TGIF

Today under COVID-19 News I summarize the upcoming report from CDC on “breakthrough” COVID-19 in fully vaccinated people. The next is an update on the review of the J&J vaccine still on pause.

Under Journal Review I start with an article on possible breakthrough rates of SARS-CoV-2 variants of concern in BNT162b2 mRNA vaccinated individuals. The next article looks at response to single dose Pfizer and AstraZeneca vaccines. The third article uses a patient registry to look at anticoagulants in hospitalized COVID-19 patients. The last article studied patients diagnosed as having cerebral venous thrombosis (CVT) in the 2 weeks after they received either their COVID-19 diagnosis or their first dose of the Pfizer/BioNTech or Moderna vaccine.

Have a wonderful weekend

Ed

COVID-19 News

5,800 COVID-19 Infections Detected Among 77 Million Fully Vaccinated People: CDC
Highlights

1. **Breakthrough infections are rare, but not unexpected.** No vaccine is 100 percent effective. Moderna's vaccine was 94.1 percent effective in a 30,000-person trial, and Pfizer's was 95 percent effective in a 38,000-person trial. The J&J vaccine was 100 percent effective at preventing COVID-19 hospitalization and death, 85 percent effective at protecting against severe cases and 72 percent effective at preventing moderate illness in U.S. trials.
2. Though the exact number of breakthrough cases to date is unknown, states reporting such cases show a 0.01 percent incidence rate.
3. **Most people who experience breakthrough infections do not have a severe case.**
4. **The reason breakthrough infections occur in rare instances is still unclear**.
5. These so-called breakthrough cases, which are defined as positive Covid-19 test results received at least two weeks after patients receive their final vaccine dose, represent 0.008% of the fully vaccinated population.
6. The experience so far is that the vaccine remains highly effective and those who did have breakthrough infections have had very mild and manageable illnesses.
7. Of the breakthrough cases identified by the CDC, more than 40% occurred in people older than 60, while 65% of the cases were in female patients. The CDC found that 29% of breakthrough infections were asymptomatic and 7% of patients experiencing a breakthrough infection were hospitalized. So far, 74 people have died after experiencing breakthrough infections. The agency is expected to publish some of these findings next week.

Comment: This report is very encouraging as vaccinated people begin to normalize their activities. No vaccine is perfect, but this report is very encouraging.

J&J Vaccine Update
In an April 14 emergency meeting, the Advisory Committee on Immunization Practices (ACIP) recommended continuing the suspension until more data become available. The CDC recommends that persons who experience a thrombotic event and thrombocytopenia after administration of the Johnson

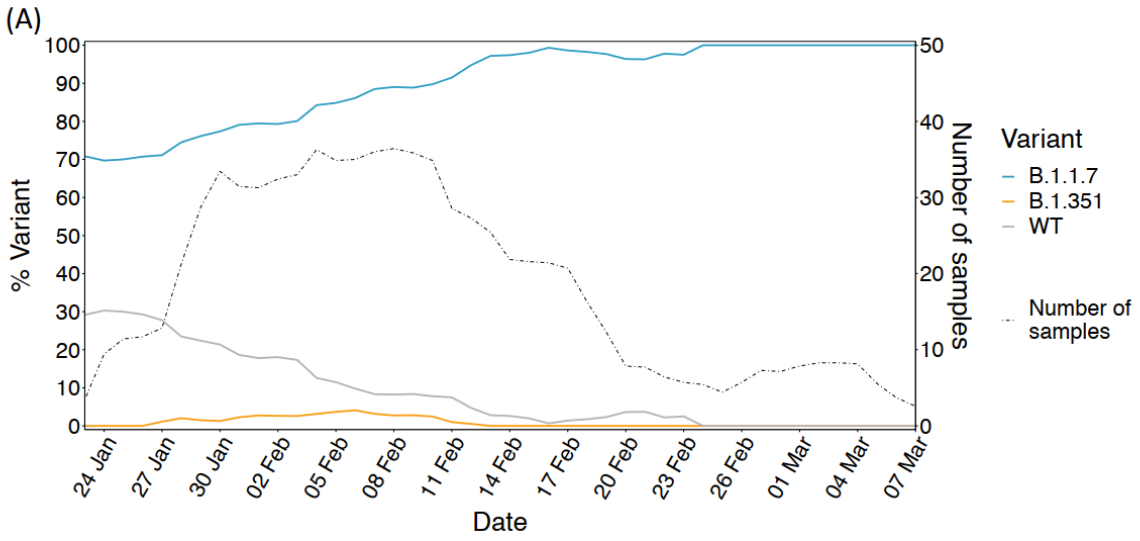
& Johnson vaccine be screened with a PF4 HIT enzyme-linked immunosorbent assay (ELISA) and referred to a hematologist. If the assay is positive or cannot be completed, heparin should not be used for thrombosis management; other anticoagulants and intravenous immune globulin should be considered instead.

Comment: See last article for some perspective on cerebral venous sinus thrombosis (CVST). CVST with thrombocytopenia has also been reported with the AstraZeneca adenovirus-based COVID-19 vaccine (not authorized for use in the US). With both adenovirus-based vaccines, incidence of CVST with thrombocytopenia has been associated with high serum levels of antibodies against platelet factor 4 (PF4)-polyanion complexes similar to those that occur in heparin-induced thrombocytopenia (HIT). No cases of CVST with thrombocytopenia have been associated with the ~180 million Pfizer and Moderna mRNA-based COVID-19 vaccine doses administered in the US. Despite this report, CVST is still very rare with a rate ~1 per million versus 125 out of every 1 million Americans between 18 and 48 who have died of COVID-19 since early last year.

Journal Review

Evidence for Increased Breakthrough Rates of SARS-CoV-2 Variants of Concern in BNT162b2 mRNA Vaccinated Individuals
medRxiv published online April 6, 2021
doi.org/10.1101/2021.04.06.21254882
The investigators performed a case-control study done in Israel that examined whether BNT162b2 vaccinees (Pfizer) with documented SARS-CoV-2 infection were more likely to become infected with B.1.1.7 or B.1.351 compared with unvaccinated individuals.

Vaccinees infected at least a week after the second dose were disproportionally infected with B.1.351 (odds ratio of 8:1). [very small numbers] Those infected between two weeks after the first dose and one week after the second dose, were disproportionally infected by B.1.1.7 (odds ratio of 26:10), suggesting reduced vaccine effectiveness against both VOCs (variants of concern) under different dosage/timing conditions.



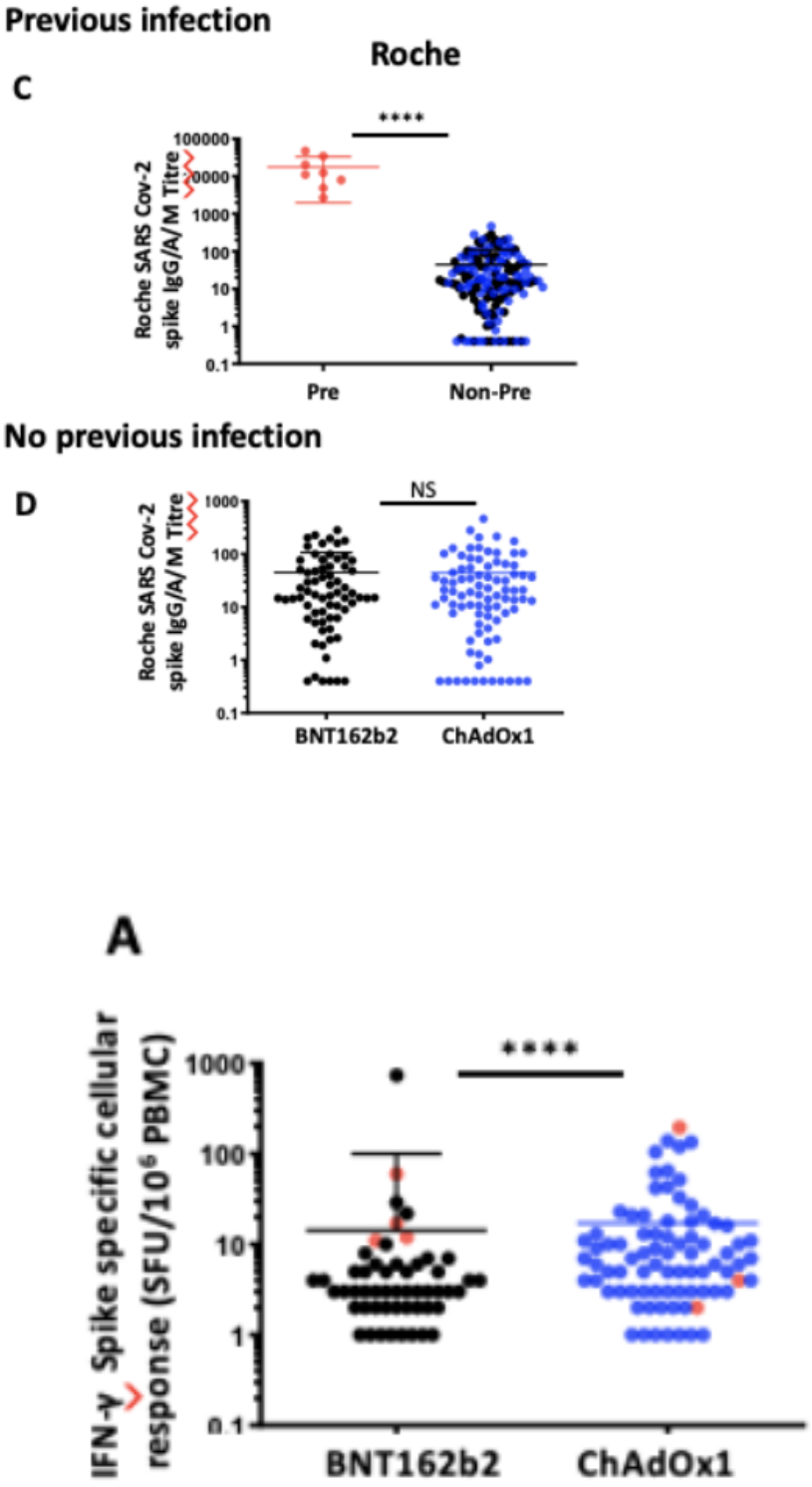
Comment: The B.1.351 incidence in Israel to-date remains low and vaccine effectiveness remains high against B.1.1.7, among those fully vaccinated under real world conditions. The main caveat of this study was the small sample size of both the WT (wild type) and B.1.351 variants. These small samples sizes are a product of a dramatic increase in frequency of the B.1.1.7 variant. The study design was not intended to deduce vaccine effectiveness against either variant, since they observe VOCs conditioned on infection, and did not measure absolute infection rates in the vaccinated or control population. Thus, they can only cautiously speculate on vaccine effectiveness against the B.1.1.7 and B.1.351 strains from these dates. Previous real-world work has shown a remarkably high effectiveness of the BNT162b2 vaccine starting a week after the second dose [Dagan N Engl J Med, 2021]. During the period of the latter study, B.1.1.7 likely rose to a high frequency, suggesting high vaccine effectiveness also against this strain. These results overall suggest that vaccine breakthrough infection may be more frequent with B.1.351, yet a combination of mass-vaccination with two doses coupled with non-pharmaceutical interventions control and has contained spread. The study did not address whether the fully vaccinated Israelis with the South African variant - eight people in total - developed serious illness.

Single Vaccination with BNT162b2 or ChAdOx1 in Older People Induces Equivalent Antibody Generation but Enhanced Cellular Responses After ChAdOx1

Lancet published online April 13, 2021

The investigators recruited 165 participants aged 80+ years who had received a single dose of either Pfizer or AstraZeneca vaccine and studied the adaptive immune response at 5 weeks.

Antibody responses against spike protein were detectable in 93% and 87% of mRNA or ChAdOx1 recipients respectively. Spike-specific T cell responses were observed in 12% and 31% of mRNA or ChAdOx1 recipients respectively. Median responses were 3-fold higher in ChAdOx1 vaccinees at 2 vs 6 spots/million respectively ($p=<0.0001$). Evidence of previous natural infection was seen in 8 donors and associated with 691-fold and 4-fold increase in humoral and cellular immune response.



Comment: Single doses of either the BNT162b2 or ChAdOx1vaccine in older persons induce strong humeral response in most donors and was markedly increased with prior infection. Cellular responses, however, were weaker, with ChAdOx1vaccine showing a stronger response. The mechanisms that lead to improved cellular response are not clear but may potentially relate to an adjuvant effect from the

adenovirus vector. Cellular responses were somewhat lower than has been reported for younger donors after single dose vaccination and this may reflect the impact of immune senescence in the older population. Cellular-specific immune responses may also be of value in supporting and maintaining humoral immunity over time. This finding advocates for receiving the second dose to optimize the longer-term benefit of vaccination.

Anticoagulation Therapy in Patients with Coronavirus Disease 2019: Results from a Multicenter International Prospective Registry (Health Outcome Predictive Evaluation for Corona Virus Disease 2019 [HOPE-COVID19])

Crit Care Med published online April 2021
DOI: 10.1097/CCM.0000000000005010

The investigators used an observational registry. Data was from a cohort study of 5,838 patients with COVID-19 infection enrolled in the multicenter international Health Outcome Predictive Evaluation for Corona Virus Disease 2019 (HOPE-COVID19) Registry. All patients were diagnosed with COVID-19 according to WHO interim guidance through PCR testing. Among patients in the general population without previous anticoagulation therapy, anticoagulation was not associated with better survival rate (81% vs 81%; $p = 0.94$) but with higher risk of bleeding (2.7% vs 1.8%; $p = 0.03$). In this setting, lower mortality rates were associated with prophylactic parenteral anticoagulation when compared with therapeutic anticoagulation therapy including oral or IV administration.

However, among patients admitted with respiratory failure (49%, 2,859 patients, including 391 and 583 patients requiring invasive and noninvasive ventilation, respectively), anticoagulation started during hospitalization was associated with lower mortality rates (32% vs 42%; $p < 0.01$) (log-rank $p < 0.001$) and not significant higher risk of bleeding (3.4% vs 2.7%; $p = 0.3$). In this subset of patients, 40% received prophylactic dose and 11% therapeutic dose. Three-hundred ninety-one patients (14%) underwent invasive ventilation; of these, 154 received (39%) prophylactic dose anticoagulation and 110 (28%) therapeutic dose. Additional anticoagulation therapy was associated with lower mortality rates (53% vs 64%; $p = 0.05$) without increased rates of bleeding (9% vs 8%; $p = 0.88$)

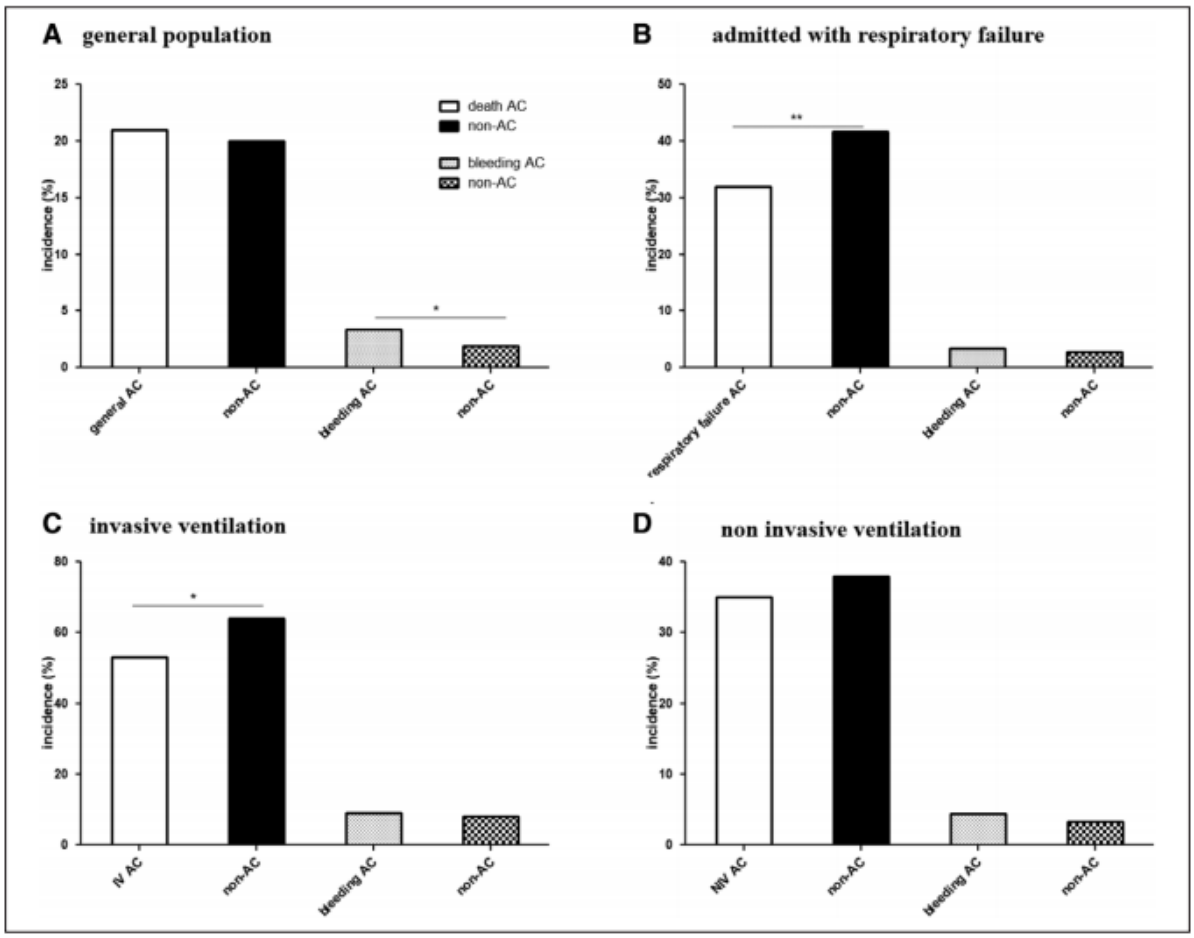


Figure 2. Rates of occurrence of death and bleeding in general population (**A**), naive subjects with respiratory failure (**B**), invasive ventilation (IV) (**C**), and noninvasive ventilation (NIV) (**D**), according to anticoagulant therapy during hospitalization. *Differences that are statistically different ($p < 0.05$). AC = anticoagulation.

Comment: Anticoagulation therapy in general population with COVID-19 was not associated with better survival rates but with higher bleeding risk. Better results were observed in patients admitted with respiratory failure and requiring invasive ventilation. Recent data from registries and autopsies suggested a potential role for coagulopathy in influencing outcome of COVID-19 patients. Data on standard of care for anticoagulation therapy in COVID-19 are limited and therapy is mainly based on physician choice. Some clinicians use prophylactic dosing and others intermediate- or full-dose (therapeutic) parenteral anticoagulation to prevent microvascular thrombosis. The study is a large multicenter international prospective registry, and not an RCT of different therapies. Timing of anticoagulation initiation during hospitalization was not prospectively collected, while anticoagulation dosage was not available in all patients. Most of the patients have 28 days follow-up, and no conclusion can be done for long-term outcome. The lack of several clinical and individual variables did not allow a propensity score matching analysis. The NIH COVID-19 guidelines state: Hospitalized nonpregnant adults with COVID-19 should receive prophylactic dose anticoagulation (AIII)**.** Anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside of the usual standard of care for patients without COVID-19 (AIII). There are currently insufficient data to recommend either for or against the use of thrombolytics or higher than the prophylactic dose of anticoagulation for VTE prophylaxis in hospitalized COVID-19 patients outside of a clinical trial.

Cerebral Venous Thrombosis: A Retrospective Cohort Study of 513,284 Confirmed COVID-19 Cases and a Comparison with 489,871 People Receiving a COVID-19 mRNA Vaccine

Published preprint server OSF

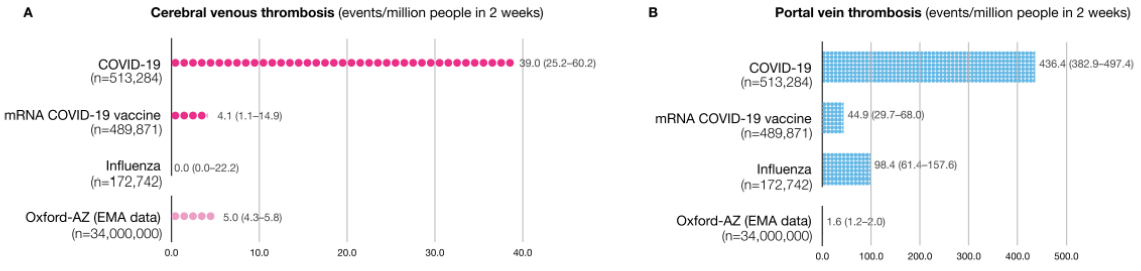
The researchers studied patients diagnosed as having cerebral venous thrombosis (CVT) in the 2 weeks after they received either their COVID-19 diagnosis or their first dose of the Pfizer/BioNTech or Moderna vaccine from Jan 20, 2020, to Mar 25, 2021. The researchers then compared those with rates of CVT in an unmatched cohort who had the flu and in the general population over the same period. They used an electronic health records network (TriNetX) of 81 million patients at 59 healthcare systems, mainly in the United States.

The risk of CVT was 8 to 10 times higher in the 513,284 patients with a COVID-19 diagnosis than in the 489,871 vaccinees and 100 times greater than in the general population. There were only two cases of CVT in the vaccine population, one after vaccination with the Pfizer vaccine and one after receipt of an undetermined mRNA vaccine. Patients younger than 30 years accounted for 30% of coronavirus-related CVT. The rate in the 172,742 flu patients was 0 per 1 million. Laboratory test results available in a subset of the COVID-19 patients provide preliminary evidence suggestive of raised D-dimer, lowered fibrinogen, and an increased rate of thrombocytopenia in the CVT and PVT groups.

CVT in all patient groups was rare, at 39 per 1 million COVID-19 patients and 4 in 1 million vaccine recipients. The risk of CVT after COVID-19 was about 10 times higher than those from a single dose of the Pfizer or Moderna vaccines and, according to the European Medicines Agency (EMA), about eight times higher than after the AstraZeneca/Oxford vaccine.

The death rate among COVID-19 patients was 20% for those who had CVT and 18.8% for portal vein (liver) thrombosis (PVT), which was assessed in the same populations. The incidence of PVT was 436.4 per 1 million people with COVID-19, 98.4 per 1 million among flu patients, and 44.9 per 1 million after vaccination with the Pfizer or Moderna vaccine. Twenty-two cases of PVT were diagnosed among vaccinees, 11 after the Pfizer vaccine, 2 after the Moderna vaccine, and 9 after a vaccine of an undetermined brand (either Pfizer or Moderna).

Figure 1 – Incidence of CVT (A) and PVT (B) per million people in the two weeks after different health events. The numbers in parentheses on the right of each bar represent the 95% confidence intervals. Data for the ChAdOx1 nCoV-19 vaccine are presented for reference and inferred from the European Medicines Agency data (posted 7 April 2021).



Comment: COVID-19—the actual disease—posed 8 to 10 times the threat of CVT than do COVID-19 vaccines. Recent reports of CVT after receipt of the AstraZeneca and Johnson & Johnson COVID-19 vaccines in young women have led to pauses in the rollouts of the two adenovirus vaccines in Europe (AstraZeneca) and the United States (J&J). This study showed the dramatic increase in risk of CVT from COVID-19 higher than the risk from vaccination even for those under 30. This should be considered when considering the balances between risks and benefits for vaccination especially with the viral vector vaccines. The authors could not verify the accuracy of the diagnosis of CVST [cerebral venous sinus thrombosis] and they were not able to look at the risks of CVST associated with the AstraZeneca vaccine in the same population. The investigators are not claiming that vaccines do not increase the risk at all compared to the risk in people who have not been vaccinated and have also not had COVID-19—but they say the CVT risk in people who have had COVID-19 is about 100 times the risk in the general population.