Good afternoon

I usually publish on Tuesday AM, but there is so much new to report since Friday. So, I thought for a change I would send Tuesday's Briefing this afternoon.

Under Covid-19 News I actually have written two short opinion pieces on religious exemptions and mandatory vaccinations. Your comments are welcome. Next is a report on a rare complication with the AZ vaccine. EMA's safety committee has concluded that people who have previously had capillary leak syndrome should not be vaccinated with the AZ vaccine. Next, the announcement that Moderna has applied for EUA for 12-18-year-olds. The fifth piece is a report on Novavax late-stage data from its U.S.-based clinical trial showing its vaccine is more than 90% effective against COVID-19 across a variety of variants of the virus. Next, CDC is encouraging hospitals, emergency departments, and emergency care facilities to administer COVID-19 vaccines to unvaccinated patients at discharge. Lastly, CDC has seen an increase in new cases in the US and their concern over the emergence of the delta variant.

Under Journal Review the first is a CDC report that shows a significant reduction in COVID-19 cases and severe illness in populations with high vaccination coverage. The next two articles look at therapeutic versus prophylactic doses for VTE prophylaxis in patients hospitalized with Covid-19. The last article is a comparison of symptoms and RNA levels in children and adults with SARS-CoV-2 infection.

Have a wonderful week.

Ed

VII-Religious Exemptions

For years I have tried to understand what is a valid religious exemption to vaccinations? Recently [April 28, 2021] the state of Connecticut removed the existing legal exemption for religious reasons. Connecticut has now joined California, New York, and Maine as states where religious exemptions have been withdrawn. West Virginia and Mississippi had already decided against permitting religious exemptions. All states require school vaccinations. Mississippi and West Virginia only permit a health exemption. Most other states permit either a philosophical objection or a religious exemption in addition to legitimate health exemptions. We know that when parents exempt their children from childhood vaccination, outbreaks do occur. Recent outbreaks of measles and mumps are well described. Just like with Covid-19 vaccinations, if someone refuses to be vaccinated, not only does it put that person at risk, but they also put others in the community at risk.

Next, I looked at major religions to find if any of them actually oppose vaccination. The Catholic Church, Muslim traditions, Buddhism, Hinduism, and Judaism are in favor of vaccination. They want their communities protected. Even Christian Scientists leave it to conscience as to whether you want to take a preventive action to try to stop a communicable disease. Christian Scientists recognize that you should honor political authorities and try to be a good citizen in making decisions about what to do with a requirement like vaccination. So, I ask all of you if religions do not oppose vaccination should we follow the states like Connecticut and eliminate religious exemptions?

Houston Methodist Can Require Employees to Get Covid-19 Vaccine

June 12, 2021

A federal judge in Texas ruled that Houston Methodist can require its employees to be vaccinated against Covid-19, dismissing a lawsuit brought by workers who claimed the mandate unlawfully forced

them to be human "guinea pigs." More than 100 of its workers filed suit against the requirement in late May. They contended that the federally approved vaccines are experimental and dangerous and likened Houston Methodist's requirement to Nazi medical experiments on concentration camp prisoners during the Holocaust. Among other claims, the suit said the system's policy violated a federal law governing the protection of "human subjects." In a five-page ruling, Judge Hughes said the Nazi comparison was "reprehensible" and that the lawsuit's legal assertions misinterpreted the law and completely lacked merit. Houston Methodist's policy allowed employees to request exemptions based on a documented medical condition or a conflict with their sincerely held religious beliefs. [see above on religious exemptions] It also allowed pregnant employees to delay their shots. The policy aligned with updated guidance from the U.S. Equal Employment Opportunity Commission (EEOC) issued last month that said employers could require workers entering a workplace to be vaccinated.

VII Comment: The recognition of HCW vaccination as an essential component of patient and HCW safety programs emerged in the mid-2000s with a focus on influenza vaccination. Patient safety focused programs at hospitals like Virginia Mason and HCA paved the way for stronger expectations surrounding HCW vaccination. [Infect Control Hosp Epidemiol. 2010; 31:881-888 and JAMA 2011; 305:999-1001] In 2009 I was Medical Director of Infection Prevention and Epidemiology at HCA when HCA implemented their mandatory patient safety program and seasonal influenza vaccination of HCWs. Influenza vaccination rates went from 62% to >90%. Both Virginia Mason and HCA were also sued. Mandatory influenza vaccination programs for HCW have been associated with high vaccination rates and a significant decrease in HCW absenteeism and health care associated influenza among hospitalized patients. [Open Forum Infect Dis. 2019;6(4):ofz096] HCW should not spread vaccine preventable infections like measles, pertussis, and influenza to their patients and other HCW. The data is becoming clear: Covid-19 vaccines have been shown to be safe and have excellent effectiveness against both symptomatic and asymptomatic COVID-19 infection. It is time is to add COVID-19 to that list for mandatory vaccination.

Tom Talbot has written a very thoughtful Viewpoint in JAMA published online June 7, 2021 [doi:10.1001/jama.2021.8901], entitled "COVID-19 Vaccination of Health Care Personnel as a Condition of Employment: A Logical Addition to Institutional Safety Programs." He reviews experience with influenza vaccine mandates and current information on safety and efficacy of current Covid-19 vaccines, HCW risk of contracting Covid-19, and impact of vaccination on transmission.

AstraZeneca Vaccine: EMA (European Medicines Agency) Advises Against Use in People with History of Capillary Leak Syndrome

June 11, 2021

EMA's safety committee has concluded that people who have previously had capillary leak syndrome must not be vaccinated with the AstraZeneca (AZ) vaccine. The Committee carried out an in-depth review of 6 cases of capillary leak syndrome in people who had received AZ vaccine. Most of the cases occurred in women and within 4 days of vaccination. Three of those affected had a history of capillary leak syndrome and one of them subsequently died. Capillary leak symptoms include hypotension, rapid swelling of arms and legs, and sudden weight gain.

Moderna Seeks FDA OK for Adolescent COVID Vaccine

June 11, 2021

Moderna has filed for emergency use authorization from the U.S. Food and Drug Administration to give its vaccine to adolescents aged 12-17. The company released early results from a clinical trial that

enrolled 3,732 adolescents, including two-thirds who received two doses. Blood tests showed that the vaccine created an immune response similar to that in adults.

Comment: I do not expect any difficulty for FDA granting EUA.

Novavax COVID-19 Vaccine Update
Yesterday Novavax reported late-stage data from its U.S.-based clinical trial showing its vaccine is more than 90% effective against COVID-19 across a variety of variants of the virus. Novavax's protein-based COVID-19 vaccine candidate was more than 93% effective against the predominant variants of COVID-19 that have been of concern among scientists and public health officials. During the trial, the B.1.1.7 variant [Alpha] first discovered in the United Kingdom became the most common variant in the United States, the vaccine was 91% effective among volunteers at high risk of severe infection and 100% effective in preventing moderate and severe cases of COVID-19. The vaccine was generally well tolerated. Side effects included headache, fatigue, and muscle pain and were generally mild. A small number of participants experienced side effects described as severe. Novavax is on track to file for EUA in the United States in the third quarter of 2021.

Comment: This is great news. If all goes as planned Novavax could be the third vaccine given EUA in the US. In addition, Novavax is working with countries like India. Novavax has begun its regulatory filing in India in partnership with the Serum Institute of India. Novavax remains on track to produce 100 million doses per month by the end of the third quarter of 2021 and 150 million doses per month in the fourth quarter of 2021. The addition of Novavax will be a welcome addition in the worldwide effort to vaccinate as many people as possible across the globe to end this pandemic.

CDC Urges COVID-19 Vaccinations at Discharge
The CDC is encouraging hospitals, emergency departments and emergency care facilities to administer COVID-19 vaccines to unvaccinated patients at discharge.

- EDs serve as the primary—and often only—health care access point for up to a fifth of the U.S. population.
- Urgent care clinics handle about 89 million patient visits each year, or more than 29% of all primary care visits in the country, and nearly 15% of all outpatient physician visits.
- Expanding COVID-19 vaccine availability via these settings can therefore increase access to vaccinations.

US COVID-19 Cases No Longer Declining; Delta Variant's Rapid Spread

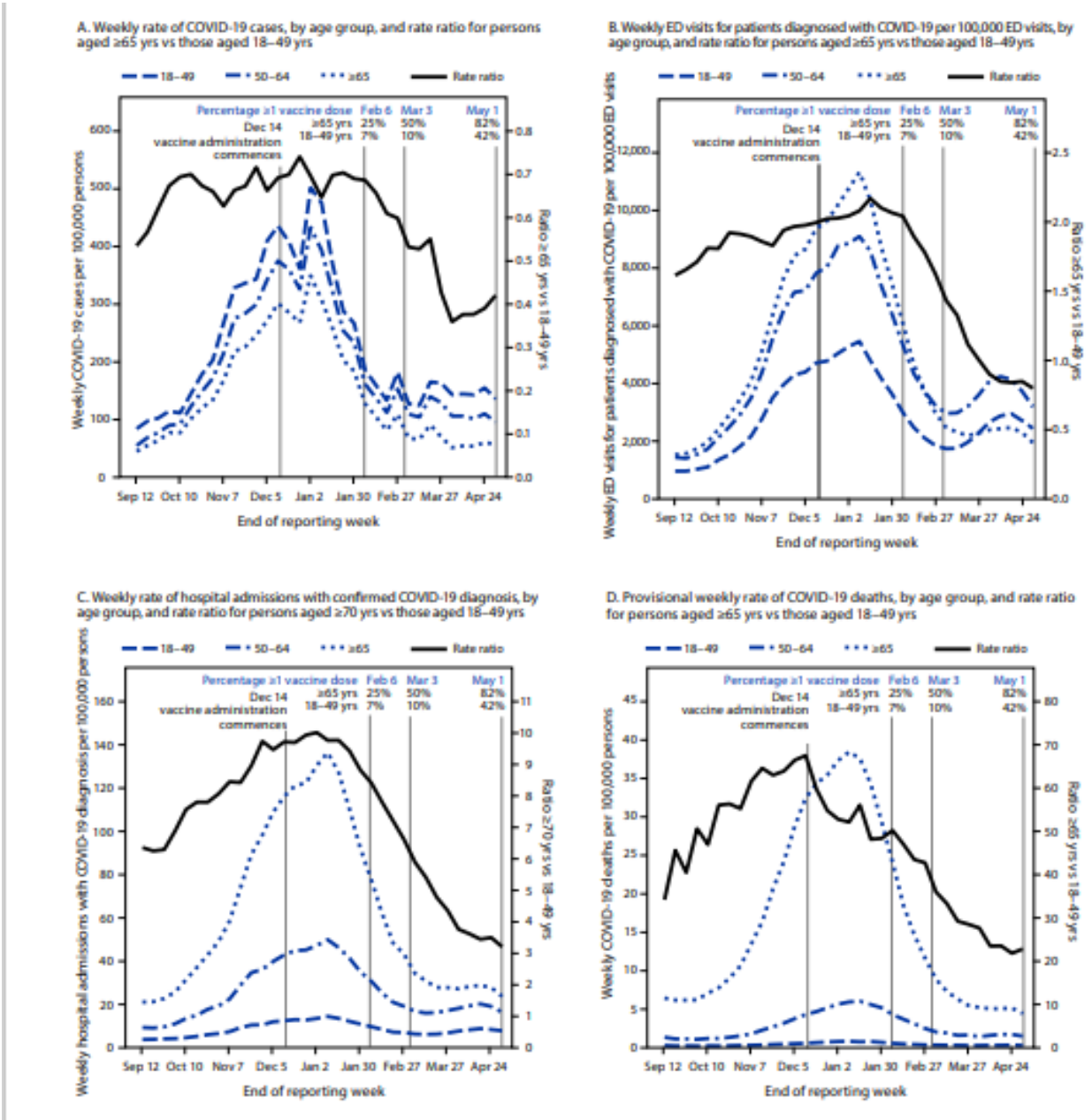
- Total cases in US increased by 9000.
- The U.S. vaccination campaign has slowed, and nearly a third of Americans are hesitant about getting vaccinated.
- The delta variant, first identified in India, now accounts for about 10 percent of U.S. cases and is doubling every two weeks**.**
- The delta variant appears to be more contagious and more severe than earlier variants.
- The good news is the data suggests that, if you have been fully vaccinated, you remain protected.

Journal Review

Decreases in COVID-19 Cases, Emergency Department Visits, Hospital Admissions, and Deaths Among Older Adults Following the Introduction of COVID-19 Vaccine — United States, September 6, 2020–May 1, 2021

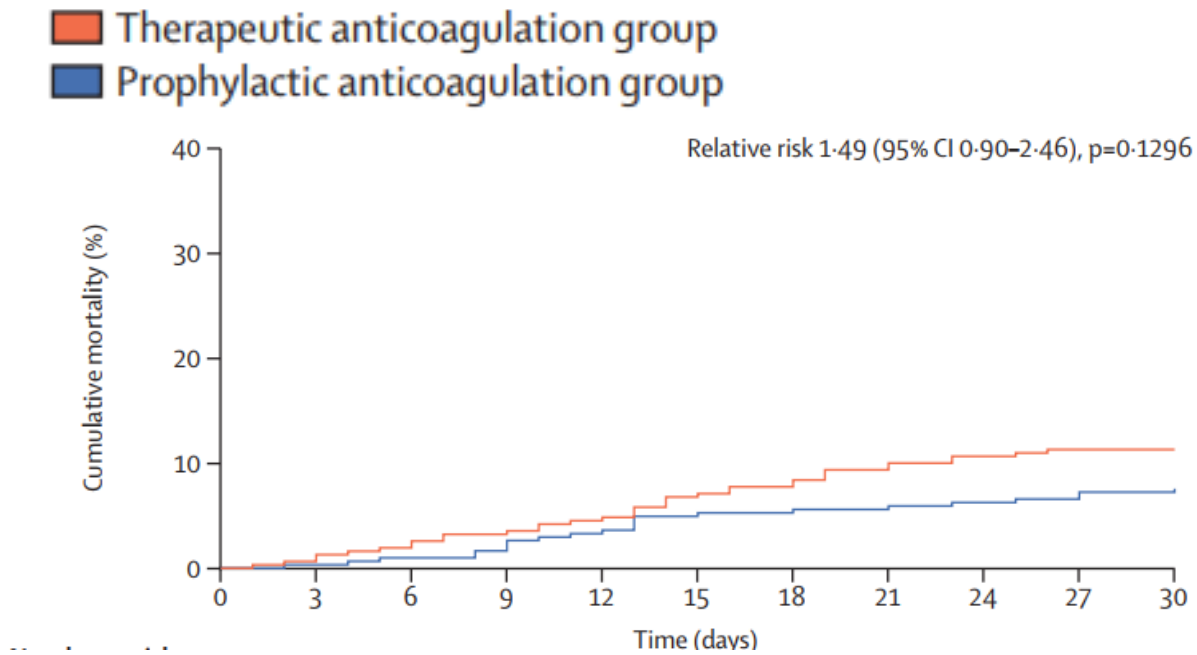
MMWR 2021; 70:858-864

By May 1, 2021, 82%, 63%, and 42% of adults aged ≥65, 50-64, and 18-49 years, respectively, had received ≥1 vaccine dose. From November 29-December 12, 2020, to April 18-May 1, 2021, the rate ratios of COVID-19 incidence, emergency department visits, hospital admissions, and deaths among adults aged ≥65 years (≥70 years for hospitalizations) to adults aged 18-49 years declined 40%, 59%, 65%, and 66%, respectively.



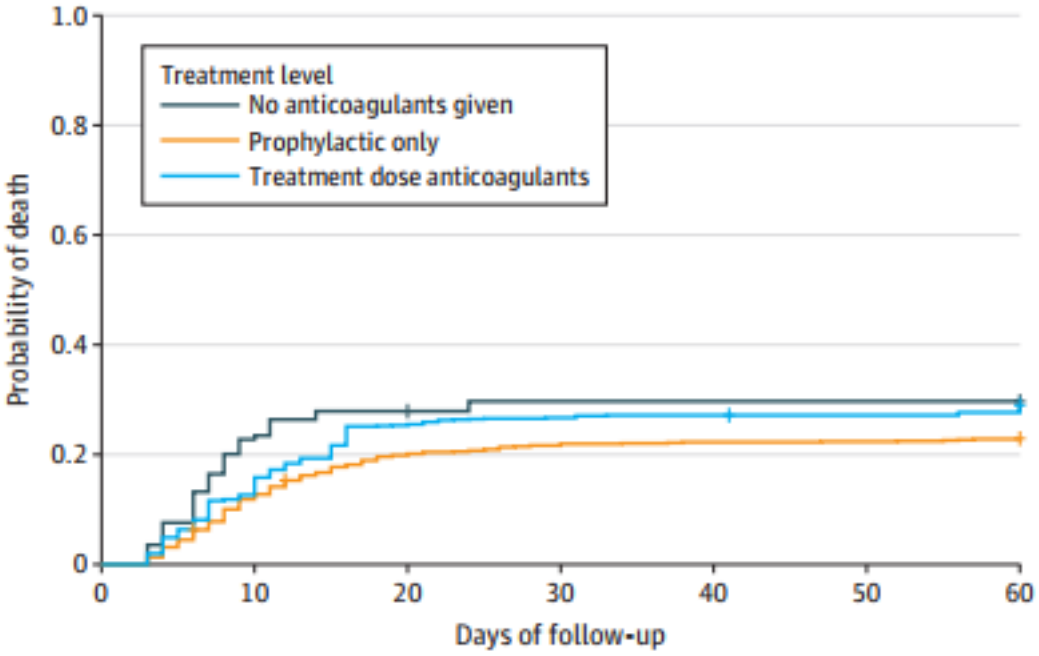
Comment: These data are consistent with other reports showing a reduction in COVID-19 cases and severe illness in populations with high vaccination coverage. A study from Israel found the ratio of COVID-19 patients aged ≥70 years requiring mechanical ventilation to those aged <50 years declined 67% within 3 months of a nationwide vaccination campaign prioritizing persons aged >60 years (MMWR 2021; 70:326–8). In separate studies analyzing the Israeli experience, COVID-19 incidence, hospitalizations, and deaths markedly declined across all age groups as cumulative vaccination coverage increased (Lancet 2021;397:1819–29), and vaccine effectiveness of 46% for COVID-19 infection, 74% for hospitalization, and 72% for death, was observed during 2-3 weeks after the first dose (N Engl J Med 2021;384:1412–23). The alpha variant (B.1.1.7) accounted for ~80% of cases in Israel. The current study was an ecologic real-world analysis based on aggregated data that may not account for variability in reporting or vaccination coverage among jurisdictions, between rural and urban areas, or by race and ethnicity. The populations eligible and timing of each vaccination phase varied across different states and cities. There was also reporting inconsistencies and delays. Nonetheless, the greater decline in COVID-19 morbidity and mortality in older adults, the age group with the highest vaccination rates and risk, demonstrates the impact of increasing population level vaccination coverage.

Therapeutic Versus Prophylactic Anticoagulation for Patients Admitted to Hospital with COVID-19 and Elevated D-Dimer Concentration (ACTION): An Open-Label, Multicentre, Randomised, Controlled Trial
Lancet published online June 4, 2021
doi.org/10.1016/ S0140-6736(21)01203-4
This is a pragmatic, open label (with blinded adjudication), multicenter, randomized, controlled trial, at 31 sites in Brazil. Patients (aged ≥18 years) hospitalized with COVID-19 and elevated D-dimer concentration, and who had COVID-19 symptoms for up to 14 days before randomization, were randomly assigned (1:1) to receive either therapeutic or prophylactic anticoagulation. Therapeutic anticoagulation was in-hospital oral rivaroxaban (20 mg or 15 mg daily) for stable patients, or initial subcutaneous enoxaparin (1 mg/kg twice per day) or intravenous unfractionated heparin (to achieve a 0·3–0·7 IU/mL anti-Xa concentration) for clinically unstable patients, followed by rivaroxaban to day 30. Prophylactic anticoagulation was standard in-hospital enoxaparin or unfractionated heparin. The primary efficacy outcome was a hierarchical analysis of time to death, duration of hospitalization, or duration of supplemental oxygen to day 30. 615 were randomly allocated (311 [50%] to the therapeutic anticoagulation group and 304 [50%] to the prophylactic anticoagulation group). 576 (94%) were clinically stable and 39 (6%) clinically unstable. The primary efficacy outcome was not different between patients assigned therapeutic or prophylactic anticoagulation, with 28,899 (34·8%) wins in the therapeutic group and 34 288 (41·3%) in the prophylactic group (win ratio 0·86 [95% CI 0·59–1·22], p=0·40). Consistent results were seen in clinically stable and clinically unstable patients. The primary safety outcome of major or clinically relevant non-major bleeding occurred in 26 (8%) patients assigned therapeutic anticoagulation and seven (2%) assigned prophylactic anticoagulation (relative risk 3·64 [95% CI 1·61–8·27], p=0·0010).



Comment: To my knowledge this is the first randomized clinical trial with an adequate sample size to calculate the effect of the therapeutic use of an oral anticoagulant on clinical outcomes in patients hospitalized with COVID-19 and elevated D-dimer concentration in comparison with prophylactic anticoagulation. The results of the current study show that, in patients hospitalized with COVID-19 and elevated D-dimer concentration, therapeutic anticoagulation with rivaroxaban in clinically stable patients and heparin in clinically unstable patients did not improve clinical outcomes or reduce death, and increased bleeding when compared with thromboprophylaxis with heparin. The open label design has a potential risk of bias, especially with respect to clinical event ascertainment. Adherence to the medication at the end of the study was assessed through pill count done by patients via telephone call and not in an in-person medical evaluation. See below.

Trends in Venous Thromboembolism Anticoagulation in Patients Hospitalized with COVID-19
JAMA Netw Open published online June 11, 2021
doi:10.1001/jamanetworkopen.2021.11788
This is a multicenter cohort study to evaluate the use of anticoagulation in hospitalized patients with COVID-19 infection across 30 hospitals in Michigan. The study included 1351 patients with COVID-19 and evaluated in-hospital mortality and 60-day mortality based on anticoagulation strategy, as well as anticoagulation nonadherence rates, during the first several months of the COVID-19 pandemic from March to June 2020. The study found that in-hospital use of both prophylactic- and treatment-dose anticoagulation for adults hospitalized with COVID-19 was associated with reduced in-hospital mortality; however, at 60 days, only prophylactic-dose anticoagulation remained associated with lower mortality. Additionally, the authors demonstrated that anticoagulation nonadherence, defined as missing 2 days or more of anticoagulation, was associated with a higher 60-day mortality but not an increase in in-hospital mortality. Anticoagulation adherence increased significantly over the course of time within the study.



Comment: In addition to confirming recent findings suggesting both prophylactic- and treatment-dose anticoagulation strategies are associated with lower in-hospital mortality, they found that only prophylactic-dose anticoagulation was associated with lower 60-day mortality. The current study showed a mortality benefit in line with other recently published studies of patients infected with COVID-19. Numerous recent studies have focused on the question of optimal anticoagulation dosing for patients with COVID-19. Unfortunately, results thus far have been quite varied; both increases and reductions in mortality rate associated with treatment-dose anticoagulation have been observed. Similarly, the data in the current study are not robust enough to recommend one anticoagulation dose over another. Comparison of outcomes between the 2 doses observed (prophylactic and treatment doses) is limited by the study design (i.e., nonrandomized), lack of sufficient granular clinical data (i.e., bleeding rate was not reported for both groups), and potentially inadequate matching. Nonetheless, these findings suggest that prophylactic-dose VTE anticoagulation may be optimal therapy for patients hospitalized with COVID-19. See above.

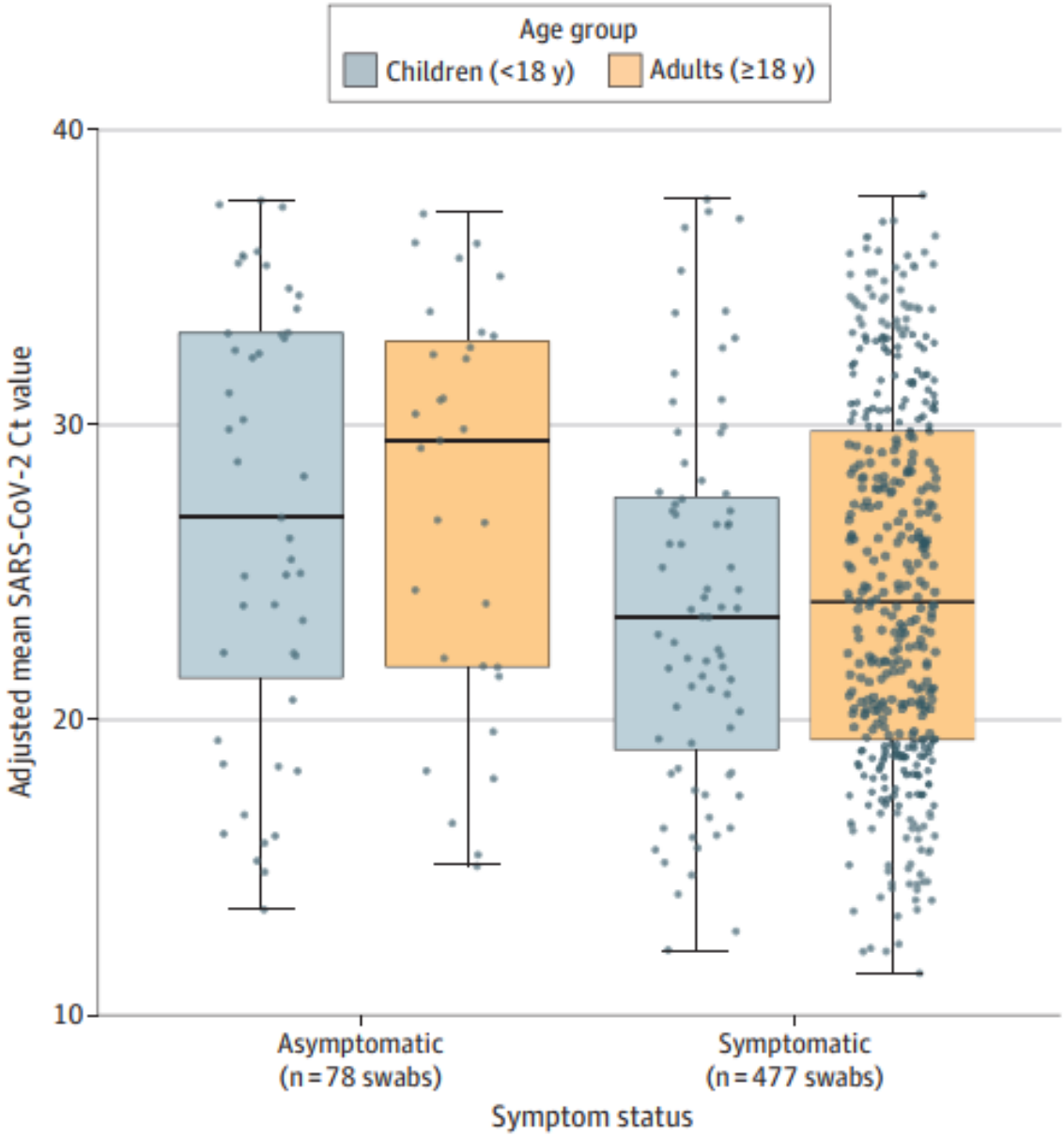
Comparison of Symptoms and RNA Levels in Children and Adults With SARS-CoV-2 Infection in the Community Setting

JAMA Pediatr published online June 11, 2021.
doi:10.1001/jamapediatrics.2021.2025

This is cross-sectional study which used a respiratory virus surveillance platform in persons of all ages to detect community COVID-19 cases from March 23 to November 9, 2020. A population-based convenience sample of children younger than 18 years and adults in King County, Washington, who enrolled online for home self-collection of upper respiratory samples for SARS-CoV-2 testing by PCR were included. After signing an electronic consent form, all participants, or parents or guardians for participants younger than 18 years, completed an electronic questionnaire to collect data on sociodemographic and clinical characteristics, exposures, and health-related behaviors. Race and ethnicity were self-classified by participants using provided standard race and ethnic categories. Race and ethnicity data were collected to examine disparities between racial/ethnic groups in study participation as well as in outcomes, such as SARS-CoV-2 positivity. Samples were self-collected by

participants 13 years and older via unsupervised middle turbinate (MTB) or anterior nares (AN) swabs. Parents or guardians performed swab collection for children younger than 13 years.

In this cross-sectional study of 555 children and adults with SARS-CoV-2 confirmed by PCR, symptomatic individuals had higher SARS-CoV-2 RNA levels (as indicated by lower mean cycle threshold values) compared with asymptomatic individuals. No significant differences in RNA levels were found between asymptomatic children and asymptomatic adults or between symptomatic children and symptomatic adults.



Comment: Regardless of age, in this community-based study, SARS-CoV-2 RNA levels were higher in symptomatic individuals. This publication is consistent with recent studies of asymptomatic children and

studies of viral load by age. To put these data into the perspective of transmission risk, a recent study demonstrated that SARS-CoV-2 Ct values almost linearly inversely correlated with transmission. [medRxiv. published online March 05, 2021. doi:10.1101/ 2021.02.28.21252608] Furthermore, a meta-analysis found that the risk of asymptomatic transmission is significantly lower than that of symptomatic transmission (relative risk, 0.58; 95% CI, 0.34-0.99; *P* = .047). [JAMMI. 2020;5(4):223-234] Taken together, these findings suggest that children may be less likely to transmit SARS-CoV-2 because of reduced frequency and severity of symptoms, which are associated with reduced viral load. In schools, transmission typically follows trends in community transmission, rather than preceding or amplifying them. Schools have generally not been associated with frequent outbreaks or substantial increases in community transmission as measured by COVID-19-associated hospitalizations. [Lancet Infect Dis. 2021;21(3): 344-353] Recent data demonstrate that although the risk of COVID-19 may appear greater among children who are attending school in person, this risk disappears with layered prevention measures. [Science. 2021;eabh2939. Published online April 29, 2021].