Good morning.

Under Covid-19 News I start with the news about Molnupiravir. Next a number of updates on rates, hospitalizations, and deaths. Next a report from Israel on impact of boosters in older adults. Last is the FDA announcement on hearings.

Under Journal Review I start with VE in adolescents. The second article reports on the sides effects of getting a third dose. I conclude with a model of predictive symptoms of Covid-19. This may help as we approach the viral respiratory season.

Have a great week.

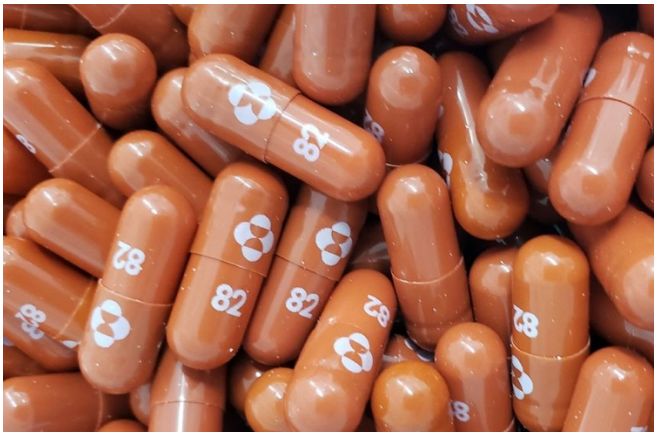
Ed

## COVID-19 News

**Molnupiravir**
Molnupiravir instead targets the viral polymerase, an enzyme needed for the virus to make copies of itself. It is designed to work by introducing errors into the genetic code of the virus.

Last week the results of a randomized, double-blind, placebo-controlled phase 3 trial (MOVe-OUT) in non-hospitalized adult patients with mild to moderate COVID-19 was released. Eligible patients had laboratory-confirmed SARS-CoV-2 infection with symptom onset within 5 days of randomization and at least one risk factor associated with poor disease outcome (e.g., obesity, age >60 years, diabetes, or heart disease). According to the results of a planned interim analysis released by Merck, among 775 patients who were initially enrolled in the trial, molnupiravir reduced the risk of hospitalization or death through day 29 by approximately 50% (7.3% vs 14.1% with placebo). (*P*=0.0012). There were no deaths in the molnupiravir group compared to 8 deaths in the placebo group. The efficacy of the drug appears to be similar among the Gamma, Delta, and Mu variants. Based on these interim results, enrollment in MOVe-OUT was stopped. Adverse effects in MOVe-OUT were similar with molnupiravir and placebo. The dosage of molnupiravir in the clinical trial was 800 mg twice daily for 5 days.

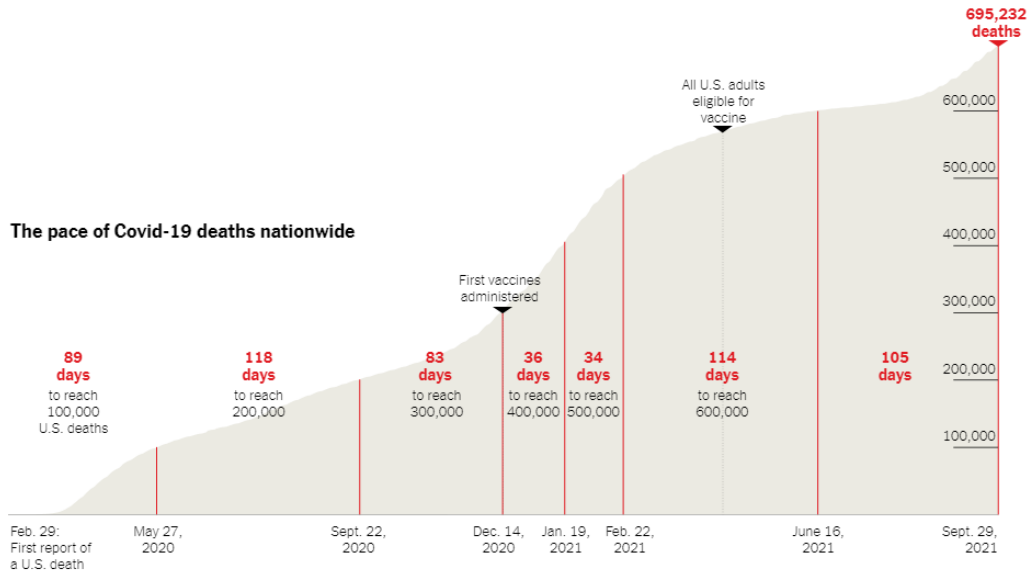
The company has a U.S. government contract to supply 1.7 million courses of molnupiravir at a price of $700 per course. That is about one-third the current cost of a monoclonal antibody (MCA) treatment, which is typically given to patients via IV infusion or SC.



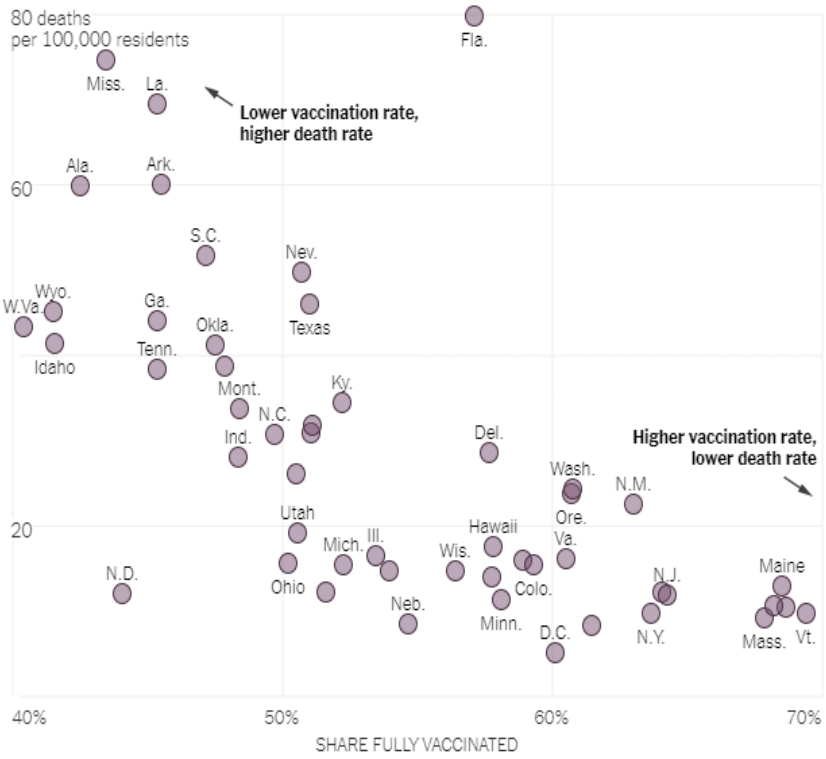
**Comment:** Molnupiravir appears to be less effective than MCA treatments, which have been in high demand. Studies have shown that they reduce hospitalizations and deaths by at least 70 percent in high-risk Covid patients. But the MCA treatments are expensive, are typically given intravenously or SQ and logistically are challenging for hospitals and clinics to administer. However, the pill burden and the duration of therapy may decrease compliance compared to a one-time infusion. Overall if molnupiravir is approved it will add an important oral option for early treatment. In the future I would like to know if this drug can be used for post-exposure prophylaxis and will prophylaxis/treatment decrease spread. Last week I reported on the preliminary results on the use of RDV in the outpatient setting with good results in terms of preventing progression.

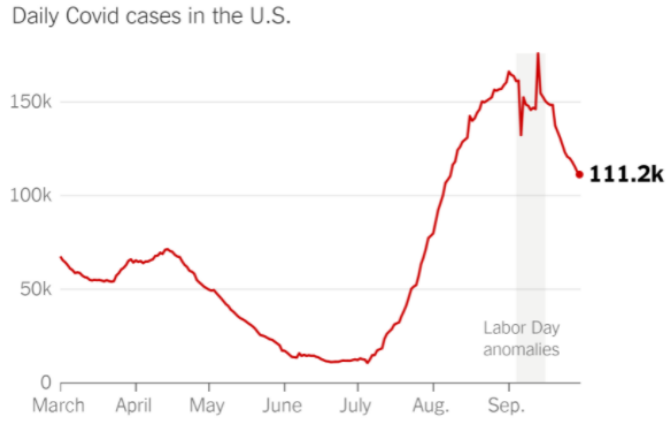
Let me be clear, **vaccination is still, first and foremost, the most effective and least risky thing that you can do**. I hope molnupiravir's promising results do not discourage people from getting vaccinated. The results haven't been published in a peer-reviewed scientific journal. I also look forward to trials with fluvoxamine.

## COVID-19 Updates

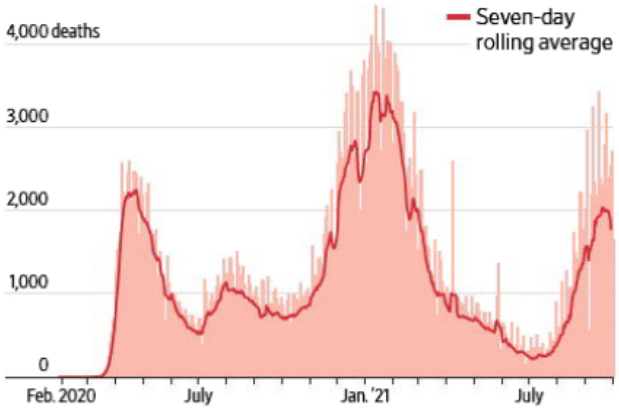


## Recent Covid-19 deaths compared with state vaccination rates



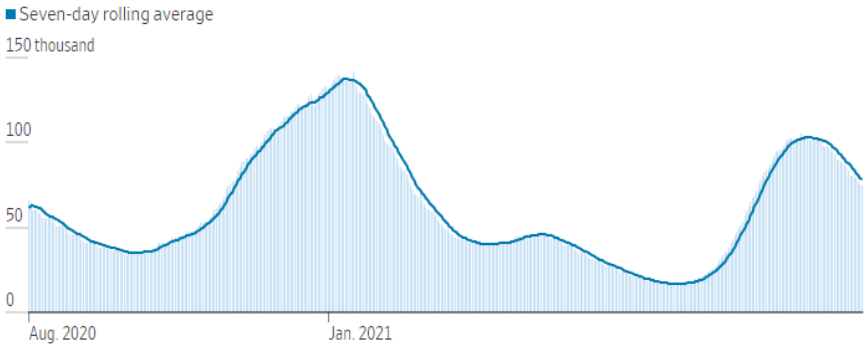



**Daily reported Covid-19 deaths in the U.S.**

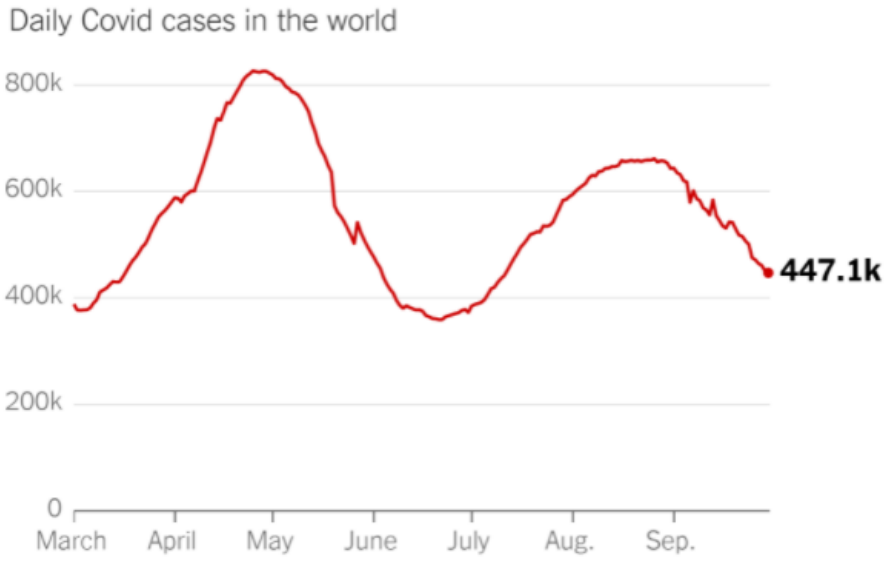



Note: For all 50 states and D.C., U.S. territories and cruises. Last updated Oct. 1, at 4:21 p.m. ET
Source: Johns Hopkins University

**Number of Covid-19 patients hospitalized in the U.S.**




Note: Last updated Oct. 1
Source: U.S. Department of Health & Human Services



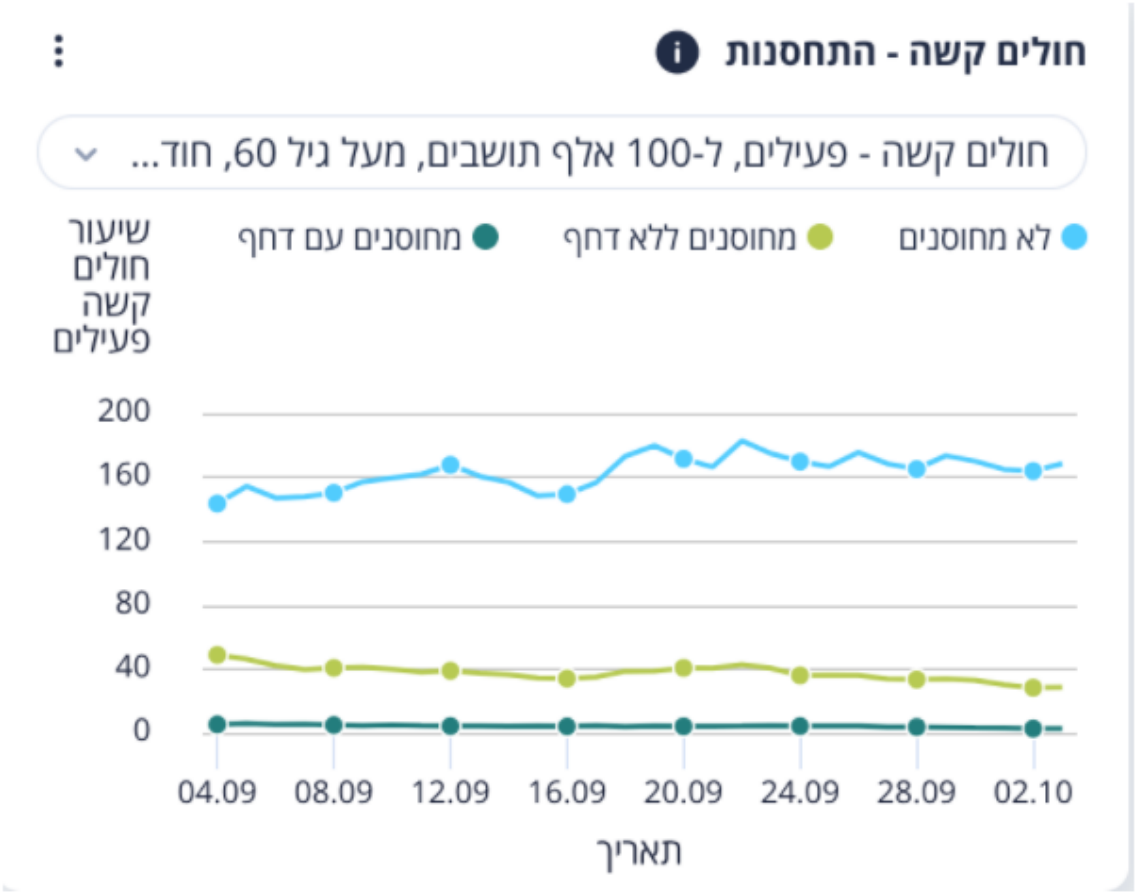
**Comment:** Worldwide, cases have also dropped more than 30 percent since late August. Since SARS-CoV-2 began spreading in early 2020, cases have often surged for about two months and then declined for about two months. Public health officials do not completely understand why. Explanations, like seasonality or variability of NPIs do not seem to completely explain this pattern. The two-month cycle has occurred during different seasons of the year and occurred even when human behavior has not significantly changed. Perhaps a variant needs about two months to circulate through an average-sized community. The recent declines have occurred despite millions of American children starting back to school. There are, however, exceptions. In the UK, for example, caseloads have seesawed over the past two months, rather than consistently fallen.

However, there are some legitimate reasons for Covid optimism. The share of Americans 12 and over who have received at least one vaccine shot has reached 76 percent, and the growing number of vaccine mandates — along with the likely authorization of the Pfizer vaccine for children ages 5 to 11 — will increase the number of vaccinations this fall. Almost as important, about 30-50% of Americans have probably had Covid already, giving them some natural immunity. I hope immunity will become widespread enough that another wave as large and damaging as the Delta wave will be blunted. More than 700,000 Americans have died from Covid (see above), but tragically nearly 200,000 probably could have been saved if they had chosen to take a vaccine. Recent deaths are related to state vaccination rates. (See above)

Covid isn't likely to be going away anytime soon. I think it will continue to circulate for years. But vaccination and therapeutics like MCA and Molnupiravir can and have transformed Covid into a manageable disease, like flu or the common cold. Whatever this fall and winter brings, it is my sincere hope the worst of the pandemic may be behind us.

**Israel Data: Boosters Cut Elderly's Risk of COVID Death**
October 3, 2021 – article provided by Rabbi Daniel Septimus
Over-60s who shun vaccines are not only at much greater risk of death than triple-vaccinated, but also have 65 times the chance of getting seriously ill. After boosters, elderly Israelis who are fully inoculated have just one fiftieth of the chance of COVID death compared to unvaccinated people in the same age bracket.

According to Health Ministry data for the last seven days of September, there were 6.43 daily deaths per 100,000 Israelis aged 60-plus. For older people who were vaccinated three times, the average was 0.13. Among triple-vaccinated Israelis aged 60-plus, there are 2.6 people per 100,000 in serious condition. Among the unvaccinated the figure is 168.5. Boosters are shown to be working well in keeping people out of serious condition. There are 28.5 serious cases per 100,000 people among 60-plus Israelis who got just two shots, compared to 2.6 for the triple-vaccinated.




A graph showing the rate of Israelis per 100,000 citizens aged 60-plus who are seriously ill with COVID-19. The vertical axis is the number of people per 100,000, and the horizontal axis shows the date. The top line on the graph, in light blue, denotes unvaccinated people, the next line (light green) denotes people who received two shots, and the bottom line (dark green) denotes the triple-vaccinated.

**Comment:** This report supports the FDA and CDC recommendation about a third shot for persons >65. [Israel used >60] Israel almost exclusively uses the Pfizer vaccine.

**FDA**

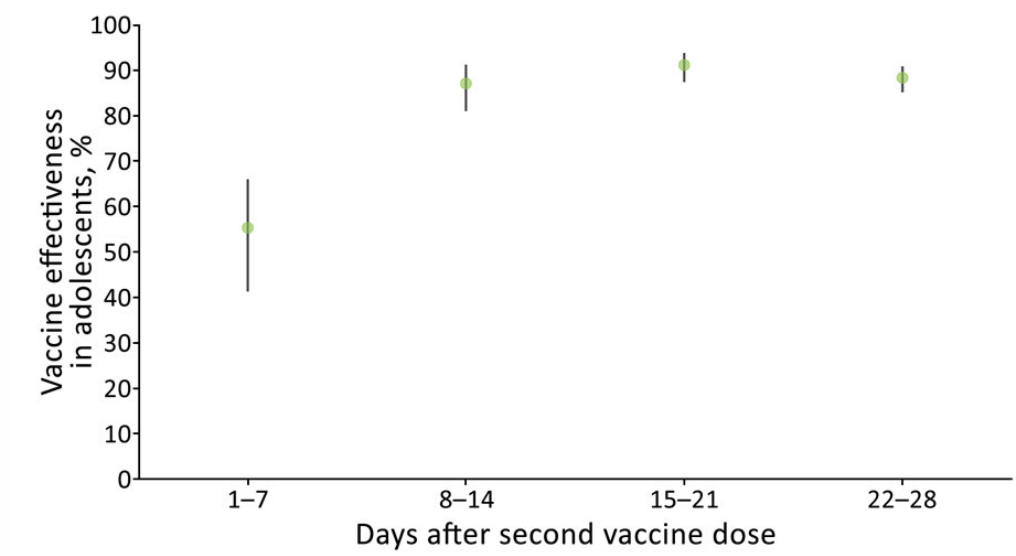
FDA on Friday scheduled three days of public meetings with its panel of independent vaccine experts for later this month, as the agency prepares to make high-profile decisions on whether to authorize emergency use of the Pfizer-BioNTech vaccine for children ages 5 to 11 and booster shots for adult recipients of the Moderna and Johnson & Johnson vaccines. The panel will meet on Oct. 14 and 15 to discuss booster doses and is tentatively scheduled to discuss Pfizer's pediatric vaccine on Oct. 26, the agency said. The decision to have the committee discuss the evidence for Moderna and Johnson & Johnson booster shots two weeks before it does so for Pfizer's children's vaccine may reflect the FDA's priorities and the availability of data.

## Journal Review

**Effectiveness of BNT162b2 Vaccine in Adolescents during Outbreak of SARS-CoV-2 Delta Variant Infection, Israel, 2021**

Emerg Infect Dis published online September 27, 2021
doi.org/10.3201/eid2711.211886
The investigators performed a nationwide retrospective cohort study to estimate vaccine effectiveness against PCR-confirmed SARS-CoV-2 infections among adolescent Israel residents 12-15 years of age who had received the second Pfizer vaccine dose during July 1-24, 2021. They estimated vaccine effectiveness for 1-7, 8-14, 15-21, and 22-28 days after the second vaccine dose. Incidence rate ratio denotes the ratio of the rate of PCR-confirmed SARS-CoV-2 infections in the vaccinated and unvaccinated groups. The Pfizer vaccination campaign for adolescents 12-15 years of age in Israel coincided with the outbreak of the SARS-CoV-2 Delta variant. This enabled the investigators to be able to estimate vaccine effectiveness against SARS-CoV-2 infection for this age group during predominant circulation of the Delta variant.

The results demonstrated high vaccine effectiveness against SARS-CoV-2 infection in this population starting the second week after the second vaccine dose. These estimates are somewhat lower than those that had been estimated for persons 16-39 years of age during the same time intervals after the second vaccine dose during circulation of the SARS-CoV-2 Alpha variant and wild-type virus in Israel (EBioMedicine. 2021; 72:103574) Specifically, adjusted vaccine effectiveness against SARS-CoV-2 infection for persons 16-39 years of age was 93.2% (95% CI 91.9%-94.2%) at 8-14 days, 96.7% (95% CI 95.8%-97.4%) at 15-21 days, and 96.6 (95% CI 95.7%-97.3%) at 22-28 days after receipt of the second vaccine dose. Although vaccine effectiveness estimates and 95% Cis during the circulation of the Alpha variant and the wild-type virus were adjusted for age, sex, and epidemiologic week, only minor differences in point estimates and 95% CIs were noted between crude and adjusted vaccine effectiveness.



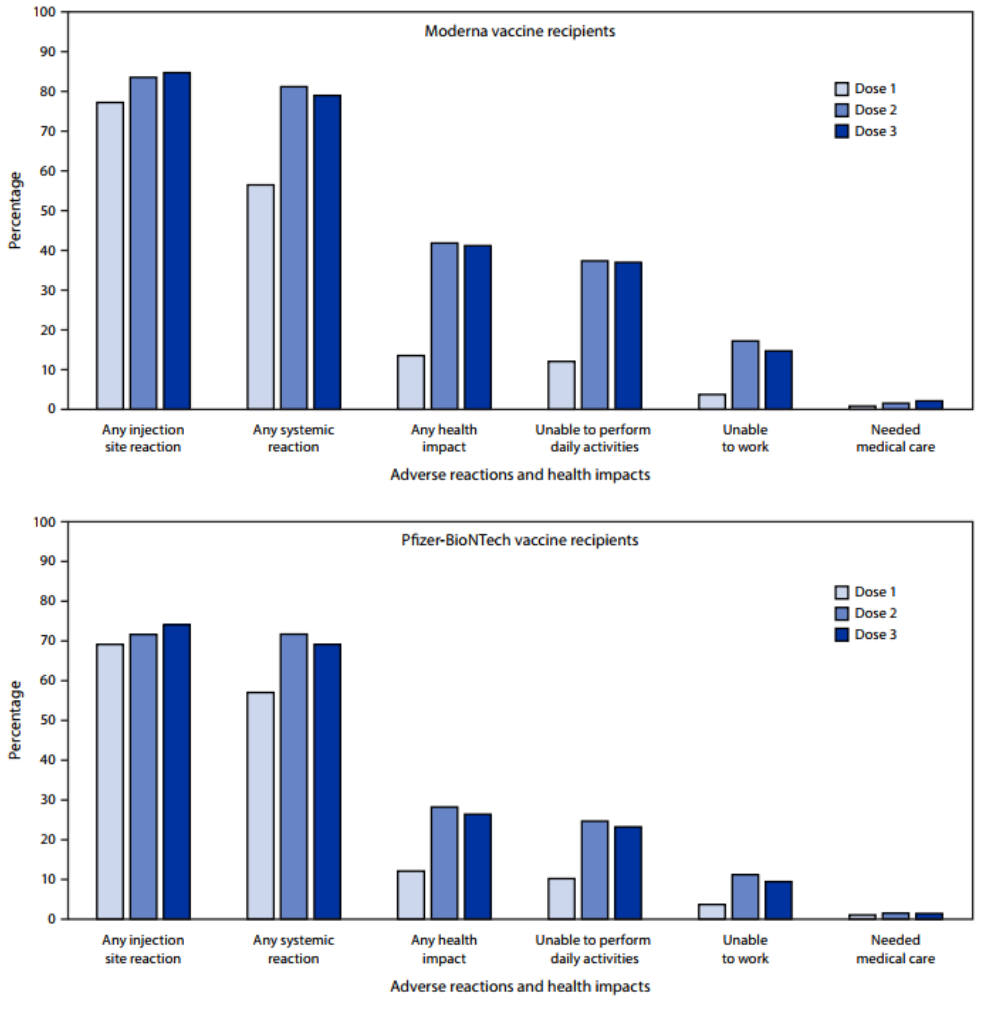

**Comments:** Their findings are consistent with those of a recent study from the UK, which demonstrated vaccine effectiveness of 88.0% (95% CI 85.3%-90.1%) against symptomatic disease caused by the SARS-CoV-2 Delta variant, compared with vaccine effectiveness of 93.7% (95% CI 91.6%-95.3%) against disease caused by the Alpha variant among persons >16 years of age who had received 2 doses of Pfizer (N Engl J Med. 2021;385:585-94)

**Safety Monitoring of an Additional Dose of COVID-19 Vaccine — United States, August 12-September 19, 2021**

MMWR published online September 28, 2021

During August 12-September 19, 2021, a total of 22,191 v-safe registrants reported receipt of an additional dose of COVID-19 vaccine. The investigators used V-safe a voluntary, smartphone-based U.S. safety surveillance system; vaccinated persons eligible to receive authorized or licensed vaccine product may register in v-safe. The v-safe platform allows existing registrants to report receiving an additional dose of COVID-19 vaccine and new registrants to enter information about all doses of COVID-19 vaccine received. V-safe health surveys are sent during days 0-7 after each dose of vaccine and include questions about local injection site and systemic reactions and health impacts. Most (97.6%) reported a primary 2-dose mRNA vaccination series followed by a third dose of the same vaccine. Among those who completed a health check-in survey for all 3 doses (12,591; 58.1%), 79.4% and 74.1% reported local or systemic reactions, respectively, after dose 3, compared with 77.6% and 76.5% who reported local or systemic reactions, respectively, after dose 2. The findings indicate no unexpected patterns of adverse reactions after an additional dose of COVID-19 vaccine; most of these adverse reactions were mild or moderate.

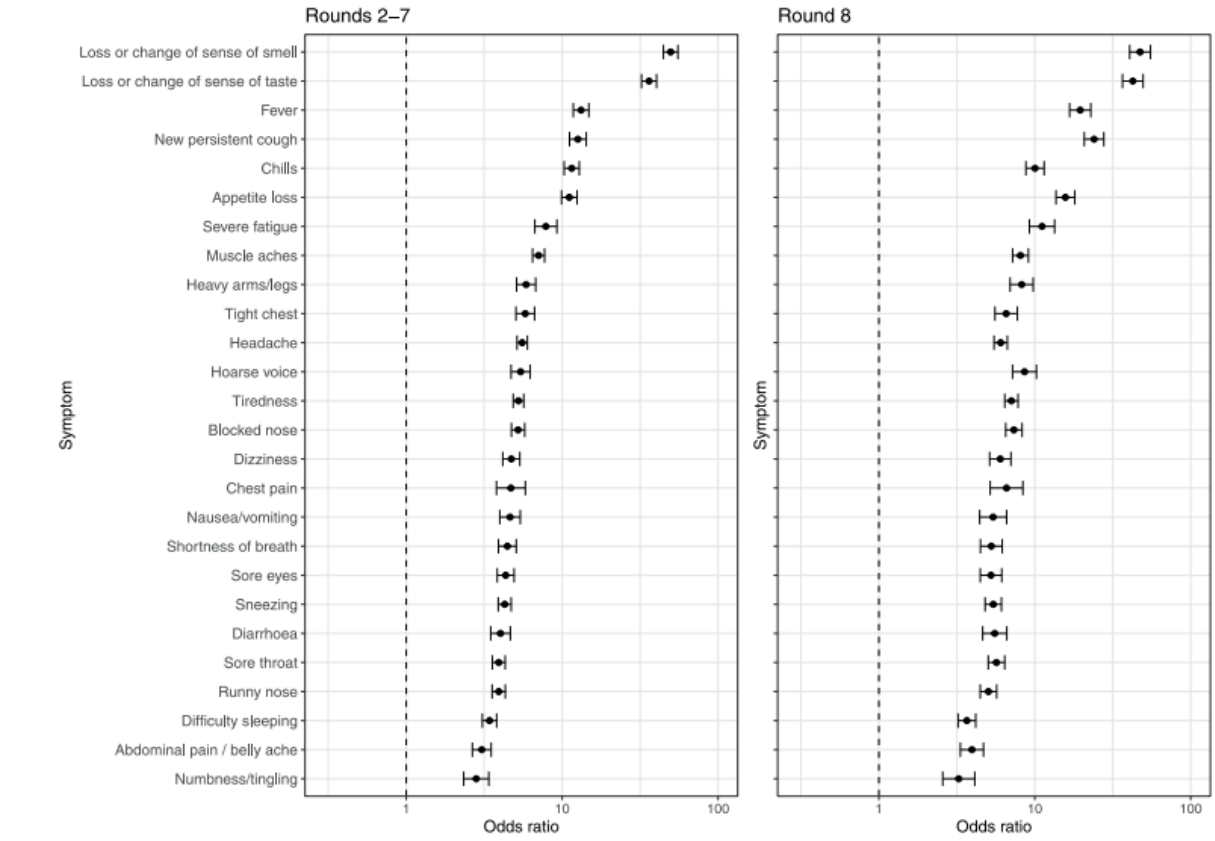
**FIGURE. Adverse reactions and health impacts reported by persons who received 3 doses* of Moderna (N = 6,283) or Pfizer-BioNTech (N = 6,308) COVID-19 vaccine and completed at least one v-safe health check-in survey on days 0–7 after each dose, by dose number — United States, August 12–September 19, 2021**



**Comment:** Voluntary reports to v-safe found no unexpected patterns of adverse reactions after an additional dose of COVID-19 vaccine. Enrollment in v-safe is voluntary and likely not representative of the vaccinated U.S. population; the majority of participants identified themselves as White and non-Hispanic. Second, during this study period, additional dose recommendations were limited to persons with immunocompromising conditions who completed a primary mRNA COVID-19 vaccination series; however, v-safe does not include information about immune status.

An additional dose of mRNA COVID-19 vaccine is recommended for persons with moderately to severely immunocompromising conditions. CDC also recommends an additional dose of Pfizer vaccine ≥6 months after completion of the primary vaccine series among persons aged ≥65 years, residents in long-term care settings, and persons aged 50-64 years with underlying medical conditions. Persons aged 18-49 years with underlying medical conditions and persons aged 18-64 years at increased risk for COVID-19 exposure and transmission because of occupational or institutional setting may receive an additional dose based on their individual benefits and risks.

**Predictive Symptoms for COVID-19 in the Community: REACT-1 Study of Over 1 Million People**
PLOS ONE published September 28, 2021
doi.org/10.1371/journal.pmed.1003777
A model was developed based on the data obtained during rounds 2 to 7, with 7 symptoms selected as jointly positively predictive of PCR positivity: loss or change of smell, loss or change of taste, fever, new persistent cough, chills, appetite loss, and muscle aches. The first 4 of those symptoms are currently used in the UK to determine eligibility for community PCR testing. In round 8 of testing, the resulting model predicted PCR positivity with an area under the curve of 0.77 and testing people in the community with at least 1 of the 7 selected positively predictive symptoms gave sensitivity, specificity, and positive predictive values of 74%, 64%, and 9.7%, respectively. Modeling suggested that the use of the 7 symptoms identified for PCR test allocation would result in 30% to 40% of symptomatic individuals in England being eligible for a test (versus 10% currently) and, if all those eligible were tested, would result in the detection of 70% to 75% of positive cases.




**Comment:** They identified 7 symptoms that were jointly predictive of PCR positivity and appeared to vary only marginally across age groups: loss or change of sense of smell, loss or change of sense of taste, fever, new persistent cough, chills, appetite loss, and muscle aches. Loss of taste and smell seems to be most predictive and may help differentiate Covid from other respiratory viruses.