Good morning. Just when you thought things were beginning to calm down, we now have the pause of the J&J vaccine reviewed under COVID-19 News.

Under Journal Review, in keeping with the theme of vaccines, the first article looks at the mechanism of this rare thrombotic event associated with the AstraZeneca vaccine. The second article showed previous history of SARS-CoV-2 infection was associated with an 84% lower risk of infection, with median protective effect observed 7 months following primary infection. The third article confirms emerging evidence of increased transmissibility of B.1.1.7. However, they did not identify an association of the variant with more severe disease. The last article confirms that the AstraZeneca vaccine still maintains strong protection against B.1.1.7 also shown with the mRNA vaccines.

Stay tuned for the ACIP hearing later today.

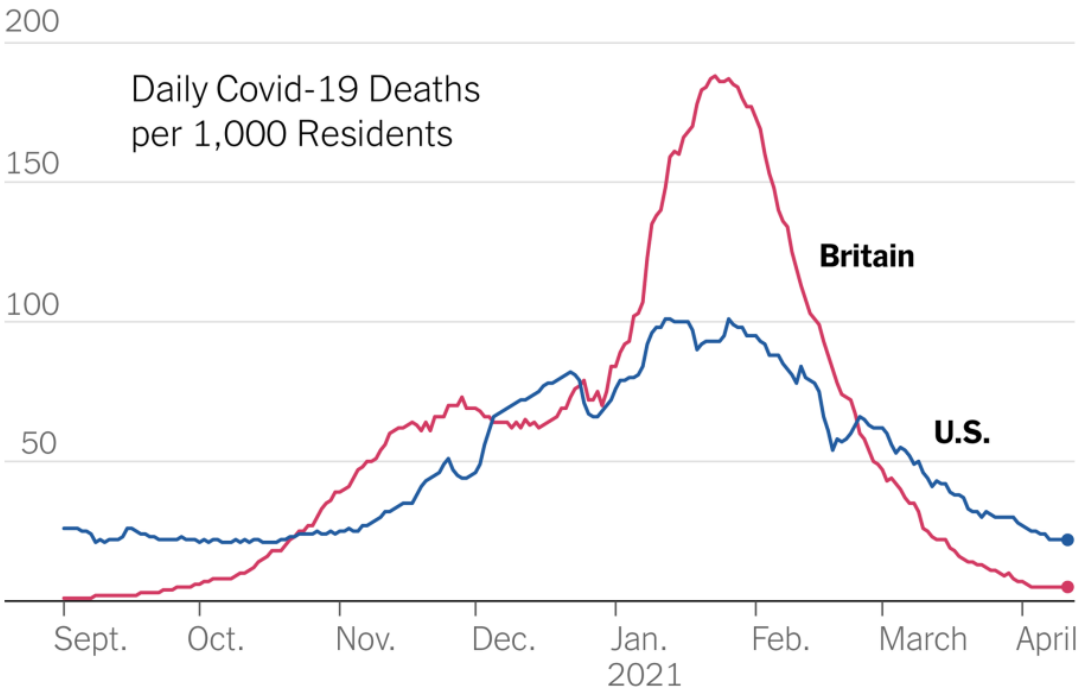
Ed

COVID-19 News

Joint CDC and FDA Statement on Johnson & Johnson COVID-19 Vaccine
As of April 12, more than 6.8 million doses of the Johnson & Johnson (Janssen) vaccine have been administered in the U.S. CDC and FDA are reviewing data involving six reported U.S. cases of a rare and severe type of blood clot in individuals after receiving the J&J vaccine. One patient has died. In these cases, a type of blood clot called cerebral venous sinus thrombosis (CVST) was seen in combination with thrombocytopenia. All six cases occurred among women between the ages of 18 and 48, and symptoms occurred 6 to 13 days after vaccination. Treatment of this specific type of blood clot is different from the treatment that might typically be administered. Usually, an anticoagulant is used to treat blood clots. In this setting, administration of an anticoagulant may be dangerous, and alternative treatments need to be given. See below.

CDC is convening a meeting of the Advisory Committee on Immunization Practices (ACIP) today to further review these cases and assess their potential significance. FDA will review that analysis as it also investigates these cases. Until that process is complete, they have recommended a pause in the use of this vaccine out of an “abundance of caution”.

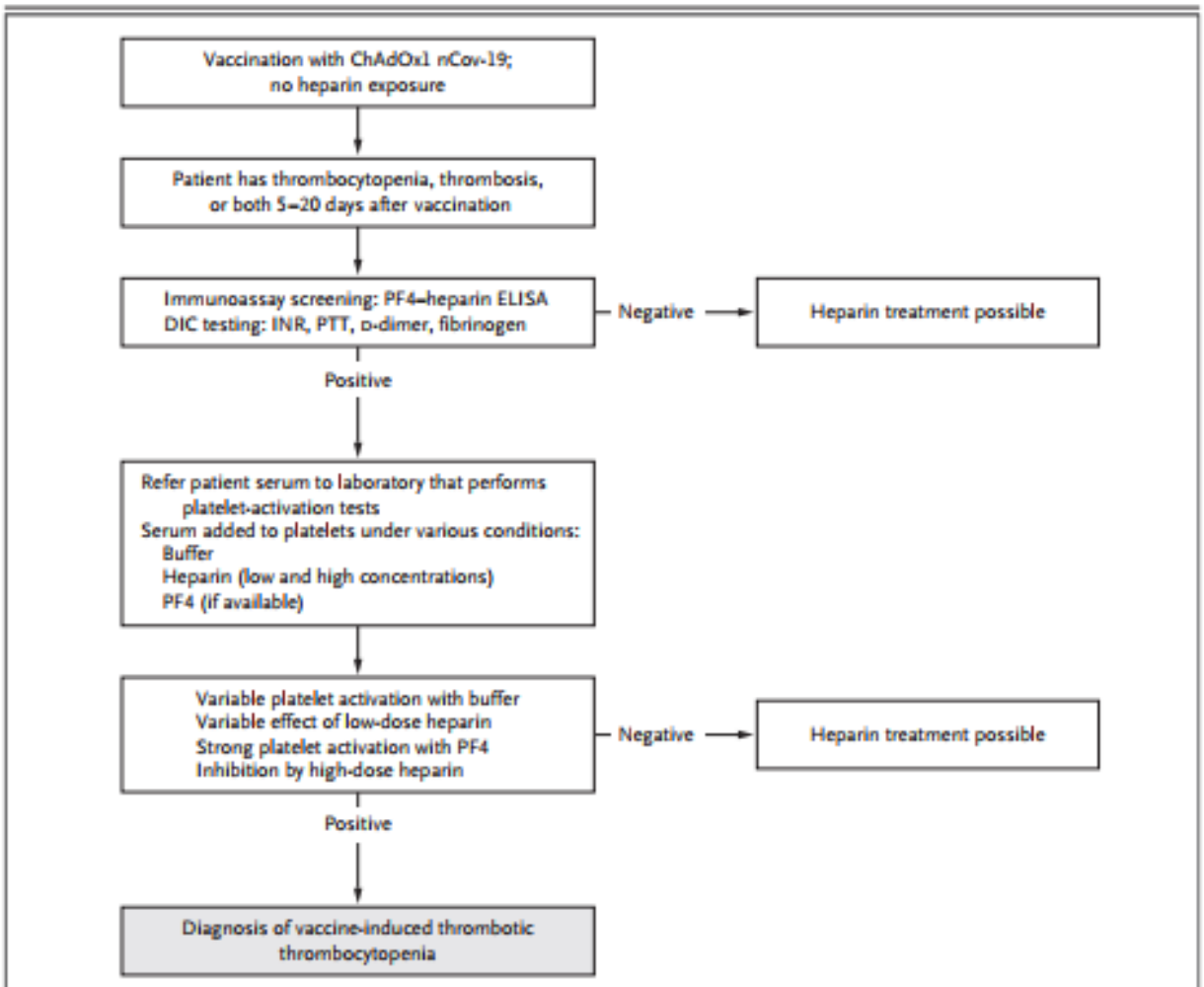
Comment: This risk appears to be similar to what has been reported with the AstraZeneca vaccine. Both vaccines are viral vector vaccines using a non-replicating adenovirus. The mechanism may be development of immune thrombotic thrombocytopenia mediated by platelet-activating antibodies against PF4. (see below) As with the AstraZeneca vaccine, this complication appears to affect younger women. The Europeans still feel the benefits outweigh the risks and have decided to use the vaccine in older people. Given the vaccination success in the UK (see below) I tend to agree with the Europeans and the importance of immunization on the pandemic overweigh this rare complication, but we need to continue to carefully monitor and follow the science. Consider this fact that the risk of clots is much higher with BCP and natural COVID-19! If we pull all medications for a 1 in >1 million chance of a serious side effect what will be left? On the other hand, it is a credit to our monitoring system that we can pick up such a rare event. We must follow the science as we investigate this rare event, but I have a concern people will be even more reluctant to be vaccinated.



Journal Review

Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination
N Engl J Med published online April 9, 2021
DOI: 10.1056/NEJMoa2104840
The investigators assessed the clinical and laboratory features of 11 patients in Germany and Austria in whom thrombosis or thrombocytopenia had developed after vaccination with ChAdOx1 nCov-19(AstraZeneca). They used a standard enzyme-linked immunosorbent assay to detect platelet factor 4 (PF4)-heparin antibodies and a modified (PF4-enhanced) platelet-activation test to detect platelet-activating antibodies under various reaction conditions. Included in this testing were samples from patients who had blood samples referred for investigation of vaccine-associated thrombotic events, with 28 testing positives on a screening PF4-heparin immunoassay.

Of the 11 original patients, 9 were women, with a median age of 36 years (range, 22 to 49). Beginning 5 to 16 days after vaccination, the patients presented with one or more thrombotic events, with the exception of 1 patient, who presented with fatal intracranial hemorrhage. Of the patients with one or more thrombotic events, 9 had cerebral venous thrombosis, 3 had splanchnic-vein thrombosis, 3 had pulmonary embolism, and 4 had other thromboses; of these patients, 6 died. All 28 patients who tested positive for antibodies against PF4-heparin tested positive on the platelet-activation assay in the presence of PF4 independent of heparin. Platelet activation was inhibited by high levels of heparin, Fc receptor-blocking monoclonal antibody, and immune globulin (10 mg per milliliter). Below are suggested diagnostic and therapeutic options for patients with suspected vaccine immune thrombotic thrombocytopenia.



Treatment Options	Comment
High-dose intravenous immune globulin (1 g per kg for 2 days)	Raises platelet count and decreases hypercoagulability (by analogy with autoimmune HIT); inhibits platelet activation by platelet-activating anti-PF4 antibodies (platelet Fcγ receptors)
Anticoagulants often used to treat heparin-induced thrombocytopenia	Direct oral Xa inhibitors (apixaban, rivaroxaban) Direct thrombin inhibitors (argatroban, bivalirudin) Indirect (antithrombin-dependent) Xa inhibitors: danaparoid (not available in U.S.), fondaparinux
Platelet transfusions	Avoid unless presence of bleeding (theoretical prothrombotic risk)
Vitamin K antagonist	Contraindicated during acute thrombocytopenia and disseminated intravascular coagulation (microthrombosis associated with protein C depletion)

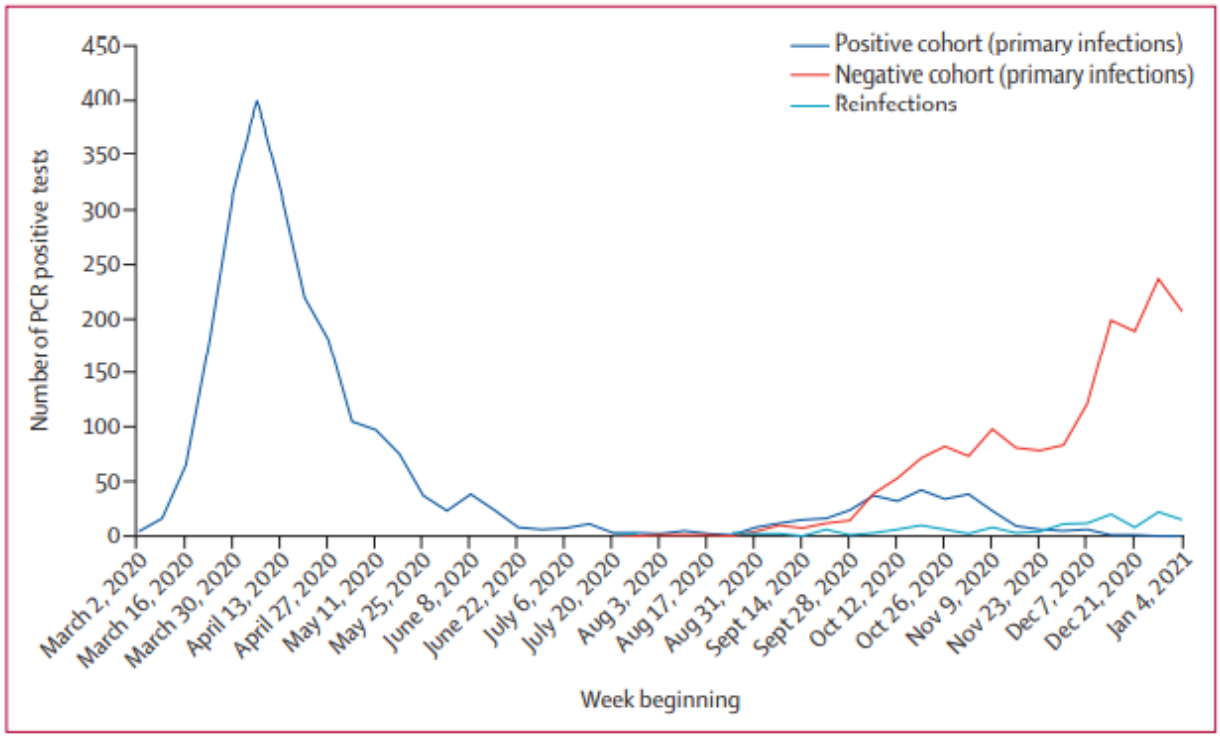
Comment: The clinical picture of moderate-to-severe thrombocytopenia and thrombotic complications at unusual sites beginning approximately 1 to 2 weeks after vaccination against SARS-CoV-2 with ChAdOx1 nCov-19 suggests a disorder that clinically resembles severe heparin-induced thrombocytopenia. Vaccination with ChAdOx1 nCov-19 can result in the rare development of immune thrombotic thrombocytopenia mediated by platelet-activating antibodies against PF4, which clinically mimics autoimmune heparin-induced thrombocytopenia. It is well known that adenovirus

binds to platelets and causes platelet activation. [Blood 2007; 109:2832-9] This week, J&J (another adenovirus vaccine) has reported a similar syndrome now under investigation by the FDA. See above.

SARS-CoV-2 Infection Rates of Antibody-Positive Compared with Antibody-Negative Health-Care Workers in England: A Large, Multicentre, Prospective Cohort Study (SIREN)
Lancet published online April 9, 2021
doi.org/10.1016/ S0140-6736(21)00675-9
This is a prospective cohort SARS-CoV-2 Immunity and Reinfection Evaluation (SIREN) study involving 25,661 workers at public hospitals throughout England who were tested for SARS-CoV-2 every 2 to 4 weeks and antibodies at enrollment and every 4 weeks. Volunteers also completed questionnaires on symptoms and exposures every 2 weeks.

Of the 25,661 participants, 32.3% were assigned to the baseline positive (possibly or probably previously infected) group, and 67.7% were assigned to the negative group. Of the 8,278 positive participants, 91.2% had SARS-CoV-2 antibodies at study enrollment, while 7.0% were negative for antibodies but had a previously positive antibody and/or COVID-19 test, and 1.8% had tested positive for COVID-19 but did not have linked antibody data.

From June 2020 to January 2021, 1.4% of the 8,278 participants who previously had COVID-19 were infected, compared with 9.8% of 17,383 initially coronavirus-naïve participants. Infections in the baseline-positive group peaked in the first week of April, while they peaked in the negative group the last week of December. Among the baseline-positive group, 50.3% of infections were symptomatic, with 32.3% involving usual COVID-19 symptoms. Among the baseline-negative cohort, 80.3% of infections were symptomatic, 66.1% of them involving usual COVID-19 symptoms.



Comment: This study showed previous history of SARS-CoV-2 infection was associated with an 84% lower risk of infection, with median protective effect observed 7 months following primary infection. This study shows that previous infection with SARS-CoV-2 induces effective immunity to future infections in most individuals. Now add prior infected people now getting at least on dose of a vaccine this will further lower the risk of reinfection.

Genomic Characteristics and Clinical Effect of the Emergent SARS-CoV-2 B.1.1.7 Lineage in London, UK: A Whole-Genome Sequencing and Hospital-Based Cohort Study
Lancet Infect Dis published online April 12, 2021
doi.org/10.1016/ S1473-3099(21)00170-5
This is a cohort study, based on samples positive for SARS-CoV-2 on PCR that were collected from Nov 9, 2020, for patients acutely admitted to one of two hospitals on or before Dec 20, 2020, in London, UK, were sequenced and analyzed for the presence of VOC (variant of concern)-defining mutations. We fitted Poisson regression models to investigate the association between B.1.1.7 infection and severe disease (defined as point 6 or higher on the WHO ordinal scale within 14 days of symptoms or positive test) and death within 28 days of a positive test and did supplementary genomic analyses in a cohort of chronically shedding patients and in a cohort of remdesivir-treated patients. Viral load was compared by proxy, using PCR cycle threshold values and sequencing read depths.

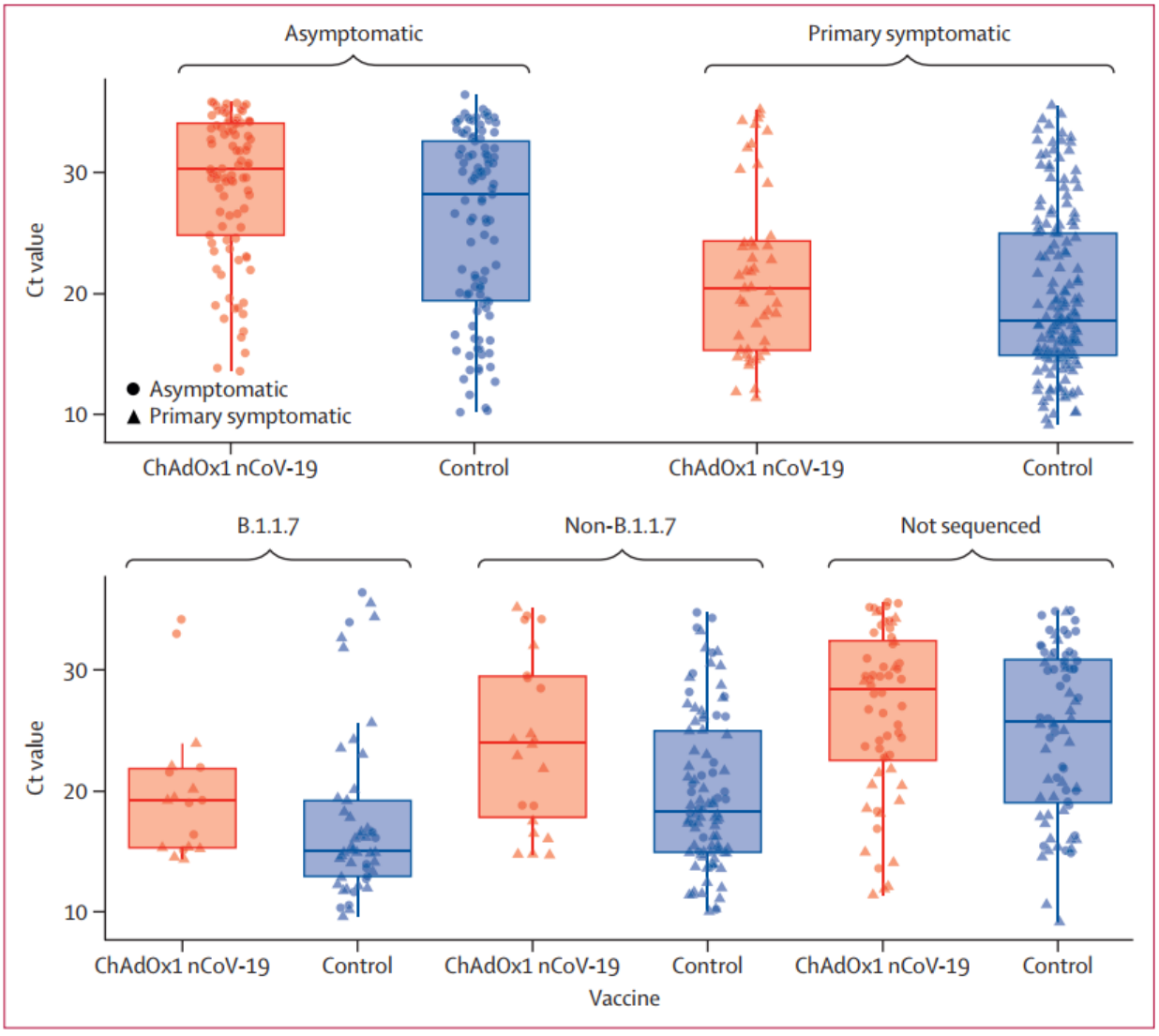
Of 496 patients with samples positive for SARS-CoV-2 on PCR and who met inclusion criteria, 341 had samples that could be sequenced. 198 (58%) of 341 had B.1.1.7 infection and 143 (42%) had non-B.1.1.7 infection. They found no evidence of an association between severe disease and death and lineage (B.1.1.7 *vs* non-B.1.1.7) in unadjusted analyses (prevalence ratio [PR] 0·97 [95% CI 0·72–1·31]), or in analyses adjusted for hospital, sex, age, comorbidities, and ethnicity (adjusted PR 1·02 [0·76–1·38]). They detected no B.1.1.7 VOC-defining mutations in 123 chronically shedding immunocompromised patients or in 32 remdesivir-treated patients. Viral load by proxy was higher in B.1.1.7 samples than in non-B.1.1.7 samples, as measured by cycle threshold value (mean 28·8 [SD 4·7] *vs* 32·0 [4·8]; p=0·0085) and genomic read depth (1280 [1004] *vs* 831 [682]; p=0·0011).

Comment: This report confirmed emerging evidence of increased transmissibility of B.1.1.7, by using increased virus load as a proxy for B.1.1.7 transmissibility. However, they did not identify an association of the variant with severe disease in this hospitalized cohort. Prior to this publication, two independent unpublished studies from the London School of Hygiene & Tropical Medicine and Imperial College London (both in the UK) detected a relative hazard of death of 1·35 (95% CI 1·08–1·68), and a case fatality rate of 1·35 (1·18–1·56). However, these population cohort studies, based predominately on community testing, were limited by the data available, with a low percentage of reported deaths, potential variation in case ascertainment, and transmission-setting bias. Further updates by NERVTAG include an unpublished analysis of patients admitted to hospital showing no significant increase in mortality associated with B.1.1.7.

Efficacy of ChAdOx1 nCoV-19 (AZD1222) Vaccine Against SARS-CoV-2 Variant of Concern 202012/01 (B.1.1.7): An Exploratory Analysis of a Randomised Controlled Trial
Lancet 2021; 397: 1351–62
doi.org/10.1016/ S0140-6736(21)00628-0
Volunteers (aged ≥18 years) who were enrolled in phase 2/3 vaccine efficacy studies in the UK, and who were randomly assigned (1:1) to receive ChAdOx1 (AstraZeneca) or a meningococcal conjugate control (MenACWY) vaccine, provided upper airway swabs on a weekly basis and also if they developed symptoms of COVID-19 disease (a cough, a fever of 37·8°C or higher, shortness of breath, anosmia, or

ageusia). Swabs were tested by NAAT for SARS-CoV-2 and positive samples were sequenced through the COVID-19 Genomics UK consortium. Neutralizing antibody responses were measured using a live virus microneutralization assay against the B.1.1.7 lineage and a canonical non-B.1.1.7 lineage (Victoria-Wuhan). The efficacy analysis included symptomatic COVID-19 in seronegative participants with a NAAT positive swab more than 14 days after a second dose of vaccine. Vaccine efficacy was calculated as 1-relative risk (ChAdOx1 *vs* MenACWY groups) derived from a robust Poisson regression model.

Of 8534 participants in the primary efficacy cohort, 6636 (78%) were aged 18–55 years and 5065 (59%) were female. Between Oct 1, 2020, and Jan 14, 2021, 520 participants developed SARS-CoV-2 infection. 1466 NAAT positive nose and throat swabs were collected from these participants during the trial. Of these, 401 swabs from 311 participants were successfully sequenced. Laboratory virus neutralization activity by vaccine-induced antibodies was lower against the B.1.1.7 variant than against the Victoria lineage (geometric mean ratio 8·9, 95% CI 7·2–11·0). Clinical vaccine efficacy against symptomatic NAAT positive infection was 70·4% (95% CI 43·6–84·5) for B.1.1.7 and 81·5% (67·9–89·4) for non-B.1.1.7 lineages.



Comment: The B.1.1.7 variant is currently responsible for the majority of COVID-19 disease in the UK (and now the US). This publication showed ChAdOx1 was efficacious against both the B.1.1.7 variant and non-B.1.1.7 variants. Furthermore, vaccination reduced viral load and length of NAAT positivity against both B.1.1.7 and non-B.1.1.7 lineages. [remember higher Ct lower viral load] Neutralization assays have showed that sera from BNT162b2 (Pfizer) and ChAdOx1 vaccinees had a 2·0-3·3 times reduction in neutralization activity against B.1.1.7. Despite the large reduction in measured live neutralizing activity against B.1.1.7 virus, the vaccine still provided strong protection against B.1.1.7 variant disease, [especially severe disease and deaths] with the lower bound of the 95% CI above the 30% threshold recommended by WHO. In line with previously published data, protection was also shown against the non-B.1.1.7 strains, the majority of which were due to the B.1.1.7 lineage. Real world experience in the UK supports the use of ChAdOx1 in mass vaccination programs to both prevent symptomatic B.1.1.7 disease and reduce the opportunity for viral transmission. See graph above on deaths in UK and US.