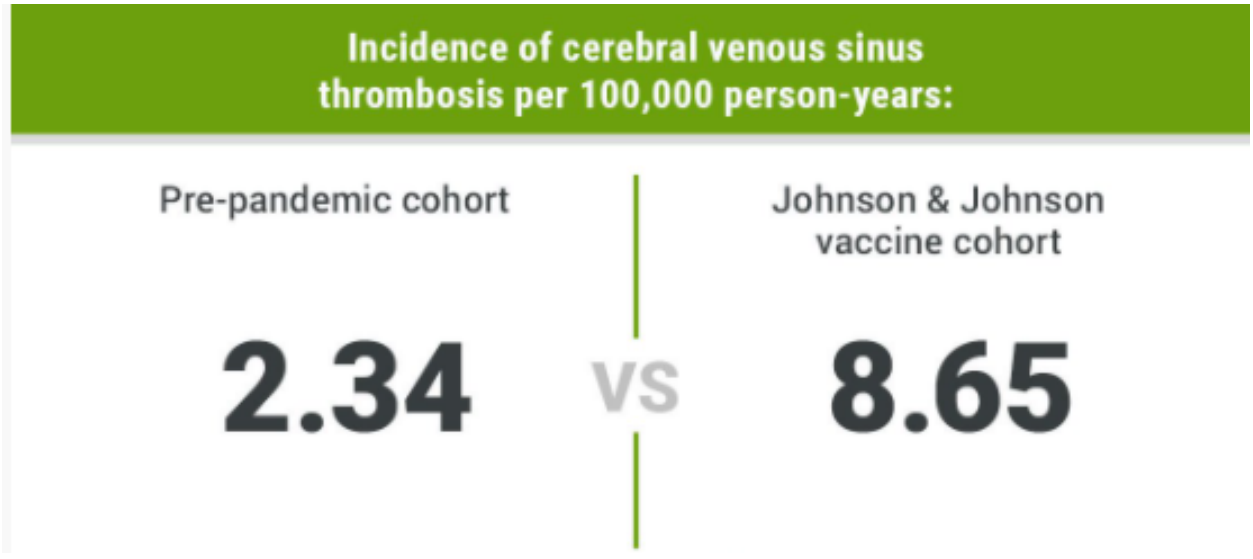
**Age- and Sex-Specific Incidence of Cerebral Venous Sinus Thrombosis Associated with Ad26.COV2.S COVID-19 Vaccination**

JAMA Intern Med published online November 1, 2021
doi:10.1001/jamainternmed.2021.6352

They used CDC Vaccine Adverse Event Reporting System (VAERS) data from February 28, 2021 (vaccine approval date) to May 7, 2021, to estimate the incidence of CVST after J&J vaccination in Olmstead County. They then compared post-J&J vaccination CVST rates with prepandemic rates to estimate postvaccination CVST risk.

From 2001 through 2015, 39 Olmsted County residents developed acute incident CVST. A total of 29 patients (74.4%) had a predisposing venous thromboembolism risk factor (e.g., infection, active cancer, or oral contraceptives [for women]) within 92 days before the event. The median age at diagnosis was 41 years (range, 22-84 years); 22 residents with CVST (56.4%) were female. The overall age- and sex-adjusted CVST incidence was 2.34 per 100,000 person-years (PY) (95% CI, 1.60-3.08 per 100,000 PY). Age-adjusted CVST rates for female and male individuals were 2.46 per 100,000 PY (95% CI, 1.43-3.49 per 100,000 PY) and 2.34 per 100,000 PY (95% CI, 1.22-3.46 per 100,000 PY), respectively. Men aged 65 years or older had the highest CVST rate (6.22 per 100,000 PY; 95% CI, 2.50-12.82 per 100,000 PY), followed by women aged 18 to 29 years (4.71 per 100,000 person-years; 95% CI, 2.26-8.66 per 100,000 PY).

The overall incidence rate of post-J&J vaccination CVST was 8.65 per 100,000 PY (95% CI, 5.88-12.28 per 100,000 PY) at 15 days, 5.02 per 100,000 PY (95%CI, 3.52-6.95 per 100,000 PY) at 30 days, and 1.73 per 100,000 PY (95% CI, 1.22-2.37 per 100,000 PY) at 92 days. The 15-day postvaccination CVST incidence rates for female and male individuals were 13.01 per 100,000 PY (95% CI, 8.24-19.52 per 100,000 PY) and 4.41 per 100,000 PY (95% CI, 1.90-8.68 per 100,000 PY), respectively. The postvaccination CVST rate among females was 5.1-fold higher compared with the pre-COVID-19 pandemic rate (13.01 vs 2.53 per 100,000 PY; $P < .001$). This risk was highest among women aged 40 to 49 years (29.50 per 100,000 PY; 95% CI, 13.50-55.95 per 100,000 PY), followed by women aged 30 to 39 years (26.50 per 100,000 PY; 10.65-54.63 per 100,000 PY).



**Comment:** As expected in this population-based cohort study, they found that the CVST incidence rate 15 days after J&J vaccination was significantly higher than the prepandemic rate. Most CVST events occurred within 15 days after vaccination, which is likely the highest at-risk period. The postvaccination CVST rate among females was higher than the prepandemic rate among females. The highest risk was among women aged 30 to 49 years, but the absolute CVST risk was still in this group (up to 29.5 per 100,000 PY among women aged 40-49 years). The incidence in this study was slightly higher than prior publications since they captured all objectively diagnosed incident CVST cases in a well-defined population, including those discovered at autopsy. This rare adverse effect must be considered in the context of the effectiveness of the vaccine in preventing COVID-19 with a second dose.

**SARS-CoV-2 Vaccine Protection and Deaths Among US Veterans During 2021**

published online November 4, 2021
DOI: 10.1126/science.abm0620

Researchers found that protection against any COVID-19 infection declined for all vaccine types, with overall vaccine protection declining from 87.9% in February to 48.1% by October 2021.

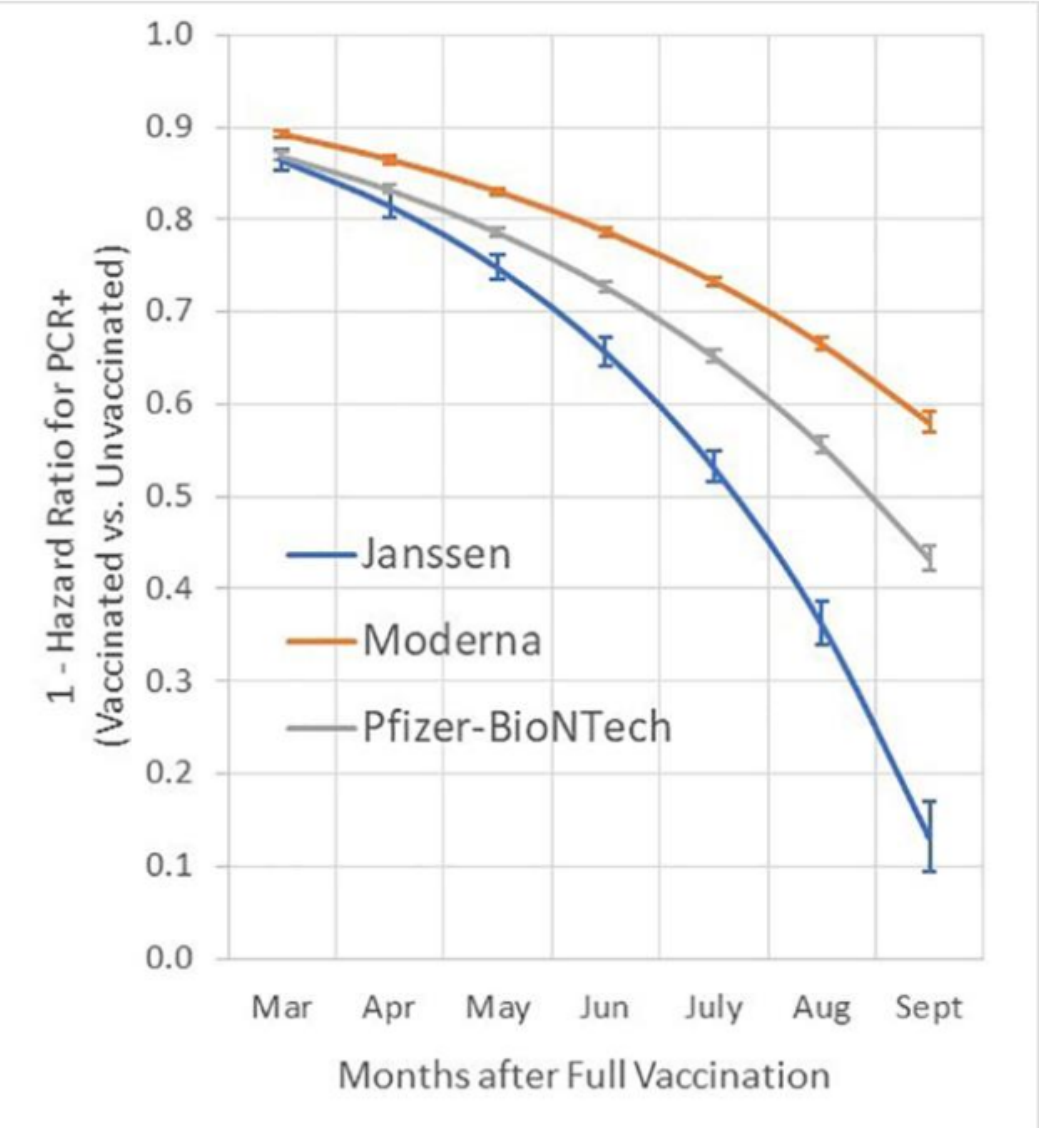
- The decline was greatest for the J&J vaccine, with protection against infection declining from 86.4% in March to 13.1% in September.
- Declines for Pfizer were from 86.9% to 43.3%.
- Declines for Moderna were 89.2% to 58%.

The study demonstrated that the risk of death from COVID infection was highest in unvaccinated Veterans, regardless of age and comorbidities. While some breakthrough infections resulted in death, vaccination remained protective against death in those who became infected during the Delta surge. For those under 65 years old, vaccines overall were 81.7% effective against death.

- Protection against death was greatest for the Pfizer vaccine, at 84.3%.
- Moderna was the next most effective, at 81.5%.
- J&J was 73% effective.

For those 65 and over, overall vaccine effectiveness against death was 71.6%.

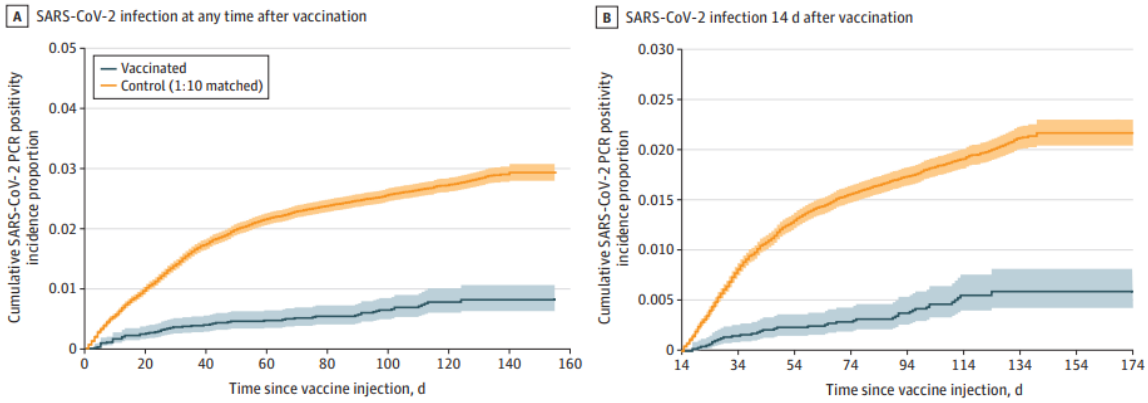
- Moderna was 75.5% effective.
- Pfizer was 70.1% effective.
- Janssen was 52.2% effective.




**Comment:** Given the declines in vaccine protection and the emergence of the more transmissible Delta variant, this article and others reviewed in recent months in the Briefing support recent recommendations for boosters. This manuscript supports the strong evidence that vaccination still protects against death even for persons with breakthrough infections, compared to persons who become infected and are not vaccinated. As reviewed in the November 1, 2021 Briefing, vaccinated people over age 80 have higher deaths rates compared to younger vaccinated persons.

**Analysis of the Effectiveness of the Ad26.COV2.S Adenoviral Vector Vaccine for Preventing COVID-19**
JAMA Netw Open published online November 2, 2021
doi:10.1001/jamanetworkopen.2021.32540
The investigators provide valuable data for the real-world effectiveness of the J&J vaccine in an observational, retrospective, comparative effectiveness research study. This study consisted of 8889 vaccinated and 88,898 unvaccinated individuals, with matching based on age, sex, zip code, race, ethnicity, and previous number of SARS-CoV-2 polymerase chain reaction tests. The investigators found that the VE of the J&J vaccine was 73.6%, which is in accordance with the effectiveness of 66.9%

reported in the phase 3 clinical trial of this vaccine and other publications. [see above] In addition, this study shows that the J&J vaccine reduces the risk of hospitalization and intensive care unit admission.




**Comment:** This study is part of a growing body of work surrounding humoral responses to a single dose of the J&J vaccine and VE. Several studies have showed that the recipients of the J&J vaccine have lower neutralization activity against virus variants. In terms of VE, 2 studies have shown that the effectiveness of the J&J vaccine is stable over time (before and after the emergence of the Delta variant), with a moderate decrease in effectiveness for individuals older than 75 years. The emergence of the Delta variant occurred in the final weeks of this study thus, there were not enough cases to determine VE against this variant. In the Briefing October 19, 2021, data presented to the FDA demonstrated with one dose, the vaccine is 71% protective. Based on the recent findings in this publication as well as the growing body of literature, it appears that the single-dose J&J vaccine, although providing protection against infection and serious disease in most recipients, still has room for improvement. This may ultimately come in the form of a second dose of the same vaccine, as reported recently VRBPAC members said the J&J vaccine should be considered a two-dose product. A booster increases effectiveness to 94%. (mRNA as second dose may provide a better response)