Good morning

Today under COVID News an update on the Astra Zeneca vaccine and a new mutant (E484K)

Under Journal Review: First a nice systemic review on long term effects of COVID-19. The second article is an interim analysis of the phase 3 trial of Gam-COVID-Vac (Sputnik V) It actually looks pretty good! The last article is a fascinating study looking at vaccine response between seropositive individuals and seronegative individuals. Individuals who already have had COVID-19 probably only need one dose and vaccine response is greater than natural disease.

Have a wonderful day

Ed

COVID-19 News

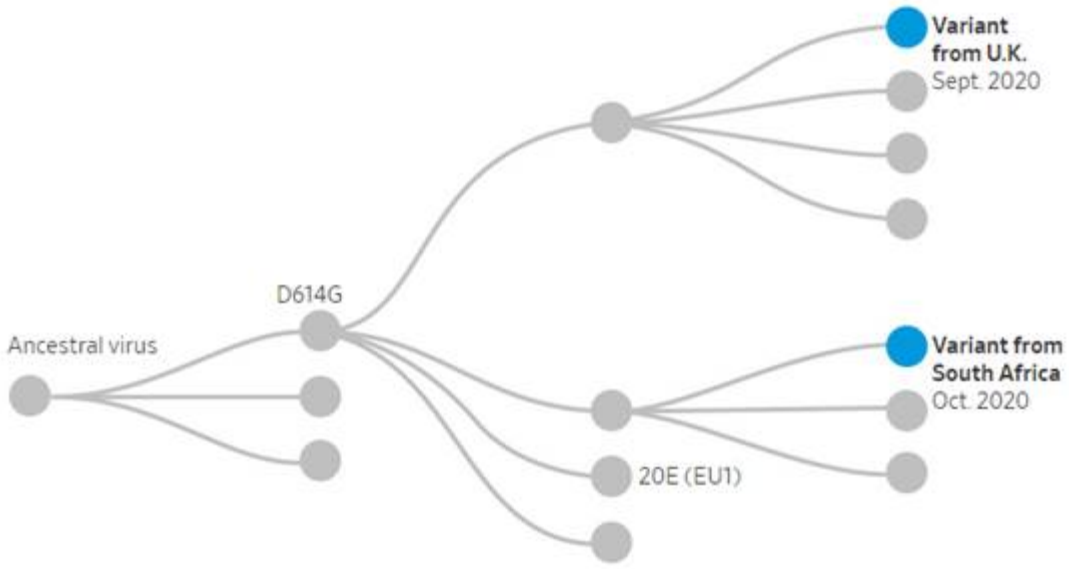
Astra Zeneca Vaccine
Researchers from the University of Oxford said Tuesday its Covid-19 vaccine could have a substantial effect on curbing virus transmission after one dose, and said that spacing doses apart by as long as three months improved effectiveness, according to data adding to previously published finding. [seems weird to me] Oxford said the vaccine may reduce symptomatic transmission of the virus by 67%, based on positive swab tests of vaccinated trial volunteers after a single dose, though those swab tests were only done in the UK, showed that effectiveness against symptomatic Covid-19 was well-sustained at 76% from 22 days after the first dose and until 90 days later. The data build on results from December, and include data involving more than 17,000 volunteers in Oxford-run late-stage trials in the UK, Brazil, and South Africa. Oxford said Tuesday that trial participants showed 82.4% effectiveness after receiving two doses spaced 12 weeks apart, compared with just 54.9% if the doses were spaced less than six weeks apart. [does not make sense to me] They said protection wasn't reduced over a three-month period. The additional data are based on results up to Dec. 7 and don't address levels of effectiveness against newer variants common in the UK and South Africa. Data in coming days are expected to shed light on how well the vaccine protects against those fast-spreading versions of the virus.

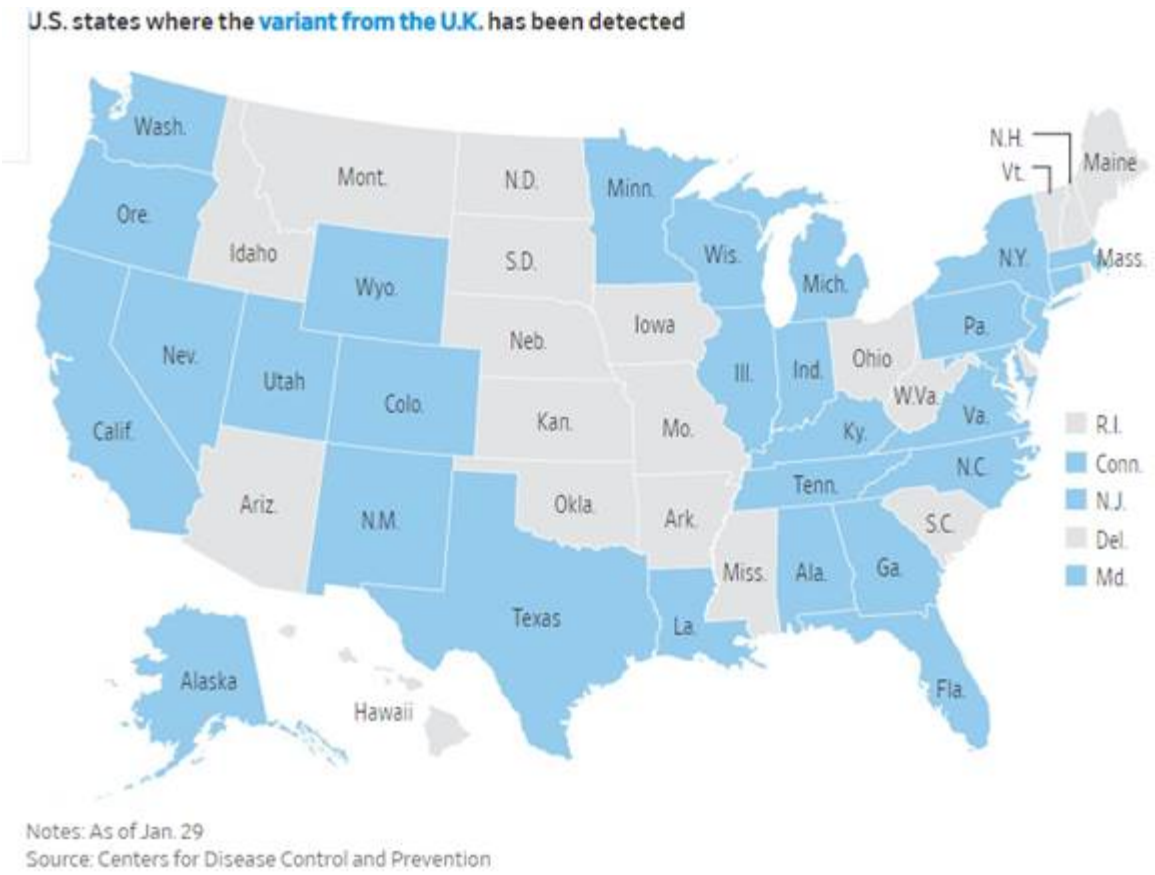
Comment: Not peered review and many unanswered questions!

New UK Mutant-E484K
UK authorities say they have discovered a potentially new version of the country's more-contagious coronavirus variant (B.1.17) with a new mutation (E484K)—one also detected in strains in South Africa and Brazil—that appears to make some vaccines less effective. Researchers say they have discovered 11 people around the southwest city of Bristol infected with the UK's more transmissible B.1.1.7 variant that also has the E484K mutation. The additional mutation, identified by genomic testing, appears to have arisen independently in both the UK variant and its predecessor, since there are no known links to international travel among the cases and they don't appear to be linked to a single infection. The additional mutation, known as E484K, is part of variants that have driven powerful new waves of infections in South Africa and Brazil. Scientists believe it protects the virus from antibodies triggered by vaccines or earlier COVID-19 infections by changing the shape of the virus's spike protein.

Recent clinical trials in South Africa showed that the not-yet-authorized shots developed by Novavax Inc. and Johnson & Johnson were less effective at preventing Covid-19 there compared with clinical trials in the US and the UK. Moderna Inc. and Pfizer Inc. have said that based on laboratory studies, they expect their vaccines to still work against variants with the E484K mutation. Moderna and Novavax have said that they are already working to update their vaccines to better tackle the South African variant.

Comment: On the surface things may appear bleak, but I view the ability to detect and potentially modify vaccines very encouraging. In addition, it still appears currents vaccines have a good efficacy against severe COVID-19. What bothers me more are the vaccine skeptics (like the mask skeptics), a sign of mistrust in public health and the government. If we do not get vaccinated against this pandemic we will only prolong and select for further mutations.



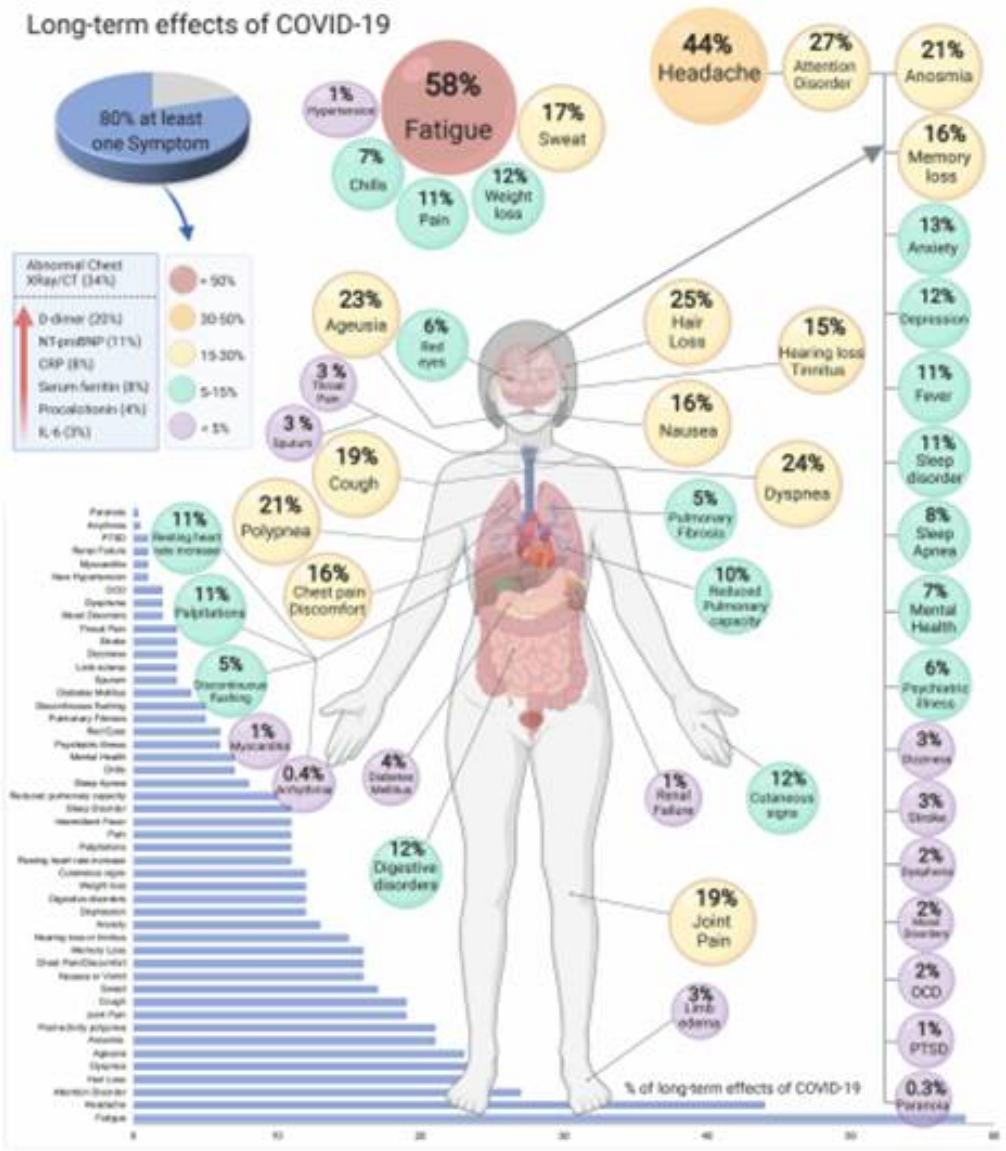


Journal Reviews

More than 50 Long-Term Effects of COVID-19: A Systematic Review and Meta-Analysis
medRxiv published online January 29, 2021
doi: https://doi.org/10.1101/2021.01.27.21250617
This is a systematic review and meta-analysis to identify studies assessing long term effects of COVID-19 and estimates the prevalence of each symptom, sign, or laboratory parameter of patients at a post-COVID-19 stage. PubMed and Medline and Embase were searched by two independent researchers. All articles with original data for detecting long term COVID-19 published before 1st of January 2021 and with a minimum of 100 patients were included. For effects reported in two or more studies, meta-analyses using a random-effects model were performed using the MetaXL software to estimate the pooled prevalence with 95% CI. Heterogeneity was assessed using I 2 statistics. The Preferred Reporting Items for Systematic Reviewers and Meta-analysis (PRISMA) reporting guideline was followed.

A total of 18,251 publications were identified, of which 15 met the inclusion criteria. The prevalence of 55 long term effects was estimated, 21 meta-analyses were performed, and 47,910 patients were included. The follow-up time ranged from 15 to 110 days post-viral infection. The age of the study participants ranged between 17 and 87 years. It was estimated that 80% (95% CI 65-92) of the patients that were infected with SARS-CoV-2 developed one or more long-term symptoms. The five most common symptoms were fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%), and dyspnea (24%). All meta-analyses showed medium (n=2) to high heterogeneity (n=13). To have a better understanding, future studies need to stratify by sex, age, previous comorbidities, severity of COVID-19

(ranging from asymptomatic to severe), and duration of each symptom. During follow-up, 34% of patients had an abnormal chest x-ray or CT. Elevated markers also were seen, including D-dimer (20%), NT-proBNP (11%), CRP (8%), serum ferritin (8%), procalcitonin (4%), and IL-6 (3%). Other lingering symptoms were pulmonary (cough, chest discomfort, reduced pulmonary diffusing capacity, sleep apnea, pulmonary fibrosis), cardiovascular (arrhythmias, myocarditis), or neurologic or psychiatric (memory loss, depression, anxiety, sleep disorders).



Comment: The Daily Briefing on January 13th reviewed a paper in Lancet (doi.org/10.1016/ S0140-6736(20)32656-8) that showed at 6 months after acute infection, COVID-19 survivors were mainly troubled with fatigue or muscle weakness, sleep difficulties, and anxiety or depression. Patients who were more severely ill during their hospital stay had more severe impaired pulmonary diffusion capacities and abnormal chest imaging manifestations. Reviewed. To have a better understanding, future studies need to stratify by sex, age, previous comorbidities, severity of COVID-19 (ranging from

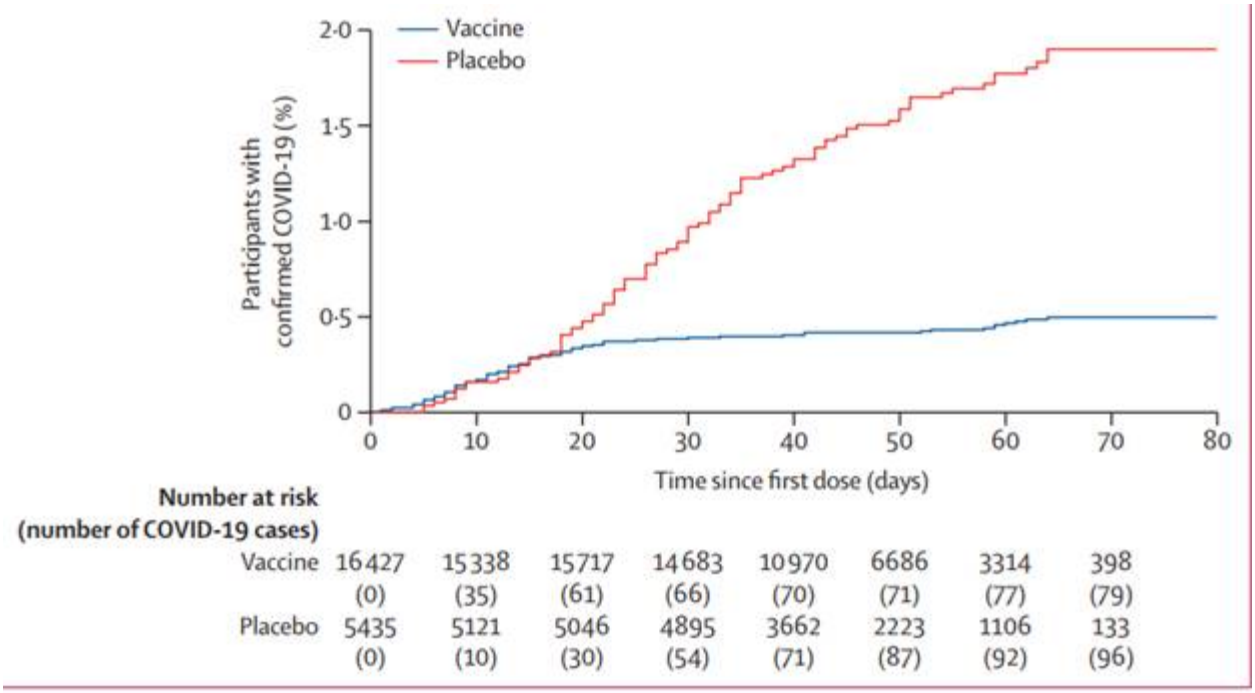
asymptomatic to severe), and duration of each symptom. Preventive measures, rehabilitation techniques, and clinical management strategies designed to address prevalent long-term effects of COVID-19 are urgently needed.

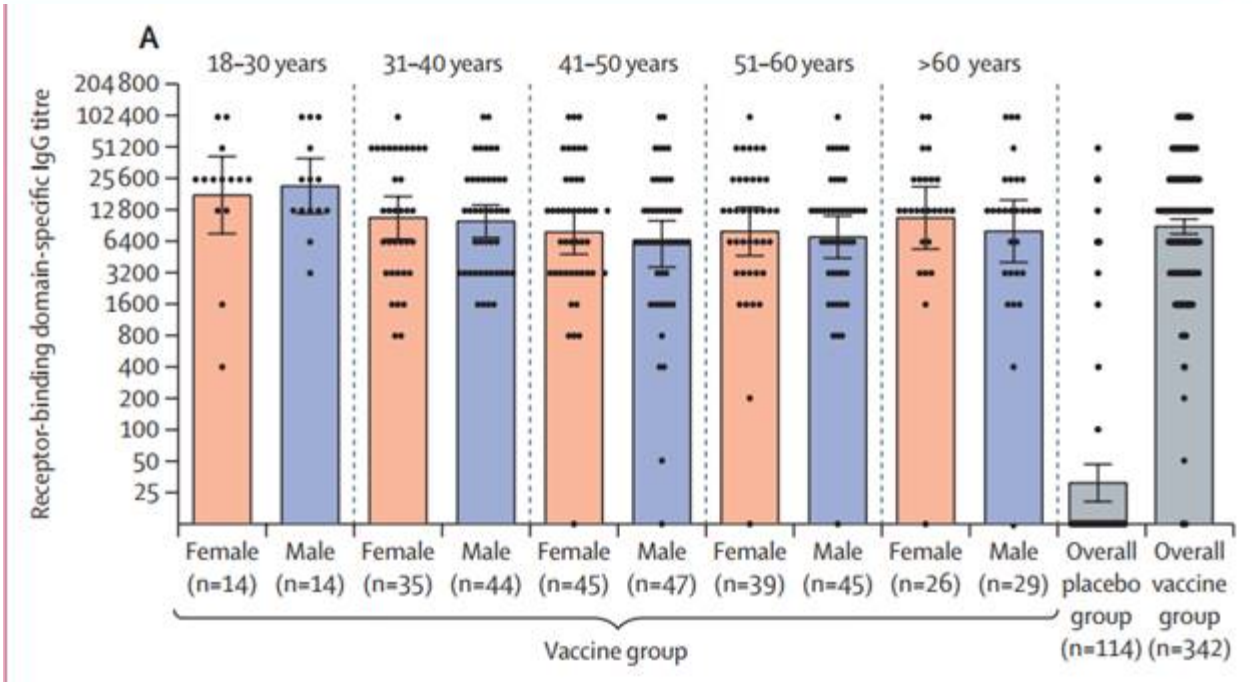
Safety and Efficacy of an rAd26 and rAd5 Vector-Based Heterologous Prime-Boost COVID-19 Vaccine: An Interim Analysis of a Randomised Controlled Phase 3 Trial in Russia

Lancet published online February 2, 2021
article provided by Josh Septimus
doi.org/10.1016/ S0140-6736(21)00234-8

Adenoviral vector delivered antigens are known to induce both cellular and humoral immunity after a single immunization. A heterologous recombinant adenovirus (rAd)-based vaccine, Gam-COVID-Vac (Sputnik V), showed a good safety profile and induced strong humoral and cellular immune responses in participants in phase 1/2 clinical trials. Here, the investigators report preliminary results on the efficacy and safety of Gam-COVID-Vac from the interim analysis of this phase 3 trial.

They performed a randomized, double-blind, placebo-controlled, phase 3 trial at 25 hospitals and polyclinics in Moscow, Russia. They included participants aged at least 18 years, with negative SARS-CoV-2 PCR and IgG and IgM tests, no infectious diseases in the 14 days before enrolment, and no other vaccinations in the 30 days before enrollment. Participants were randomly assigned (3:1) to receive vaccine or placebo. The vaccine was administered (0.5 mL/dose) intramuscularly in a prime-boost regimen: a 21-day interval between the first dose (rAd26) and the second dose (rAd5), both vectors carrying the gene for the full-length SARS-CoV-2 glycoprotein S. The primary outcome was the proportion of participants with PCR-confirmed COVID-19 from day 21 after receiving the first dose. Between Sept 7 and Nov 24, 2020, 21,977 adults were randomly assigned to the vaccine group (n=16501) or the placebo group (n=5476). 19,866 received two doses of vaccine or placebo and were included in the primary outcome analysis. From 21 days after the first dose of vaccine (the day of dose 2), 16 (0.1%) of 14,964 participants in the vaccine group and 62 (1.3%) of 4,902 in the placebo group were confirmed to have COVID-19; vaccine efficacy was 91.6% (95% CI 85.6-95.2). Most reported adverse events were grade 1 (7485 [94.0%] of 7,966 total events). The results also showed that the two-component vaccine Gam-COVID-Vac was able to induce a virus-neutralizing humoral response in participants older than 60 years. Furthermore, vaccine efficacy in this group of participants did not differ significantly from the efficacy of the age 18–60 years group. The observed vaccine effectiveness includes a 91.8% efficacy in volunteers older than 60 years.





Comment: This interim analysis of the phase 3 trial of Gam-COVID-Vac showed 91.6% efficacy against COVID-19 and was well tolerated. The limitations of the interim analysis of efficacy include the small sample sizes within age strata. Further data collection will allow for clarification of efficacy data within age groups. Furthermore, COVID-19 cases were detected through self-report of symptoms by participants, followed by a PCR test, so only symptomatic cases of COVID-19 are included in the efficacy analyses. Therefore, study did not examine asymptomatic disease similar to the initial trials with the Pfizer and Moderna vaccine. In this interim analysis, they were not able to assess duration of protection; median follow-up time was 48 days after first dose. Although the study enrolled participants with

comorbidities, not all risk groups were represented. There is a need to further investigate the vaccine in adolescents and children, as well as pregnant and lactating women. Most participants in this trial were white, so additional studies are necessary to investigate a more diverse cohort. This vaccine, along with other SARS-CoV-2 vaccines, helps to diversify the world SARS-CoV-2 vaccine pipeline. This is the third adenovirus vector vaccine in phase 3 trials. J&J just reported their preliminary results and Astra Zeneca is being used in the UK and Europe under EUA. In addition, adeno-vector vaccines, like Sputnik V, the one produced by AstraZeneca/University of Oxford and the J&J vaccine generate a robust response even after the first dose [J&J only recommends a single dose] and don't require ultra-cold storage.

Robust Spike Antibody Responses and Increased Reactogenicity in Seropositive Individuals after a Single Dose of SARS-CoV-2 mRNA Vaccine

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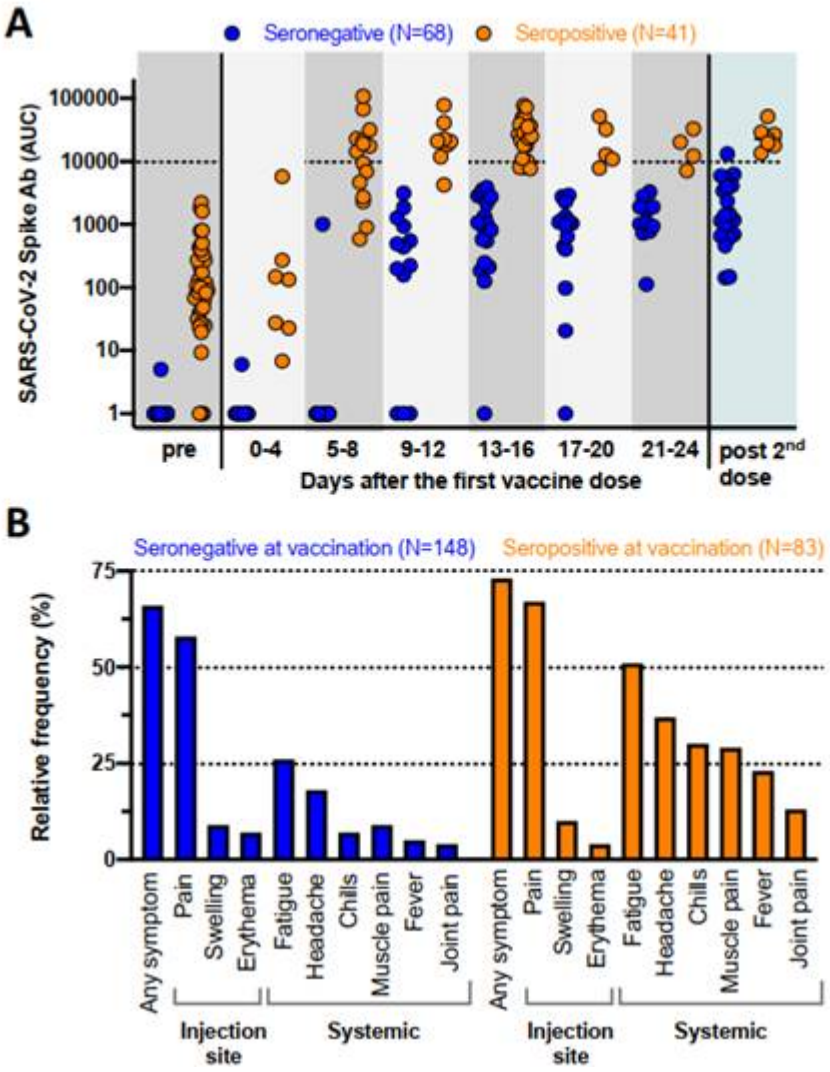
doi.org/10.1101/2021.01.29.21250653

The investigators report the antibody responses in 109 individuals with and without documented pre-existing SARS-CoV-2 immunity (seronegative: 68, seropositive: 41) who received their first vaccine dose in 2020 (mRNA). Repeated sampling after the first dose indicates that the majority of seronegative individuals mount variable and relatively low SARS-CoV-2 IgG responses within 9-12 days after vaccination (median AUC pre-vaccination: 1 [N=68]; 9-12 days: 439 [N=13]; 13-16 days: 1037 [N=15], 17-20 days: 1,037 [N=15], 21-24 days: 1,075 [N=11], and post 2nd dose 1,399 [N= 21]). In contrast, individuals with pre-existing SARS-CoV-2 immune responses (as evidenced by SARS-CoV-2 antibodies) rapidly develop uniform, high antibody titers within days of vaccination (median AUC pre vaccination: 91 [N=41]; 5-8 days: 14,208 [N=15], 9-12 days: 20,783 [N=8]; 13-16 days: 25,927 [N=20], 17-20 days: 12,661 [N=5], 21-24 days: 16,263 [N=4] and post 2nd dose: 22,509 [N=7]). The antibody titers of vaccinees with pre-existing immunity are not only 10-20 times higher than those of naïve vaccinees at the same time points ($p < 0.0001$, two tailed Mann Whitney test), but also exceed the median antibody titers measured in naïve individuals even after the second vaccine dose by more than 10-fold. Ongoing follow-up studies will show whether these early differences in immune responses are maintained over time. In addition, we compared frequency of local, injection side related as well as systemic reactions after the first dose of vaccination in 231 individuals (148 seronegative and 83 seropositive)

Overall, both vaccines are well tolerated without any side effects requiring additional medical attention. 159/231 of the participants completing the survey after the first dose experienced any kind of side effect (66% seronegative and 73% seropositive). Most common were localized injection site symptoms (e.g., pain, swelling and erythema), which occurred with equal frequency independent of the serostatus at the time of vaccination and resolved spontaneously within days of vaccination. Vaccine recipients with pre-existing immunity experienced systemic side effects with a significantly higher frequency than antibody naïve vaccinees (e.g., fatigue, headache, chills, fever, muscle or join pains, in order of decreasing frequency, $P < 0.001$ for all listed symptoms).



Comment: These findings suggest that a single dose of mRNA vaccine elicits very rapid immune responses in seropositive individuals with post-vaccine antibody titers that are comparable to or exceed titers found in naïve individuals who received two vaccinations. We also noted that vaccine reactogenicity after the first dose is substantially more pronounced in individuals with pre-existing immunity. These observations are in line with the first vaccine dose serving as a boost in naturally infected individuals providing a rationale for updating vaccine recommendations to consider a single vaccine dose to be sufficient to reach immunity. Bottom line – people who have already been infected (seropositive) with SARS-CoV-2 only need one dose of the mRNA vaccine.