Good morning

I start today's Briefing with my reaction to Governor Abbott's announcement to lift restrictions in the state of Texas.

On the journal front, the first two articles look at thromboprophylaxis. The next two articles examine the humoral and T-cell responses in people who had prior infection with SARS-CoV-2 given a single dose of vaccine compared to infection-naïve people. The last article explores the question does antecedent statin use decrease mortality in patients with COVID-19.

Have a great day.

Ed

COVID-19 News

The big buzz surrounds Texas Governor Abbott's decision to lift restrictions to end state mask mandate and allow businesses to operate with no capacity limits. On Tuesday, Mississippi Gov. Tate Reeves also said he would be dropping the state's mask mandate and all business-capacity restrictions. Below is my take on Governor Abbott's decision.

VII editorial
Today Governor Greg Abbott announced that effective March 10, he is lifting the statewide mask mandate and capacity limits on businesses, however the Governor also encouraged people to continue following medical advice and safe practices to prevent the spread of COVID.

Average daily hospital admissions have dropped but case counts are still too high and might be plateauing. The pandemic is not over, and we do not have community control. The impact of the winter storm on transmission is yet to play out and vaccinations are now a week behind due to the storm. We also have spring break approaching in the next few weeks. Finally, current levels of immunity are not enough to reach herd immunity and new variants may gain a foothold here in Houston and around the state. Certain variants are known to be more contagious and may be more deadly.

As of yesterday, only 6.6% of the Texas population had been fully vaccinated against Covid-19 and the state had a 13.5% positivity rate for Covid-19 tests, according to Johns Hopkins University.

Given current unknowns and community rates of COVID-19, now is not the time to rapidly relax safety measures. Although there is reason for cautious optimism as COVID-19 cases have declined and vaccination rates are increasing, I think it is a mistake to lift these mandates too early.

Journal Review

Pharmacologic Thromboprophylaxis and Thrombosis in Hospitalized Patients with COVID-19: A Pooled Analysis
Thromb Haemost 2021;121:76–85
doi: 10.1055/s-0040-1721664

Thrombosis, Bleeding, and the Observational Effect of Early Therapeutic Anticoagulation on Survival in Critically Ill Patients With COVID-19

Ann Intern Med published online January 26, 2021
doi:10.7326/M20-6739

The first article is a meta-analysis. The authors pooled data from 35 cohort studies to compare pharmacologic dosing strategies among nearly 11,000 hospitalized COVID-19 patients. Pooled incidence of venous thromboembolism (VTE) and arterial thromboembolism was significantly lower in patients who received any pharmacologic prophylaxis, but the various dosing strategies did not yield significant differences in outcomes.

	No pharmacologic prophylaxis	**Standard-dose prophylaxis** (e.g., 40-mg enoxaparin [SQ] daily)	**Intermediate-dose prophylaxis** (e.g., 0.5 mg/kg enoxaparin [SQ] twice daily)	**Therapeutic anticoagulation** (e.g., 1 mg/kg enoxaparin [SQ] twice daily)
Venous thromboembolism (DVT or PE)	42%	20%	12%	11%
Arterial thromboembolism	11.3%	2.5%	2.1%	1.3%
Bleeding	6.7%	1.7%	2.1%	6.3%

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The second article is a retrospective cohort study of 3200 intensive care unit (ICU) patients with COVID-19 who received at least standard-dose prophylaxis at 69 U.S. hospitals. Investigators found a low-to-moderate incidence of radiologically confirmed VTE (6.2%) and major bleeding (2.8%) at 14 days. Men and patients with elevated d-dimer levels had significantly higher risk for developing VTE. After median follow-up of 27 days, no survival advantage was seen among patients who received early therapeutic-dose anticoagulation (by the second ICU day — 12% of the cohort) versus any other anticoagulation protocol; any effect might have been mitigated by an additional 30% of patients receiving full anticoagulation after day 2 and before day 14 of their ICU stay.

Comment: These studies show the hospitalized COVID-19 patients benefit from VTE prophylaxis, but it is unclear if outcomes improve with more intensive strategies. Larger trials risk stratified might clarify optimal dosing for VTE prophylaxis.

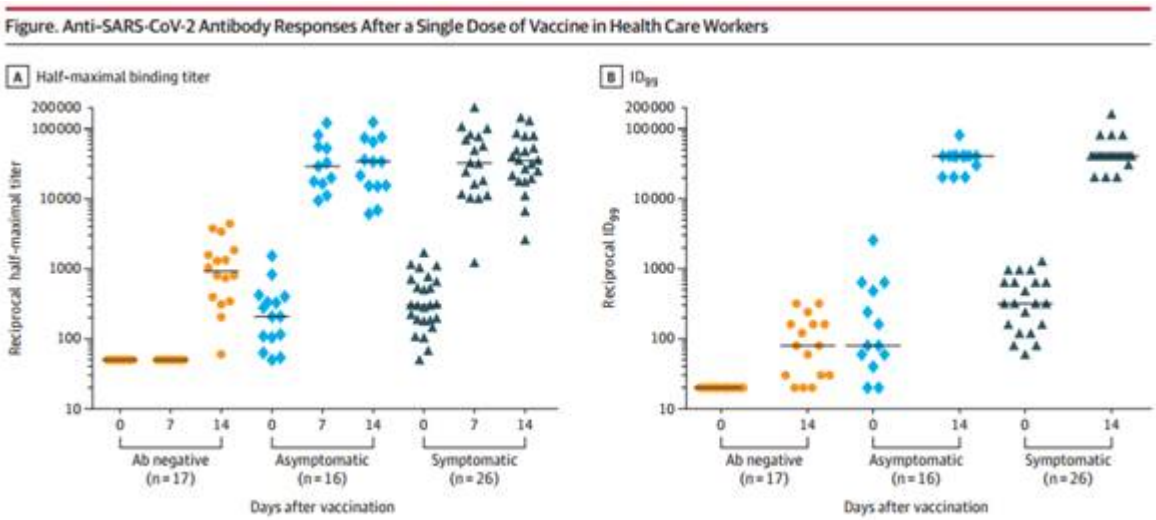
Binding and Neutralization Antibody Titers After a Single Vaccine Dose in Health Care Workers Previously Infected With SARS-CoV-2

JAMA published online March 1, 2021
doi:10.1001/jama.2021.3341

HCWs who had previously enrolled in a hospital-wide serosurvey study were randomly contacted based on stratification into 3 groups: SARS-CoV-2 IgG-antibody negative (Ab-negative); IgG-positive asymptomatic COVID-19 (asymptomatic); and IgG-positive with history of symptomatic COVID-19 (symptomatic). Participants were vaccinated with either the Pfizer or Moderna vaccine, depending on personal preference and availability. Blood was drawn at days 0 (baseline), 7, and 14 postvaccination. Plasma was tested using enzyme-linked immunosorbent assay (ELISA) for IgG to spike trimer.

Of the volunteers, 17 had no evidence of prior infection with SARS-CoV-2 (antibody [Ab]-negative), 16 were antibody-positive but never experienced COVID-19 symptoms, and 26 were antibody-positive and had a history of symptomatic COVID-19. The median age was 38 years for the Ab-negative, 40 years for the asymptomatic, and 38 years for the symptomatic group. The percentage of women was 71% for the Ab-negative, 75% for the asymptomatic, and 88% for the symptomatic group.

At 0, 7, and 14 days, median reciprocal half-maximal binding titers were higher in each of the asymptomatic (208; 29,364; and 34,033) and symptomatic (302; 32,301; and 35,460) groups compared with the Ab-negative group (<50; <50; and 924; *P* < .001 for all). Day 0 and 14 samples were also tested for the 99% inhibitory dose (ID99), which is the highest dilution at which 99% of cells were protected by live virus neutralization (presented as reciprocals). At 0 and 14 days, median reciprocal ID99 virus neutralization titers were higher in the asymptomatic (80 and 40,960) and symptomatic (320 and 40,960) groups compared with the Ab-negative group (<20 and 80; *P* < .001 for all).



Comment: The study clearly showed HCWs with previous COVID-19 infection, based on laboratory-confirmed serology testing, had higher antibody titer responses to a single dose of mRNA vaccine than those who were not previously infected. The results as well as other studies suggest a single-dose vaccination strategy may be enough for those with prior COVID-19. Limitations of the study are the small sample size, lack of demonstration of vaccine efficacy, and potential bias introduced by those enrolling not being representative of the larger original population.

Effect of Previous SARS-CoV-2 Infection on Humoral and T-cell Responses to Single-Dose BNT162b2 Vaccine

Lancet published online February 25, 2021

doi.org/10.1016/S0140-6736(21)00502-X

This study included 72 HCWs from Imperial College Healthcare NHS Trust vaccinated between December 23 and December 31, 2020 who provided blood samples at the time of receiving their first dose of BNT162b2 vaccine (Pfizer) and 21-25 days after vaccination. The authors investigated immunological responses to single-dose BNT162b2 using a combination of serology, live virus neutralization, and T-cell enzyme-linked immunospot (ELISpot) assays.

Of the HCWs, 21 (29%) had evidence of previous SARS-CoV-2 infection, of whom 16 had positive baseline serology, while five had strong T-cell responses to non-spike antigens post-vaccination (>100 spot forming units [SFU] per 10^6 peripheral blood mononuclear cells [PBMC]). Meanwhile, 51 HCWs had negative baseline serology and cellular responses post-vaccine limited to spike antigens; this group was defined as infection-naive.

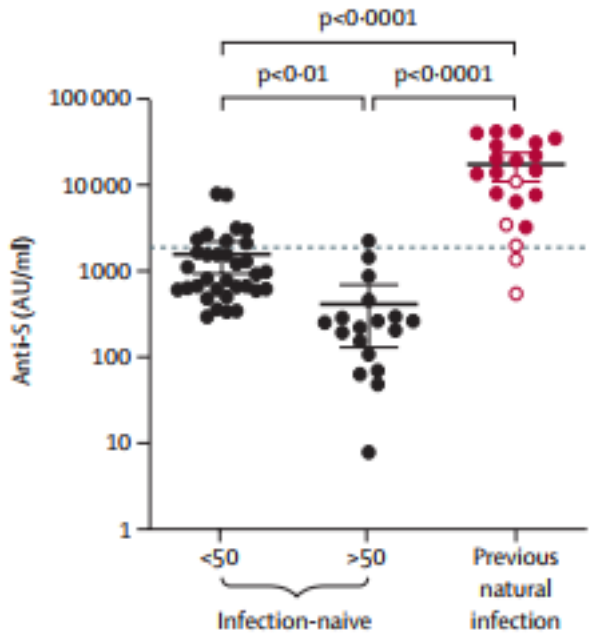
Researchers found that anti-S titers were significantly higher in individuals with previous natural infection than in infection-naive individuals (median 16,353 arbitrary units [AU] per mL [IQR 4741–28 581] vs 615.1 AU/mL (286.4–1491), *P* <0.0001). The five participants with previous natural infection yet negative serology at baseline developed post-vaccination anti-S titers that were intermediate between the infection-naive and previously infected groups.

Infection-naive individuals showed an inverse correlation between post-vaccination anti-S titer and age, with individuals older than 50 years generating a significantly weaker serological response than those younger than 50 years (median 230.1 AU/mL vs 888.9 AU/mL, *P* <0.0001). This correlation was not seen in the group with previous natural infection.

In individuals with previous exposure, they found that the vaccine induced very strong neutralizing antibody titers even in those without detectable or very low virus neutralization titers (NT) at baseline. Meanwhile, in infection-naive individuals, vaccination induced detectable neutralizing antibodies in 15 of 16 sera, but titers were all lower than those of previously infected individuals (median NT_{50} 1/29.50, range from below lower limit of detection to 1/68).

In addition, post-vaccination T-cell responses to spike peptides were significantly weaker in the infection-naive group compared with individuals with previous infection (median 38 SFU/10^6 PBMC [IQR 26–110] vs 400 SFU/10^6 PBMC [IQR 287–544], *P* <0.0001). Further, 24 (50%) of 48 infection-naive patients generated T-cell responses that could be considered negative (<40 SFU/10^6 PBMC). Unlike humoral responses, there was no correlation between age and degree of T-cell response.

Serological response to BNT162b2 inversely correlates with age. They found median anti-S titers post-vaccination in the infection-cohort to be lower than those seen 2–8 weeks after natural infection alone, and this difference was particularly striking in those older than 50 years. In a setting where prioritization of groups of HCWs for second vaccination might be necessary, consideration must be given to protocolized vaccination of infection-naive individuals or those over the age of 50 (who are at increased risk of both severe COVID-19 and minimal vaccine response).



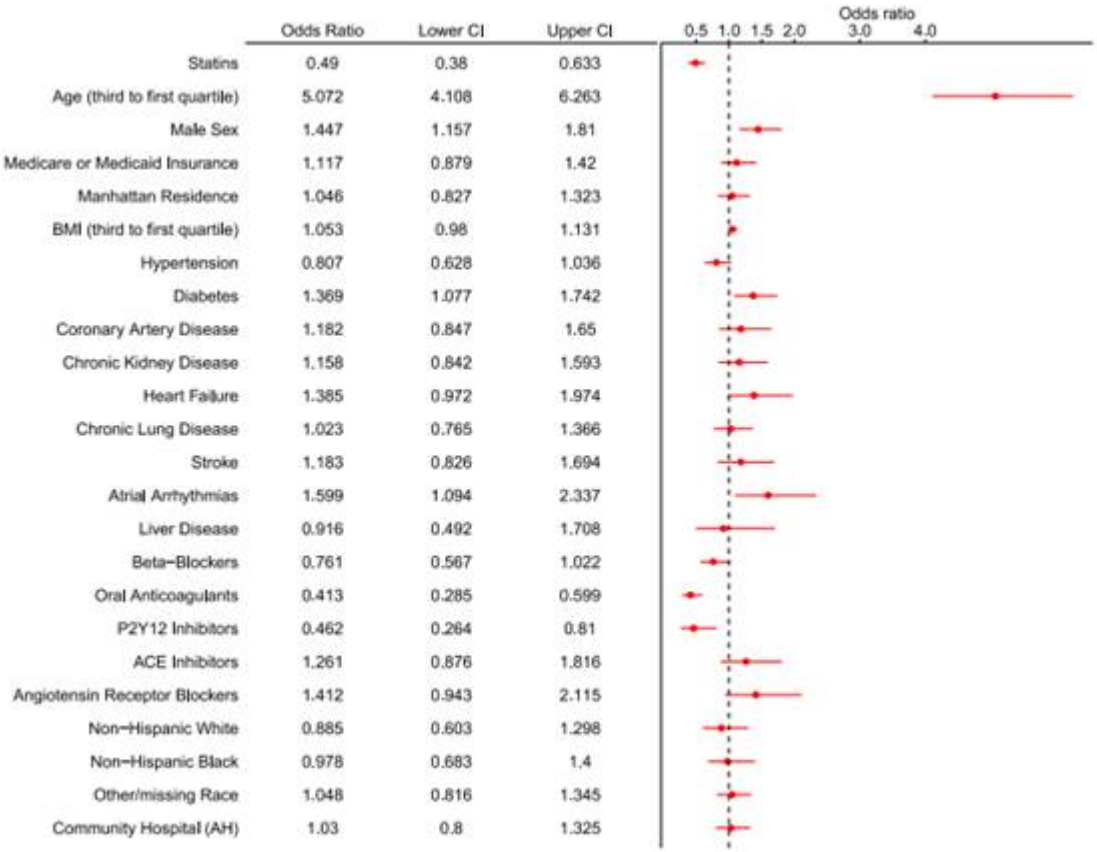
Comment: This study like the one above shows that individuals with previous SARS-CoV-2 infection generated "strong" humoral and cellular responses to one dose of the BNT162b2 vaccine, with evidence of high titers of in-vitro live virus neutralization. In contrast, most individuals who were infection-naive generated both weak T-cell responses and low titers of neutralizing antibodies to a single dose. Age may need to be considered in determining need for a second dose in persons with prior infection.

Association Between Antecedent Statin Use and Decreased Mortality in Hospitalized Patients with COVID-19

Nature Comm published online February 26, 2021

doi.org/10.1038/s41467-021-21553-1

This is a retrospective analysis of patients admitted with COVID-19. Antecedent statin use was assessed using medication information available in the electronic medical record. We constructed a multivariable logistic regression model to predict the propensity of receiving statins, adjusting for baseline sociodemographic and clinical characteristics, and outpatient medications. The primary endpoint includes in-hospital mortality within 30 days. A total of 2626 patients were admitted during the study period, of whom 951 (36.2%) were antecedent statin users. Among 1296 patients (648 statin users, 648 non-statin users) identified with 1:1 propensity-score matching, statin use is significantly associated with lower odds of the primary endpoint in the propensity-matched cohort (OR 0.47, 95% CI 0.36–0.62, $p < 0.001$). They conclude that antecedent statin use in patients hospitalized with COVID-19 is associated with lower inpatient mortality.



	Odds Ratio	Lower CI	Upper CI
Statins	0.49	0.38	0.633
Age (third to first quartile)	5.072	4.108	6.263
Male Sex	1.447	1.157	1.81
Medicare or Medicaid Insurance	1.117	0.879	1.42
Manhattan Residence	1.046	0.827	1.323
BMI (third to first quartile)	1.053	0.98	1.131
Hypertension	0.807	0.628	1.036
Diabetes	1.369	1.077	1.742
Coronary Artery Disease	1.182	0.847	1.65
Chronic Kidney Disease	1.158	0.842	1.593
Heart Failure	1.385	0.972	1.974
Chronic Lung Disease	1.023	0.765	1.366
Stroke	1.183	0.826	1.694
Atrial Arrhythmias	1.599	1.094	2.337
Liver Disease	0.916	0.492	1.708
Beta−Blockers	0.761	0.567	1.022
Oral Anticoagulants	0.413	0.285	0.599
P2Y12 Inhibitors	0.462	0.264	0.81
ACE Inhibitors	1.261	0.876	1.816
Angiotensin Receptor Blockers	1.412	0.943	2.115
Non−Hispanic White	0.885	0.603	1.298
Non−Hispanic Black	0.978	0.683	1.4
Other/missing Race	1.048	0.816	1.345
Community Hospital (AH)	1.03	0.8	1.325

Fig. 1 Forest plot for in-hospital mortality within 30 days. Forest plot demonstrating the odds ratio (OR) and 95% confidence interval (CI) for in-hospital mortality within 30 days with antecedent statin use (vs. no antecedent statin use) after multivariable logistic regression in the overall cohort. A number of

Comment: SARS-CoV-2 infection can result in a hyperinflammatory state, leading to ARDS, myocardial injury, and thrombotic complications, among other sequelae. Statins, which are known to have anti-inflammatory and antithrombotic properties, have been studied in the setting of other viral infections, but their benefit has not been assessed in COVID-19. They performed propensity matched analysis and multivariable adjustment to minimize the likelihood for confounding. As a retrospective analysis of electronic medical record data, however, there remains the potential for unmeasured confounders.