Good morning,

Today I review in COVID-19 News, the CDC updated contraindications and precautions on mRNA vaccines and the FDA response in advising on alternative vaccine schedules.

Under journal review I start with 3 articles just published in the Ann Intern Med in favor of an altered vaccine schedule. The next article reviews the experience of a rapid antigen test versus PCR on two college campuses. The next article is a small prospective study using canakinumab an IL-1β antibody. I included since this is the first mention, I have seen using this therapeutic in SARS-CoV-2 infected persons. The last article is a complicated but relevant article on impact of tiered restrictions and lockdowns. In my comment I try and put all of this into perspective with recent experience over the holidays and what is happening around the world. Would love to hear from you about my take on the subject.

Stay safe, get vaccinated, and have a good day.

Ed

COVID-19 News

CDC Updated Contraindications and Precautions to mRNA Vaccines

Contraindications

CDC considers a history of the following to be a contraindication to vaccination with both the Pfizer-BioNTech and Moderna COVID-19 vaccines:

- Severe allergic reaction (e.g., anaphylaxis) after a previous dose of an mRNA COVID-19 vaccine or any of its components
- Immediate allergic reaction of any severity to a previous dose of an mRNA COVID-19 vaccine or any of its components (including polyethylene glycol [PEG])
- Immediate allergic reaction of any severity to polysorbate (due to potential cross-reactive hypersensitivity with the vaccine ingredient PEG)

Persons with an immediate allergic reaction to the first dose of an mRNA COVID-19 vaccine should not receive additional doses of either of the mRNA COVID-19 vaccines. Providers should attempt to determine whether reactions reported following vaccination are consistent with immediate allergic reactions versus other types of reactions commonly observed following vaccination, such as a vasovagal reaction or post-vaccination side effects (which are not contraindications to receiving the second vaccine dose).

Precautions

CDC considers a history of any immediate allergic reaction to any other vaccine or injectable therapy (i.e., intramuscular, intravenous, or subcutaneous vaccines or therapies not related to a component of mRNA COVID-19 vaccines or polysorbate) as a precaution but **not** a contraindication to vaccination for both the Pfizer-BioNTech and Moderna COVID-19 vaccines. These persons should be counseled about the unknown risks of developing a severe allergic reaction and balance these risks against the benefits of vaccination. Deferral of vaccination and/or consultation with an allergist-immunologist may be considered until further information on the risk of anaphylaxis is available. The following considerations can be used to help the provider conduct a risk assessment for mRNA COVID-19 vaccination in these individuals:

- Risk of exposure to SARS-CoV-2 (e.g., because of residence in a congregate setting such as a long-term care facility, occupation)
- Risk of severe disease or death due to COVID-19 (e.g., because of age, underlying medical conditions)
- Whether the patient has previously been infected with SARS-CoV-2 and, if so, how long ago
    - Note: Vaccination is recommended for persons with a history of COVID-19; however, because reinfection is uncommon in the 90 days following infection, persons with a precaution to vaccination and recent COVID-19 may choose to defer vaccination until further information is known about the risk of anaphylaxis following vaccination.
- The unknown risk of anaphylaxis (including fatal anaphylaxis) following mRNA COVID-19 vaccination in a person with a history of an immediate allergic reaction to other vaccines or injectable therapies
- Ability of the patient to be vaccinated in a setting where appropriate medical care is immediately available for anaphylaxis

Neither contraindications nor precautions to vaccination
Allergic reactions (including severe allergic reactions) not related to vaccines, injectable therapies, components of mRNA COVID-19 vaccines (including PEG), or polysorbates, such as food, pet, venom, or environmental allergies, or allergies to oral medications (including the oral equivalents of injectable medications) are **not** a contraindication or precaution to vaccination with either mRNA COVID-19 vaccine. The vial stoppers of these mRNA vaccines are not made with natural rubber latex, and there is no contraindication or precaution to vaccination for persons with a latex allergy. In addition, as the mRNA COVID-19 vaccines do not contain eggs or gelatin, persons with allergies to these substances do not have a contraindication or precaution to vaccination.

FDA Vaccine Schedule
FDA officials on Monday cautioned against altering the two-dose schedules for the two authorized COVID-19 vaccines. To reach more people faster, some have suggested stretching the time between the first and second doses, giving single doses, or giving two half doses.

"At this time, suggesting changes to the FDA-authorized dosing or schedules of these vaccines is premature and not rooted solidly in the available evidence," Dr. Stephen Hahn, FDA commissioner, and Dr. Peter Marks, director of the FDA's Center for Biologics Evaluation and Research, said in a statement. "Without appropriate data supporting such changes in vaccine administration, we run a significant risk of placing public health at risk." They noted that people might wrongly assume they are fully protected and might take risks they would not otherwise take. See articles below.

Journal Review

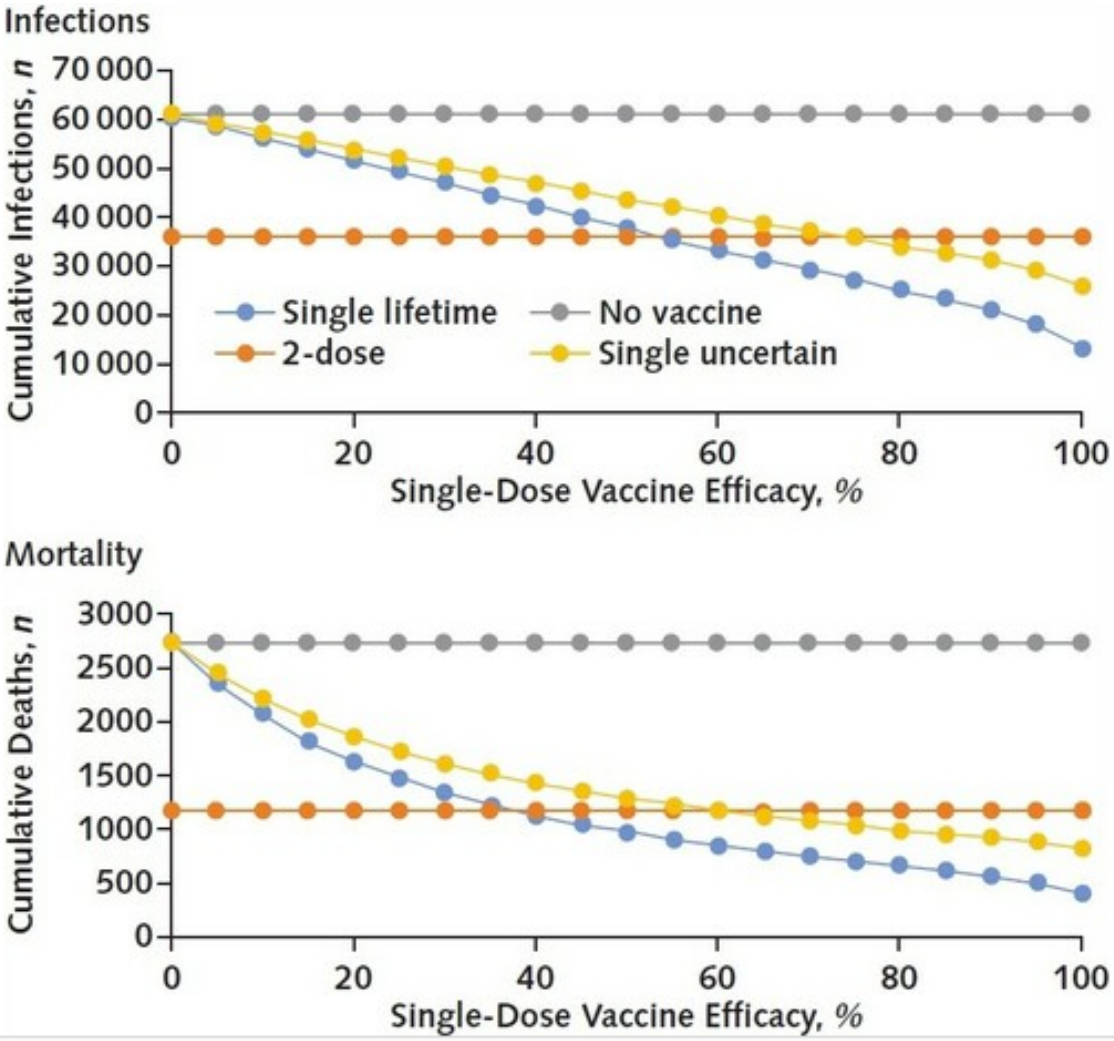
Speed Versus Efficacy: Quantifying Potential Tradeoffs in COVID-19 Vaccine Deployment
Ann Intern Med published online January 5, 2021
doi.org/10.7326/M20-7866

Alternative Dose Allocation Strategies to Increase Benefits from Constrained COVID-19 Vaccine Supply
Ann Intern Med published online January 5, 2021
doi.org/10.7326/M20-8137

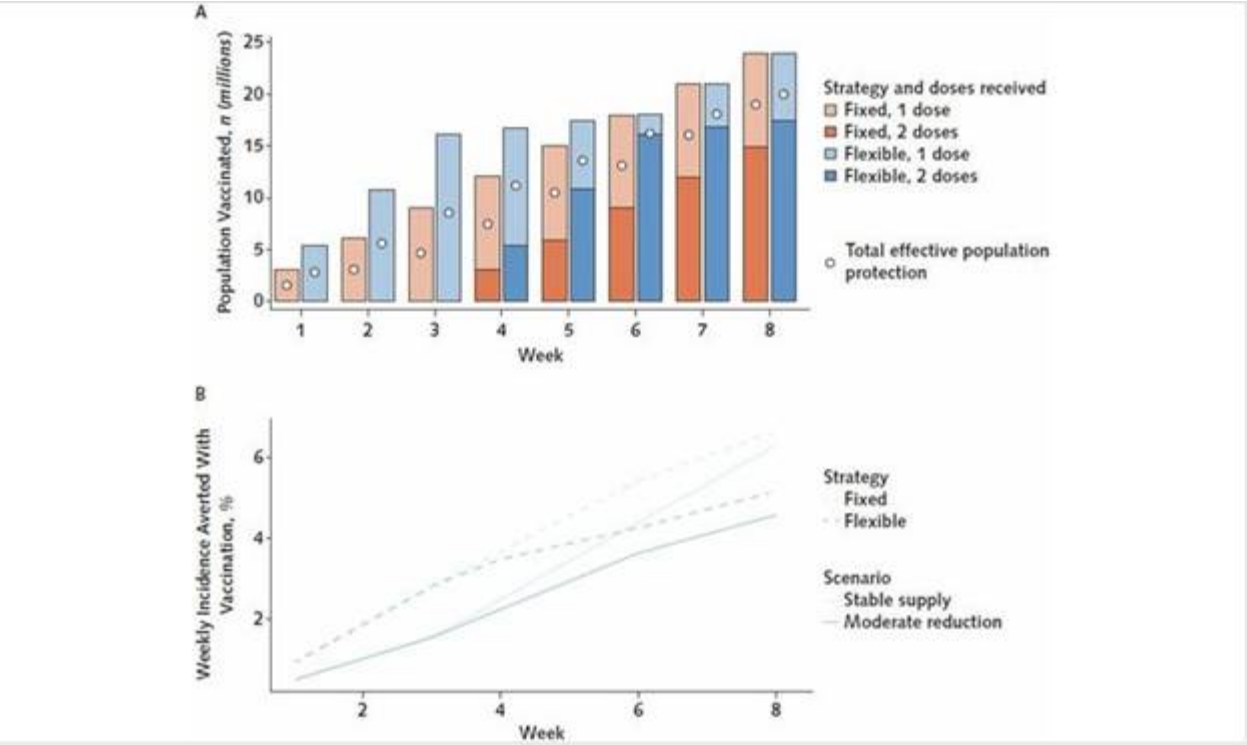
A Public Health COVID-19 Vaccination Strategy to Maximize the Health Gains for Every Single Vaccine Dose

Ann Intern Med published online January 5, 2021
doi.org/10.7326/M20-8060

Three articles in favor of an altered vaccine schedule were just published in the Ann Intern Med. The first study found that depending on the duration of protection provided, a single-dose vaccine that has 55% effectiveness could provide a greater population benefit than a two-dose regimen that is 95% effective.



A second study compared the current fixed allocation strategy, in which 50% of vaccines are held back for second doses, with a flexible strategy that focuses on vaccinating more people initially. For the flexible strategy, 10% of the vaccine supply is reserved for second doses in the initial 3 weeks, 90% is held back in each of the following 3 weeks, and 50% is held back for the remaining period. Over 8 weeks, the authors calculate that an additional 23% to 32% of cases could be averted with a flexible rather than a fixed strategy.



In the third article under "Ideas & Opinions", the authors propose several reasons why single-dose vaccination makes sense without long-term efficacy data, including accelerating pandemic control and the ethics of administering the first dose to more people. See table below.

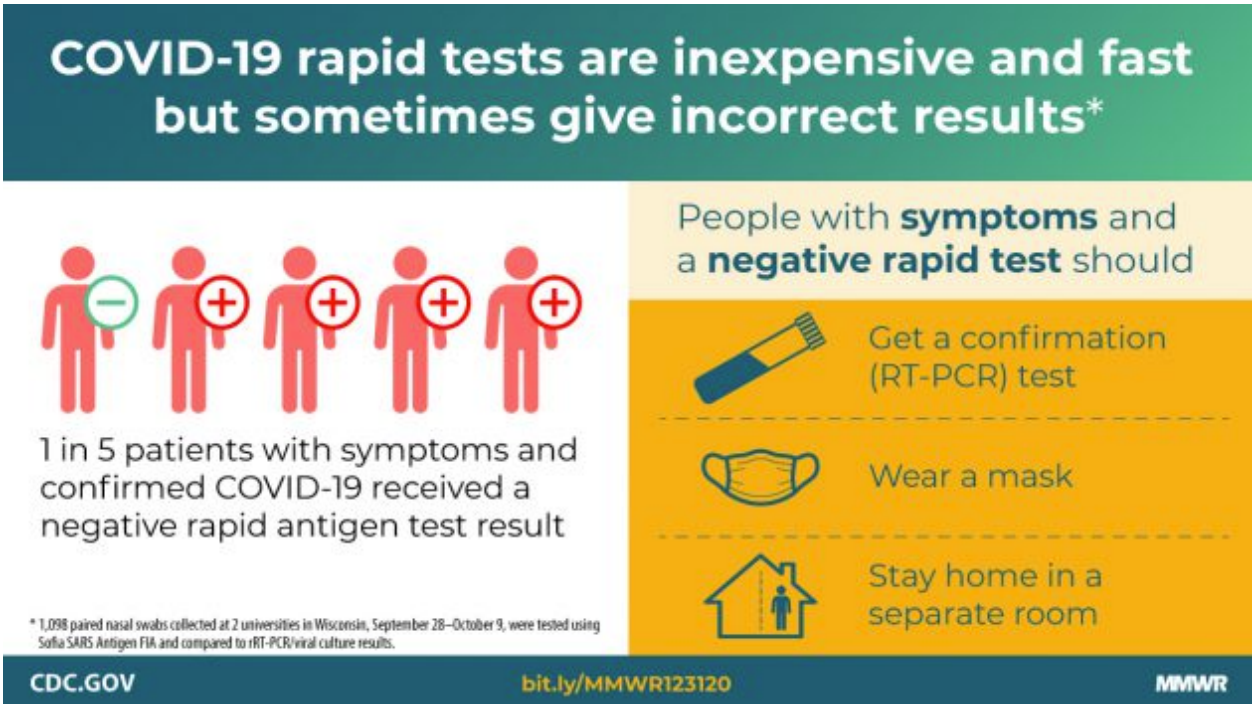
Table. Pros and Cons of Two-Dose Versus Single-Dose Vaccination Strategy

Vaccination Strategy	Pros	Cons
2-dose vaccine	Very high efficacy Closely mirrors the clinical trial Prevents severe disease	Requires delivery of 2 doses May exacerbate inequities May lead to behavioral disinhibition Doubles time required for a critical proportion of the population to be vaccinated
Single-dose vaccine	Higher proportion of population protected Promotes equity Reduces sequelae of reactogenicity Potential to accelerate pandemic control	Partial efficacy

Comment: The priority should be to grow the evidence base by pursuing clinical testing and observational studies to determine whether a single dose or a delayed second dose of the current vaccines will generate immunity similar to that of the FDA-authorized 2-dose regimen. As the authors point out in public health emergencies an argument can be made for doing something less than perfect to help more people quickly; however, the proposed alternative approaches with current vaccines are far from clear. Investing in a strong public health system, increasing vaccine production [with Astra Zeneca and J&J hopefully on the way by February (fingers crossed)], equitable vaccine distribution, and vaccine strategies driven by science we can control this pandemic.

Performance of an Antigen-Based Test for Asymptomatic and Symptomatic SARS-CoV-2 Testing at Two University Campuses — Wisconsin, September–October 2020
MMWR 2021; 69:1642-1647

Researchers studied antigen and PCR samples from over 1100 people presenting for COVID-19 testing. Among symptomatic people, the Sofia antigen test had a sensitivity of 80%, a specificity of 99%, a positive predictive value (PPV) of 94%, and a negative predictive value (NPV) of 96%. Among those without symptoms, the test had a sensitivity of 41%, a specificity of 98%, a PPV of 33%, and an NPV of 99%.



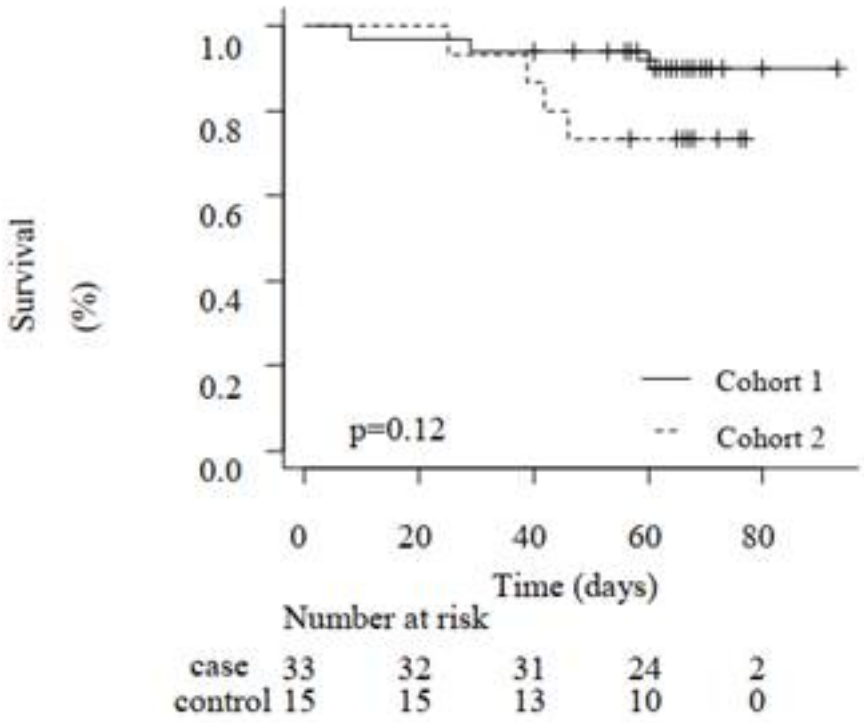
Comment: This article confirms limitation of rapid antigen tests especially if asymptomatic. One must also be aware of the FDA report reviewed last month about false-positive rapid antigen tests in asymptomatic individuals. Some of the limitations of rapid antigen testing can be overcome with more frequent testing as reviewed last month in the Daily Briefing.

Canakinumab as Treatment for COVID-19-Related Pneumonia: A Prospective Case-Control Study
Int J Infect Dis published online December 29, 2020
doi.org/10.1016/j.ijid.2020.12.073
Canakinumab is an IL-1β antibody that neutralizes the activity of IL-1β. Forty-eight patients with moderate COVID-19-related pneumonia were asked to participate in the prospective case control study; 33 patients (Cases) signed informed consent and received canakinumab; 15 patients (Controls) refused to receive the experimental drug and received institutional standard of care (SoC).

Results: Hospital discharge within 21 days was seen in 63% of patients in canakinumab vs. 0% in control (median 14 vs 26 days, respectively; $p<0.001$). There was significant clinical improvement in ventilation regimens following administration of canakinumab compared to control. (Stuart-Maxwell test for paired data, $p<0.001$). Patients treated with canakinumab experienced a significant increase in PaO2:FiO2 ($p<0.001$) and reduction in lung damage by CT ($p=0.01$), along with significant decreases in immune/inflammation markers that were not observed in control. Only mild side effects were seen in patients treated with canakinumab; survival at 60 days.

With regards to inflammatory markers, canakinumab treatment was associated with prompt reductions in serum CRP (p<0.001), IL-6 (p<0.03), and ferritin (p<0.001). In control, only a reduction in the level of D-dimer was noted (p=0.05) which was likely due to the higher dose of heparin used compared to canakinumab group.

Figure 3a: Overall survival in cohort 1 and cohort 2.



Cohort 1-canakinumab; Cohort 2 control

Comment: This is the first study I have seen looking at an IL-1β antibody. Treatment with canakinumab did rapidly restore normal oxygen status and was also associated with a more favorable prognosis versus standard of care was 90.0% (95% CI: 71.9-96.7) in patients treated with canakinumab and 73.3% (95%. CI: 43.6-89.1) for control. This study should be interpreted with caution. First it was a prospective but non-randomized study. The numbers are small. However, based on these results, a randomized, controlled trial with canakinumab in COVID-19-pneumonia is warranted. A randomized phase III clinical trial with intravenous canakinumab in hospitalized patients with COVID-19-induced pneumonia is ongoing (NCT04362813), but this study will only assess the efficacy of a higher dose (administered IV and by body weight).

Association of Tiered Restrictions and a Second Lockdown with COVID-19 Deaths and Hospital Admissions in England: A Modelling Study
Lancet Infect Dis published online December 23, 2020
doi.org/10.1016/ S1473-3099(20)30984-1

The investigators examined the impact of tiered restrictions, and alternatives for lockdown stringency, timing, and duration, on SARS-CoV-2 transmission and hospital admissions and deaths from COVID-19. They searched PubMed, bioRxiv, and medRxiv from database inception to Nov 9, 2020, for English-language articles with the search terms ("COVID-19" OR "SARS-CoV-2" OR "coronavirus") AND ("lockdown") AND ("model"). This search returned 676 results, of which 23 were modelling studies that fit models to data and examined a second round of physical distancing restrictions, such as lockdowns or tiered restrictions. 19 of the 23 studies used a model to assess the impact of lockdowns, often on a national scale and occasionally regionally.

The UK Government announced a program of regionally differentiated physical distancing measures using a three-tiered approach, known as alert levels. By default, regions were placed into tier 1, the least restrictive tier, but could be moved into tiers 2 or 3 if incidence of infection increased. Regions in tier 1 had a 10 PM curfew for "hospitality venues" and restrictions on the number of individuals who could meet (the so-called rule of six). Tier 2 regions had additional restrictions on individuals from different households mixing, and residents were advised to avoid making unnecessary journeys. Regions in tier 3 had additional closures of hospitality and leisure venues, such as pubs and restaurants. In the weeks following the announcement, the UK Government placed several local authority districts—particularly in the north of England—into the highest restriction category, tier 3. Despite these measures, incidence continued to rise in all regions of England. Consequently, on Oct 31, a new 4-week national lockdown for England was announced, beginning on Nov 5. The restrictions were broadly similar to those of the initial spring lockdown, but schools and universities were allowed to remain open. It remains unclear how effective the tiered restrictions were in reducing transmission and what additional reduction in transmission might have been accomplished by the second lockdown.

They estimated a reduction in the effective reproduction number (*R*t) of 2% (95% credible interval [CrI] 0–4) for tier 2, 10% (6–14) for tier 3, 35% (30–41) for a Northern Ireland-stringency lockdown with schools closed, and 44% (37–49) for a Wales-stringency lockdown with schools closed. From Oct 1, 2020, to March 31, 2021, a projected COVID-19 epidemic without tiered restrictions or lockdown results in 280,000 (95% projection interval 27,4000–287,000) hospital admissions and 58,500 (55,800–61,100) deaths. Tiered restrictions would reduce hospital admissions to 238,000 (231,000–245,000) and deaths to 48,600 (46,400–50,700). From Nov 5, 2020, a 4-week Wales-type lockdown with schools remaining open—similar to the lockdown measures announced in England in November 2020—was projected to further reduce hospital admissions to 186,000 (179,000–193,000) and deaths to 36,800 (34,900–38,800).

Closing schools was projected to further reduce hospital admissions to 157,000 (152, 000–163,000) and deaths to 30,300 (29,000–31,900). [I am not sure the science supports this projection since studies do not support schools as a major source for transmission] A projected lockdown of greater than 4 weeks would reduce deaths but would bring diminishing returns in reducing peak pressure on hospital services. An earlier lockdown would have reduced deaths and hospitalizations in the short term but would lead to a faster resurgence in cases after January 2021. In a post-hoc analysis, they estimated that the second lockdown in England (Nov 5–Dec 2) reduced *R*t by 22% (95% CrI 15–29), rather than the 32% (25–39) reduction estimated for a Wales-stringency lockdown with schools open.

Comment: This article indicated lockdown measures outperform less stringent restrictions in reducing cumulative deaths. However, although **earlier** lockdowns may have saved lives in the short term, this resulted in substantial susceptibility in the population, which may result in a larger resurgence after January 2021, requiring the introduction of further non-pharmaceutical interventions (NPIs) [3Ws].

Following completion of the analysis, they analyzed new data from November 2020, and found that despite similarities in policy, the second lockdown in England had a smaller impact on behavior [? Covid fatigue] than did the second lockdown in Wales, resulting in more deaths and hospitalizations than they originally projected when focusing on a Wales-stringency scenario for the lockdown. Their model is subject to certain limitations and uncertainties. The authors they did not consider the implementation of any further interventions after the lockdown periods and adherence to NPIs, aside from a continuation of tiered restrictions at the level imposed before the lockdown. [as we have seen in the US, restrictions have been eased in stages] Changes in behavior are likely to occur over the time frames that they are modelling, particularly over the winter break. Behavioral changes are difficult to predict, and it is possible that there will be a return to more typical behaviors after the lockdown. [I think we saw multiple examples of reduction in adherence to the 3Ws over the holidays] Obviously, the UK is experiencing a surge in part driven by a new mutant that appears to be more contagious. Bottom line, lock downs can reduce infections and “blunt the curve”, but lockdown may only delay infections. In addition, as this study suggests and experience in the US also confirms it is difficult to maintain appropriate behavior over time, so despite lock downs transmissions can continue due to small gatherings etc. I hate to say this but given human behavior and what we have witnessed in the last few months, the only realistic hope to control this pandemic is through vaccinations. The good news I think we will see an acceleration of vaccinations and the addition of one or more new vaccines over the next several months.