TGIF
First, keep the American spirit alive by honoring this special weekend. Have a safe and happy July 4th . We have much to celebrate in 2021. What a difference a year makes.

Today under COVID-19 News the NIH has revised guidance on dosing monoclonals. Next APIC announced support for mandatory Covid-19 vaccinations in healthcare facilities. I then discuss differences in masking policy between the WHO and the CDC. The last two segments discuss impact of vaccinations on the risk of dying and the continued increase in delta variant across the US. A theme continues that if you are fully vaccinated your risk of dying is very low and you have very good protection from infection even against the delta variant. [see Journal Review]

Under the Journal Review an update of the efficacy of the NVX vaccine, the first protein-based, adjuvanted vaccine to report information on phase 3 trials in a top tier peer reviewed journal. The next article reinforces the need to recognize the increased protection offered by a second vaccine dose as COVID-19 cases associated with the B.1.617.2-delta variant. The last article demonstrates that current mRNA vaccines are highly effective among working-age adults in preventing SARS-CoV-2 infection when administered in real-world conditions.

Ed

COVID-19 News

The NIH COVID-19 Treatment Guidelines Panel's Statement on the Updated Emergency Use Authorization of the Anti-SARS-CoV-2 Monoclonal Antibody Combination Casirivimab Plus Imdevimab for the Treatment of COVID-19 June 17, 2021
On June 3, 2021, the Food and Drug Administration (FDA) updated the Emergency Use Authorization (EUA) of the anti-SARS-CoV-2 monoclonal antibody combination casirivimab plus imdevimab for the treatment of nonhospitalized individuals with COVID-19. The authorized dosage has been reduced from a single intravenous (IV) infusion of casirivimab 1,200 mg plus imdevimab 1,200 mg to casirivimab 600 mg plus imdevimab 600 mg. In addition, the same doses of casirivimab and imdevimab may now be administered by subcutaneous (SQ) injection when IV infusion is not feasible or may delay treatment. It should be noted that SQ administration requires four injections (2.5 mL per injection) at four different sites.

- Using the dose of casirivimab 600 mg plus imdevimab 600 mg (AIIa).
- Using IV infusion of casirivimab plus imdevimab (AIIa).
- When IV infusion is not feasible or would lead to delay in treatment, SQ injection of casirivimab plus imdevimab can be used as an alternative route of administration (BIII).

APIC Supports Mandatory COVID-19 Vaccine Policies in Healthcare Facilities June 30, 2021

The Association for Professionals in Infection Control and Epidemiology (APIC) announced Wednesday its support for hospitals and health systems that are requiring all employees and clinical team members to be vaccinated against COVID-19 as a condition of employment. Vaccinations have brought about a sharp decline in COVID-19 cases, but vaccinations have stalled in recent weeks, likely short of the necessary threshold to adequately halt the spread of the virus. COVID-19 so far has claimed the lives of more than 600,000 Americans. Mandatory healthcare worker vaccination policies for influenza and other infectious diseases already exist and have proven effective. APIC urges everyone who is eligible to receive the COVID-19

vaccine. All the COVID-19 vaccines available in the U.S. under the FDA emergency use authorization are safe, effective, and readily available.

WHO versus CDC Mask Policy June 30, 2021

The director of the CDC, Dr. Rochelle Walensky, on Wednesday stood by advice that people fully vaccinated against the coronavirus do not need to wear masks in most situations but added that there are instances where local authorities might impose more stringent measures to protect the unvaccinated.
The comments came after the WHO recently reiterated longstanding guidance that everyone, vaccinated or not, wear masks and take other precautions, following a global surge in infections of the more contagious Delta variant. Dr. Walensky added that the WHO's blanket suggestion that both vaccinated and unvaccinated individuals wear masks was informed by its global purview.
Comment: Vaccines (fully vaccinated) consistently protect people from the variants circulating in the United States, including the Delta variant. Masking policies are not to protect the vaccinated — they are to protect the unvaccinated. Most new infections are in unvaccinated individuals. To remind readers, in the Briefing on June 8th I reviewed a MMWR publication on hospitalizations of adolescents aged 12-17. Although adolescents are less likely than adults to be hospitalized with COVID-19, their risk of hospitalization is about three times greater than for influenza and they can spread infection to other unvaccinated people. It is time that individuals take personal responsibility and get vaccinated to not only protect themselves, but our communities.

Almost All US COVID-19 Deaths Now in the Unvaccinated AP June 29, 2021

An AP report based on governmental data (CDC) in May shows that "breakthrough" infections in fully vaccinated people accounted for fewer than 1200 of more than 107,000(~1.1%) Covid-19 hospitalizations. About 150 of more than 18,000 Covid-19 deaths in May were in fully vaccinated people. They say that translates to ~0.8% or five deaths per week on average.

Comment: The AP analysis included only 45 states that report breakthrough infections. Earlier this month Andy Slavitt (a former advisor to the Biden administration on Covid-19) suggested that 98% of Americans dying of Covid-129 were unvaccinated. In Seattle, the health department found only three deaths during a 60-day period in people who were fully vaccinated. The rest, some 95% had had no vaccine or just one dose. I think you get the picture!

Delta Most Common Covid-19 Variant in U.S. June 30, 2021

An analysis of genetic sequencing data as of June 27th showed that the Delta strain now makes up about 40% of positive Covid-19 test samples, according to Helix, a population genomics company that collects and analyzes test samples from several U.S. states. Most Helix's data comes from pharmacies in 10 states, including Florida and California. Helix's data showed that the Delta strain is now more prevalent than Alpha, which had been the most common strain in the U.S. since March. Helix said Alpha has dropped below 20% of positive test samples sequenced. Another variant, called Gamma, or P.1, appears to be plateauing. CDC data

showed that as of June 19th, Delta made up only 26.1% of positive Covid-19 samples sequenced, while Alpha made up 47.8%.

Comment: Full doses of the Pfizer, Moderna, and AstraZeneca Covid-19 vaccines protect against the Delta variant, according to data from Public Health England.[reviewed recently in the COVID-19 Briefing] To repeat from the Briefing on June 29th, a recent study confirms that fully vaccinated individuals(both doses) given the Pfizer vaccine had an 88% effective effectiveness against symptomatic disease caused by delta, but only a 33% effectiveness if a single dose of the vaccine was given. (see Lancet article below) The time has come for vaccine refusers to take personal responsibility for their hesitancy. We must stop making excuses for them. They not only put their health at risk, but they also put others at risk as well. Because of the unvaccinated we may need to reinstate burdensome precautions. Lastly, although we have made progress, we need more robust genomic surveillance.

Journal Review

Safety and Efficacy of NVX-CoV2373 Covid-19 Vaccine N Engl J Med published online June 30, 2021

DOI: 10.1056/NEJMoa2107659

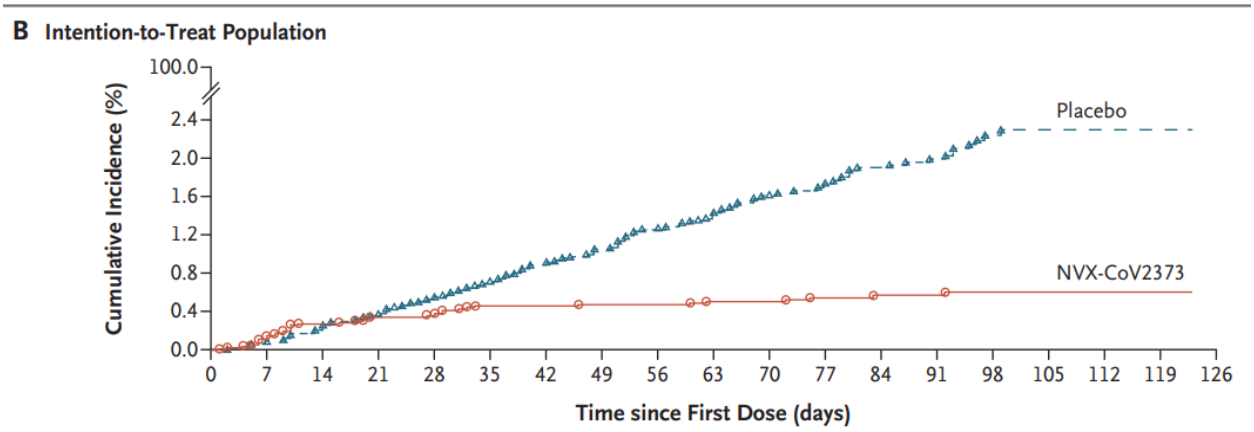
This is a Phase III randomized controlled trial enrolled 15,187 participants at 33 sites in the UK from September 28 to November 28, 2020. Eligible participants were men and nonpregnant women between the ages of 18 and 84 years who were healthy or had stable chronic medical conditions, including HIV infection (for which they were receiving highly active antiretroviral therapy) and cardiac and respiratory diseases. Participants were randomly assigned to receive two intramuscular 5-μg doses of NVX, or placebo administered 21 days apart. NVX is a protein-based, adjuvanted vaccine.

A total of 15,139 participants who received at least one dose of NVX (n = 7,569) or placebo (n = 7,570) were included in the safety population. The primary efficacy endpoint was virologically confirmed symptomatic mild, moderate, or severe SARS-CoV-2 infection with an onset at least 7 days after the second injection in participants who were serologically negative at baseline.

The per-protocol efficacy population included 14,039 participants (7,020 in the vaccine group and 7,019 in the placebo group) with a median age of 56 years and 27.9% of the participants were 65 years of age or older. Overall, cases of virologically confirmed, symptomatic mild, moderate, or severe COVID-19 with an onset at least 7 days after receiving a second dose occurred in 10 of 7,020 vaccine recipients (6.53 per 1,000 person-years; 95% confidence interval [CI], 3.32-12.85) and in 96 of 7,019 placebo recipients (63.43 per 1,000 person-years; 95% CI, 45.19-89.03), for a vaccine efficacy of 89.7% (95% CI, 80.2-94.6).

No hospitalizations or deaths were reported among the 10 cases in the vaccine group, whereas 5 cases of severe infection were reported in the placebo group. Of the 10 vaccine breakthrough cases, 8 were caused by the B.1.1.7 variant(alpha), 1 was caused by a non-B.1.1.7 variant, and 1 viral strain could not be identified. Among the participants who were 65 years of age or older, overall vaccine efficacy was 88.9% (95% CI, 20.2-99.7). Meanwhile, a post hoc analysis showed an efficacy of 86.3% (95% CI, 71.3-93.5) against the B.1.1.7 variant and 96.4% (95% CI, 73.8-99.5) against non-B.1.1.7 variants.

Side effects were reported to be generally mild or moderate, and reactions were less common and milder in older participants and more common after the second dose. Injection-site tenderness and pain, fatigue, headache, and muscle pain were the most reported local and systemic adverse events.



Comment: A two-dose regimen of the NVX vaccine administered to adult participants conferred 89.7% protection against SARS-CoV-2 infection and showed high efficacy against the B.1.1.7 variant. The incidence of serious adverse events was low and similar in the two groups. NVX can be stored at standard refrigeration temperatures and can induce a broad epitope response to the spike protein antigen. Efficacy estimates reported here are derived from a relatively short duration of observation (median, 3 months after dose 2). Thus, the ongoing follow-up will provide data regarding the durability of vaccine efficacy. The big question now is how NVX performs against the delta variant.

AZD1222-induced neutralising antibody activity against SARS-CoV-2 Delta VOC Lancet published online June 28, 2021

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The authors set out to determine delta variant sensitivity to AZ-induced neutralizing antibodies (NAbs) and to compare this to their previous measurements of NAbs induced by Pfizer vaccine. They also carried out a second initial analysis of Legacy study participants vaccinated with AZ. Legacy was initiated in early 2021 by University College London Hospitals and the Francis Crick Institute in London, UK, to track serological responses to vaccination during the national COVID-19 vaccination program in prospectively recruited healthy staff volunteers.

Using a high-throughput live-virus SARS-CoV-2 neutralization assay, they determined NAb titers (NAbTs) against five SARS-CoV-2 strains in 106 participants (median age 34 years, IQR 29–42) after either one dose of AZ (n=50, median time after first dose 41 days [IQR 30–51]) or two doses of AZ (n=63, median
time after second dose 31 days [IQR 19·5–46·0]. The median interval between doses was 63 days (IQR 62·0–69·5).

Two doses of AZ generated NAb activity against the wildtype strain bearing a spike identical to that encoded by the vaccine in all participants (median NAbT IC50=419), with a 2·1–fold (95% CI 2·0–2·2) reduction in median NAbT relative to two doses of Pfizer vaccine. Moreover, median

NAbTs against all SARS-CoV-2 variants were further reduced relative to Pfizer: 2·4-fold (95% CI 2·3–2·6) against D614G(wild type), 2·4-fold against B.1.1.7 [alpha UK] (2·2–2·5), 2·5-fold (1·3–2·8) against B.1.351[beta So African], and 2·5-fold (1·4–2·7) against B.1.617.2.[delta] Nearly all participants had a quantifiable NAbT against the D614G(wild type) and B.1.1.7 variants (55 [87%] of 63 [95% CI 76–94%], significantly fewer participants had quantifiable NAbTs against B.1.351 and B.1.617.2 VOCs after two doses of AZ (38 [60%] of 63 [95% CI 47–72%] against B.1.351; and 39 [62%] of 63 [49–74%] against B.1.617.2), relative to the former two variants (χ^2 test p<0·0011). Analysis of these data by ordered logistic regression confirmed vaccine type was associated with decreased NAbTs, independent of SARS-CoV-2 strain, in two-dose vaccine recipients (p=0·0017). After a single AZ dose, participants with prior COVID-19 symptoms (16 [32%] of 50) had significantly higher NAbTs against all strains than those without prior COVID symptoms ($5{\cdot}1 \times 10^{-5} \leq p \leq 3{\cdot}1 \times 10^{-4}$). Analysis by ordered logistic regression confirmed that a previous history of COVID-19 symptoms was associated with increased NAbTs, independent of SARS-CoV-2 strain, in single-dose AZ recipients.

These data, together with their previous findings, reveal that AZ recipients have lower NAbTs than Pfizer recipients against SARS-CoV-2 variants, including B.1.617.2. Notably, their data are consistent with preliminary observational estimates based on rates of *S* gene target failure during PCR testing in England (MedRxiv 2021; published online May 24. doi.org/10.1101/2021.05.22.21257658) and more recent data from Scotland,(Lancet 2021; 397**:** 2461–62 review in the Briefing). which reports 19% reduced AZ efficacy following two doses (60%) relative to two doses of Pfizer (79%) against the B.1.617.2 variant and similar to reduced efficacy against the B.1.1.7 variant(alpha) following two doses (73% for AZ *vs* 92% for Pfizer).

Comment: Their data also suggest that further booster immunizations might be needed, especially for more susceptible groups that have received vaccines that induce lower than average NAbTs. The UK is considering booster doses before next winter.

Prevention and Attenuation of Covid-19 with the BNT162b2 and mRNA-1273 Vaccines N Engl J Med published online June 30, 2021

DOI: 10.1056/NEJMoa2107058

The investigators conducted a prospective cohort study involving 3975 health care personnel, first responders, and other essential and frontline workers. From December 14, 2020, to April 10, 2021, the participants completed weekly SARS-CoV-2 testing by providing mid-turbinate nasal swabs for qualitative and quantitative RT-PCR analysis.

SARS-CoV-2 was detected in 204 participants (5%), of whom 5 were fully vaccinated (≥14 days after dose 2), 11 partially vaccinated (≥14 days after dose 1 and <14 days after dose 2) and 156 unvaccinated. Of the 93 genetically sequenced viruses, 12 were detected in participants with indeterminate vaccination status and were excluded. Of the remaining viruses, 10 were variants of concern (8 were the B.1.429 variant and 1 was the B.1.427 variant [epsilon] and 1 was the B.1.1.7 variant [alpha]); 1 was a variant of interest (the P.2 variant [zeta]). There were 10 genetically sequenced viruses detected in partially or fully vaccinated participants; 3 of these 10 viruses (30%) were variants of concern (all the B.1.429 variant [epsilon]), as compared with 7 of the 70 viruses (10%) detected in unvaccinated participants (excluding the variant of interest. The rest were wild type.

Adjusted vaccine effectiveness was 91% (95% confidence interval [CI], 76 to 97) with full vaccination and 81% (95% CI, 64 to 90) with partial vaccination. Among participants with SARS-CoV-2 infection, the mean viral RNA load was 40% lower (95% CI, 16 to 57) in partially or fully vaccinated participants than in unvaccinated participants. In addition, the risk of febrile symptoms was 58% lower (relative risk, 0.42; 95% CI, 0.18 to 0.98) and the duration of illness was shorter, with 2.3 fewer days spent sick in bed (95% CI, 0.8 to 3.7).

Table 3. Viral RNA Load, Duration of Viral RNA Detection, Frequency of Febrile Symptoms, and Duration of Illness in Vaccinated and Unvaccinated Participants with SARS-CoV-2 Infection.*

Variable	Unvaccinated	Partially or Fully Vaccinated	Difference (95% CI)
Viral RNA load			
No. assessed	155	16	—
Mean — $\log_{10}$ copies/ml†	3.8±1.7	2.3±1.7	40.2 (16.3–57.3)‡
Duration of viral RNA detection			
No. assessed	155	16	—
Mean — days	8.9±10.2	2.7±3.0	6.2 (4.0–8.4)
Detection of viral RNA for >1 week — no./total no. (%)	113/156 (72.4)	4/16 (25.0)	0.34 (0.15–0.81)§
Febrile symptoms — no./total no. (%)¶	94/149 (63.1)	4/16 (25.0)	0.42 (0.18–0.98)‖
Total days of symptoms			
No. assessed	148	16	—
Mean — days	16.7±15.7	10.3±10.3	6.4 (0.4–12.3)
Days spent sick in bed			
No. assessed	147	15	—
Mean — days	3.8±5.9	1.5±2.1	2.3 (0.8–3.7)

Comment: The current mRNA vaccines are highly effective among working-age adults in preventing SARS-CoV-2 infection when administered in real-world conditions, and in addition the vaccines attenuated the viral RNA load, risk of febrile symptoms, and duration of illness among those who had breakthrough infection despite vaccination. This study include the focus on working-age adults without previous laboratory documented SARS-CoV-2 infection and the use of weekly testing for SARS-CoV-2 infection and illness with high adherence to surveillance. The investigators did not perform genetic sequencing for all viruses. The majority were wild type, so this study does not address effectiveness against delta variant. [see above] Because there was a relatively small number of breakthrough infections, they could not differentiate attenuation effects associated with partial vaccination from effects associated with full vaccination. Results for febrile symptoms and duration of illness were based on participant-reported data, which can be subject to recall and confirmation biases. As with other studies like this, the detection of viral RNA may not be equivalent to actual isolation the virus; however, low cycle thresholds on PCR assay have been associated with the ability to isolate SARS-CoV-2 in culture, and both the level and the duration of viral RNA detection are associated with infectivity and transmission in other viral infections.

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