Good morning. Lots to share. Next edition will review the updated AAP guidance for safe schools which includes universal masking. I will try and put this recommendation in perspective. Just what we needed – more controversy. ☹

For today under COVID-19 News I report that ACIP will be meeting tomorrow to consider booster doses. Next the disappointing announcement of setting a deadline of 2022 for full approval for mRNA vaccines. I was hoping for September. Next from ECCMID, a promising report on the antiviral molnupiravir. Next an update on COVID-19 from CDC. Last, another retraction – this time from JAMA Pediatrics on the controversial study suggesting that masks may harm children. [Hint, not true]

Under Journal Review I start with a sobering report on impact of caseload of COVID-19 patients and outcomes. Personally, I am concerned about burn out and post-traumatic stress. Next an article on long-term symptoms for children post COVID-19 infection. Next is another negative article on use of RDV. The last article highlights the complications of patients hospitalized with SARS-CoV-2.

Last, words of encouragement, despite Delta we will get through this "bump in the road."

Have a good day

Ed

? Booster Dose
A federal advisory panel is expected later this week to consider whether health-care workers should be allowed to give additional Covid-19 shots to patients with fragile immune systems, even as top U.S. health officials have said an additional dose of vaccine is not widely needed. The prospect of booster shots emerged last week as the maker of a two-dose coronavirus vaccine, Pfizer, announced it would seek regulatory approval for a third inoculation amid rising global concern about the highly transmissible Delta variant. The advisory panel next week plans to focus on the 2 to 4 percent of U.S. adults who have suppressed immunity, a population that includes organ transplant recipients, people on cancer treatments, and people living with rheumatologic conditions, HIV, and leukemia.

The ACIP, which makes vaccine recommendations to the Centers for Disease Control, is scheduled to discuss the clinical considerations involved with giving additional doses to immunocompromised patients at a July 22 meeting.

FDA Sets 2022 Deadline to Decide on Full Approval of Pfizer Vaccine
July 16, 2021
Pfizer also is seeking approval of a booster dose, but official from CDC and NIH have indicated they did not think booster doses are necessary at this time. See above.

Comment: This is a disappointment. I do not want the FDA to take any shortcuts, but as I have indicated a few weeks ago, the RNA vaccines have been studied extensively and hundreds of millions of doses have been administered worldwide. With vaccination slowdown and vaccine hesitancy and emergence of variants such as Delta, full authorization could provide an additional push to get more people vaccinated who are hesitant.

Molnupiravir Shows Promise for Treatment of Moderate COVID-19 in Phase 2/3 Trial
ECCMID July 14, 2021

The ongoing phase 2/3, randomized, placebo-controlled, double-blind, multi-site study is evaluating the efficacy, safety, and pharmacokinetics of orally administered molnupiravir in non-hospitalized participants with a PCR confirmed case of COVID-19 was presented at ECCMID. Findings from part 1 of the trial demonstrated that the percentage of patients who were hospitalized and/or died was lower in the combined molnupiravir-treated groups versus the placebo arm. Additionally, those participants who received 800 mg of the therapy had the largest overall antiviral effect, in comparison to those who received 200 mg or 400 mg. Part 2 of the trial, the phase 3 portion, will evaluate an 800 mg dose of molnupiravir administered twice daily.

Comment: Although early molnupiravir shows promise, I look forward to seeing the results of phase 3 trials using the 800 mg dose. Molnupiravir was developed at Emory (University) Institute for Drug Discovery (EIDD) as part of a program against Venezuelan equine encephalitis virus, and preclinical models have shown antiviral activity against both influenza and respiratory syncytial viruses. As SARS-CoV-2 emerged, molnupiravir showed potent anti-SARS-CoV-2 activity both in vitro and in animal models. It is currently in phase 2-3 testing both in outpatient settings and in hospitalized COVID-19 patients.

COVID-19 Cases Rising in All 50 States CDC Updates

- The nation's current seven-day case average was 26,306 as of July 16, a 69.3 percent increase from the previous week's average.
- Nationwide, hospitalizations are also rising, particularly in states with lower vaccination levels and outbreaks involving the delta variant, such as Arkansas, Mississippi, and Missouri.
- The nation's seven-day hospitalization average for July 7-13 was 2,794, a 35.8 percent increase from the previous week's average.
- The seven-day average number of vaccines administered daily was 270,592 as of July 15, a 35.7 percent decrease from the previous week.
- As of July 18, 68.2 percent of American adults have received at least one COVID-19 vaccine dose, while 59.4 percent are fully inoculated.
- The current seven-day death average is 211, up 26.3 percent from the previous week's average.

Notice of Retraction: Walach H, et al. Experimental Assessment of Carbon Dioxide Content in Inhaled Air With or Without Face Masks in Healthy Children: A Randomized Clinical Trial
JAMA Pediatr. Published online June 30, 2021. Editorial published online July 16, 2021
This controversial study suggesting that masks may harm children by exposing them to high carbon dioxide levels was retracted on Friday. The research letter released in JAMA Pediatrics on June 30 had reported unacceptably high levels of carbon dioxide by German air standards inside masks worn by children in a laboratory environment.

In the retraction notice, the journal editors cited "numerous scientific issues," that also included questions over the applicability of the CO2 measurement device and the validity of the study conclusions. Following publication, numerous scientific issues were raised regarding the study methodology, including concerns about the applicability of the device used for assessment of carbon dioxide levels in this study setting, and whether the measurements obtained accurately represented carbon dioxide content in inhaled air, as well as issues related to the validity of the study conclusions. In their invited responses to these and other concerns, the authors did not provide sufficiently convincing evidence to resolve these issues, as determined by editorial evaluation and additional scientific review. Given fundamental concerns about the study methodology, uncertainty regarding the validity of the

findings and conclusions, and the potential public health implications, the editors have retracted this Research Letter.

Comment: CDC does not list any known risk to children from wearing face masks, and in fact, recently recommended that unvaccinated children wear masks when school reopens in the fall. I commend JAMA Pediatrics for taking immediate action in retraction of this study.

Journal Review

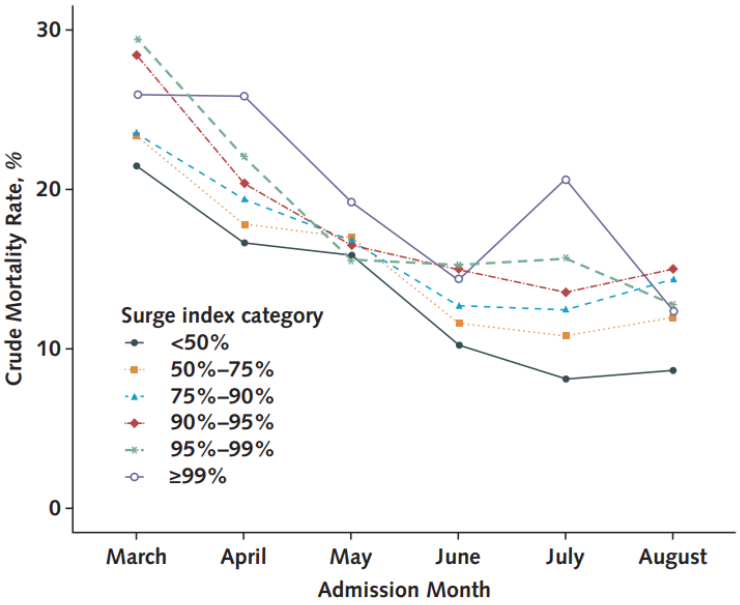
Association Between Caseload Surge and COVID-19 Survival in 558 U.S. Hospitals, March to August 2020

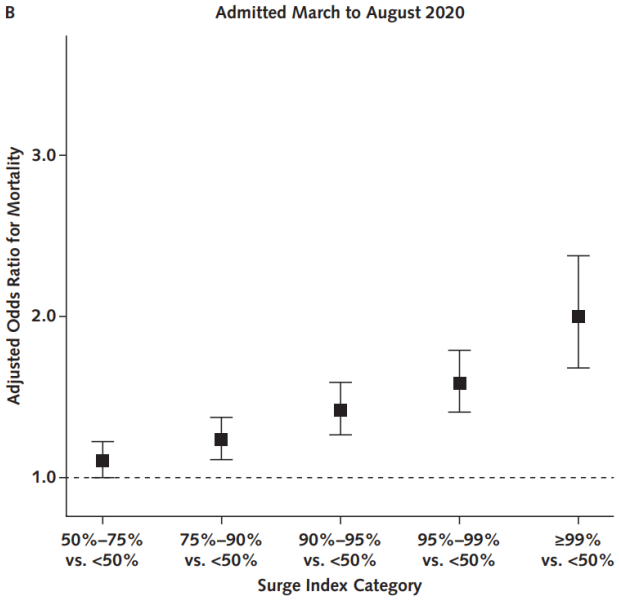
Ann Intern Med published online July 6, 2021
doi:10.7326/M21-1213

Several U.S. hospitals had surges in COVID-19 caseload, but their effect on COVID-19 survival rates remains unclear, especially independent of temporal changes in survival. This is a retrospective cohort study in 558 U.S. hospitals in the Premier Healthcare Database. Adult COVID-19-coded inpatients admitted from March to August 2020 with discharge dispositions by October 2020 were included. Each hospital-month was stratified by percentile rank on a surge index (a severity-weighted measure of COVID-19 caseload relative to pre-COVID-19 bed capacity). The effect of surge index on risk-adjusted odds ratio (aOR) of in-hospital mortality or discharge to hospice was calculated using hierarchical modeling; interaction by surge attributes was assessed.

In the cohort of 558 U.S. hospitals that included approximately 1 of every 7 COVID-19 deaths reported in the United States, they found an association between surge index (a severity-weighted metric of COVID-19 caseload adjusted for baseline hospital capacity) and escalating COVID-19 mortality risk. This association was robust to multiple parameterizations of the surge index and several sensitivity analyses.

Importantly, nearly 1 in 4 COVID-19 deaths in their cohort might have been attributable to hospital strain related to COVID-19 caseload. Although baseline inpatient COVID-19 survival improved over the study period, after adjustment for changing case mix and treatment patterns and other hospital factors, mortality risk associated with hospitals experiencing surges was found to increase even more in later study months.





Comment: This volume-outcome relationship was stronger in later pandemic months despite greater use of corticosteroids and more selective intubation in later and higher surging months. (See above) Residual confounding may have occurred due to social determinants of health, prone positioning, and finer differences in severity of acute illness that were uncaptured in administrative data. However, this is at least the second paper that I am aware of that links increased to outcomes. [JAMA Netw Open. 2021;4:e2034266] We also know HAIs, especially CLABSIs, increased during the pandemic and AR remains a concern. During surges, many hospitals needed traveling nurses to adequately staff units which may have further impacted outcomes. Demand relative to staff availability and burnout, space, supplies, and personal protective equipment might also affect care.

Long-Term Symptoms After SARS-CoV-2 Infection in Children and Adolescents
JAMA Netw Open published online July 15, 2021

doi:10.1001/jama.2021.11880
Children can experience SARS-CoV-2 postviral syndromes, but it is unclear to what extent these individuals are affected by long COVID. The investigators compared symptoms compatible with long COVID in children and adolescents (hereafter "children") reported within 6 months after SARS-CoV-2 serologic testing.

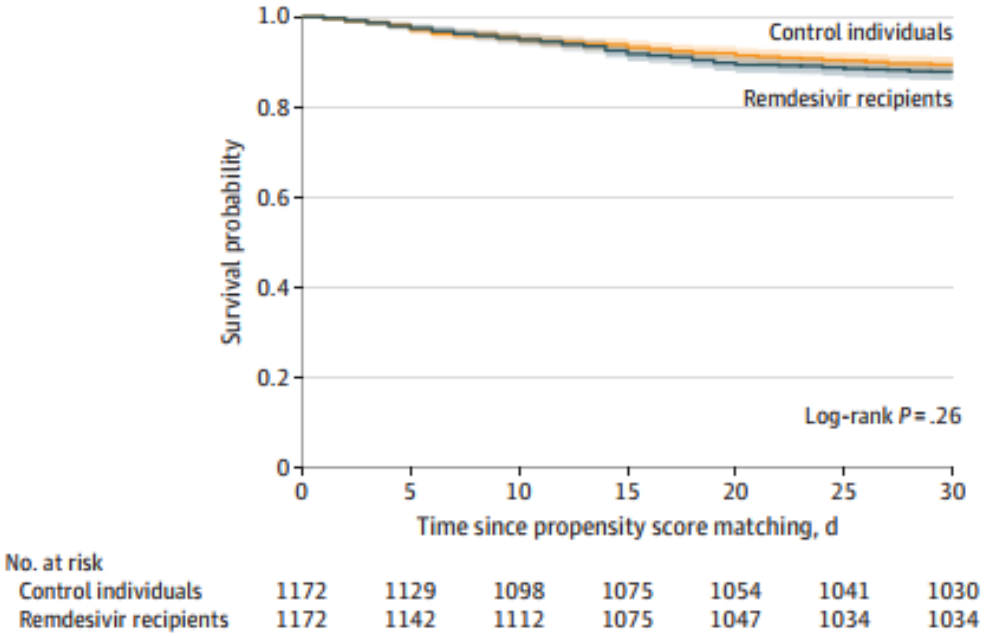
This is a longitudinal cohort study investigating SARS-CoV-2 seroprevalence in 55 randomly selected schools in Zurich in Switzerland. They compared children who tested positive for SARS-CoV-2 antibodies in October or November 2020 with those who tested negative. Overall, 1355 of 2503 children (54%) (median age, 11 years; interquartile range, 9-13; 54% girls) with a serology result in October or November 2020 were included. Between October and November 2020 and March and April 2021, 4 of 109 seropositive children (4%) vs 28 of 1246 seronegative ones (2%) reported at least 1 symptom lasting beyond 12 weeks. The most frequently reported symptoms lasting more than 12 weeks among seropositive children were tiredness (3/109, 3%), difficulty concentrating (2/109, 2%), and increased need for sleep (2/109, 2%).

Comment: This study found a low prevalence of symptoms compatible with long COVID in a randomly selected cohort of children assessed 6 months after serologic testing. This study reports the distribution of symptoms compatible with long COVID on a population level; it did not capture severe SARS-CoV-2 infections because they are rare in children. Limitations include the relatively small number of seropositive children, lack of information on the exact time of SARS-CoV-2 infection, possible misclassification of some children with false seropositive results, potential recall bias, parental report of child's symptoms, lack of information on symptom severity, and noncompletion of the questionnaire.

Association of Remdesivir Treatment with Survival and Length of Hospital Stay Among US Veterans Hospitalized with COVID-19

JAMA Netw Open published online July 15, 2021
doi:10.1001/jamanetworkopen.2021.14741
This is a retrospective cohort study using data from the Veteran Hospitals (VHA) to identify adult patients in 123 VHA hospitals who had a first hospitalization with laboratory-confirmed COVID-19 from May 1 to October 8, 2020. Propensity score matching of patients initiating remdesivir treatment to control patients who had not initiated remdesivir treatment by the same hospital day was used to create the analytic cohort. Main outcomes were time to death within 30 days of remdesivir treatment initiation (or corresponding hospital day for matched control individuals) and time to hospital discharge with time to death as a competing event.

After propensity score matching, the analysis included 1172 remdesivir recipients and 1172 controls, for a final matched cohort of 2344 individuals. Remdesivir recipients and matched controls were similar with regard to age (mean [SD], 66.6 [14.2] years vs 67.5 [14.1] years), sex (1101 men [93.9%] vs 1101 men [93.9%]), dexamethasone use (559 [47.7%] vs 559 [47.7%]), admission to the ICU (242 [20.7%] vs 234 [19.1%]), and MV use (69 [5.9%] vs 45 [3.8%]). Standardized differences were less than 10% for all measures. Remdesivir treatment was not associated with 30-day mortality (143 remdesivir recipients [12.2%] vs 124 controls [10.6%]; log rank $P = .26$; adjusted hazard ratio [HR], 1.06; 95% CI, 0.83-1.36). Results were similar for people receiving vs not receiving dexamethasone at remdesivir initiation (dexamethasone recipients: adjusted HR, 0.93; 95% CI, 0.64-1.35; nonrecipients: adjusted HR, 1.19; 95% CI, 0.84-1.69). Remdesivir recipients had a longer median time to hospital discharge compared with matched controls (6 days [interquartile range, 4-12 days] vs 3 days [interquartile range, 1-7 days]; $P < .001$).

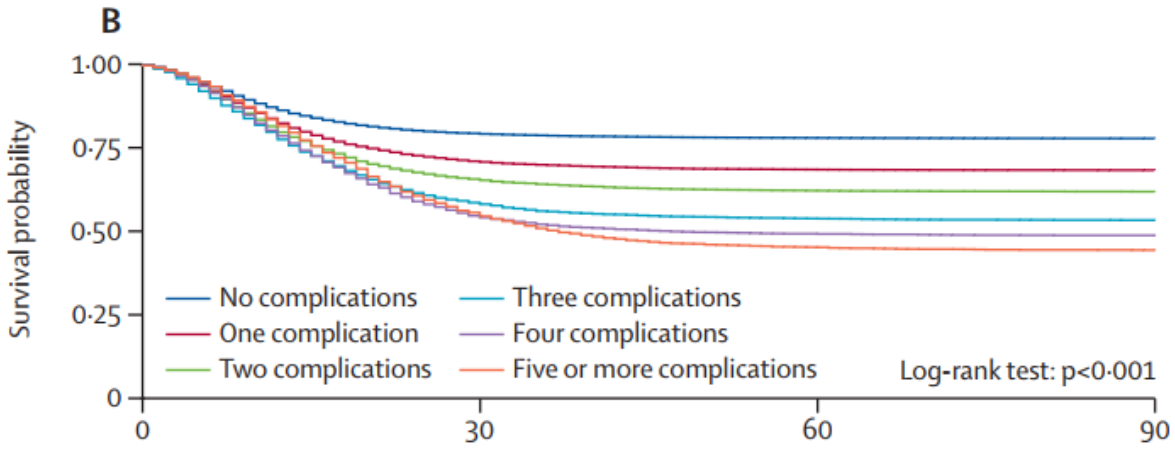


Comment: In this cohort study of 2344 US veterans hospitalized with COVID-19, remdesivir therapy was not associated with improved 30-day survival but was associated with a significant increase in median time to hospital discharge. [Part may be based that some patients were kept in hospital to complete RDV] Propensity score-matched remdesivir recipients and controls had similar illness severity based on observed variables, but there may have been residual confounding associated with both unobserved variables and imprecise measurement of observed variables. Second, the results pertain only to the 1172 remdesivir recipients (49.5% of the remdesivir recipients in the total cohort) whom they were able to match to controls. These patients had a lower propensity for remdesivir treatment and less severe illness compared with unmatched remdesivir recipients. Potential reason is that rates of remdesivir treatment were higher among the most severely ill patients, leaving few similar control patients for matching. In addition, available data prevented them from identifying specific subgroups of patients who may have been more likely to benefit from remdesivir treatment. An example, subgroup analyses in the ACTT-1 suggested that remdesivir was most effective when patients required supplemental oxygen but had not yet progressed to require mechanical ventilation or high flow heated oxygen.

Characterisation of In-Hospital Complications Associated with COVID-19 Using the ISARIC WHO Clinical Characterisation Protocol UK: A Prospective, Multicentre Cohort Study
Lancet 2021; 398: 223–37
The investigators did a prospective, multicenter cohort study in 302 UK health-care facilities. Adult patients aged 19 years or older, with confirmed or highly suspected SARS-CoV-2 infection leading to COVID-19 were included in the study. The primary outcome of this study was the incidence of in-hospital complications, defined as organ-specific diagnoses occurring alone or in addition to any hallmarks of COVID-19 illness. They used multilevel logistic regression and survival models to explore associations between these outcomes and in-hospital complications, age, and pre-existing comorbidities. Data were collected on organ-specific complications including complex respiratory (bacterial pneumonia, acute respiratory distress syndrome [ARDS], empyema, pneumothorax, and pleural effusion), neurological (meningitis, encephalitis, seizure, and stroke), cardiovascular (thromboembolism, heart failure,

myocarditis, endocarditis, arrhythmia, cardiomyopathy, myocardial ischemia, and cardiac arrest), acute kidney injury, gastrointestinal (acute liver injury, pancreatitis, and gastrointestinal hemorrhage), and other systemic complications (coagulopathy, disseminated intravascular coagulation, anemia, and bloodstream infection).

Of the patients admitted to hospital for management of COVID-19, 49·7% (36,367 of 73,197) had at least one complication. The mean age of our cohort was 71·1 years, with 56·0% being male and 81·0% having at least one comorbidity. Males and those aged older than 60 years were most likely to have a complication. Renal (24·3%), complex respiratory (18·4%), and systemic (16·3%) complications were the most frequent. Cardiovascular (12·3%), neurological (4·3%), and gastrointestinal or liver (0·8%) complications were also reported. Suspected bacterial pneumonia was the most common respiratory complication. Acute complications were associated with reduced ability to selfcare at discharge, with neurological complications being associated with the worst functional outcomes.



Comment: COVID-19 complications are likely to cause a substantial strain on health and social care in the coming years beyond just hospitalization. This dataset focuses on in-hospital complications during the index admission for COVID-19 and does not provide longer-term outcome data or data on quality of life. This study did not include a non-SARS-CoV-2 control group, which could provide useful data to compare complication burdens to other causes of critical illness or viral infection.