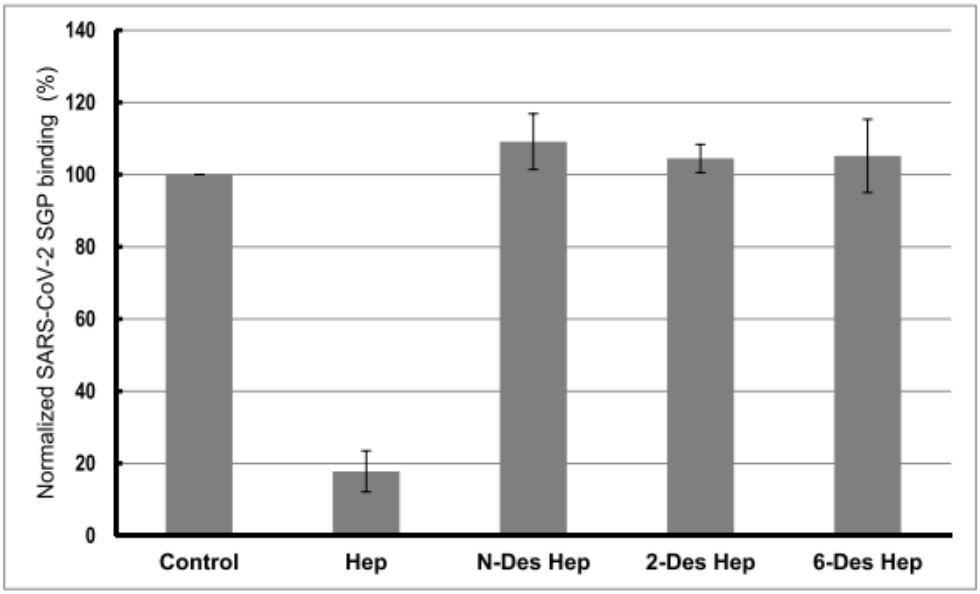
Good morning

I have chosen a diverse group of publications today. The first brings up the issue of heparin as the preferred agent for antithrombotic therapy. The next 2 article relate to use of masking. In a very interesting Perspective in the N Engl J Med the authors suggest universal masking can reduce the inoculum that may reach the respiratory track thereby reducing severity of disease. The next article on masks uses a very nice simulation model to again demonstrate the face shields are not a substitute for masking. In addition, masks with an exhalation valves should not be used. The next article contrasts clinical Features of COVID-19 vs Seasonal Influenza A and B in US Children earlier this year. The article also highlights the importance of influenza vaccination as we approach the 2020/21 influenza season. The last article explores cytokine levels in critically ill patients with COVID-19 and other critical illnesses. This article reminds us, we much to learn about the pathogenesis of ARDS in SARS-CoV-2 infections and whether IL-6 or IL-1 inhibitors have a place in our treatment protocols.

Ed

Characterization of Heparin and Severe Acute Respiratory Syndrome-Related Coronavirus 2 (SARS-CoV-2) Spike Glycoprotein Binding Interactions
Antiviral Research published July 10, 2020
The investigators discovery of a novel insertion of glycosaminoglycan (GAG)-binding motif at S1/S2 proteolytic cleavage site (681–686 (PRRARS)) and two other GAG-binding-like motifs within SARS-CoV-2 spike glycoprotein (SGP) led us to their hypothesize that host cell surface GAGs may interact SARS-CoV-2 SGPs to facilitate host cell entry. Using a surface plasmon resonance direct binding assay, they found that both monomeric and trimeric SARS-CoV-2 SGP bind more tightly to immobilized heparin than the SARS-CoV and MERS-CoV SGPs. In competitive binding studies, the IC50 of heparin, tri-sulfated non-anticoagulant heparan sulfate, and non-anticoagulant low molecular weight heparin against SARS-CoV-2 SGP binding to immobilized heparin were 0.056 μM, 0.12 μM, and 26.4 μM, respectively. Finally, unbiased computational ligand docking indicates that heparan sulfate interacts with the GAG-binding motif at the S1/S2 site on each monomer interface in the trimeric SARS-CoV-2 SGP, and at another site when the receptor-binding domain is in an open conformation.



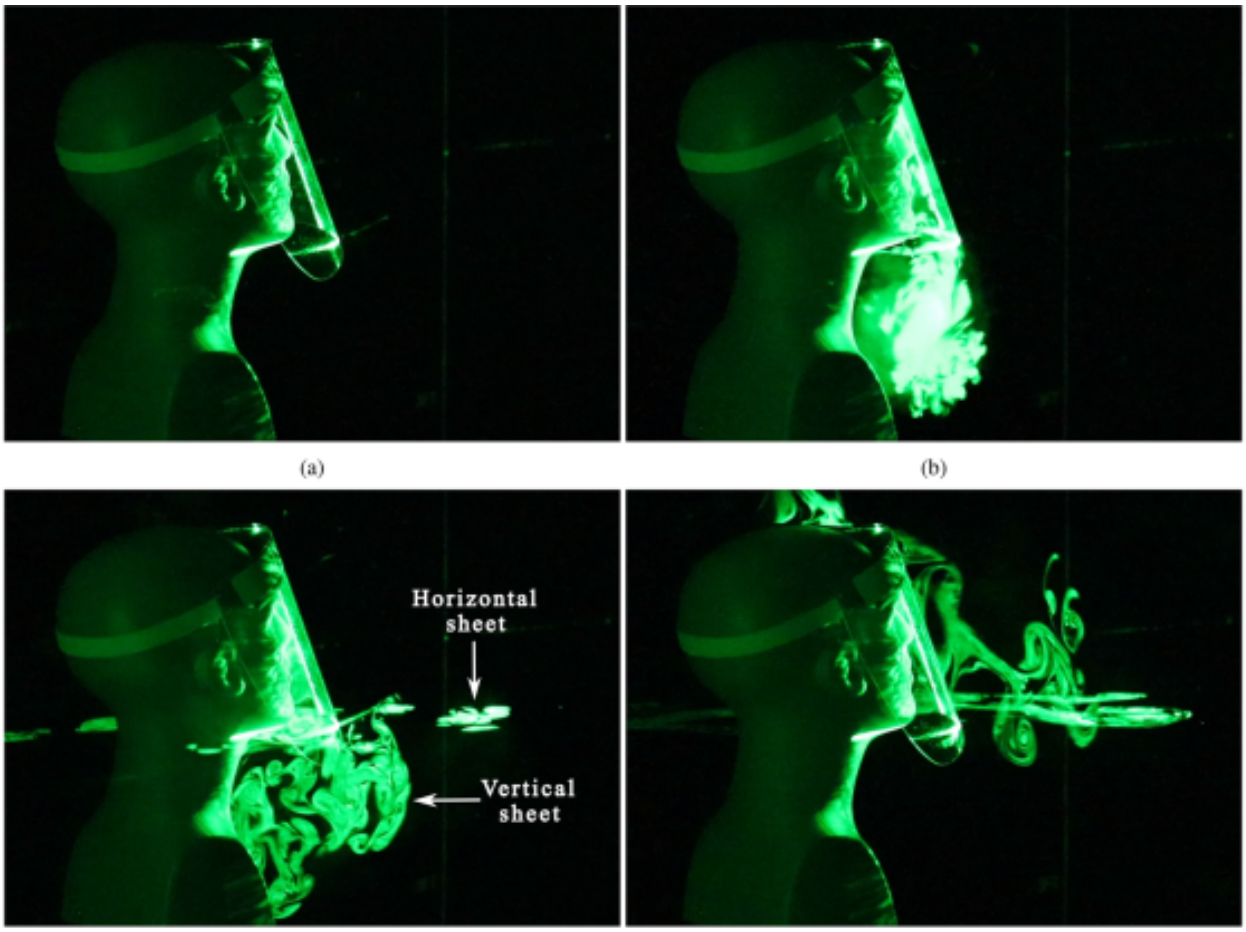
Comment: I selected this article to highlight what I consider an unresolved question: should we use enoxaparin vs heparin for VTE prophylaxis? The findings reported in this paper may provide additional basis for further heparin-based interventions for COVID-19 patients exhibiting thrombotic complications.

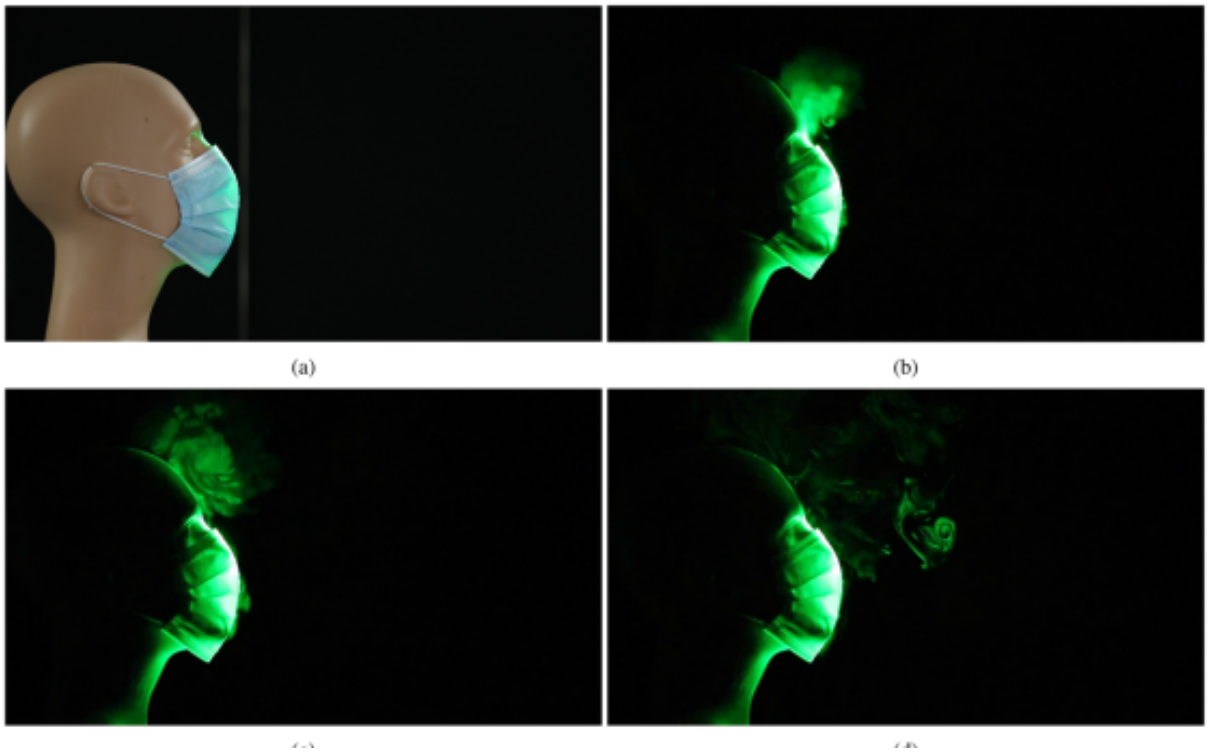
Facial Masking for Covid-19 — Potential for "Variolation" as We Await a Vaccine
N Engl J Med published online September 8, 2020
The question raised in this Perspective: Can universal masking reduce severity of disease? If this hypothesis is borne out, universal masking could become a form of "variolation" that would generate immunity and thereby slow the spread of the virus in the United States and elsewhere, as we await a vaccine. Universal facial masking may prevent transmission from asymptomatic or presymptomatic infected people. Masking can also protect the wearer from becoming infected, by blocking viral particles from entering the nose and mouth. Epidemiologic investigations conducted around the world — primarily in Asian countries that became accustomed to population-wide masking during the 2003 SARS pandemic — have suggested that there is a strong relationship between public masking and pandemic control. Recent data from colleagues in Boston demonstrate that SARS-CoV-2 infections decreased among health care workers after universal masking was implemented in hospitals in late March and April [reviewed in the Daily Briefing in July].

As proof of concept of viral inocula influencing disease manifestations, higher doses of administered virus led to more severe manifestations of Covid-19 in a Syrian hamster model of SARS-CoV-2 infection [Proc Natl Acad Sci 2020;117:16587-95]. If the viral inoculum matters in determining the severity of SARS-CoV-2 infection, an additional reason for wearing facial masks could be to reduce the viral inoculum to which the wearer is exposed and the subsequent clinical impact of the disease. Since masks can filter out some virus-containing droplets (depends on mask type), masking might reduce the inoculum that an exposed person inhale. CDC reports asymptomatic infection rates are reported to be higher than 80% in settings with universal masking, which provides observational evidence for this hypothesis.
Comment: The coronavirus variolation theory hinges on two assumptions that are difficult to prove: that lower doses of the virus lead to less severe disease, and that mild or asymptomatic infections can stimulate long-term protection against subsequent infection [especially T-cell immunity]. The theory cannot be directly proven without clinical trials that compare the outcomes of people who are masked in the presence of SARS-CoV-2 with those who are unmasked — an unethical situation. Masked exposures are no substitute for a safe and effective vaccine. But data from animals infected with the coronavirus, as well as insights gleaned from other diseases, suggest that masks, by cutting down on the inoculum that reaches a person's airway, might reduce the wearer's chances of getting symptomatic infection.

Visualizing Droplet Dispersal for Face Shields and Masks with Exhalation Valves
Phys Fluids published online September 1, 2020
There is an increasing trend of people substituting regular cloth or surgical masks with clear plastic face shields and with masks equipped with exhalation valves. One of the reasons driving this increased adoption is improved comfort compared to regular masks. To help evaluate the effectiveness (or lack of effectiveness) of these alternatives, the investigators use qualitative visualizations to examine the performance of face shields and exhalation valves in the spread of aerosol-sized droplets. The studies indicate that although face shields block the initial forward motion of the jet, the expelled droplets can move around the visor with relative ease and spread out over a large area. Visualizations for a mask

equipped with an exhalation port indicate that many droplets pass through the exhale valve unfiltered, which significantly reduces its effectiveness as a means of source control.





Comment: This study along with others clearly indicate that to minimize spread of COVID-19, it is be preferable to use high quality cloth(at least 2-ply) or surgical masks instead of face shields and masks equipped with exhale valves. Although this is a simulation, face shields are not a substitute for masks and masks with an exhalation valve should not be worn.

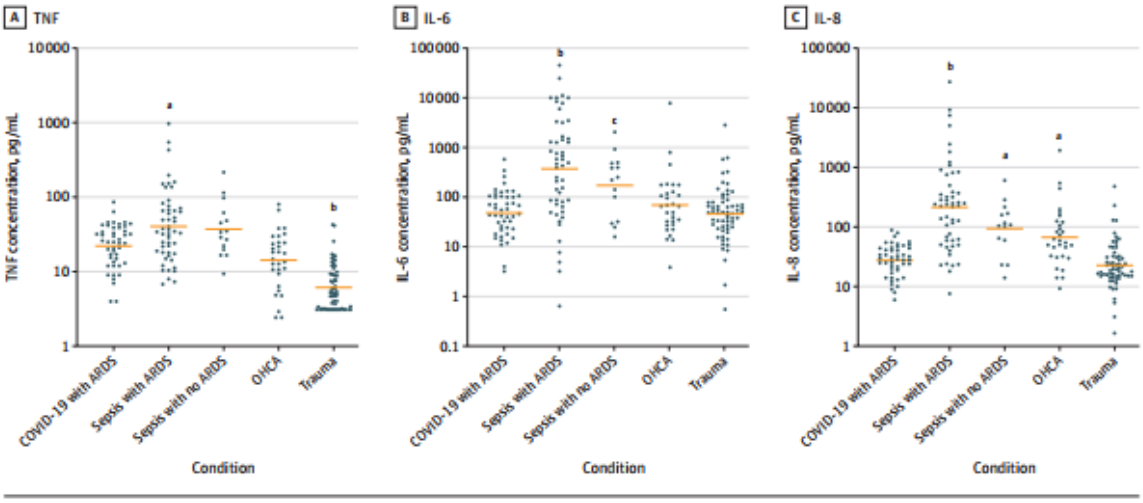
Comparison of Clinical Features of COVID-19 vs Seasonal Influenza A and B in US Children
JAMA Netw Open published online September 8. 2020
This is a retrospective cohort study of children who were diagnosed with laboratory-confirmed COVID-19 between March 25 and May 15, 2020, and children diagnosed with seasonal influenza between October 1, 2019, and June 6, 2020, at Children's National Hospital in DC.

The study included 315 patients diagnosed with COVID-19 (164 [52%] male; median age, 8.3 years and 1402 patients diagnosed with seasonal influenza (743 [53%] male; median age, 3.9 years. Patients with COVID-19 and those with seasonal influenza had a similar hospitalization rate (54 [17%] vs 291 [21%], P = .15), intensive care unit admission rate (18 [6%] vs 98 [7%], P = .42), and use of mechanical ventilators (10 [3%] vs 27 [2%], P = .17). More patients hospitalized with COVID-19 than with seasonal influenza reported fever (41 [76%] vs 159 [55%], P = .005), diarrhea or vomiting (14 [26%] vs 36 [12%], P = .01), headache (6 [11%] vs 9 [3%], P = .01), body ache or myalgia (12 [22%] vs 20 [7%], P = .001), and chest pain (6 [11%] vs 9 [3%], P = .01). No patient had both coronavirus and flu. Cases of flu dropped dramatically after pandemic-related school closures began on Mar 15 and authorities issued stay-at-home orders on Apr 1. The positivity testing rate for flu declined from 22% in mid-March to 0.3% (only one case) from Mar 22 to Jun 6. Two patients with influenza A died; no deaths were reported among COVID-19 or influenza B patients.

Comment: In this cohort study of US children with COVID-19 or seasonal influenza, there was no difference in hospitalization rates, intensive care unit admission rates, and mechanical ventilator use between the 2 groups. There were differences in clinical symptoms at the time of diagnosis. Compared with patients hospitalized with seasonal influenza, they found more patients hospitalized with COVID-19 that were older than 15 years or had underlying medical conditions. Because it was a retrospective study, the findings are subject to biases owing to recall error or missing information that were introduced during a patient encounter. However, the possibility that the upcoming influenza season could occur with SARS-CoV-2 cocirculating in the community, I believe it is imperative to ensure individuals especially with comorbidities receive the influenza vaccine to prevent severe disease courses that lead to hospitalization and possible death. Having said this, I believe all individuals over age 6 months should receive influenza vaccine.

Cytokine Levels in Critically Ill Patients With COVID-19 and Other Conditions
JAMA published online September 3, 2020
Investigators in this paper studied 46 people with COVID-19 and acute respiratory distress syndrome (ARDS) who were admitted to the ICU. All participants underwent mechanical ventilation and were treated between March 11 and April 27, 2020. The investigators measured plasma levels of cytokines, including tumor necrosis factor (TNF), interleukin-6 (IL-6), and interleukin-8 (IL-8). They compared results in this group to those in 51 patients who experienced septic shock and ARDS, 15 patients with septic shock without ARDS, 30 people with out-of-hospital cardiac arrest, and 62 people who experienced multiple traumas. They used historical data for the non-COVID-19 cohorts.

Compared to patients with septic shock and ARDS, the COVID-19 cohort had lower levels of TNF, IL-6, and IL-8. The differences were statistically significant for TNF ($P < .01$), as well as for IL-6 and IL-8 concentrations (for both, $P < .001$). In addition, the COVID-19 group had significantly lower IL-6 and IL-8 concentrations compared with the patients who had septic shock without ARDS. The researchers likewise found lower concentrations of IL-8 in patients with COVID-19 compared to the out-of-hospital cardiac arrest patients. IL-8 levels did not differ between the COVID-19 and trauma groups. Furthermore, they found no differences in IL-6 concentrations between patients with COVID-19 and those who experienced out-of-hospital cardiac arrest or trauma. However, levels of TNF in people with COVID-19 were higher than in trauma patients.



Comment: In another study published online August 21 in *PNAS,* the investigators also reported lower serum IL-6 levels among people with COVID-19 compared to patients with bacterial ARDS or sepsis. However, the authors admit COVID-19 patients can still develop severe respiratory failure, suggesting a distinct immune reaction compared to patients with bacterial sepsis. SARS-CoV-2 directly infects and activates endothelial cells rather than macrophages, as occurs in sepsis. SARS-CoV-2 infection can still cause critical illness and severe dysfunction in lungs and induces a "cytokine-like storm", even in the setting of lower but still elevated serum IL-6 levels. This study was a single center with a small sample size and used different lots of the same assays without data on lot-to-lot variability. The use of IL-6 or IL-1 inhibitors remains to be determined.