Good morning.

Today under Covid-19 News I start with the CDC Update on COVID-19 pandemic in US. Next Merck has applied to the FDA Monday for EUA for Molnupiravir. The last item is a press release on research affiliated with the ZOE Covid Study app comparing natural infection, vaccination, and natural infection plus vaccination.

Under Journal Review, the first two articles look at immunity in convalescent individuals and convalescent individuals who also receive available mRNA vaccines. The third article studied the incidence of SARS-CoV-2 primary infection and reinfection among individuals who were infected during the first wave of the pandemic in Italy. The next article set out to compare incidence rates and clinical characteristics of SARS-CoV-2 infection among adults and children and estimated household infection risks within a prospective household cohort. The next article looks at virulence of Delta variant in Canada. The last article looks at Covid symptoms one year after natural infection.

Have a great day.

Ed

COVID-19 News

CDC Updates
Reported cases
The nation's current seven-day case average is 95,448, an 11.6 percent decrease from the previous week's average. This marks the third consecutive week the national case average has declined. However, five states -- Montana, Colorado, Minnesota, Michigan and Pennsylvania -- had at least 10% more new cases this past week compared to the previous week.

Hospitalizations
The current seven-day hospitalization average for Sept. 29 to Oct. 5 is 7,440, a 13.2 percent drop from the previous week's average.

Vaccinations
About 216.3 million people — 65.1 percent of the total U.S. population — have received at least one dose of the COVID-19 vaccine, and more than 186.6 million people, or 56.2 percent of the population, have gotten both doses. About 6.4 million booster doses in fully vaccinated people have been reported. The seven-day average number of vaccines administered daily was 948,921 as of Oct. 7, a 30.5 percent increase from the previous week.

Variants
Based on projections for the week ending Oct. 2, the CDC estimates the delta variant still accounts for more than 99 percent of all U.S. COVID-19 cases.

Deaths
The current seven-day death average is 1,431, down 8.4 percent from the previous week's average.

Merck asks FDA for EUA for Molnupiravir

Merck has applied to the FDA Monday for EUA for Molnupiravir. This would be the first pill to treat Covid-19. As reported in the Briefing [October 5, 2021], Molnupiravir given within 5 days of symptom onset reduced risk of hospitalization and death by 50%.

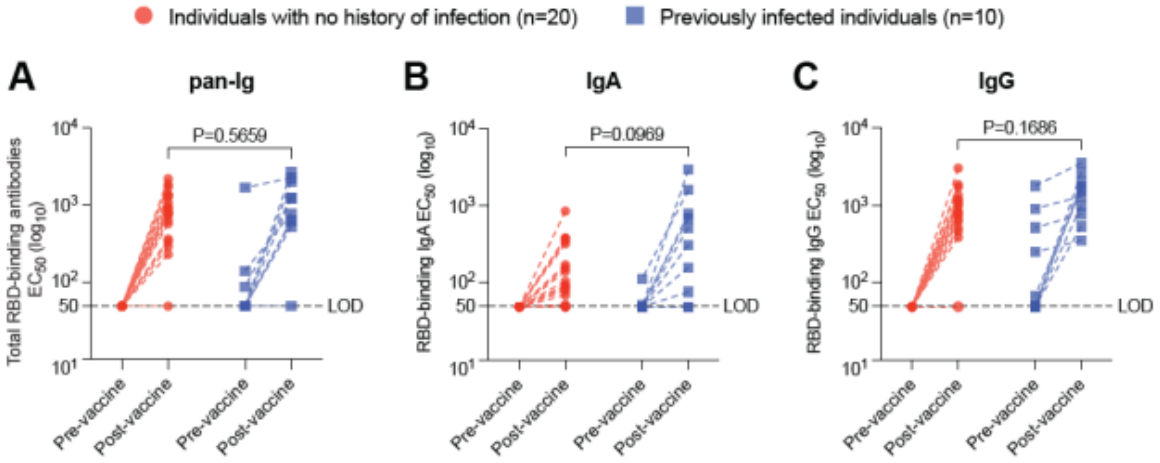
Comment: Molnupiravir is given twice per day for 5 days similar to oseltamivir. If EUA is granted, this is welcome addition to MCA which must be given via IV.

Fully Vaccinated and Had Covid-19
Last week via press release, researchers affiliated with the ZOE Covid Study app, which is for people in the U.K. to self-report symptoms and test results, said real-world infection followed by two doses of the Pfizer vaccine provided 94% protection up to six months after vaccination, compared with 80% protection from vaccination alone or 65% from only infection. The findings were based on more than 650,000 Covid-19 test results reported by app users. The findings have not been peer reviewed to date.

Comment: Several studies now suggest that people who have had natural Covid-19 and were fully vaccinated have strong protection, including against variants, and may not need a booster dose, but the research is preliminary. The studies suggest a Covid-19 exposure effectively serves as a dose of the vaccine or a primer for the immune response. Like a vaccine dose, the real-world infection prompts the immune system to generate the antibodies, memory B cells and T cells that can be recruited to defend against the virus in the future. However, some people with weakened immune systems or certain underlying medical conditions may still need a third dose. Another factor that people who were infected should weigh before getting vaccinated is whether getting two doses of an mRNA vaccine could raise their potential risk of myocarditis. If you are a young male, perhaps getting one dose of J&J may be preferred. Even if they get an mRNA vaccine, one dose may be adequate. Most cases of myocarditis occur after the second dose. [see articles below to provide additional perspective]

Journal Review

Previously Infected Vaccinees Broadly Neutralize SARS-CoV-2 Variants
medRxiv published online July 2021
https://doi.org/10.1101/2021.04.25.21256049
Naturally Enhanced Neutralizing Breadth Against SARS-CoV-2 One Year After Infection
Nature published online June 14, 2021; 595: 426–431
In the first article the authors compared the serum neutralizing antibody titers before and after two doses of the Pfizer vaccine in ten individuals who recovered from SARS-CoV-2 infection prior to vaccination to 20 individuals with no history of infection, against clinical isolates of B.1.1.7, B.1.351, P.1, and the original SARS-CoV-2 virus. Vaccination boosted pre-existing levels of anti-SARS-CoV-2 spike antibodies 10-fold in previously infected individuals, but not to levels significantly higher than those of uninfected vaccinees. However, neutralizing antibody titers increased in previously infected vaccinees relative to uninfected vaccinees against every variant tested: 5.2-fold against B.1.1.7, 6.5-fold against B.1.351, 4.3-fold against P.1, and 3.4-fold against original SARS-CoV-2. This small study indicates that Pfizer vaccine provides broad protection from SARS-CoV-2 variants in 33 individuals with previous infection.



In the second article researchers from Rockefeller University said that people who were infected with Covid-19 and later vaccinated with a messenger RNA vaccine saw 20 to 40 times greater immune response than those who weren't vaccinated. The mechanism underlying these broad-based responses involves ongoing antibody somatic mutation, memory B cell clonal turnover and development of monoclonal antibodies that are exceptionally resistant to SARS-CoV-2 RBD mutations, including those found in the variants of concern. In addition, B cell clones expressing broad and potent antibodies are selectively retained in the repertoire over time and expand markedly after vaccination.

Comment: The data from these two articles suggest that immunity in convalescent individuals will be very long lasting and that convalescent individuals who receive available mRNA vaccines will produce antibodies and memory B cells that should be protective against circulating SARS-CoV-2 variant. These articles and recent preliminary data found that hybrid immunity from infection and vaccination generally confers more immunity than vaccine-induced immunity alone, including against variants. These studies were done before Delta variant. [see next article]

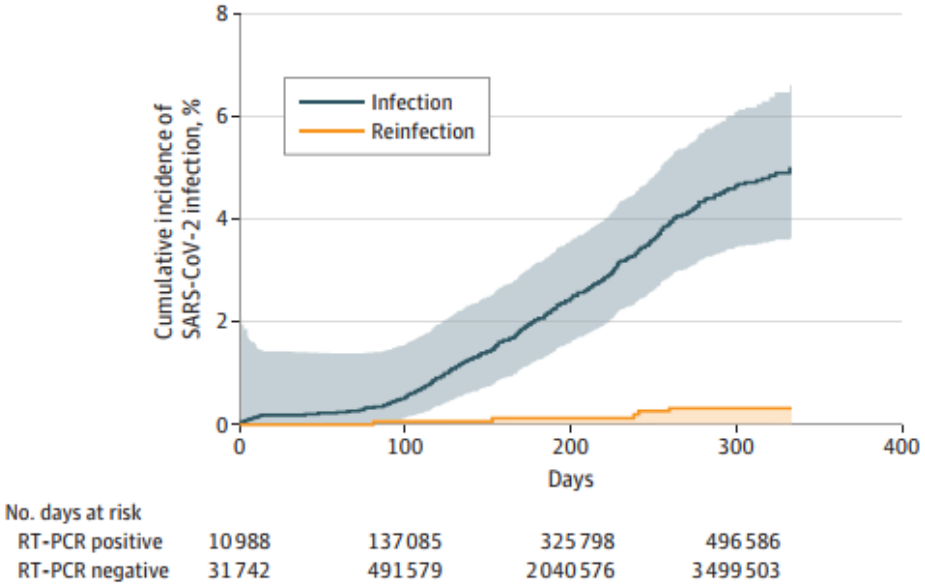
Assessment of SARS-CoV-2 Reinfection 1 Year After Primary Infection in a Population in Lombardy, Italy

JAMA Intern Med 2021; 181:1407-1408
doi:10.1001/jamainternmed.2021.2959

The investigators studied the incidence of SARS-CoV-2 primary infection and reinfection among individuals who, during the first wave of the pandemic in Italy (February to July 2020), underwent diagnostic PCR. Symptomatic and asymptomatic patients of any age, who were recruited in several screening and contact-tracing programs, were included. They defined cases (those with infection who were PCR-positive) and controls (those without infection who were PCR-negative) according to the WHO guidelines. Reinfections were defined by a second PCR positivity beyond 90 days after complete resolution of the first infection and with at least 2 consecutive negative test results between episodes.

During the follow-up (mean [SD], 280 [41] days) 5 reinfections (0.31%; 95% CI, 0.03%-0.58%) were confirmed in the cohort of 1579 positive patients. Most of these patients were evaluated, treated, and followed in hospitals or dedicated COVID-19 ambulatories. Only 1 was hospitalized, and 4 patients had a close relationship (2 patients work in hospitals, 1 patient underwent transfusions every week, and 1

patient retired in a nursing home) with health facilities. Of 13,496 persons who initially were not infected with SARS-CoV-2, 528 (3.9%; 95% CI, 3.5%-4.2%) subsequently developed a primary infection. The incidence density per 100,000 person days was 1.0 (95% CI, 0.5-1.5) for reinfections compared with 15.1 (95% CI, 14.5-15.7) for new infections. After analyzing the cumulative incidence during follow-up, they confirmed that the 2 cohorts were significantly different (hazard ratio, 0.06; 95% CI, 0.05-0.08; *P* < .001).



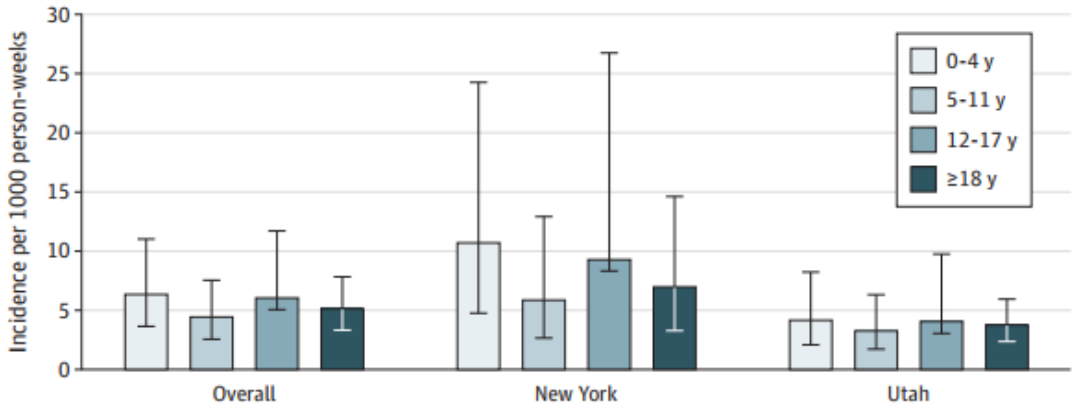
Comment: The study results suggest that reinfections are uncommon events and patients who have recovered from COVID-19 have a lower risk of reinfection. Natural immunity to SARS-CoV-2 appears to confer a protective effect for at least a year, which is similar to the protection reported in recent vaccine studies. However, this study ended before Alpha and Delta variants began to spread, and it is unknown how well natural immunity to the wild-type virus will protect against variants.

Incidence Rates, Household Infection Risk, and Clinical Characteristics of SARS-CoV-2 Infection Among Children and Adults in Utah and New York City, New York
JAMA Pediatr published online October 8, 2021 article provided by Flor Munoz
doi:10.1001/jamapediatrics.2021.4217
The investigators set out to compare incidence rates and clinical characteristics of SARS-CoV-2 infection among adults and children and estimated household infection risks within a prospective household cohort. Households with at least 1 child aged 0 to 17 years in selected counties in Utah and New York City, New York, were eligible for enrollment. From September 2020 through April 2021, participants self-collected midturbinate nasal swabs for PCR testing for SARS-CoV-2 and responded to symptom questionnaires each week. specimens with onset of COVID-19-like illness. For children unable to self-collect respiratory specimens, an adult caregiver collected the specimens.

A total of 1236 participants in 310 households participated in surveillance, including 176 participants (14%) who were aged 0 to 4 years, 313 (25%) aged 5 to 11 years, 163 (13%) aged 12 to 17 years, and 584 (47%) 18 years or older. Overall incidence rates of SARS-CoV-2 infection was 3.8 (95% CI, 2.4-5.9) and 7.7 (95% CI, 4.1-14.5) per 1000 person-weeks among the Utah and New York City cohorts, respectively. Site-adjusted incidence rates per 1000 person-weeks were similar by age group: 6.3 (95% CI, 3.6-11.0) for

children 0 to 4 years, 4.4 (95% CI, 2.5-7.5) for children 5 to 11 years, 6.0 (95% CI, 3.0-11.7) for children 12 to 17 years, and 5.1 (95% CI, 3.3-7.8) for adults (18 years). The asymptomatic fractions of infection by age group were 52%, 50%, 45%, and 12% among individuals aged 0 to 4 years, 5 to 11 years, 12 to 17 years, and 18 years or older, respectively. Among 40 households with 1 or more SARS-CoV-2 infections, the mean risk of SARS-CoV-2 infection among all enrolled household members were 52% (range, 11%-100%), with higher risks in New York City compared with Utah (80% [95% CI, 64%-91%] vs 44% [95% CI, 36%-53%]; *P* < .001).

Figure 2. SARS-CoV-2 Infection Incidences per 1000 Person-Weeks by Site and Age in Utah and New York City, New York, From September 2020 Through April 2021 (N = 1236)



Comment: Adults and children of all ages had similar risks of SARS-CoV-2 infection, but approximately half of SARS-CoV-2 infections among children were asymptomatic compared with a much smaller fraction among adults. In an excellent editorial by Flor Munoz she points out: "SARS-CoV-2 initially appeared to affect primarily older adults, who experienced the highest morbidity and mortality of COVID-19. As the pandemic evolved and children and adolescents were gradually allowed to resume social and school activities, and particularly with the relaxation of the use of public health measures such as masking and social distancing, the actual impact of SARS-CoV-2 in the pediatric population has become apparent. While relative to adults, children continue to be generally less affected from severe COVID-19, hospitalization, and death, the number of pediatric cases, hospitalizations, and complications such as multisystem inflammatory syndrome are not insignificant and continue to rise with the advent of the Delta variant in the United States." This study estimated that in households with at least 1 documented case of pediatric infection, the risk of infection among household members was 52% which is a high rate of transmission, and this was before the Delta variant. The evidence now demonstrates even very young children can transmit SARS-CoV-2. Flor appropriately points out these findings highlight the implications for pandemic control. As she points out there is a need for earlier inclusion of children in vaccine studies and vaccination strategies for their own protection, for protection of other children and the adults they are in contact with at home and in schools, and for the protection of the community. It is also imperative to include children in studies of preventive treatments such as monoclonal antibodies, antivirals, and other therapeutics for SARS-CoV-2. Individuals who participate in studies that require intensive follow-up may differ from the general population in their attitudes toward public health and science, which may influence behaviors associated with infection risk and prevention. If true, then the incidence rates from this study may underestimate community rates of infection. Persons of certain racial and ethnic backgrounds and low-income households were underrepresented in this cohort; therefore, incidence rates may not be generalizable to those populations since infection risks

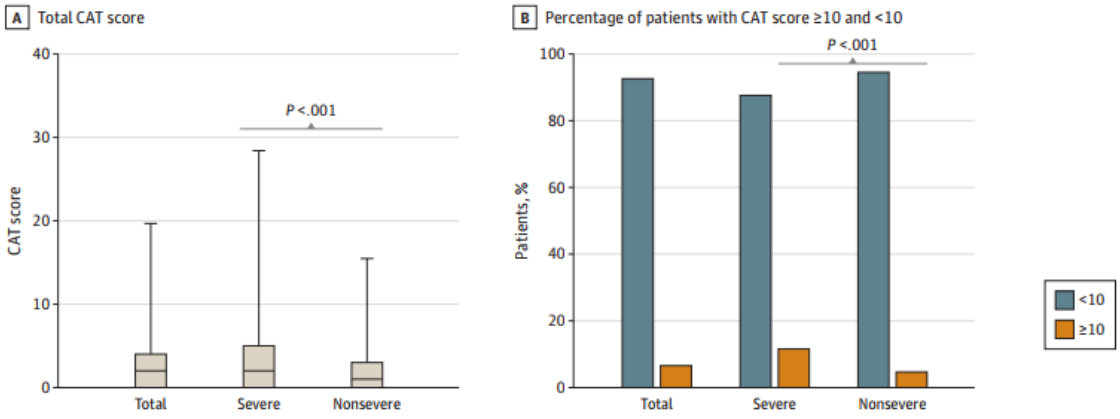
vary by race, ethnicity, or income level.

Evaluation of the Relative Virulence of Novel SARS-CoV-2 Variants: A Retrospective Cohort Study in Ontario, Canada
CMAJ published online October 4, 2021
doi: 10.1503/cmaj.211248
The investigators created a retrospective cohort of people in Ontario who tested positive for SARS-CoV-2 and were screened for VOCs, with dates of test reported between Feb. 7 and June 27, 2021. They constructed mixed-effect logistic regression models with hospitalization, ICU admission and death as outcome variables. They adjusted models for age, sex, time, vaccination status, comorbidities and pregnancy status.

Their cohort included 212,326 people. Compared with non-VOC SARS-2 CoV-2 strains, the adjusted elevation in risk associated with N501Y-positive variants was 52% (95% confidence interval [CI] 42%–63%) for hospitalization, 89% (95% CI 67%–117%) for ICU admission and 51% (95% CI 30%–78%) for death. Increased risk with the Delta variant was more pronounced at 108% (95% CI 78%–140%) for hospitalization, 235% (95% CI 160%–331%) for ICU admission and 133% (95% CI 54%–231%) for death.

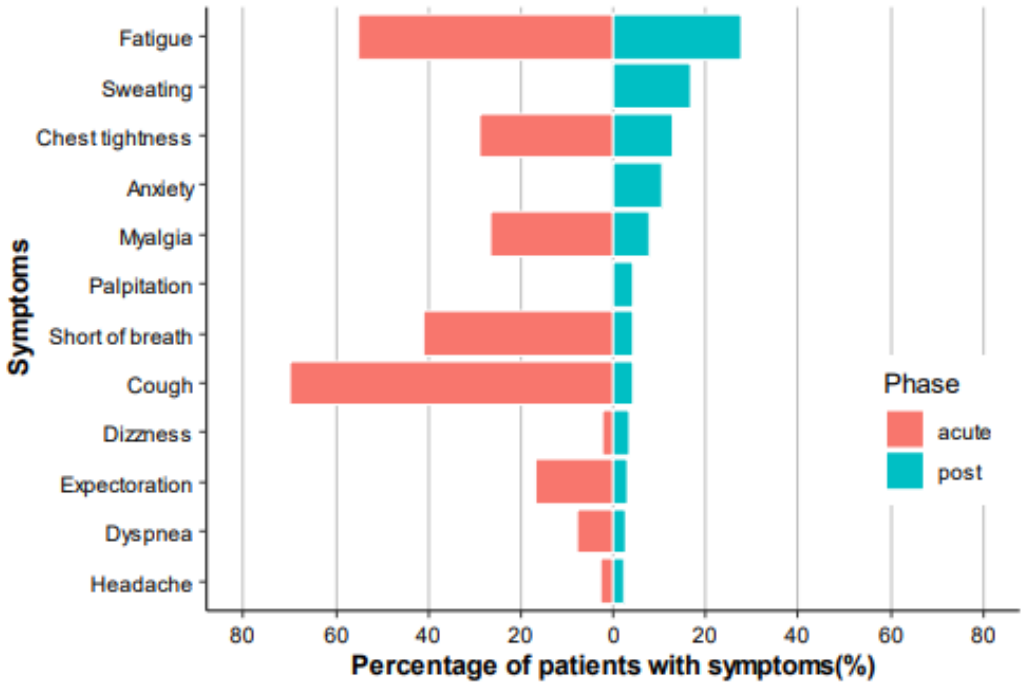
Comment: The increasing virulence of SARS-CoV-2 VOCs can lead to a considerably larger, and more deadly, pandemic. They were able to demonstrate the enhanced relative virulence of the Delta variant. Combined with increased transmissibility and immune escape, the increased virulence of VOCs represents a substantial escalation in risk to public health during the SARS-CoV-2 pandemic.

Symptoms and Health Outcomes Among Survivors of COVID-19 Infection 1 Year After Discharge from Hospitals in Wuhan, China
JAMA Network Open. 2021;4(9):e2127403
doi:10.1001/jamanetworkopen.2021.27403
2433 patients were available at 1-year follow-up, 1205 (49.5%) were men and 680 (27.9%) were women. They were categorized into the severe disease group as defined by the WHO guideline; the median (IQR) age was 60.0 (49.0-68.0) years. In total, 1095 patients (45.0%) reported at least 1 symptom. The most common symptoms included fatigue, sweating, chest tightness, anxiety, and myalgia. Older age (odds ratio [OR], 1.02; 95% CI, 1.01-1.02; *P* < .001), female sex (OR, 1.27; 95% CI, 1.06-1.52; *P* = .008), and severe disease during hospital stay (OR, 1.43; 95% CI, 1.18-1.74; *P* < .001) were associated with higher risks of fatigue. Older age (OR, 1.02; 95% CI, 1.01-1.03; *P* < .001) and severe disease (OR, 1.51; 95% CI, 1.14-1.99; *P* = .004) were associated with higher risks of having at least 3 symptoms.



2.CAT scoring Total score: _____

Symptoms	score						Symptoms
I never cough	0	1	2	3	4	5	I cough all the time
I have no phlegm (mucus) in my chest at all	0	1	2	3	4	5	My chest is completely full of phlegm (mucus)
My chest does not feel tight at all	0	1	2	3	4	5	My chest feels very tight
When I walk up a hill or one flight of stairs I am not breathless	0	1	2	3	4	5	When I walk up a hill or one flight of stairs I am very breathless
I am not limited doing any activities at home	0	1	2	3	4	5	I am very limited doing activities at home
I am confident leaving my home despite my lung condition	0	1	2	3	4	5	I am not at all confident leaving my home because of my lung condition
I sleep soundly	0	1	2	3	4	5	I don't sleep soundly because of my lung condition
I have lots of energy	0	1	2	3	4	5	I have no energy at all



Comment: This study reported prolonged symptoms of COVID-19 and found that severe disease during hospitalization was a risk factor for more symptoms and higher chronic obstructive pulmonary disease assessment test scores. As much as 19% of the eligible population was not accessible and nearly 25% of the remaining population declined to participate the current study and some of the demographic characteristics differed between enrolled patients and those lost to follow-up, predisposing a risk of survivor bias and the included patients may be less representative of the target population. However, the authors performed propensity matching and a sensitivity analysis which suggested that this bias was small.