TGIF – As Ed Sullivan used to say (many of you are too young to remember Ed Sullivan) we have a really big show – well today we have a really big Daily Briefing.

Under Covid-19 News I start with a summary of the IDSA Guideline on Rapid Antigen testing. Next is the announcement of EUA by WHO of a second Chinese vaccine. Last is the WHO decision to start labeling SARS-CoV-2 variants based on the Greek alphabet.

Under Journal Review a study comparing methylprednisolone versus dexamethasone for patients hospitalized with Covid-19. The next two articles report on risk of reinfection after natural infection in two different countries. The last is a nice analytical model used to simulate COVID-19 transmission and progression from March 24, 2020, to September 23, 2021, using different assumptions of vaccine efficacy, coverage, and use of NPI.

Have a relaxing weekend – next Daily Briefing Tuesday.

Ed

COVID-19 News

IDSA Guidelines on the Diagnosis of COVID-19: Antigen Testing Highlights
May 27, 2021 – article provided by Cesar Arias
The overall specificity of SARS-CoV-2 Ag testing was ≥ 99% compared to standard NAAT (i.e., rapid RT-PCR or laboratory-based NAAT). Therefore, routine confirmation of positive Ag results by a reference molecular method does not appear to be necessary, even in most low prevalence settings. Alternatively, Ag test sensitivity varied widely across studies and was dependent on the presence or absence of documented COVID-19 symptoms and the time of testing after symptom onset. Pooled Ag test sensitivity was 84% for symptomatic individuals tested within the first seven days of illness, 62% after seven days or more of symptoms and 49% for those without symptoms. Antigen tests performed similarly in adults and children**.**

Given the superior sensitivity of molecular diagnostics, the panel suggests the use of standard NAAT over Ag tests, especially for individuals with symptoms of COVID-19 or when the implications of missing the diagnosis of SARS-CoV-2 are significant (such as for hospitalized patients, in long-term care facilities, or when screening for asymptomatic infection before major surgery). For symptomatic patients, if Ag testing is used, negative results should be confirmed by standard NAAT when the clinical suspicion of COVID-19 is high. Ultimately, deciding whether to use rapid Ag tests in lower-risk, non-medical settings will depend on several factors including the prevalence of disease in the population combined with an assessment of the value of detecting true SARS-CoV-2 infection *versus* the detrimental effects of erroneous results (i.e., false negative and false positive results).

Recommendation 1**:** For symptomatic individuals suspected of having COVID-19, the IDSA panel suggests using standard NAAT (either rapid RT-PCR or laboratory-based NAAT) over rapid Ag tests (*conditional recommendation based on moderate certainty in test accuracy of rapid Ag test and very low certainty in comparative test accuracy of rapid RT-PCR* versus *rapid Ag tests*).

Recommendation 2**:** For asymptomatic individuals with risk for exposure to SARS-CoV-2 infection, the IDSA panel suggests using a single standard NAAT (either rapid RT-PCR or laboratory-based NAAT) over a

single rapid Ag test (*conditional recommendation based on moderate certainty in test accuracy of rapid Ag tests and very low certainty in comparative test accuracy of rapid RT-PCR* versus *rapid Ag tests*).

Recommendation 3: For asymptomatic individuals with risk for exposure to SARS-CoV-2 infection, the IDSA panel suggests a single (i.e., one-time) standard NAAT (either rapid RT-PCR or laboratory-based NAAT) rather than a strategy of two consecutive rapid Ag tests (*conditional recommendation based on moderate certainty in test accuracy of molecular testing and an evidence gap to inform the test accuracy of strategies using repeat Ag testing*).

- If two rapid Ag tests are performed, sequential testing during the same clinical encounter, when the first test is negative, does not appear to improve sensitivity. The optimal timing between two sequential tests has not been established.

Recommendation 4**:** In asymptomatic individuals with risk for exposure to SARS-CoV-2 infection, the IDSA panel suggests neither for nor against using single (i.e., one-time) rapid Ag testing over no testing (evidence gap to inform the utility of Ag testing compared to no testing).

- SARS-CoV-2 testing in the absence of COVID-like symptoms should be individualized. Vaccination status and history of prior laboratory-confirmed SARS-CoV-2 infection may affect decisions about whether to test in certain situations.

Recommendation 5**:** In asymptomatic individuals with risk for exposure to SARS-CoV-2 infection, the IDSA panel suggests neither for nor against using repeat rapid Ag testing over no testing (*evidence gap to inform the utility of a strategy of Ag testing compared to no testing)*.

- Repeat Ag testing (*versus* no testing) is likely to have utility in congregate settings experiencing an outbreak.
- Repeat Ag testing (*versus* no testing) is also expected to detect some asymptomatic infections in populations with moderate to high prevalence (i.e., ≥5%).
- If repeated Ag tests are performed, the optimal number, timing and duration of testing has not been established and may vary by the indication for testing.

Test features	Antigen tests	Nucleic acid amplification tests
Limitations	• Less sensitive (more false negatives) than standard* NAAT, especially for asymptomatic individuals or when testing is performed late in the course of infection • Negative Ag results in symptomatic persons require confirmation with NAAT • Large scale testing using LFAs may be more complicated to scale up than high-throughput laboratory-based NAAT	• Laboratory based NAAT may have long turnaround times, depending on the laboratory • Prolonged RNA shedding is detectable by sensitive NAATs during the recovery phase of COVID-19, which is potentially beyond the presumed period of infectiousness • The sensitivity of molecular assays targeting the spike gene may be affected by circulating variants (gene mutations) • NAAT is generally more expensive than Ag testing

Ag: Antigen; **LFA:** Lateral flow assay; **RT-PCR**: Reverse transcriptase polymerase chain reaction; **NAAT:** Nucleic acid amplification test; **TMA:** Transcription-mediated amplification

Comment: This is a wonderful reference. In the end, testing type should be individualized based on factors discussed above. The table above is a good summary of the limitations of antigen and NAAT. When choosing a test be aware of the limitation, the indication, and setting in which the test is used.

WHO Validates Sinovac COVID-19 Vaccine for Emergency Use

The WHO has validated the Sinovac-CoronaVac COVID-19 vaccine for emergency use in adults 18 years and older, in a two-dose schedule with a spacing of two to four weeks. Sinovac-CoronaVac is an inactivated vaccine. The review of the vaccine demonstrated prevention of symptomatic disease in 51% of those inoculated and prevented severe COVID-19 and hospitalization in almost 100% of participants in trials. The agency noted that few adults over 60 were enrolled in clinical trials of CoronaVac, so efficacy could not be estimated in this age group. Phase III clinical trials of Sinovac's vaccine have been conducted in Turkey, Chile, Indonesia, and Brazil with varying efficacy results. Protection against symptomatic COVID-19 at least 14 days after the second dose was 84% in the Turkish trial, but fell to 65% and 51%, respectively, in the studies conducted in Indonesia and Brazil. Meanwhile, vaccine efficacy in the Chilean study was 67% at least 14 days after two doses.

WHO Announced a Simple Labeling System for SARS-CoV-2 Variants

June 1, 2021

The WHO announced a labeling system for SARS-CoV-2 variants, which relies on the Greek alphabet, they claim making them easier to remember and avoids naming after places they were first detected. It said it chose the labeling system after convening an international expert group.

Variants of Concern:

WHO label	Pango lineage	GISAID clade/lineage	Nextstrain clade	Earliest documented samples	Date of designation
Alpha	B.1.1.7	GRY (formerly GR/501Y.V1)	20I/S:501Y.V1	United Kingdom, Sep-2020	18-Dec-2020
Beta	B.1.351	GH/501Y.V2	20H/S:501Y.V2	South Africa, May-2020	18-Dec-2020
Gamma	P.1	GR/501Y.V3	20J/S:501Y.V3	Brazil, Nov-2020	11-Jan-2021
Delta	B.1.617.2	G/452R.V3	21A/S:478K	India, Oct-2020	VOI: 4-Apr-2021 VOC: 11-May-2021

Variants of Interest:

WHO label	Pango lineage	GISAID clade/lineage	Nextstrain clade	Earliest documented samples	Date of designation
Epsilon	B.1.427/B.1.429	GH/452R.V1	20C/S.452R	United States of America, Mar-2020	5-Mar-2021
Zeta	P.2	GR	20B/S.484K	Brazil, Apr-2020	17-Mar-2021
Eta	B.1.525	G/484K.V3	20A/S484K	Multiple countries, Dec-2020	17-Mar-2021
Theta	P.3	GR	20B/S:265C	Philippines, Jan-2021	24-Mar-2021
Iota	B.1.526	GH	20C/S:484K	United States of America, Nov-2020	24-Mar-2021
Kappa	B.1.617.1	G/452R.V3	21A/S:154K	India, Oct-2020	4-Apr-2021

Comment: This will take getting used to and maybe more difficult to remember compared to saying UK or South African variant. It also requires some knowledge of the Greek alphabet!

Journal Review

Methylprednisolone or Dexamethasone, Which One is Superior Corticosteroid in the Treatment of Hospitalized COVID-19 Patients: A Triple-Blinded Randomized Controlled Trial
BMC Infect Dis published April 10, 2021

Methylprednisolone achieves higher lung tissue concentrations than dexamethasone, raising questions about whether it would be more effective. Investigators randomized 86 adults with confirmed SARS-CoV-2 infection who were hospitalized (with oxygen saturation ≤92% on room air) to receive either intravenous methylprednisolone (2 mg/kg daily dose tapered after 5 days; total dosing, 10 days) or intravenous dexamethasone (6 mg daily for 10 days). Patients and investigators were blinded to drug assignments.

Based on the WHO's Ordinal Scale for Clinical Improvement, patients who received methylprednisolone had significantly greater clinical improvement than patients who received dexamethasone. Methylprednisolone patients also had significantly lower ventilator requirements (18% vs. 38%; number needed to treat, 5), significantly shorter hospital length of stay (3 days fewer), and a trend toward lower mortality (19% vs. 38%; NNT, 6; *P*=0.076), compared with dexamethasone patients.

Comment: It is unclear to me if the study results are due to the type of steroid and its improved lung penetration or to the much higher relative dose of methylprednisolone prescribed. This is a small study and needs additional study. Nonetheless, this approach could be considered in patients with severe Covid-19.

SARS-CoV-2 Re-Infection Risk in Austria
Eur J Clin Invest. 2021;51:e13520.
doi.org/10.1111/eci.13520
This is a retrospective observational study using national SARS-CoV-2 infection data from the Austrian epidemiological reporting system. As the primary outcome, they aimed to compare the odds of SARS-CoV-2 re-infections of COVID-19 survivors of the first wave (February to April 30, 2020) versus the odds of first infections in the remainder general population by tracking polymerase chain reaction (PCR)-confirmed infections of both groups during the second wave from September 1 to November 30, 2020. We recorded 40 tentative re-infections in 14,840 COVID-19 survivors of the first wave (0.27%) and 253,581 infections in 8,885,640 individuals of the remaining general population (2.85%) translating into an odds ratio (95% confidence interval) of 0.09 (0.07 to 0.13).

Comment: The range of reduction of re-infection from COVID-19 was between 82% to 95% among six studies that encompassed nearly 1 million people conducted in the U.S., the U.K., Denmark, Austria, Qatar, and among U.S. Marines. The study above demonstrates that the frequency of re-infection from COVID-19 caused hospitalization in only five out of 14,840 (0.03%) people and death in one out of 14,840 (0.01%). Protection against SARS-CoV-2 after natural infection is comparable with the highest available estimates on vaccine efficacies in this study. From recent studies reviewed in the last few weeks on the Daily Briefing confirm the immune response of more than 95% of people who recovered from COVID-19 had durable memories of the virus up to 8 months to a year after natural infection.

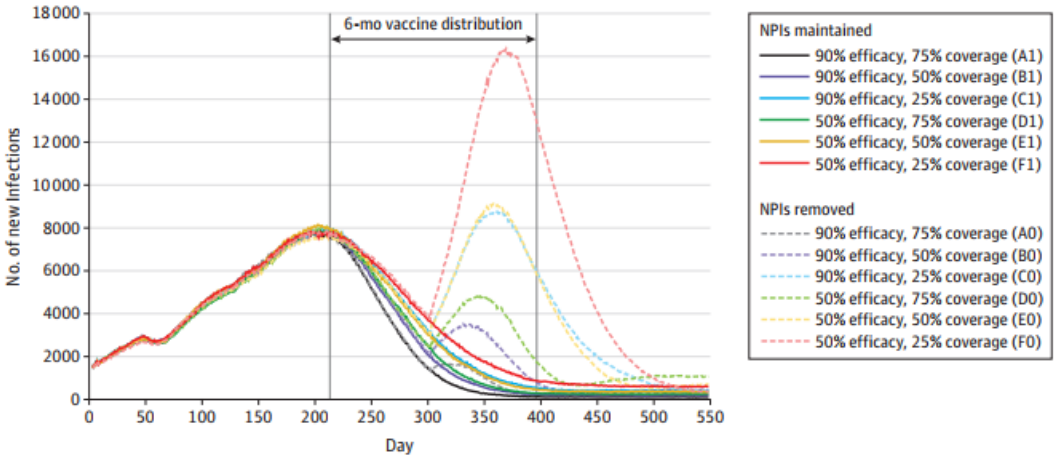
Assessment of SARS-CoV-2 Reinfection 1 Year After Primary Infection in a Population in Lombardy, Italy
JAMA Intern Med published online May 28, 2021
doi:10.1001/jamainternmed.2021.2959
The researchers followed 1,579 COVID-positive patients and 13,496 COVID-negative patients who received PCR diagnoses from February to July 2020 in Italy. After an average follow-up time of 280 days (end date, Feb 28, 2021), 5 previously COVID-infected patients tested positive again via PCR (0.3%), and 528 people were infected for the first time (3.9%).

The hazard ratio for reinfection compared with initial infection was 0.06 (95% confidence interval, 0.05 to 0.08). Incidence density was 1.0 per 100,000 person days for those with a prior infection and 15.1 for those without. Reinfection was defined as a second positive PCR test at least 90 days from the first positive diagnosis and with at least two consecutive negative diagnoses in between.

Comment: We do not know how long natural immunity lasts or if natural immunity to the wild-type virus is equally protective for SARS-CoV-2 variants but articles like this and the one above suggests some immunity. Studies to date suggest that immunization plus history of natural infection is better protection than natural infection alone; therefore, all persons should be encouraged to get vaccinated even if they have been previously infected with SARS-CoV-2. Lastly, achieving herd immunity through natural infection is a long and difficult process. Historically, the only human disease to be eradicated, smallpox, was eradicated through vaccination, not natural infection. [Polio has been eradicated in NA] In addition, one of the greatest public health achievements of the last century is significant reduction of vaccine preventable diseases.

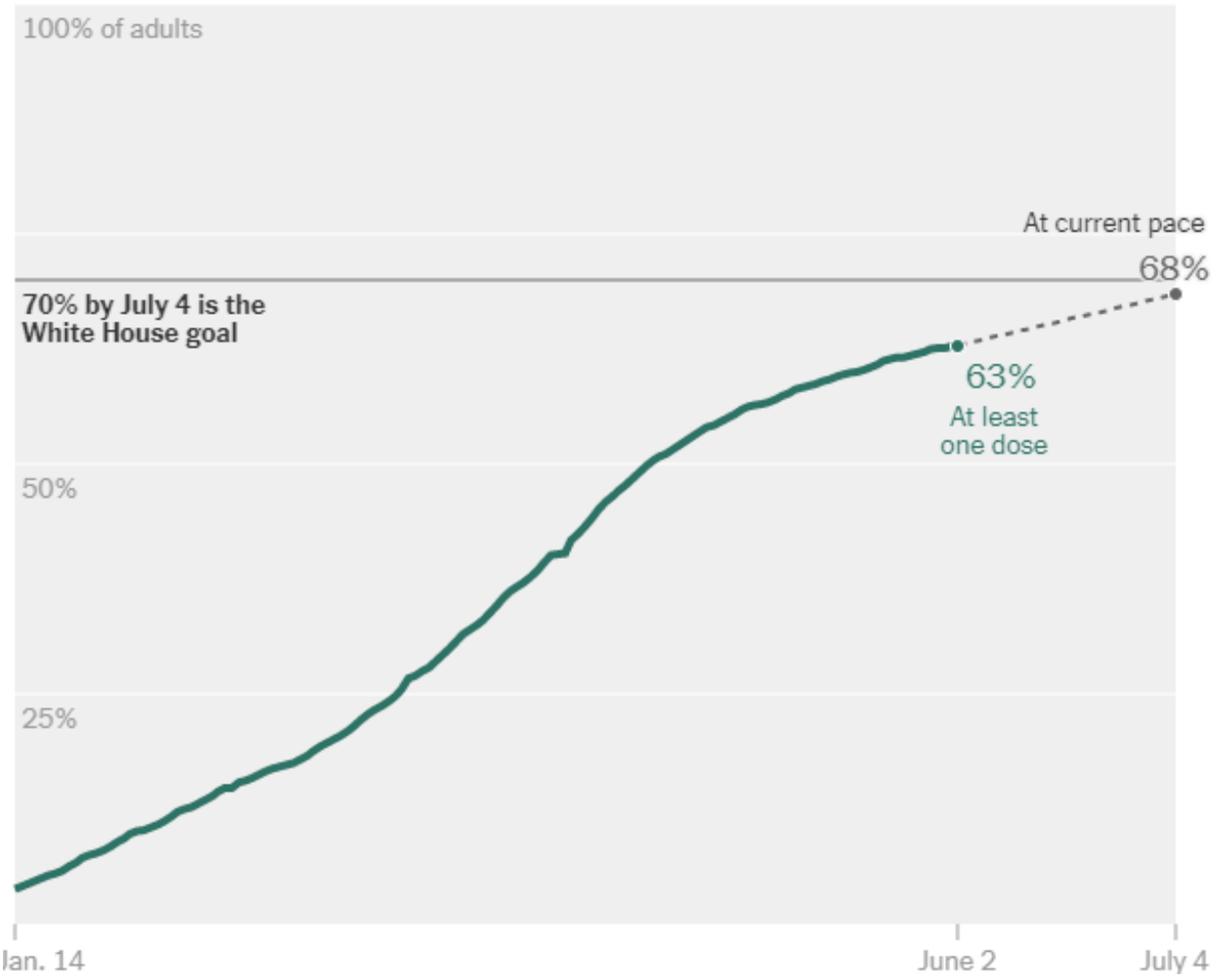
Association of Simulated COVID-19 Vaccination and Nonpharmaceutical Interventions with Infections, Hospitalizations, and Mortality
JAMA Netw Open June 1, 2021
doi:10.1001/jamanetworkopen.2021.10782
An established decision analytical model was used to simulate COVID-19 transmission and progression from March 24, 2020, to September 23, 2021. The model simulated COVID-19 spread in North Carolina, a US state of 10.5 million people. Scenarios of vaccine efficacy (50% and 90%), vaccine coverage (25%, 50%, and 75% at the end of a 6-month distribution period), and NPIs (reduced mobility, school closings, and use of face masks) maintained and removed during vaccine distribution. The main outcomes and measures were risks of infection from the start of vaccine distribution and risk differences comparing different scenarios.

In the worst-case vaccination scenario (50% efficacy, 25% coverage), a mean (SD) of 2,231,134 (117,867) new infections occurred after vaccination began with NPIs removed, and a mean (SD) of 799,949 (60,279) new infections occurred with NPIs maintained for 11 months. In contrast, in the best-case scenario (90% efficacy, 75% coverage), a mean (SD) of 527,409 (40,637) new infections occurred with NPIs removed and a mean (SD) of 450,575 (32,716) new infections occurred with NPIs maintained. With NPIs removed, lower efficacy (50%) and higher coverage (75%) reduced infection risk by a greater magnitude than higher efficacy (90%) and lower coverage (25%) compared with the worst-case scenario (mean [SD] absolute risk reduction, 13% [1%] and 8% [1%], respectively).



Comment: It is apparent that lifting NPIs while rolling out vaccinations was associated with a significant increase in the number of infections, hospitalizations, and deaths across the range of vaccine effectiveness and vaccine coverage assumptions. Second, achieving a higher vaccine coverage leads to a greater reduction in the number of infections, even with the relatively lower vaccine effectiveness in the absence of NPIs with a combination of 75% coverage and 50% efficacy, resulting in a greater risk reduction compared with 25% coverage and 90% efficacy. Lastly, the cumulative incidence of infections, hospitalizations, and deaths varied by ethnicity/race and place of residence across different scenarios, with African American persons and residents of rural areas faring the worst.

These findings highlight the need to coordinate efforts to achieve high vaccine coverage and continued adherence to NPIs before completely lifting NPIs. We know mRNA vaccines are >90% efficacious both against symptomatic and asymptomatic disease and as a country as of June 2nd, 63% of the total population has had a least 1 dose of vaccine (86%>65; 63% adults). See graph below. New infections and hospitalizations are down. Not in calculation is percent of population immune by natural infection. [difficult to get an exact number] CDC's revised masking guidance considers the impact of vaccinations and transmission based on recent studies. Bottom line: if you are fully vaccinated you can choose to remove your mask and relax social distancing. Tracking cases after Memorial Day will be a big test to see if relaxing NPI in vaccinated people is safe in a real-world setting. We have come a long way, but the pandemic is not over. I think we will see a decoupling between new cases and hospitalizations and deaths since most high-risk people have been vaccinated.


100% of adults
At current pace
68%
70% by July 4 is the White House goal
63%
At least one dose
50%
25%
Jan. 14
June 2
July 4