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Dear DCI Community,

Many of you have asked when we would have another Town Hall Meeting for our entire DCI Community. I am pleased to say that we are planning our next Town Hall for **Wednesday, August 5 at 3:00 pm (Pacific Time).**

[Zoom Link for DCI Town Hall Meeting, August 5](#)

Our August 5th Town Hall Meeting will enable us to bring our community together, provide updates on DCI initiatives and concerns, as well as enlist you in an important dialogue about how our community can become more engaged in the extraordinary and timely issues of race and social justice in the US. I am pleased to let you know that [James White \(DCI 2018\)](#) will share ideas that he and a DCI working group are assembling regarding racism and social justice. They will seek your input, guidance and involvement as to how we should move forward.

I look forward to seeing you on August 5th.

Phil

## *Notes on the Pandemic #11* *July 27, 2020*

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### **Dear DCI Community,**

It sometimes feels like whiplash as research findings or recommendations are brought forth with great conviction and authority, only to be changed or even retracted as new data emerges or new positions taken. Ideally new insights or recommendations are based on more recent data that builds on prior observations. Change is built into the science, including the refutation of prior observations as well as their modifications and affirmations. In fact, in retrospective analysis of 100 systemic reviews published in an article entitled “How quickly do

systematic reviews go out of date? A survival analysis” in the *Ann Intern Med*. 2007;147(4):224-33, Shojania et al found that new evidence occurred within 5.5 years of publication which substantially changed the conclusions about the effectiveness or harms of the originally reported results. Significant new evidence was available within two years following the original publication in 23% of systematic reviews.

Given the pace of science today and the deluge of new information since the onset of COVID-19, [according to the National Library of Medicine](#) it is not surprising that even recently reported studies and claims will be changed or proven false. In part this is related to the pace of reports on COVID-19, including the rush to their publication, sometimes before peer review has been completed or all the data are fully assembled. There have been over 36,000 articles published on COVID-19 through July 24 related to the mechanism of infection, transmission, diagnosis, treatment, prevention and overall management. The pace of change in some areas of research, including putative conclusions and recommendations, has been measured in weeks or months rather than years – creating confusion and, in some instances, the loss of public trust. This adds to the anxieties that are already felt so deeply. That said, a recent review article published online on July 10 by Wiersinga et al entitled [“Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 \(COVID-19\)”](#) provides a quite up-to-date summary of what is currently known and may be an article you would like to read.

**More on Schools:** Understandably, some of the changes in recommendations regarding COVID-19 are driven by the observations from different experimental approaches and disciplines. A recent example is the announcement by environmental scientists that SARS-CoV-2 can be transmitted by aerosolization – an issue I will comment on below. The early reluctance, including by the CDC, to recommend the wide use of masks is another example that seems in conflict with recent recommendations. In many of these situations, the differences in findings, recommendations and policies can be traced to emerging data. In other cases, changes in recommendations seem to have other drivers, including political ones. The announcement on July 24 by the CDC on the [“Importance of Reopening America’s Schools this Fall”](#) seems to be an example of a change taking place because of political pressure, especially in light of [earlier findings from the agency just weeks ago](#) coupled with public statements from the White House that the CDC recommendations were too conservative.

In fairness, the more recent statement from the CDC is consistent with the [recommendations that were put forth from the American Academy of Pediatrics](#) (AAP) that I reviewed in *Notes #10*. The case made by the CDC rests more heavily on the social and emotional wellness of children and the important role that school plays in their lives (including the advantages to in-person classroom participation to educational engagement, social and emotional skill development, safety, nutrition, and physical activity) rather than on the risks related to COVID-19 or even parents’ reactions to the rapidly changing recommendations. I doubt anyone would deny the importance of school for children. Coupled with this is the knowledge that children younger than 18 years account for less than 7% of COVID-19 cases and less than 0.1 percent of deaths. That is important and I would argue, as did the AAP and now the CDC, in supporting the return of children to school in the fall.

However, [more recent data from a study done in South Korea compiled by Young Joon Park and the COVID-19 National Emergency Response Center](#) provides follow-up on the 59,073 contacts of 5,706 COVID-19 index cases. This study found that while children less than 10 years of age had a lower rate of infection than all other age groups, those over 10 years of age become infected at the same rate as adults. That would suggest that while children in primary school grades are less likely to acquire or transmit infection, that is not the case for children in middle and high school. Even though mortality is low in these age groups, older children can contribute to transmission to classmates as well as to other members of the community, especially in households where overall transmission is highest (11.8%). This is particularly important at a time when COVID-19 cases have been increasing in much of the US, making the risks of infection for children and their households higher.

Despite the recommendations of the AAP and CDC, it seems clear that there will not be consistent state or national policies regarding the reopening of schools. We are quite aware of how this is playing out in higher education (see [Notes #9 and #10](#)) with most colleges and universities, including Stanford, planning for virtual classes or hybrid programs that will involve fewer students on campus so that social distancing can be achieved. The significance for primary and secondary schools carry additional implications with the continued rise of COVID-19 and most governors, mayors as well as school principals and parents are articulating a patchwork of plans, some completely virtual, a number exploring hybrid models with some time on campus or at school, including staggered schedules with reduced numbers of students to optimize social distancing. Few schools will be fully in-person.

The balance between the benefits of school versus the risks for infection in households and communities, must be considered in the context of the family unit and its vulnerabilities. Also important are the economic and related consequences, particularly to parents, if children are not able to enter school this fall. Of course, there is an unintended consequence of increasing the risk to grandparents and other vulnerable members of families where exposure to children enrolled in school may serve as a source of transmission to them. A number of us fall into this category. A range of opinions appeared in [an essay by Rachel Harris and Liza Tarchak in the July 25 issue of New York Times](#) that may be of interest.

**Epidemiology and Transmission:** The risk of infection with COVID-19 needs to be balanced against the seroprevalence in different parts of the US, as was reviewed in an editorial by Tyler Brown and Rochelle Walensky is [“Undetected, Uncertain and Out of Control.”](#) Their essay is based on a [report by Havers et al in the July 21 issue of JAMA Internal Medicine](#) (in which the authors conducted a cross-sectional study based on virus testing from the residual sera left over from clinical blood specimens that had been obtained between March 23 – May 12. This study included 16,025 patient samples from 10 different states. The authors reported that the proportion of individuals with prior exposure to SARS-CoV-2 was still quite low (ranging from 1% in San Francisco to 6.9% in New York City). Based on their findings they estimated the number of infected individuals was likely to be between 6-24 times higher than confirmed cases. These studies have a number of methodological limitations but affirm that, as a nation (or parts of it), we are still a long way from achieving herd immunity (where 60-70% of the population would need to be seropositive). Further complicating this is the observation that antibody

responses are short lived in individuals with asymptomatic infections from natural infection. Hopefully antibody responses will be more sustained with a vaccine (see below).

**Aerosols and Air Droplets and Transmission:** Adding to the confusion about the transmission of SARS-CoV-2 was [a highly publicized statement](#) from 239 scientists from 20 countries that raised the concern that aerosols could play a more major role in transmission than previously considered. There is no denying that under highly controlled experimental conditions, aerosols of SARS-CoV-2 (or its nucleic acid) can linger in the air for hours of time, especially in indoor settings. However, the epidemiologic evidence to date continues to support that the major mode of transmission of SARS-CoV-2 is by air droplets. An important Viewpoint article was published on this topic in the July 13<sup>th</sup> issue of *JAMA Online* by Michael Klompas et al entitled [“Airborne Transmission of SARS-CoV-2: Theoretical Considerations and Available Evidence.”](#) As you will recall, air droplets are larger particles (>0.5µm) that rapidly fall to the ground by gravitational force typically within 3-6 feet. In contrast, aerosols are smaller particles which remain suspended in the area for hours. The authors contend that if transmission was due to aerosols, the current epidemiologic data would look quite different than it does at this point. In that setting masks, face shields, and social distances of 6 feet would not be successful – which is not the case. Further we know that the transmission rate of SARS-CoV-2 is higher than influenza but dramatically different from measles, which is among the most infectious viruses and which is clearly spread by aerosols. As noted above, even though there were varying views about the value of face masks and other Personal Protective Equipment (PPE) outside of clinical settings early in the pandemic, the data supporting the use of masks in household or community settings in reducing and even preventing COVID-19 continues to emerge (see: John Brooks et. al. [“Universal Masking to Prevent SARS-CoV-2 Transmission- The Time is Now”](#)).

While anecdotal, Brooks reminds us of the case of two symptomatically infected hairstylists in Springfield, Missouri who had been required to wear face masks at all times – and did so. Follow-up surveillance demonstrated that two weeks after the exposure, there has been **no** transmission to 104 clients of these two infected hairstylists. That 90% of the exposed clients had also worn a mask also contributed to the lack of transmission. Such observations are supported by recent studies that show that masks and facial coverings can reduce transmission of infection in hospital and community settings. Despite this, the universal use of face masks is still an issue for many communities which, when coupled with the failure of social distancing, is contributing to the increasing number of cases in the US today. It is a sad reality that these simple measures are being ignored or refuted by so many Americans. Indeed, this accounts for why the US has continued to increase its number of COVID-19 infections and related deaths while most other countries are not doing so.

**Early Promising Updates on Vaccines:** Moving to a hopeful message, this past week brought forth some good news about the progress in COVID-19 vaccine development. There are over 200 vaccine candidates and some hopeful progress was reported on three of them. One is the vaccine from Oxford that is being developed with Astra Zeneca, a second from CanSino Biologics in Wuhan, China and a third from Moderna.

The Oxford and Wuhan vaccines have been engineered to elicit an antibody response against the “spike” protein of SARS-CoV-2 by inserting the genetic information into a

replicating adenovirus vector to elicit the response. These vaccines are not the coronavirus *per se* but an otherwise harmless vector that contains the specific genetic information. The latest results on the Oxford vaccine come from 1,077 healthy adults ranging in age from 18-55 years (***Lancet Online*** July 20). Importantly the vaccine appears safe and tolerable and elicited neutralizing antibodies in more than 90% of the study participants that lasted for at least 56 days. The Wuhan study enrolled 508 health subjects ranging in age from 18-83 years and also did not observe serious side-effects (although both studies reported local and some systemic symptoms similar to what is observed with other vaccines). In the Wuhan study, neutralizing antibodies were observed in 85% of participants (albeit lower in individuals over 55 years) – also in the July 20 ***Lancet Online***. Next for both vaccines will be large randomized Phase 3 trials which could provide more definitive data before year's end. Hopefully both will demonstrate benefit in older individuals.

In addition to these vaccines, the third currently promising one uses a different approach and is based on an mRNA platform. In this case the (messenger) mRNA is delivered in a lipid nanoparticle that is injected intramuscularly at two time points (day 1 and 28). In a Phase 1 safety study that explored three doses of the vaccine that was administered to groups of 15 individuals for each dose, the study demonstrated that the vaccine was safe and tolerated and that it produced an immunologic response impressive enough to support the Phase 2 clinical trial of mRNA-1273 in 600 individuals in a trial that will be ending this summer which, if successful, will also lead to a large Phase 3 trial (see [Jackson et al. \*New England Journal of Medicine\*, July 14, 2020](#)).

Sadly, it looks like we have a long way to go before we achieve any normality as we would like it. But there are things we can do now to reduce risk (like facial coverings, social distancing and handwashing) and, hopefully, there will be progress on one or more vaccines that could change the ledger on the pandemic by early 2021. We all hope so. Please stay well.

