I hope everyone had a marvelous weekend.

Today I have diverse topics I wish to share. The first is a question and commentary on school testing focusing on K1-K12. Please weigh in on your opinion and perspective which I will share Friday like last week. The first article looks at a UK study of household with persons infected with SARS-CoV-2. The second article is an Imperial College of London report on updated case fatality ratio for SARS-CoV-2 infections and introduces the term seroreversion. The last article is a fascinating prepublication article on the observation of clinically identifiable autoreactivity in severe SARS-CoV-2 Infection.

Have a good Monday!

Ed

The question this week revolves around testing in schools. Texas schools can opt into a program to be implemented in conjunction with the Texas Education Agency and the Texas Division of Emergency Management, who are working with select districts across the state to offer COVID-19 Rapid Testing at no cost to students and district employees.

The COVID-19 Rapid Testing pilot program will use BinaxNOW tests, which provide results in 15 minutes and are administered using a nasal swab. (not NP) The BinaxNOW tests are more sensitive for symptomatic versus asymptomatic, but not as sensitive at PCR.

Schools will receive monthly enough to test all on campus staff members and 15 percent of students attending in-person classes one time. It is recommended that recurring testing of all campus staff take place monthly. Tests will be available to all students (with permission from parents) who are showing symptoms of COVID-19 or who were in close contact of those who test positive.

Do you think a program like this will be effective at reducing transmission of SARS-CoV-2? Please let me know by email. See next article and my opinion at the end of this issue of the Daily Briefing.

Three Quarters of People with SARS-CoV-2 Infection are Asymptomatic: Analysis of English Household Survey Data
Clin Epidemiol 2020:12 1039–1043
The investigators used data from the Office for National Statistics Coronavirus (COVID-19) Infection Survey pilot study. They estimated sensitivity, specificity, the proportion of asymptomatic cases (1 – sensitivity), positive predictive value (PPV) and negative predictive value (NPV) of COVID-19 symptoms as a marker of infection using results of the SARS-CoV-2 test as the “gold standard”.

In total, there were 36,061 individuals with a SARS-CoV-2 test between 26 April and 27 June 2020. Of these, 625 (1.7%) reported symptoms on the day of the test. There were 115 (0.32%) with a positive SARS-CoV-2 test result. Of the 115, there were 27 (23.5%) who were symptomatic and 88 (76.5%) who were asymptomatic on the day of the test. Focusing on those with specific symptoms (cough, and/or fever, and/or loss of taste/smell), there were 158 (0.43%) with such symptoms on the day of the test. Of the 115 with a positive SARS-CoV-2, there were 16 (13.9%) reporting symptoms. In contrast, 99 (86.1%) did not report specific symptoms on the day of the test. The PPV for all symptoms was 4.3% and for the specific symptoms 10.1%. The specificity and NPV of symptoms were above 98%.

Comment: COVID-19 symptoms appear a poor marker of SARS-CoV-2 infection. Thus, 76.5% of this random sample who tested positive reported no symptoms, and 86.1% reported none of those specific to COVID-19 on the day of testing. A more widespread testing program is necessary to capture "silent" transmission and potentially prevent and reduce future outbreaks. In my opinion it will be necessary to set up test programs involving frequent and widespread SARS-CoV-2 testing of all individuals, at least where there are recent cases, and certainly in high-risk settings, for example, care homes, hospitals, or specific industries like sports in order to capture "silent" transmission and potentially prevent future outbreaks and protect high-risk people.

Report 34: COVID-19 Infection Fatality Ratio: Estimates from Seroprevalence
published October 29, 2020 [Imperial College COVID-19 response team]
This report covers a screening of 175 studies and identified 10 antibody surveys to obtain updated estimates of the infection fatality ratio (IFR) using a modelling framework. This specific framework addresses several limitations of previous estimates which have relied on data early in the epidemic and have not fully accounted for uncertainty in serological (antibody) test characteristics, and delays from onset of infection to seroconversion (specific antibody becoming detectable in the blood), death, and antibody waning.

The researchers confirm that age specific IFRs follow a pattern, with the risk of death doubling approximately every eight years of age. Age-specific IFRs increased from 0.1% and below for individuals under 40 years to greater than 5% among individuals over 80 years.

Using these age-specific estimates, the team estimates the overall IFR in a low-income country, with a population structure skewed towards younger individuals, can be expected to be approximately 0.23% (95% prediction interval 0.14-0.42). In contrast, in high income countries, with a greater concentration of elderly individuals, the report estimates that the overall IFR can be expected to be approximately 1.15% (95% prediction interval 0.78-1.79).

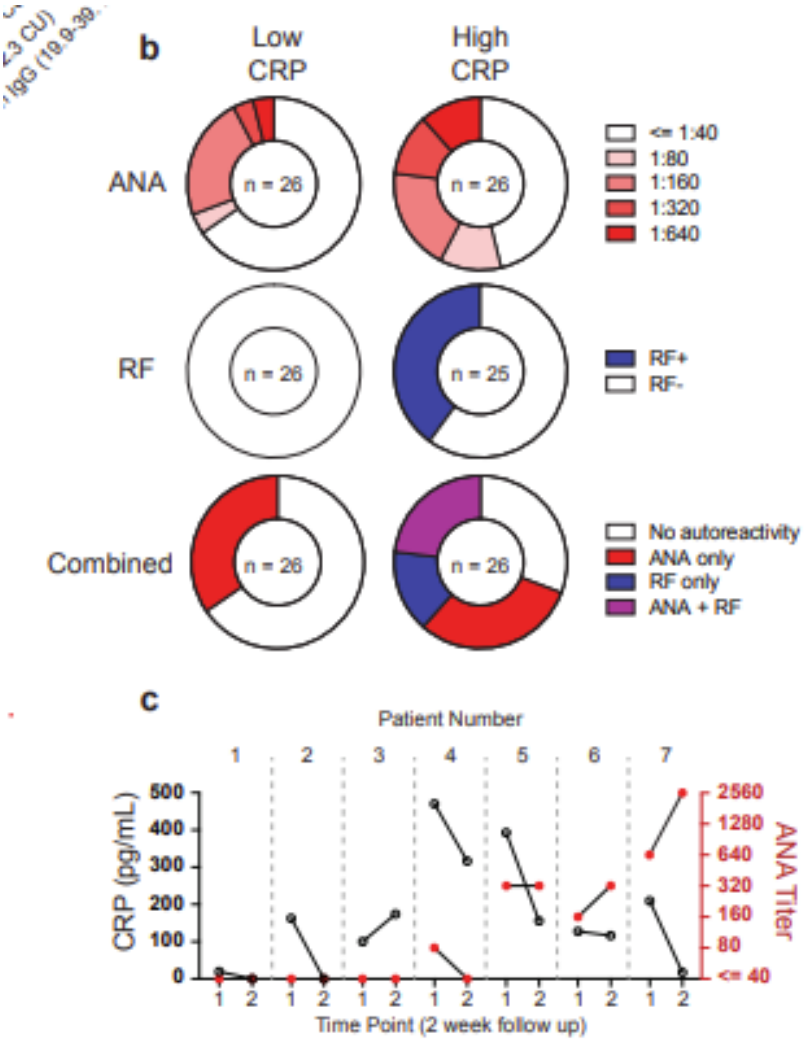
In addition, the report takes seroreversion into account. Seroreversion is the waning of antibodies, leading to a negative serological result in people who were previously infected with coronavirus and would have tested positive at an earlier time. Not accounting for seroreversion can overestimate the IFR among serosurveys conducted longer after the first wave of the outbreak (such as Italy), because we would underestimate the true number of people who had been infected.

Comment: Researchers emphasize that it will be important to continue to monitor the IFR as new treatments are introduced and population immunity increases. In addition, the researchers did not find evidence that the IFR was higher in regions with larger epidemics. Studies in US have shown a decrease in IFR probably due to better treatments and a younger population being infected during the second wave. A major limitation of this study was dependent in the serological data available. A second limitation was the use of reported deaths. Quantifying deaths from COVID-19 has been challenging for many countries, due to death counts being revised over time or countries differing in approaches to counting COVID-19 deaths.

Clinically Identifiable Autoreactivity is Common in Severe SARS-CoV-2 Infection
medRxiv published online October 21, 2020
Investigators studied 52 patients who had severe or critical COVID-19 and no history of autoimmune disorders. They found autoantibodies in about half of the patients, and among the top 50% of the most severe cases more than 70% had autoantibodies. Some of the autoantibodies were associated with

blood clotting and blood flow problems, which could be related to the coagulation issues documented in COVID-19 patients. They identified activation of an autoimmune-prone B cell response pathway as correlate of severe COVID-19, raising the possibility of de novo autoreactive antibody production during the antiviral response. Here, they identify autoreactive antibodies as a common feature of severe COVID19. These observations raised the possibility that severe SARS-CoV-2 infection frequently results in breaks of self-tolerance to a variety of autoantigens. Patients were tested for a variety of broad serologies commonly used for the initial evaluation of autoimmune rheumatic diseases. Consistent with tolerance breakdown, 44% of patients had positive levels of ANA at ≥ 1:80 predominantly speckled pattern (50%). Of positive tests, 81% displayed titers of ≥1:160. Anti-RNP and anti-centromere IgG titers were detected in only 2 of 22 ANA+ patients, while dsDNA reactivity was not detected.

Rheumatoid factor (10/52), phospholipids (3/52), prothrombin (2/52), and c-ANCA (2/52), with or without ANA reactivity was detected which may suggest broad autoimmune targeting. The presence of autoreactivity correlated with increasing serum levels of CRP. Effector B cell responses can proceed either through germinal center reactions or extrafollicular (EF) responses. Human EF responses have been best defined in SLE, where they may be induced through TLR7 by single-stranded RNA sensing, and correlate with disease severity.



Comment: This pre-publication study may indicate subsets of patients that may benefit from immunomodulation. The immunological environment of serious COVID-19 infection, including TLR7 activation by SARS-CoV2 ssRNA, may be be sufficient to drive de novo autoreactivity against a variety of self-antigens. Can we identify biomarkers that may indicate subsets of patients that may particularly benefit from immunomodulation? Should we now be including clinical testing for ANA or RF. Should we devise early rheumatological intervention strategies and establish effective long-term care protocols? This is a preliminary study but may explain a subset of patients with severe disease and offer customized interventions.

VII: School Testing and Keeping Schools Open

First, I want to go on record that I support regular testing to help prevent outbreaks and to better understand the epidemiology and transmission of SARS-CoV-2. I think Congress should provide funding for testing in schools especially in poor communities. The growing availability of inexpensive antigen tests make routine testing feasible, but there are limitations discussed below. Regular testing has been used by sports and universities but at a frequency much greater than is currently recommended by the Texas Education Agency. Schools will need a plan to follow-up testing for not just true positives and false negatives, but possible false positives and the unintended consequences. (see below) In addition local health departments should expand research to address how easily children can transmit virus in school and whether outbreaks in schools can spread to the broader community. Setting up a school COVID-19 registry and mandatory reporting may be necessary. To date, research indicates very few cases of spread in schools when mitigation strategies are in place, but more studies are needed. Since children may be asymptomatic outbreaks may go undetected. Bottom line we need to determine the most effective testing strategies (including frequency and which test) which provide actionable information that reduces spread.

1. Antigen tests are very specific for the virus but are not as sensitive as molecular PCR tests especially if asymptomatic. False negatives are more common with antigen tests.
2. Symptomatic people with a negative antigen test need to have their results confirmed with a PCR test.
3. Rapid tests alone will not halt the spread of SARS-CoV-2 by itself.
4. No test is perfect – depends on the technology used, when in the course of infection the person is, and how well the specimen is collected.
5. Antigen-based tests may be as good as PCR in the early phase of infection, when viral load and infectivity are highest. False negatives would most likely be those early infection or at the tail end of their infection, with low viral loads (not as sensitive as PCR).
6. Testing does not substitute for avoiding crowded indoor spaces, washing hands, wearing a mask, or social distancing. In addition, a negative test today does not mean that you will not be positive tomorrow.
7. In universities the successful programs test at least 2X per week-Testing monthly using an antigen test has very limited value and a negative test may give someone a false sense of security.
8. What about false positives?
    a. False positives are generally uncommon among tests that have FDA approval. But any test can be plagued by contamination, mishandling or technical glitches, leading to a false-positive.

b. In places where the rate of COVID is low, false positives may even outnumber accurate positives — eroding trust in tests and, under some circumstances, prompting outbreaks of their own.

    i. What are the unintended consequences of a false-positive test? Unnecessary isolation: According to guidelines published by the CDC, people who test positive should immediately isolate themselves for at least 10 days after their symptoms start or the first positive test if asymptomatic. That would mean 10 days spent away from friends and family, and 10 days of potential productivity in a school or workplace lost.

    ii. New outbreaks: Under certain circumstances, a false positive could expose a person who tests positive (a false positive) and maybe cohorted. Crowded facilities, such as nursing homes, prisons, or hospitals, might isolate COVID-19 positive people together.

    iii. A false sense of security**:** Mounting evidence suggests that most people who have recovered from COVID-19 have some level of immunity. C.D.C. guidelines note that reinfection is unlikely within 90 days. So, people within this time window do not need to be tested again. Therefore, what happens if your test is a false-positive and you develop symptoms within this 90-day window?

Bottom line testing does **not** substitute for the mitigation strategies and a negative test can give you a false sense of security. **Remember transmission in large part is caused by human behavior.**