Good morning. I hope everyone has had a much better week. There is so much to report today, so I have several important articles in the queue for Monday including the peer reviewed REMAP-CAP tocilizumab trial now published in the N Engl J Med and others.

Under COVID-19 News, the FDA review on the J&J vaccine. The FDA meeting as all of you know is today. I expect EUA to follow shortly. Report of new variants in CA and NY. Also, a remarkable report of the dramatic decline in NH deaths.

Under journal reviews in addition to the NY variants, Israel publication on their vaccine rollout which estimated vaccine effectiveness during the follow-up period starting 7 days after the second dose was 92% for documented infection, 94% for symptomatic Covid-19, 87% for hospitalization, and 92% for severe Covid-19. The next article is an analysis of data from the UK and US registries of pregnancies with SARS-CoV-2 infection which showed that preterm delivery occurred in a higher proportion of women with SARS-CoV-2 infection compared to contemporaneous and historical national data. The last article is an excellent review on the patterns of clinical presentation and organ involvement that distinguish between patients with MIS-C and severe acute COVID-19 in children.

Have a wonderful weekend

Ed

J&J Vaccine

The vaccine is more than 85 percent effective at preventing severe illness and 66 percent effective at preventing moderate and severe disease four weeks after the shot. The vaccine also showed 86 percent efficacy against severe forms of Covid-19 in the United States, and 82 percent against severe disease in South Africa. Novavax vaccine has an efficacy of 49% in South Africa and the AstraZeneca vaccine did not provide much protection.

The vaccine's protection was consistent across Black, Hispanic, and white volunteers, and across different ages. The newly released documents presented evidence that the vaccine was safe, with noticeably milder side effects than the Pfizer and Moderna vaccines and without any reports of severe allergic reactions like anaphylaxis to date.

The next very important question: do the vaccines prevent asymptomatic disease? J&J looked for asymptomatic infections by checking for coronavirus antibodies 71 days after volunteers got a vaccine or a placebo. The new analyses estimate that the vaccine has an efficacy rate of 74 percent against asymptomatic infections. But that calculation was based on a relatively small number. Moderna's trial found that vaccinated people were less likely to develop an infection without symptoms. And AstraZeneca found that its vaccine reduced asymptomatic infections by about half. Pfizer is evaluating if their vaccine prevents asymptomatic disease.

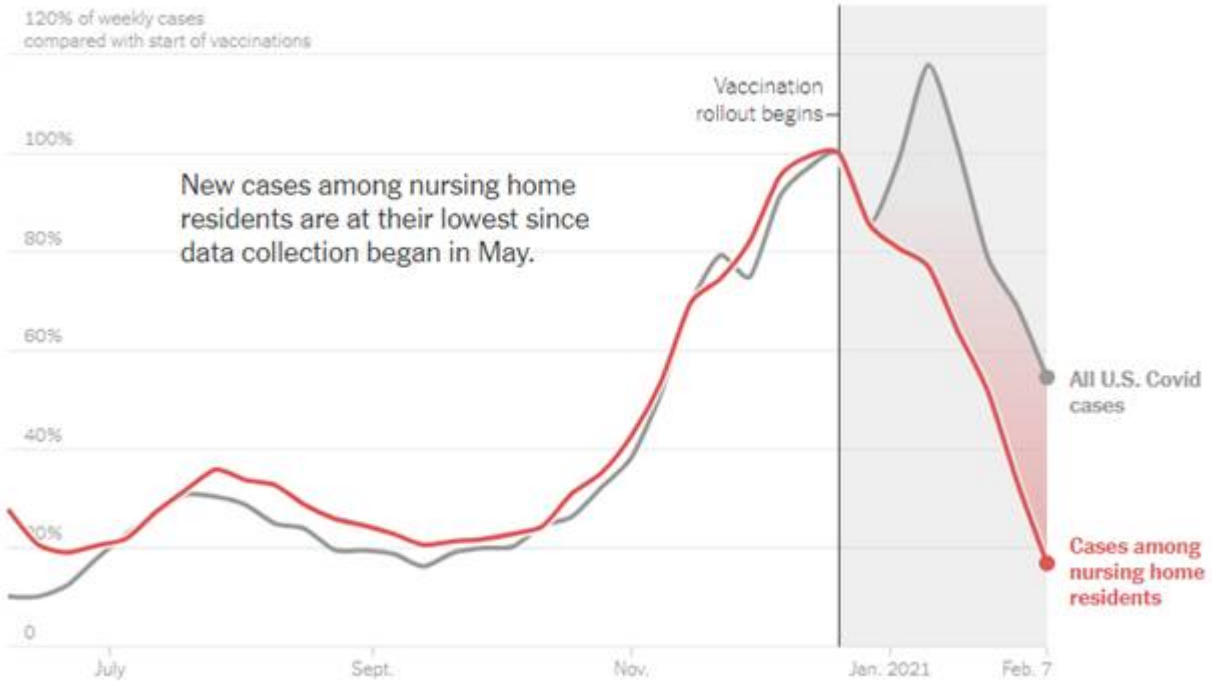
Comment: Although if appears the J&J vaccine has lower protective efficacy than Moderna and Pfizer, their trials were done later when variants were emerging; nonetheless, the fact that the vaccine provided more than 85 percent effective at preventing severe illness is significant. The vaccine appears to have fewer side effects, is one dose, and can be stored at refrigerator temperatures for at least three months which makes the distribution much easier. Hopefully the FDA will give EUA this weekend which will give access to millions who wish to vaccinated getting us closer to control of this pandemic.

New Variants

CA: Dr. Chiu and his colleagues in CA analyzed 2,172 virus samples collected from across the state between September and January. At the start of September, the researchers found no sign of B.1.427/B.1.429. But by late January, it had become the predominant variant in California. The researchers also ran experiments in the lab to look for evidence that the new variant had a biological edge. In one study (not published), they showed that it was at least 40 percent more effective at infecting human cells than earlier variants were. And when they measured the genetic material found on swabs used for coronavirus tests, the researchers found that people infected with the variant produce a viral load twice as large as that of other variants. The investigators found that people had a 35 percent chance of getting infected if someone in their house had B.1.427/B.1.429. If the person was infected with another variant, the rate was only 26 percent. This variant has shown up in 45 states to date, and in several other countries, including Australia, Denmark, Mexico and Taiwan. But it has so far taken off only in California. Investigators feel the UK variant (B.1.1.7) will win out.

Comment: As we increase genomic surveillance, we will continue to see new variants/mutations. The key question revolves around vaccine efficacy and does prior infections with SARS-CoV-2 protect against these new variants. Below is a prepublication on a new variant from NY. Despite the new variants, infections continue to decrease throughout much of the country.

Nursing Home Deaths



Source: New York Times database; U.S. Department of Health and Human Services · Data shown is normalized compared with the weekly deaths for the week ending Dec. 20, 2020 and is through Feb. 7.

Comment: Since the arrival of vaccines, which were prioritized to long-term care facilities starting in late December, new cases and deaths in nursing homes, a large subset of long-term care facilities, have fallen steeply, outpacing national decline. This is something to celebrate.

SARS-CoV-2 Lineage B.1.526 Emerging in the New York Region Detected by Software Utility Created to Query the Spike Mutational Landscape
bioRxiv published online February 23, 2021
doi.org/10.1101/2021.02.14.431043
A Novel SARS-CoV-2 Variant of Concern, B.1.526, Identified in New York
medRxivpublished online February 23, 2021
doi.org/10.1101/2021.02.23.21252259
The new variant, called B.1.526, first appeared in samples collected in the city in November. By the middle of this month, it accounted for about one in four viral sequences appearing in a database shared by scientists.

The Caltech researchers discovered the rise in B.1.526 by scanning for mutations in hundreds of thousands of viral genetic sequences in a database called GISAID. Colleagues found two versions of the coronavirus increasing in frequency: one with the E484K mutation seen in South Africa and Brazil, which is thought to help the virus partially dodge the vaccines; and another with a mutation called S477N, which may affect how tightly the virus binds to human cells. By mid-February, the two together accounted for about 27 percent of New York City viral sequences.

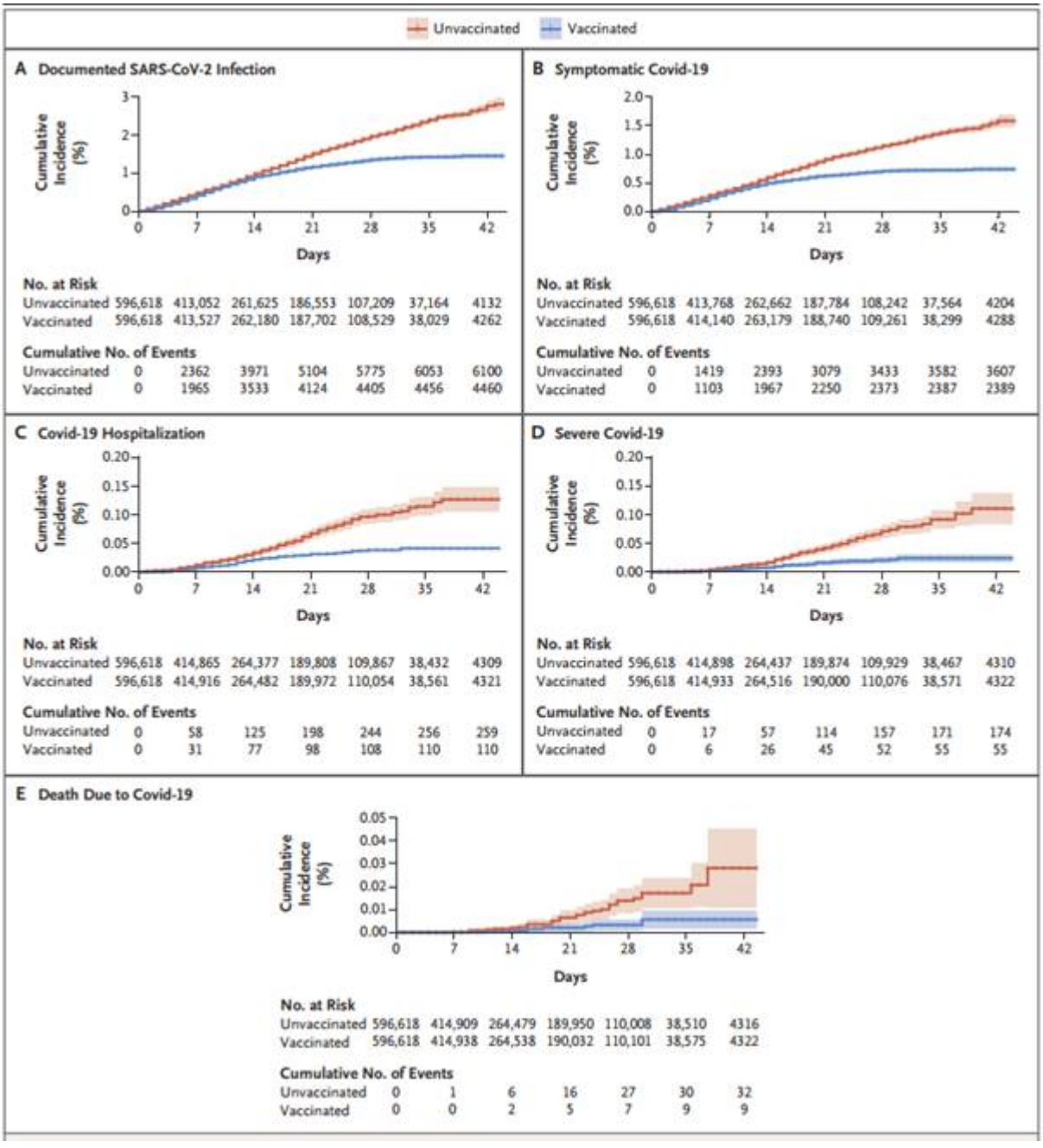
In the second paper Columbia University investigators took a different approach. They analyzed 1,142 samples from patients at their medical center and found that 12 percent of people with SARS-CoV-2 had been infected with the variant that contains the mutation E484K. Patients infected with virus carrying the E484K mutation were about six years older on average and more likely to have been hospitalized.

Comment: Several studies have now shown that variants containing the E484K mutation are less susceptible to the vaccines than was the original form of the virus. The mutation interferes with the activity of a class of antibodies that nearly everyone makes. Some mutations showed reduced neutralization but importantly even with the reduced activity, the serum was still able to neutralize variants including the B.1.351. Therefore, scientists still believe that persons who have recovered from SARS-CoV-2 infection or who have been vaccinated are very likely to be able to be protected from severe disease due to this variant, but there is still some uncertainty.

BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting
N Engl J Med
published online February 24, 2021
DOI: 10.1056/NEJMoa2101765
All persons who were newly vaccinated during the period from December 20, 2020, to February 1, 2021, were matched to unvaccinated controls in a 1:1 ratio according to demographic and clinical characteristics. Study outcomes included documented infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), symptomatic Covid-19, Covid-19-related hospitalization, severe illness, and death. They estimated vaccine effectiveness for each outcome as one minus the risk ratio, using the Kaplan-Meier estimator.

Estimated vaccine effectiveness for the study outcomes at days 14 through 20 after the first dose and at 7 or more days after the second dose was as follows: for documented infection, 46% (95% confidence

interval [CI], 40 to 51) and 92% (95% CI, 88 to 95); for symptomatic Covid-19, 57% (95% CI, 50 to 63) and 94% (95% CI, 87 to 98); for hospitalization, 74% (95% CI, 56 to 86) and 87% (95% CI, 55 to 100); and for severe disease, 62% (95% CI, 39 to 80) and 92% (95% CI, 75 to 100), respectively. Estimated effectiveness in preventing death from Covid-19 was 72% (95% CI, 19 to 100) for days 14 through 20 after the first dose. Estimated effectiveness in specific subpopulations assessed for documented infection and symptomatic Covid-19 was consistent across age groups, with potentially slightly lower effectiveness in persons with multiple coexisting conditions.



Comment: Estimated vaccine effectiveness during the follow-up period starting 7 days after the second dose was 92% for documented infection, 94% for symptomatic Covid-19, 87% for hospitalization, and

92% for severe Covid-19. This is a real-world experience on a nationwide mass vaccination program. As with any observational study, the study may have been affected by residual confounding due to differences between vaccinated persons and unvaccinated controls. To adjust, they performed rigorous matching on a wide range of factors that may be expected to confound the causal effect of the vaccine on the various outcomes. After the matching process, they continued to find a consistent pattern of similarity between the groups. The date of onset of symptoms was not available for the analysis. Instead, for infection outcomes, the date was set to the date of swab collection for the first positive PCR test.

Pregnancy and Neonatal Outcomes of COVID-19: Co-Reporting of Common Outcomes from PAN-COVID and AAP SONPM Registries

Ultrasound in OB GYN published online February 24, 2021
doi/epdf/10.1002/uog.23619

The investigators used data from the UK and global Pregnancy and Neonatal outcomes in COVID-19 (PAN-COVID) registry and the US American Academy of Pediatrics Section on Neonatal Perinatal Medicine (AAP SONPM) National Perinatal COVID-19 registry.

The study team looked at data of 4,005 pregnant women with suspected or confirmed SARS-CoV-2 infection. Of these women, 1,606 were from the PAN-COVID registry, which includes pregnancies with suspected or confirmed maternal SARS-CoV-2 infection at any stage in pregnancy, while 2,399 were from the AAP SONPM registry, which includes pregnancies with positive maternal testing for SARS-CoV-2 from 14 days before delivery to 3 days after delivery. All the women gave birth between January and August 2020.

The investigators found that preterm delivery occurred in 12.0% of all women in PAN-COVID, in 16.2% of those women with confirmed infection in PAN-COVID and in 15.7% of women in AAP SONPM, which they noted was 60% higher in PAN-COVID than is expected for England and Wales based on the Office of National Statistics (ONS) data for January-September 2020 (7.5%), and 57% higher in AAP SONPM than expected based on US National Vital Statistics Reports for 2018 (10%). The majority of preterm deliveries occurred between 32+0 and 36+6 weeks' gestation. Meanwhile, spontaneous onset of pre-term labor followed by preterm vaginal delivery occurred in 2.5% of all women in PAN-COVID, in 3.5% of those with confirmed infection and in 3.7% of those in AAP SONPM.

As the proportion of women with spontaneous labor and preterm vaginal delivery was low, a high proportion of preterm deliveries may have been due to physician concern about adverse effects of SARS-CoV-2 infection on the mother or fetus.

On the other hand, neither registry reported any neonatal deaths attributable to SARS-CoV-2 infection. The proportion of pregnancies affected by early neonatal death was no higher than would be expected based on England and Wales ONS data (0.2%) or the US CDC data (0.38%). Similarly, the proportion of pregnancies resulting in stillbirth (1 in 200) was comparable to that reported in a UK population surveillance study (5.64 per 1,000 total births), slightly greater than that reported in provisional ONS data for January to September 2020 (0.39%), and comparable to that reported in the US National Vital Statistics System data (611.7 per 100,000 live births). In both registries, the authors reported that suspected or confirmed SARS-CoV-2 infection resulted in fewer than 10% of babies being born small for gestational age and did not change the expected distribution of birth weight z-scores.

The investigators also found that maternal deaths related to suspected or confirmed SARS-CoV-2 infection were uncommon in both the PAN-COVID and AAP SONPM registries, with the rates of 0.50% in all women in PAN-COVID, 0.46% in those women with confirmed infection and 0.17% in women in AAP SONPM. Nonetheless, they pointed out that the rate was higher than expected based on UK and US population data.

Comment: Analysis of data from the UK and US registries of pregnancies with SARS-CoV-2 infection shows that preterm delivery occurred in a higher proportion of women with SARS-CoV-2 infection compared to contemporaneous and historical national data. Meanwhile, the proportions of pregnancies affected by stillbirth, a small-for-gestational-age infant or early neonatal death were comparable to those in historical and contemporaneous UK and US data. The data presented support strong guidance for enhanced precautions to prevent SARS-CoV-2 infection in pregnancy, particularly in the context of increased risks of preterm delivery and maternal mortality, and for priority vaccination of women planning pregnancy.

Characteristics and Outcomes of US Children and Adolescents with Multisystem Inflammatory Syndrome in Children (MIS-C) Compared with Severe Acute COVID-19

JAMA published online February 24, 2021
doi:10.1001/jama.2021.209

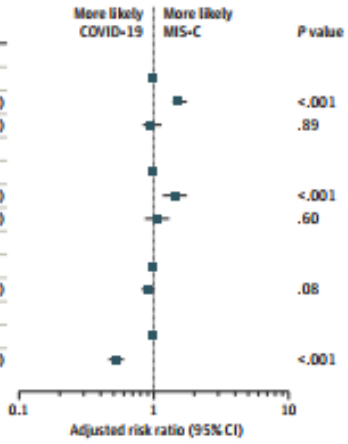
This article compared clinical characteristics and outcomes of children and adolescents with MIS-C vs those with severe COVID-19. Case series of 1116 patients aged younger than 21 years hospitalized between March 15 and October 31, 2020, at 66 US hospitals in 31 states were included. Final date of follow-up was January 5, 2021. Patients with MIS-C had fever, inflammation, multisystem involvement, and positive for SARS-CoV-2 by PCR or antibody test results or recent exposure with no alternate diagnosis. Patients with COVID-19 had positive PCR test results and severe organ system involvement.

Of 1116 patients (median age, 9.7 years; 45% female), 539 (48%) were diagnosed with MIS-C and 577 (52%) with COVID-19. Compared with patients with COVID-19, patients with MIS-C were more likely to be 6 to 12 years old (40.8% vs 19.4%; absolute risk difference [RD], 21.4% [95% CI, 16.1%-26.7%]; aRR, 1.51 [95% CI, 1.33-1.72] vs 0-5 years) and non-Hispanic Black (32.3% vs 21.5%; RD, 10.8% [95% CI, 5.6%-16.0%]; aRR, 1.43 [95% CI, 1.17-1.76] vs White). Compared with patients with COVID-19, patients with MIS-C were more likely to have cardiorespiratory involvement (56.0% vs 8.8%; RD, 47.2% [95% CI, 42.4%-52.0%]; aRR, 2.99 [95% CI, 2.55-3.50] vs respiratory involvement), cardiovascular without respiratory involvement (10.6% vs 2.9%; RD, 7.7% [95% CI, 4.7%-10.6%]; aRR, 2.49 [95% CI, 2.05-3.02] vs respiratory involvement), and mucocutaneous without cardiorespiratory involvement (7.1% vs 2.3%; RD, 4.8% [95% CI, 2.3%-7.3%]; aRR, 2.29 [95% CI, 1.84-2.85] vs respiratory involvement). Patients with MIS-C had higher neutrophil to lymphocyte ratio (median, 6.4 vs 2.7, $P < .001$), higher C-reactive protein level (median, 152 mg/L vs 33 mg/L; $P < .001$), and lower platelet count (<150 ×103 cells/µL [212/523 {41%} vs 84/486 {17%}, $P < .001$]). A total of 398 patients (73.8%) with MIS-C and 253 (43.8%) with COVID-19 were admitted to the intensive care unit, and 10 (1.9%) with MIS-C and 8 (1.4%) with COVID-19 died during hospitalization. Among patients with MIS-C with reduced left ventricular systolic function (172/503, 34.2%) and coronary artery aneurysm (57/424, 13.4%), an estimated 91.0% (95% CI, 86.0%-94.7%) and 79.1% (95% CI, 67.1%-89.1%), respectively, normalized within 30 days.

Figure 2. Multivariable Analyses of MIS-C vs COVID-19

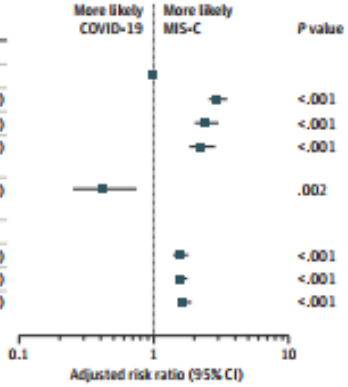
A Comparison of baseline demographic and clinical characteristics[a]

	No. (%)				
	MIS-C (n = 539)	Severe acute COVID-19 (n = 577)	Absolute risk difference, % (95% CI)[b]	Adjusted risk ratio (95% CI)[c]	P value
Age, y					
0-5	178 (33.0)	211 (36.6)	-3.5 (-9.1 to 2.0)	1 [Reference]	
6-12	220 (40.8)	112 (19.4)	21.4 (16.1 to 26.7)	1.51 (1.33 to 1.72)	<.001
13-20	141 (26.2)	254 (44.0)	-17.9 (-23.4 to -12.4)	0.99 (0.84 to 1.17)	.89
Race/ethnicity[d]					
White, non-Hispanic	63 (11.7)	106 (18.4)	-6.7 (-10.8 to -2.5)	1 [Reference]	
Black, non-Hispanic	174 (32.3)	124 (21.5)	10.8 (5.6 to 16.0)	1.43 (1.17 to 1.76)	<.001
Hispanic or Latino	193 (35.8)	262 (45.4)	-9.6 (-15.3 to -3.9)	1.06 (0.86 to 1.30)	.60
Sex					
Male	312 (57.9)	307 (53.2)	4.7 (-1.1 to 10.5)	1 [Reference]	
Female	227 (42.1)	270 (46.8)	-4.7 (-10.5 to 1.1)	0.90 (0.81 to 1.01)	.08
≥1 Underlying medical conditions					
No	372 (69.0)	219 (37.9)	31.1 (25.5 to 36.6)	1 [Reference]	
Yes	167 (31.0)	358 (62.1)	-31.1 (-36.6 to -25.5)	0.52 (0.45 to 0.60)	<.001



B Comparison of clinical phenotypes and laboratory values[a]

	No./Total No. (%)				
	MIS-C (n = 539)	Severe acute COVID-19 (n = 577)	Absolute risk difference, % (95% CI)[b]	Adjusted risk ratio (95% CI)[c]	P value
Clinical group by complication					
Respiratory without cardiovascular	130/539 (24.1)	408/577 (70.7)	-46.6 (-51.8 to -41.4)	1 [Reference]	
Cardiorespiratory	302/539 (56.0)	51/577 (8.8)	47.2 (42.4 to 52.0)	2.99 (2.55 to 3.50)	<.001
Cardiovascular without respiratory	57/539 (10.6)	17/577 (2.9)	7.7 (4.7 to 10.6)	2.49 (2.05 to 3.02)	<.001
Mucocutaneous without respiratory or cardiovascular	38/539 (7.1)	13/577 (2.3)	4.8 (2.3 to 7.3)	2.29 (1.84 to 2.85)	<.001
Other without respiratory, cardiovascular, or mucocutaneous	12/539 (2.2)	88/577 (15.3)	-13.1 (-16.2 to -9.8)	0.43 (0.25 to 0.74)	.002
Laboratory value within first 48 h					
Neutrophil to lymphocyte ratio >5	321/515 (62.3)	154/464 (33.2)	29.1 (23.2 to 35.1)	1.59 (1.40 to 1.80)	<.001
Platelets <150 × 10^3/μL	212/523 (40.5)	84/486 (17.3)	23.2 (17.9 to 28.6)	1.58 (1.43 to 1.75)	<.001
C-reactive protein level >100 mg/L	325/491 (66.2)	67/285 (23.5)	42.7 (36.2 to 49.1)	1.70 (1.51 to 1.92)	<.001



Comment: In this case series that included 539 patients with MIS-C and 577 patients with severe COVID-19, patients with MIS-C were more likely than those with severe COVID-19 to be 6 to 12 years old, be non-Hispanic Black, and have severe cardiovascular or mucocutaneous involvement and more extreme inflammation. Mortality was <2%. This article is an excellent review which should help clinicians differentiate severe COVID-19 from MIS-C.