Today I have reviewed the John Hopkins Center for Health Security document on resetting our response to the pandemic. The next article is a very nice review of site and timing of SARS-CoV-2 detection. The third article will add additional confusion and emotion around the national conversation about reopening schools. The last two articles report on rhesus macaques responses to two different vaccines-one mRNA and the other adenovirus vector vaccine. Both show promise.

On Monday I will "attempt" to review recent literature on the role of aerosol transmission of SARS-CoV-2. Another confusion and emotional topic.

Have a great weekend

Ed

Resetting Our Response: Changes Needed in the US Approach to COVID-19 published July 30, 2020 John Hopkins Center for Health Security

Summary of Recommendations:

1. Encourage and, where appropriate, mandate nonpharmaceutical interventions. [masks]
2. Close higher risk activities and settings in jurisdictions where the epidemic is worsening and reinstitute stay-at-home orders where healthcare systems are in crisis.
3. Bolster PPE supply chains and stockpiles and make information about the PPE manufacturing base and supply chain publicly available, with the goal of expanding PPE availability.
4. Bolster test supply chains, plan for shortages, and collaborate with states and commercial laboratories to expand capacity and improve test turnaround times.
5. Conduct and make public detailed analyses of epidemiologic data collected during case investigations and contact tracing.
6. Curate and fund a rapid research agenda to cope with major challenges that have arisen. [like data sharing and collaboration as suggested in the Daily Briefing last week]
7. Scale up contact tracing and continue to improve performance.
8. Identify and disseminate best practices for improving the public health response.
9. Plan for a vaccine, including production, allocation, distribution, and community engagement, to ensure a successful rollout.
10. Develop policies and best practices to better protect group institutions.

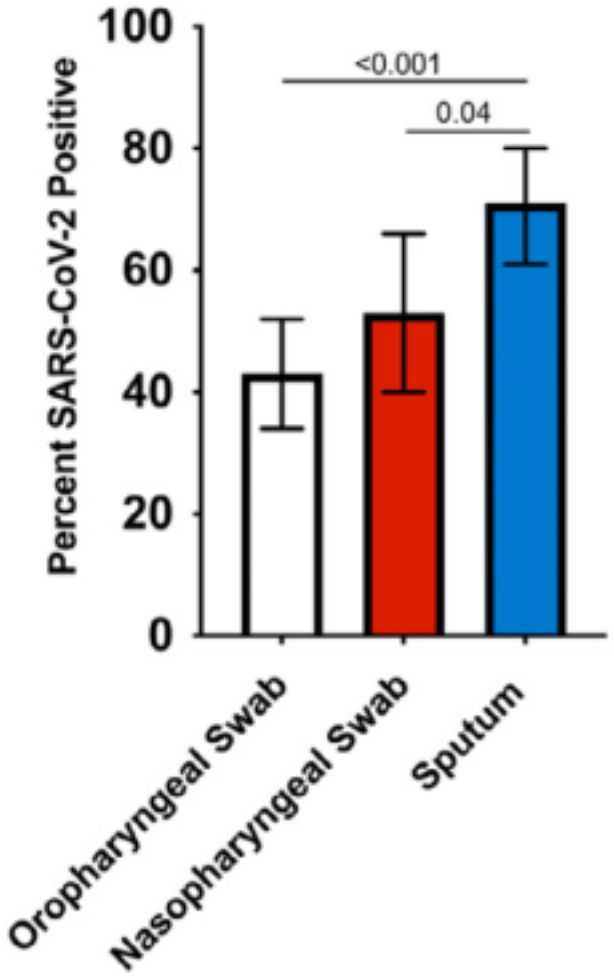
Comment: The documents states closures do not need to mirror those implemented in the spring.(not full shelter in place except if hospitals are in crisis) They state closures should include high-risk indoor settings where people congregate, like bars, restaurants, entertainment venues, gyms, and indoor religious spaces, and possibly indoor offices where transmission risk cannot be lowered through mitigation efforts. I think we need to focus on wearing masks, social distancing including avoiding indoor gatherings, improve testing and contact tracing.

SARS-CoV-2 detection in different respiratory sites: A systematic review and meta-analysis EBioMedicine published online July 18, 2020

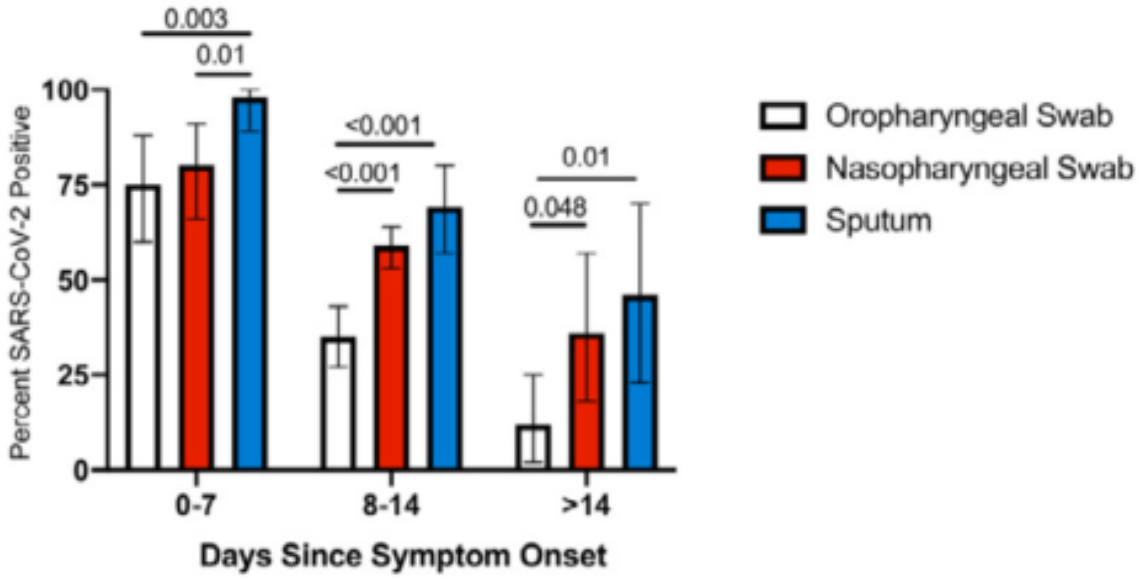
The authors performed a systematic review and meta-analysis of studies comparing respiratory sampling strategies for the detection of SARS-CoV-2 RNA. The inclusion criteria were studies that assessed at least two respiratory sampling sites (oropharyngeal swab, nasopharyngeal swab, and sputum) in participants with COVID-19. The percentage positive tests were compared between sampling modalities by constructing a Z test assuming independence and using the standard errors obtained from the random effects meta-analysis.

They identified 11 studies that met our inclusion criteria, with SARS-CoV-2 testing results from a total of 3442 respiratory tract specimens. Compared to nasopharyngeal swab sampling, sputum testing resulted in significantly higher rates of SARS-CoV-2 RNA detection while oropharyngeal

swab testing had lower rates of viral RNA detection. Earlier sampling after symptom onset was associated with improved detection rates, but the differences in SARS-CoV-2 RNA



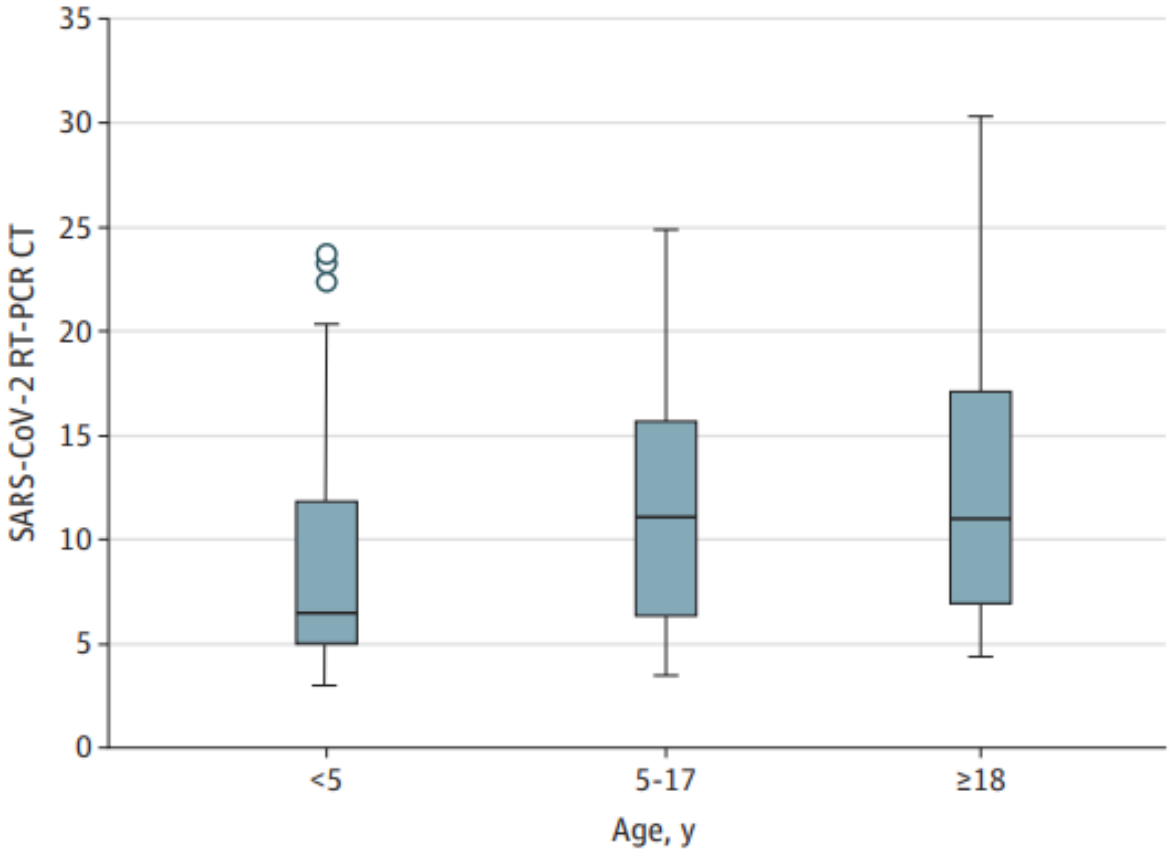
detection by sampling method was consistent regardless of the duration of symptoms.



Comment: The results support sputum sampling as a valuable method of COVID-19 diagnosis and monitoring and highlight the importance of early testing after symptom onset to increase the rates of COVID-19 diagnosis. Obviously, sensitivity of the assay used and how a specimen is collected will also influence results. The studies included were hospitalized patients and it is unclear how the results may differ for individuals with asymptomatic infection or only mild symptoms.

Age-Related Differences in Nasopharyngeal Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Levels in Patients with Mild to Moderate Coronavirus Disease 2019 (COVID-19) JAMA Pediatr published online July 30, 2020

Early reports did not find strong evidence of children as major contributors to SARS-CoV-2 spread. As public health systems look to reopen schools and day cares, understanding transmission potential in children will be important to guide public health measures. The authors report that replication of SARS-CoV-2 in older children leads to similar levels of viral nucleic acid as adults, but significantly greater amounts of viral nucleic acid are detected in children younger than 5 years. Lower CT values means higher viral RNA- the more virus present in the sample, the fewer cycles needed for a clear result.
The final cohort included 145 patients with mild to moderate illness within 1 week of symptom onset. They compared 3 groups: young children younger than 5 years (n = 46), older children aged 5 to 17 years (n = 51), and adults aged 18 to 65 years (n = 48).We found similar median (interquartile range) CT values for older children (11.1 [6.3-15.7]) and adults (11.0 [6.9- 17.5]). However, young children had significantly lower median (interquartile range) CT values (6.5 [4.8-12.0]), indicating that young children have equivalent or more viral nucleic acid in their upper respiratory tract compared with older children and adults



Comment: This analysis suggests children younger than 5 years with mild to moderate COVID-19 have high amounts of SARS CoV-2 viral RNA in their nasopharynx compared with older children and adults. It is a small study, and did not specify the participants' race or sex, or whether they had underlying conditions. The tests looked for viral RNA only, rather than the live virus itself. C.T. values ha been use as a reasonable proxy for the amount of SARS-CoV-2 virus. This study contrasts with recent publications that suggest children < age 9 are less likely to spread SARS-CoV-2 compared with older children and adults. Dr. Schultz-Cherry believes some RNA viruses multiply quickly and are prone to genetic errors that render the virus incapable of infecting cells. Therefore, some RNA detected in children could represent defective viruses. We obviously need to understand how much actually represents actual infectious virus that is capable of transmission. We still do not know what the inoculum size that is required for transmission. This will add additional confusion and emotion around the national conversation about reopening schools This is another example that we still have a lot to learn.

Evaluation of the mRNA-1273 Vaccine against SARS-CoV-2 in Nonhuman Primates N Engl J Med published online July 28, 2020

Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques Nature published online July 30,2020

In the first article rhesus macaques received 10 or 100 µg of mRNA-1273, a vaccine encoding the prefusion-stabilized spike protein of SARS-CoV-2 at time zero and at week 4, or no vaccine(PBS). Antibody and T-cell responses were assessed before upper- and lower-airway challenge with SARS-CoV 2. Active viral replication and viral genomes in bronchoalveolar-lavage (BAL) fluid and nasal swab

specimens were assessed by polymerase chain reaction, and histopathological analysis and viral quantification were performed on lung-tissue specimens. The mRNA-1273 vaccine candidate induced antibody levels exceeding those in human convalescent-phase serum, with live-virus reciprocal 50% inhibitory dilution (ID 50) geometric mean titers of 501 in the 10-µg dose group and 3481 in the 100-µg dose group. Vaccination induced type 1 helper T-cell (Th1)–biased CD4 T-cell responses and low or undetectable Th2 or CD8 T-cell responses. Viral replication was not detectable in BAL fluid by day 2 after challenge in seven of eight animals in both vaccinated groups. No viral replication was detectable in the nose of any of the eight animals in the 100-µg dose group by day 2 after challenge, and limited inflammation or detectable viral genome or antigen was noted in lungs of animals in either vaccine group.

In this second article, fifty-two rhesus macaques were immunized with Ad26 vectors encoding S variants or sham control and were challenged with SARS-CoV-2 by the intranasal and intratracheal routes. The optimal Ad26 vaccine induced robust neutralizing antibody responses and provided complete or near-complete protection in bronchoalveolar lavage and nasal swabs following SARS-CoV-2 challenge. Vaccine-elicited neutralizing antibody titers correlated with protective efficacy, suggesting an immune correlate of protection. These data demonstrate robust single-shot vaccine protection against SARS-CoV-2 in nonhuman primates. The optimal Ad26 vector-based vaccine for SARS-CoV-2, termed Ad26.COV2 is currently being evaluated in clinical trials

Comment: In the first article mRNA-1273(two doses) induced robust SARS-CoV-2 neutralizing activity, rapid protection in the upper and lower airways, and no pathologic changes in the lung. The second article theinvestigators showed the immunogenicity and protective efficacy of a single dose of adenovirus serotype 26 (Ad26) vector-based vaccines expressing the SARS-CoV-2 spike (S) protein in nonhuman primates. The two vaccines work in different ways. The first vaccine delivers genetic material messenger RNA into cells. The cells use the vaccine RNA to produce spike a protein found on the surface of the coronavirus which then hopefully prompts an immune response. In contrast,the second vaccine is based on a virus called Ad26, which researchers have modified so that it carries the coronavirus spike protein gene. The Ad26 virus can slip into human cells but cannot replicate once inside them. Its host cell then uses the spike gene to make the coronavirus proteins. The second vaccine only required a single dose. This week has been good — now we have two vaccines that work in monkeys, but we need safety and efficacy studies in humans.

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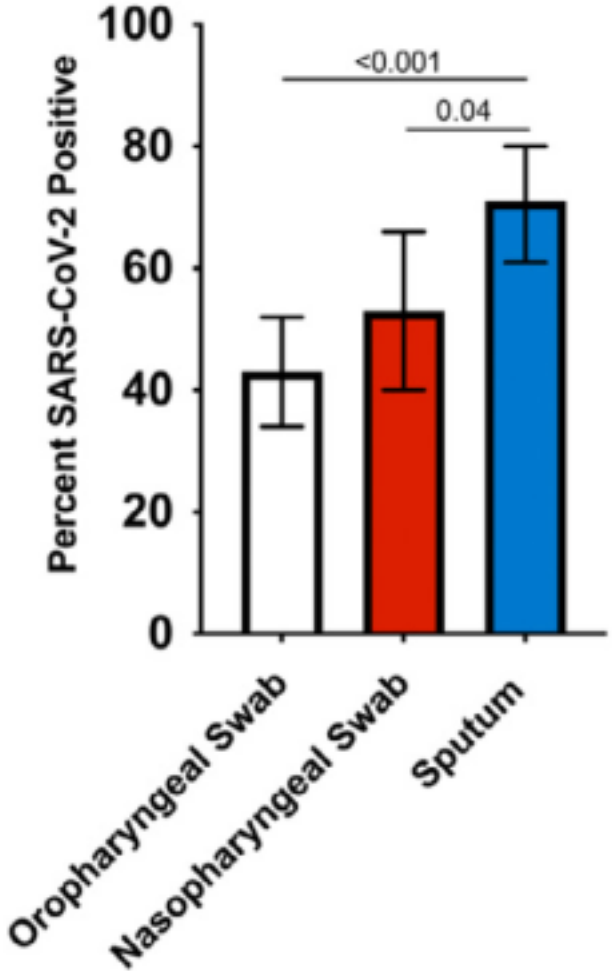
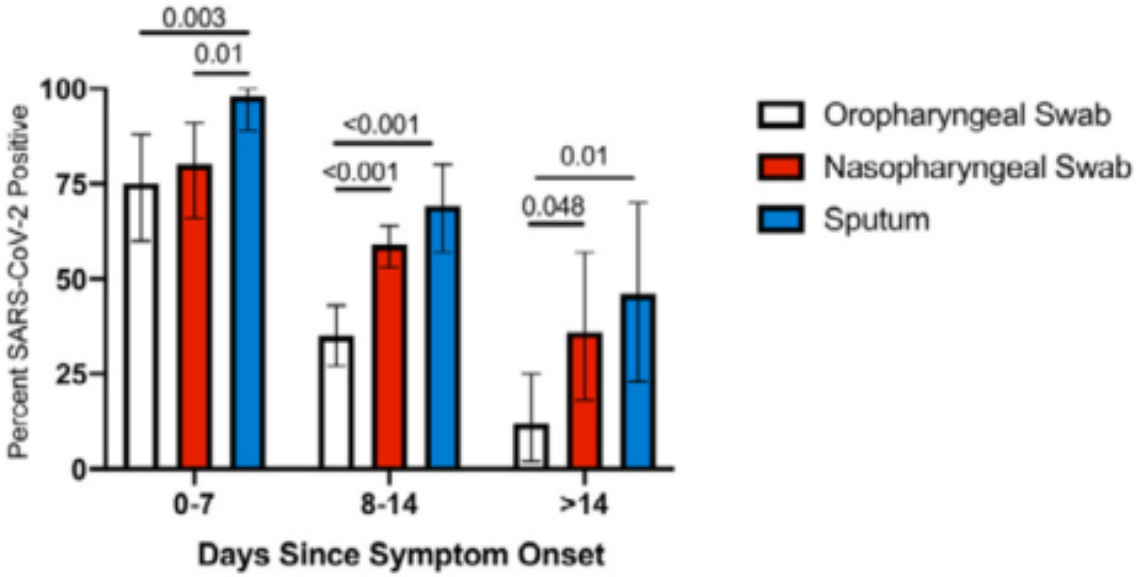
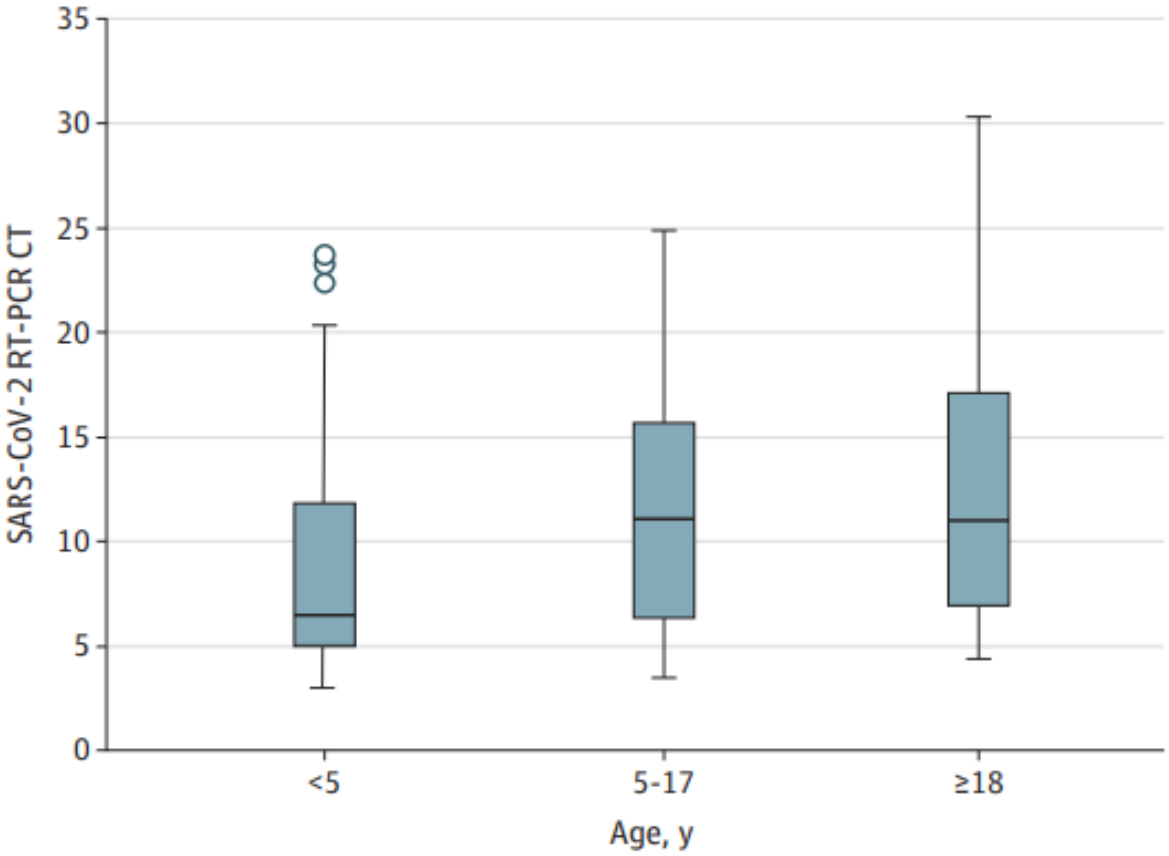

Percent SARS-CoV-2 Positive
100
80
60
40
20
0
<0.001
0.04
Oropharyngeal Swab
Nasopharyngeal Swab
Sputum


0.003
0.01
<0.001
<0.001
0.01
0.048
100
75
50
25
0
Percent SARS-CoV-2 Positive
0-7
8-14
>14
Days Since Symptom Onset
Oropharyngeal Swab
Nasopharyngeal Swab
Sputum


35
30
25
20
15
10
5
0
SARS-CoV-2 RT-PCR CT
<5
5-17
≥18
Age, y