Good morning. I start out with the announcement that HHS will be releasing doses reserved for second doses and urging states to give vaccine to anyone over age 65. The first two articles are on long term impact of patients who have recovered from COVID-19. The next article looks at gut microbiota and dysfunctional immune response. The last article is a review on the sensitivity and costs of testing for SARS-CoV-2 infection with saliva versus nasopharyngeal swabs (by PCR).

Have a pleasant day!

Ed

New Vaccine Recommendation
U.S. federal health officials on Tuesday urged state governors to "strongly recommend" COVID-19 vaccination for all adults aged 65 years and older and for those 18 and older with medical comorbidities. Only 9.3 million of the 27.7 million vaccine doses that have been shipped to states have been administered.

At a news briefing, CDC Director Dr. Robert Redfield noted that more vaccine is available than is being requested by states. Dr. Redfield and Alex Azar, Secretary of Health and Human Services, emphasized that the CDC's vaccine priority groups were not meant to be exclusive, and that states should not wait for one priority group to be fully vaccinated before moving on to another group.

Accordingly, the way vaccine doses are allocated will change in 2 weeks: they will be distributed based on the pace of vaccine administration and the size of the population age 65 and older in each state. The aim is to get doses to states where they can get out quickly to the most vulnerable.

Comment: The new guidance makes sense to me. The risk of severe illness increases with age, which is why the HHS is correct to urge states to administer the vaccine to anyone 65 and older. By one estimate a 70-year-old is about four times more likely to die than a 60-year-old and seven times more likely than a 50-year-old. This may sound controversial, but I see no reason a 25+-year-old teacher or grocery worker should get the vaccine before a 65-year-old. I also agree to release most vaccine doses that have been held back for second inoculations and send more shots to states that are administering them faster.

6-Month Consequences of COVID-19 in Patients Discharged from Hospital: A Cohort Study
Lancet published online January 8, 2021.
doi.org/10.1016/ S0140-6736(20)32656-8
This is a cohort study of patients with confirmed COVID-19 who had been discharged from the hospital in Wuhan, China between Jan 7, 2020, and May 29, 2020. Study participants were discharged from the hospital from Jan 7 to May 29, 2020, and the researchers followed-up a median of 186 days (more than 6 months) later, from Jun 16 to Sep 3. Out of 1,733 people in the cohort, 1,172 (67.6%) needed oxygen therapy, 122 (7.0%) needed ventilation or a similar procedure, and 76 (4.4%) were admitted to the intensive care unit (ICU).

The researchers assessed 17 symptoms. Besides fatigue/muscle weakness and sleeping difficulties, they included low-grade fever (0.0% prevalence), disordered taste (7.3%) or smell (10.6%), palpitations (9.3%), and hair loss (21.7%). They also found that 22.2% out of 1,617 were experiencing anxiety or depression. The researchers gave a subset of 390 patients pulmonary exams in follow-up and found diffusion impairment in 21.7% of those who did not need supplemental oxygen, 29.1% of those who

received supplemental oxygen, and 55.8% of those who needed ventilation of any kind or a similar procedure. The investigators were not surprised and was consistent with findings that the most common abnormal CT pattern was pulmonary interstitial change (GGO [ground glass opacity]), which were similar to the long-term lung manifestations of SARS or influenza pneumonia. Patients in the most severe infection group had 4.60-increased adjusted odds (95% confidence interval [CI], 0.80 to 3.25) for diffusion impairment than those who did not need any supplemental oxygen. Other physical follow-up examinations found that 13% of 822 patients had decreased kidney function after discharge and 23% of 1,692 patients performed at subnormal levels at a 6-minute walking test. None of the 390 patients who received follow-up ultrasounds had deep venous thrombosis of the legs.

The seropositivity of the neutralizing antibodies, N-IgM, RBD-IgM, and S-IgM, N-IgA, RBD-IgA, and S-IgA antibodies, and RBD-IgG, and neutralizing antibody titers at follow-up were significantly lower compared with the acute phase.

Comment: At 6 months after acute infection, COVID-19 survivors were mainly troubled with fatigue or muscle weakness, sleep difficulties, and anxiety or depression. Patients who were more severely ill during their hospital stay had more severe impaired pulmonary diffusion capacities and abnormal chest imaging manifestations. This study underscores the need for outpatient follow-up to better study the long-term effects and to assess the efficacy of therapeutic interventions to mitigate the long-term consequences of COVID-19 on multiple organs and tissues. The decline of neutralizing antibodies raises concern for SARS-CoV-2 re-infection which has been rare to date. The risk of re-infection should be monitored for patients who present with new symptoms of COVID-19.

Persistent Poor Health Post-COVID-19 Is Not Associated with Respiratory Complications or Initial Disease Severity

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They evaluated respiratory recovery and self-reported health following infection at time of outpatient attendance. Infection severity was graded into three groups: (i) not requiring admission, (ii) requiring hospital admission, and (iii) requiring ICU care. Participants underwent chest radiography and six-minute-walk test (6MWT). Fatigue and subjective return to health were assessed and levels of C-reactive protein (CRP), interleukin-6, soluble CD25 and D-dimer were measured. The association between initial illness and abnormal chest x-ray, 6MWT distance and perception of maximal exertion was investigated. To assess subjective recovery from COVID-19 illness, participants were asked a binary question regarding their perception of having returned to full health. Fatigue was assessed using the validated Chalder Fatigue Scale (CFQ-11) (35, 36). Participants are asked to answer these questions with reference to the past month in comparison to their pre-COVID-19 baseline, with responses measured on a Likert scale (0-3).

487 patients were offered an outpatient appointment, of which 153 (31%) attended for assessment at a median of 75 days after diagnosis. 74 (48%) had required hospital admission during acute infection. Persistently abnormal chest x-rays were seen in 4%. The median 6MWT distance covered was 460m. Reduced distance covered was associated with frailty and length of inpatient stay. 95 (62%) felt that they had not returned to full health, while 47% met the case definition for fatigue. Ongoing ill-health and fatigue were associated with increased perception of exertion. None of the measures of persistent respiratory disease were associated with initial disease severity.

Comment: Of the patients that attended for outpatient follow-up, they report reassuring findings regarding objective post-COVID respiratory complications at a median follow-up timepoint of 75 days, however, there is clear evidence that many patients have not returned to full fitness.

Gut Microbiota Composition Reflects Disease Severity and Dysfunctional Immune Responses in Patients with COVID-19
Gut published online January 2021
doi.org/10.1136/gutjnl-2020-323020
Researchers compared blood and stool samples of roughly 100 patients with COVID-19 in Hong Kong with samples from other people taken before the pandemic. Nearly half the COVID-19 patients had mild disease.

Several bacteria species were associated with disease severity after adjustment for antibiotic use. For instance, compared with controls, patients with COVID-19 had smaller populations of *Faecalibacterium prausnitzii* and *Eubacterium rectale*, which have known immunomodulatory potential. This altered composition exhibited stratification with disease severity concordant with elevated concentrations of inflammatory cytokines and blood markers such as C reactive protein, lactate dehydrogenase, aspartate aminotransferase and gamma-glutamyl transferase. Even among those who had recovered from COVID-19, the gut remained distinct from non-COVID patients a median of 6 days after testing negative.

Comment: Associations between gut microbiota composition, levels of cytokines and inflammatory markers in patients with COVID-19 suggest that the gut microbiome is involved in the magnitude of COVID-19 severity possibly via modulating host immune responses. Furthermore, the gut microbiota dysbiosis after disease resolution could contribute to persistent symptoms, highlighting a need to understand how gut microorganisms are involved in inflammation and COVID-19. The gut microbiota dysbiosis after disease resolution could contribute to persistent symptoms, highlighting a need to understand how gut microorganisms are involved in inflammation and COVID-19.

The Sensitivity and Costs of Testing for SARS-CoV-2 Infection with Saliva Versus Nasopharyngeal Swabs: A Systematic Review and Meta-Analysis
Ann Intern Med published online January 12, 2021
doi:10.7326/M20-6569
Saliva-based sampling for SARS-CoV-2 detection via RT-PCR has the potential to address many of the barriers associated with nasopharyngeal swab sampling. Saliva samples can be collected by the persons being tested themselves. This reduces exposure to health care workers and the need for personal protective equipment during collection. Saliva can be collected in sterile containers, without the need for swabs.

The purpose of this review was to evaluate the difference in sensitivity for SARS-CoV-2 detection between nasopharyngeal swabs and saliva and estimate the incremental cost per additional SARS-CoV-2 infection detected with nasopharyngeal swabs. To accomplish this goal, they conducted a systematic review and meta-analysis to estimate the comparative sensitivity of saliva versus nasopharyngeal swabs for detection of SARS-CoV-2.

Thirty-seven studies with 7332 paired samples were included. Against a reference standard of a positive result on either sample, the sensitivity of saliva was 3.4 percentage points lower (95% CI, 9.9 percentage points lower to 3.1 percentage points higher) than that of nasopharyngeal swabs. Among persons with

previously confirmed SARS-CoV-2 infection, saliva's sensitivity was 1.5 percentage points higher (CI, 7.3 percentage points lower to 10.3 percentage points higher) than that of nasopharyngeal swabs.

Among persons without a previous SARS-CoV-2 diagnosis, saliva was 7.9 percentage points less (CI, 14.7 percentage points less to 0.8 percentage point more) sensitive. In this subgroup, if testing 100,000 persons with a SARS-CoV-2 prevalence of 1%, nasopharyngeal swabs would detect 79 more (95% uncertainty interval, 5 fewer to 166 more) persons with SARS-CoV-2 than saliva, but with an incremental cost per additional infection detected of $8093.

Population Characteristic	Studies, *n*	Paired Samples Tested, *n*	Positive Results on Nasopharyngeal Swab, *n*	Positive Results on Saliva, *n*	Positive Results on Any Sample (Reference), *n*	Saliva Sensitivity		Difference in Sensitivity (Saliva - Nasopharyngeal)	
						Estimate (95% CI), %	I^2, %	Estimate (95% CI), *percentage points*	I^2, %
Population sampled*									
Persons with confirmed SARS-CoV-2 infection	17	1158	637	701	808	87.3 (81.3 to 91.6)	74	1.5 (−7.3 to 10.3)	78
Persons presenting for SARS-CoV-2 testing	22	5599	1243	1100	1381	85.4 (78.1 to 90.6)	89	−7.9 (−16.7 to 0.8)	89
Symptoms at the time of sampling†									
Symptomatic	24	3605	1292	1221	1437	87.0 (81.6 to 90.9)	82	−4.9 (−10.2 to 0.4)	75
Asymptomatic	8	800	226	317	357	85.8 (69.6 to 94.1)	83	−1.6 (−37.4 to 34.1)	96
Setting‡									
Outpatient	20	4429	899	862	1039	87.9 (81.5 to 92.2)	82	−4.3 (−11.8 to 3.2)	79
Inpatient	14	1917	865	784	950	85.3 (77.3 to 90.9)	85	−6.6 (−14.7 to 1.4)	79

Comment: In this meta-analysis of 37 studies comprising 7169 participants providing 7332 paired saliva samples and nasopharyngeal swabs, they found no statistically significant difference in sensitivity between these specimens for SARS-CoV-2 detection. A limitation of this study they assumed that tests would not result in false positives. This precludes estimation of specificity and results in the sampling method with the most positive results being the most sensitive method. Different methods of saliva collection and transport media were used, although in most cases they did not think it affected results. Lastly, in the subgroup of participants with paired samples who already had confirmed SARS-CoV-2 infection, the method of initial diagnosis was by pharyngeal swab in all studies. This might be expected to bias estimates in favor of nasopharyngeal swabs, but sensitivity differences were nonsignificant.