I hope everyone had a great weekend.

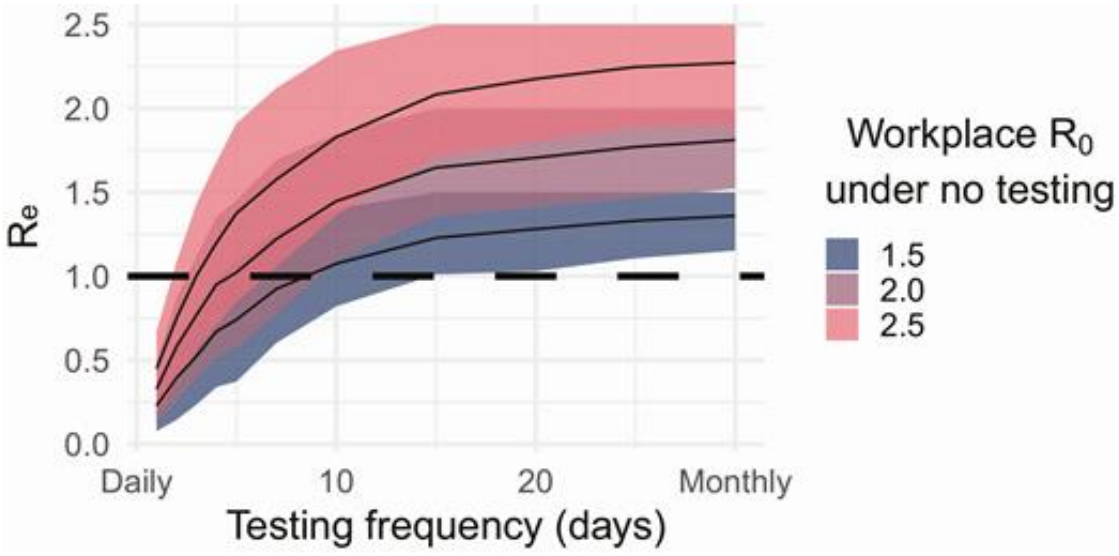
Today I start out with a timely paper on optimal frequency of testing for COVID-19 in healthcare settings. This is a nice companion article to complement discussions from last week. The second article is a fascinating report on different antibody responses between children and adults. The third article is a review article on MIS-C comparing three continents. The last article is on trends risk-adjusted mortality for COVID-19.

Have a great week

Ed

Frequency of Routine Testing for Coronavirus Disease 2019 (COVID-19) in High-risk Healthcare Environments to Reduce Outbreaks
Clin Infect Dis published online October 26, 2020
https://doi.org/10.1093/cid/ciaa1383
The authors developed a simulation model of SARS-CoV-2 transmission to evaluate the effectiveness of various frequencies of routine PCR testing of all persons in a high-risk healthcare environment (i.e., long-term residents or patients admitted to hospitals, daily healthcare workers) to reduce cases of COVID-19. The primary study outcome for each strategy was the simulated reduction in the mean effective control reproduction number (R_e) in the healthcare environment, corresponding to the average number of secondary infections caused by an infected person averaged over the simulation period, starting with a fully susceptible population, and accounting for the impact of interventions. For interpretation, a mean effective reproduction number below one would ensure decline in the number of cases when averaged over time.

The optimal testing frequency to bring R_e below one was dependent on baseline R_0 (see below). In an environment with R_0 = 2.5, [this is thought to be the R_o for SARS-CoV-2] testing would have to occur almost every other day to bring R_e below one. If R_0 = 2, testing would need to occur at least twice weekly (every 3–4 days), unless other measures were added to testing and self-isolation. If assuming R_0 = 1.5, testing weekly would suffice.



Comment: This is a timely article given our discussions last week. This simulation study found that in high-risk settings with ongoing community-based transmission, frequent (twice-weekly) routine asymptomatic viral testing may be required to prevent outbreaks and reduce case counts of COVID-19. They point out that PCR testing is not perfect and false negatives can occur especially early in the natural history, meaning that even with frequent testing, a meaningful proportion of infected persons may be missed. They also found that strategies with less frequent testing—such as once-a-week testing—may be sufficient in settings with low community incidence, especially when implemented with additional infection control measures. Their model assumed that results of testing would be available after one day, which may only be possible in higher resource settings, but they also tested the impact of slower turnaround time, which reduced the overall effectiveness of this strategy. Although testing strategies may help this should be combined with other complementary strategies to reliably prevent outbreaks of COVID-19. We need evidence on the use of strategies in combination with testing, including masking, ventilation changes, disinfection, and physical distancing.

Distinct Antibody Responses to SARS-CoV-2 in Children and Adults Across the COVID-19 Clinical Spectrum

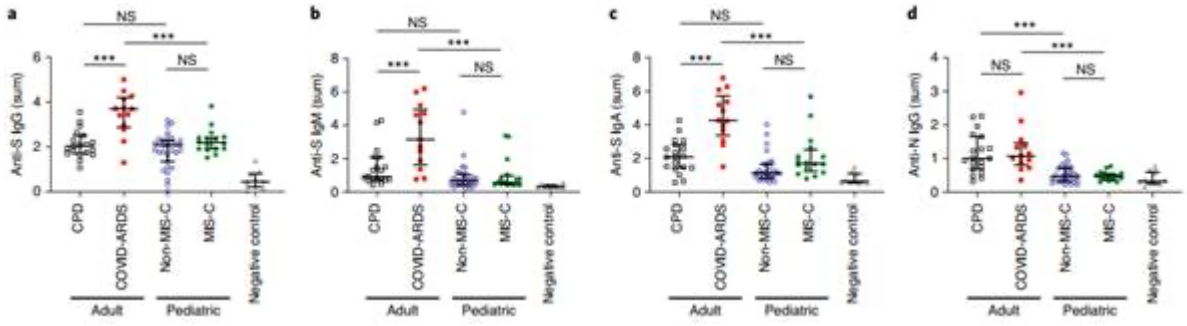
Nature Immunol published online November 6, 2020

doi.org/10.1038/s41590-020-00826-9

The investigators analyzed antibodies to the coronavirus in four groups of patients: 19 adult convalescent plasma donors who had recovered from COVID-19 without being hospitalized; 13 adults hospitalized with acute respiratory distress syndrome resulting from severe COVID-19; 16 children hospitalized with multi-system inflammatory syndrome, the rare condition affecting some infected children; and 31 infected children who did not have the syndrome.

About half of this last group of children had no symptoms at all. They showed distinct antibody responses in children and adults after SARS-CoV-2 infection.

Adult COVID-19 cohorts had anti-spike (S) IgG, IgM and IgA antibodies, as well as anti-nucleocapsid (N) IgG antibody, while children with and without MIS-C had reduced breadth of anti-SARS-CoV-2-specific antibodies, predominantly generating IgG antibodies specific for the S protein but not the N protein. Moreover, children with and without MIS-C had reduced neutralizing activity as compared to both adult COVID-19 cohorts, indicating a reduced protective serological response.



Comment: We need to be cautious in interpreting the results because they represent samples taken from people at only one point in time and the number of cases is small. In addition, samples from the more severely affected children and adults were collected within 24 to 36 hours of being admitted or

intubated for respiratory failure; those from children with mild or no symptoms were banked after medical procedures. Studies reviewed over the last several months in the Daily Briefing suggested that children have a powerful innate immune system, intended to combat the many new pathogens they encounter, and that this first line of defense may clear the infection early without needing to rely on later antibodies. Another study suggested the possibility is that the children have some protection — in the form of immune cells called memory T cells — from previous encounters with common cold coronaviruses common in children under the age of 2 or 3. [cross immunity] The reduced functional antibody response in children compared to adults could also be due to efficacious immune-mediated viral clearance resulting in fewer respiratory symptoms and severe illness. The authors conclude further studies looking at the differences in adult and pediatric immune responses to SARS-CoV-2 are needed. However, their results suggest there may be a distinct infection course and immune response in children independent of whether they develop MIS-C, with implications for developing age-targeted strategies for testing.

A Systematic Review of Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2 Infection

Pediatr Infect Dis J 2020;39:e340-e346
doi: 10.1097/INF.0000000000002888

A systemic review was conducted by combining the terms multisystem inflammatory syndrome in children and coronavirus infection or using the term multisystem inflammatory syndrome in children in bibliographic electronic databases (PubMed, EMBASE, and CINAHL) and in preprint servers (BioRxiv.org and MedRxiv.org) following the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines to retrieve all articles published from January 1, 2020, to July 31, 2020. Observational cross-sectional, cohort, case series, and case reports were included.

A total of 328 articles were identified. Sixteen studies with 655 participants (3 months–20 years of age) were included in the final analysis. Most of the children in reported studies presented with fever, gastrointestinal symptoms, and Kawasaki Disease-like symptoms. The majority of patients required critical care; 40% needed pressors; 34% received anticoagulation; and 15% required mechanical ventilation. More than two-thirds of the patients received intravenous immunoglobulin and 49% received corticosteroids. Remdesivir and convalescent plasma were not commonly used. About 1/3 of patients had evidence of left ventricular dysfunction. Among patients presenting with KD-like symptoms, 23% developed coronary abnormalities and 26% had circulatory shock. The majority recovered; only 11 (1.7%) children died.

Increased levels of C-reactive protein, troponin, and B-type natriuretic peptide (BNP) were reported in all studies. Patients were tested for SARS-CoV-2 PCR and serology. A total of 218 (33%) patients tested positive for SARS-CoV-2 by RT-PCR, while 352 (54%) patients had antibodies against SARS-CoV-2.

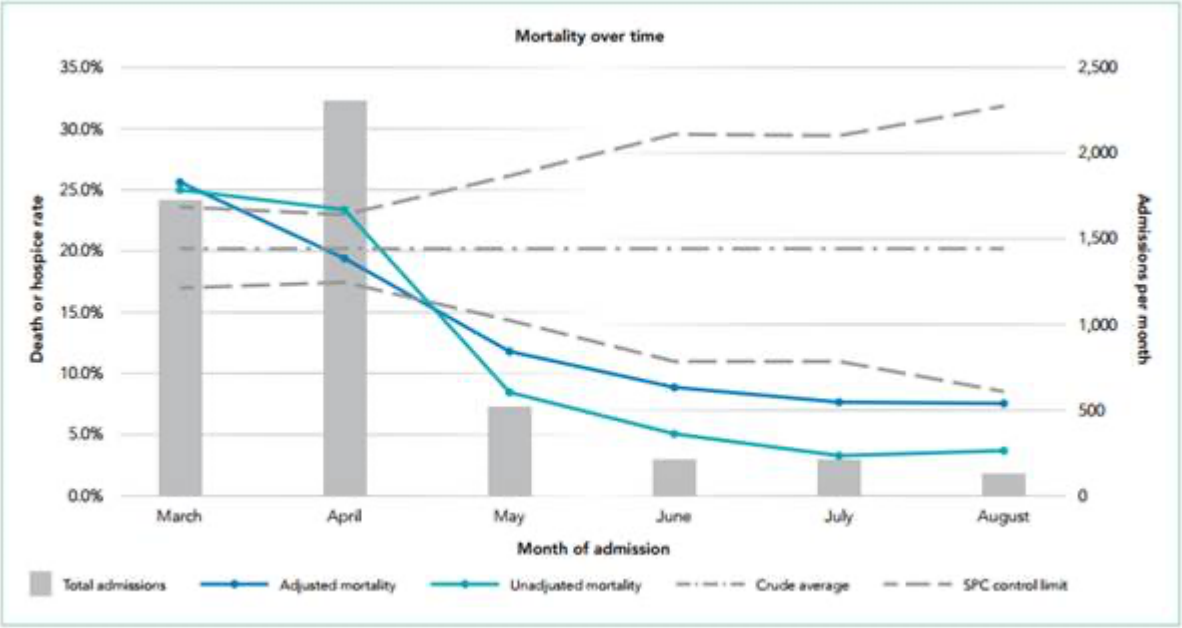
TABLE 3. Geographic Variation in Presenting Symptoms of MIS-C

	United States (n = 445)	Europe (n = 207)	India (n = 3)
Presenting symptoms (% of patients)			
Fever	100	80	100
Rash	57	59	67
Conjunctival injection	48	23	33
Gastrointestinal symptoms	84	74	67
Cardiovascular symptoms	59	74	67
Neurologic symptoms	21	12	33
Respiratory symptoms	19	11	33

Comment: MIS-C currently is thought to be a postinfectious immune-mediated phenomenon, as seen from a lag of 2–4 weeks between occurrence of peak incidence of COVID-19 cases in communities and the recognition of MIS-C. Moreover, the high percentage of seropositivity for SARS-CoV-2 with MIS-C, as also seen in this review, also supports this hypothesis. The age of MIS-C tends to be older than the traditional KD. The major limitation of this publication is that all studies were observational, and all of the data was collected retrospectively. To date there are no randomized control trial on MIS-C.

Trends in COVID-19 Risk-Adjusted Mortality Rates
J Hosp Med published online October 23, 2020
DOI 10.12788/jhm.3552
Mortality rates have recently been lower, raising hope that treatments have improved. However, some have said patients are also now younger, with fewer comorbidities. The authors reviewed whether hospital mortality was associated with changing demographics at a 3-hospital academic health system or due to better therapeutics and/or both. They chose in-hospital mortality or discharge to hospice from March through August 2020, adjusted for demographic and clinical factors, including comorbidities, admission vital signs, and laboratory results.

Among 5,121 hospitalizations, adjusted mortality dropped from 25.6% (95% CI, 23.2-28.1) in March to 7.6% (95% CI, 2.5-17.8) in August. The standardized mortality ratio dropped from 1.26 (95% CI, 1.15-1.39) in March to 0.38 (95% CI, 0.12- 0.88) in August, at which time the average probability of death (average marginal effect) was 18.2 percentage points lower than in March. This reduction remained even after risk adjustment.



Comment: In this study mortality over 6 months found that changes in demographics and severity of illness at presentation did not fully explain decreases in mortality seen over time. Even after risk adjustment for a variety of clinical and demographic factors, including severity of illness at presentation, mortality was significantly and progressively lower over the course of the study period.

The report is similar to risk-adjusted results preliminarily reported among intensive care unit patients in a preprint from the UK. Incremental improvements in outcomes in my opinion is from a combination of increasing clinical experience, decreasing hospital volume [in some areas], growing use of new therapeutics (such as systemic corticosteroids, remdesivir, and anticoagulation), nonpharmacologic treatments (such as placing the patient in the prone position, or proning), earlier intervention, community awareness, and, potentially, lower viral load exposure from increased mask wearing and social distancing. This study does have limitations. All patients were from a single geographic region and treated within a single health system. There was changing admission thresholds and not all confounders may have been identified.