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Forum for Evidence-Based Medicine

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COVID–19
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SARS-CoV-2 viral levels in young children are high

Young children are known to produce large amounts of virus often without manifesting severe clinical disease in many viral infections. Researchers at Ann & Robert H. Lurie Children's Hospital, Chicago and Northwestern have shown this to be true in SARS-CoV-2 infection as well.[1] They looked at the presence of virus in bilaterally collected nasopharyngeal swabs from 145 individuals. Three age groups were studied: less than 5 years of age, 5 to 17 years of age and 18 to 65 years of age. The amount of virus present was estimated using cycle threshold (CT) values of the standard PCR assay. The CT value refers to the number of amplification cycles through which a given NP sample needs to run in order to turn the PCR assay positive. The higher the viral load in the NP sample, the fewer cycles are needed to turn the test positive. CT values are therefore inversely correlated with the amount of virus present. The youngest age group had significantly higher viral loads (shown as lower CT values, see table). Older children and adults had similar viral levels.

Table 1. Viral levels by age: Estimated by cycle threshold value

Age range (years old)	Cycle threshold (median)	Interquartile range
Less than 5	6.5	4.8–12.0
5–17	11.1	6.3–15.7
18–65	11.0	6.9–17.5

Young children's behavioral habits combined with these high nasal viral loads mean young children, often with minimal or no symptoms, are likely an important part of COVID-19 viral spread.

Pregnant patients and fetuses at risk for complications from COVID-19

There has been concern about the effects of SARS-CoV-2 infection on pregnant women and their fetuses or neonates from the onset of the pandemic. Increasingly, data indicates that COVID-19 infection can have adverse effects on both women and their unborn children. Researchers at the CDC have confirmed excess hospitalizations in pregnant women infected with SARS-CoV-2.[2] Of 91,412 laboratory-confirmed cases of COVID-19, 8,207 (9%) were in pregnant women. This is higher than would be expected given that the number of pregnant women in the population at any single time is 5%. Pregnant woman with COVID-19 infection reported cough (>50%) and shortness of breath (30%) in equal proportion presentation than non-pregnant individuals. However, they were less likely to have minor symptoms. After adjustment for age and comorbid conditions, pregnant COVID-19 patients more frequently needed ICU care (RR 1.5 (95% CI 1.2-1.8)) and mechanical ventilation (RR 1.7 (95% CI 1.2-2.4)). There was not an increase in mortality seen in the pregnant patients. Incomplete data prevented more detailed analysis of the patients.

Additionally, a team in Paris has reported evidence of transplacental infection.[3] A 23-year-old, gravida 1, para 0 woman was admitted with cough and fever. She subsequently tested positive for SARS-CoV-2 with PCR.

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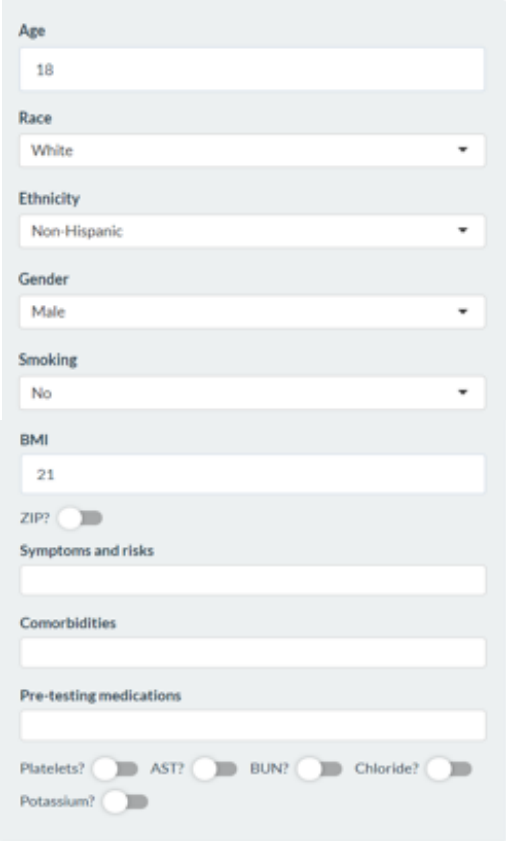
Amniotic fluid obtained prior to rupture of membranes, blood (mother and newborn), bronchoalveolar lavage fluid (newborn) and placental tissue were also positive for SARS-CoV-2 RNA using PCR. Evidence of ongoing neonatal infection was demonstrated by serial nasal swab testing. Transient neurologic symptoms occurred in the newborn with bilateral gliosis of the central nervous system believed to be the result of SARS-CoV-2 vascular inflammation. Neurologic findings had largely resolved at follow-up examination at two months of life. This is among the first extensively documented cases strongly suggesting transplacental SARS-CoV-2 transmission.

These two studies provide compelling evidence that pregnant women are at higher risk of a complicated clinical course with COVID-19 and their unborn children are at risk for transplacental infection.

Online calculator to predict risk of hospital admission with COVID-19 infection

In the last edition of the COVID Forum, dated August 7, 2020, we discussed the use of the National Early Warning Score 2 (NEWS2) to predict the severity of infection with SARS-Co-V-2 based upon the presenting signs and symptoms. This tool can be helpful in determining ER or hospital referral in intermediate to severely ill individuals. It would also be useful if we could assess the risk of requiring hospitalization in any given patient based on their individual comorbidities. The risk of hospitalization with COVID-19 varies from a low of 6 per 100k in young children to 274 per 100k in those over age 65. Researchers at the Cleveland Clinic looked at a large retrospective cohort of patients hospitalized with COVID-19. They examined the outcomes of 2,852 patients and developed a statistical model that allows individualized prediction of future hospitalization risk for a patient newly diagnosed with COVID-19. This was then validated in a second cohort of 1,684 patients. The area under the curve (AUC) in the initial cohort was 0.90 and the AUC in the validation cohort was 0.81. As would be expected, the major risk factors were age and BMI. Interestingly, the next most predictive of hospitalization were several lab parameters, followed by race and ethnicity. Shortness of breath, fatigue and loss of appetite were the only symptoms found to be predictive of hospitalization. Multiple medical comorbidities and the drugs used to treat these also reached statistical significance. Lastly, social determinant of health measures including lower median income and higher housing density were statically significant. From these results, an online tool was developed, pictured on the right. The link to the online tool is **https://riskcalc.org/COVID19Hospitalization/**.[4]



Which face masks are best for the general population?

Accumulating evidence has firmly established the value of face masks in reducing spread of SARS-Co-V-2. The data is indirect but compelling, ranging from population transmission studies to case studies. One of the best demonstrations of this was reviewed in the COVID Forum edition 15, dated July 24, 2020, and involved two infected hair stylists who continued to work in a small shop with both the stylists and their clients wearing face masks. Recall that they both worked for over a week while infected, saw 139 clients for prolonged close contact exposure and not a single SARS-Co-V-2 transmission occurred. Assuming the benefit of face masks is established, the next logical question given the wide range of face coverings currently being used is "What will work best for the general population"? Ideally, this would be studied in a controlled environment using infectious subjects studied with a variety of face coverings looking at the actual viral load being shed though the different masks. Until such data becomes available, a study done at Duke can serve as a useful surrogate. The study looked at healthy volunteers using 15 different types of face coverings and speaking the same sentence in a conversational volume into an expanded laser beam. The laser was used to quantitate the number of droplets that escaped through each mask. The results were consistent with repeated trials and with four different subjects speaking the text. Although the methodology only approximates the full

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spectrum of respiratory droplets and aerosols that are expelled with normal respiration, there is reason to assume that the results will be directionally proportionate to a more sophisticated measurement technique and relatively proportionate for the purposes of comparing one face covering to another.[5]

The results showed that the N-95 mask without valves was the superior mask, blocking almost 100% of droplets. This was followed very closely by the three-layer ear loop surgical mask which blocked over 95% of the droplets. Most of the masks tested, including the cotton masks, blocked over 80% of the droplets. The N-95 with valves performed decidedly worse than the N-95 without valves. This is an important point as there are two reasons for mask wearing. One is to prevent acquisition of infection, which the valve N-95 would be expected to do as well as the non-valve version since the valves are closed on inspiration. However, the other critical importance of the mask is to prevent transmission of infection, and the presence of exhaust valves that open with exhalation would be expected to increase droplet transmission, which is exactly what was observed. Also of importance was the observation that bandanas were statistically no better than not wearing any mask and fleece face coverings were actually associated with a higher droplet count than not wearing a mask. Because a box of 50 three-layer ear loop masks can now be easily purchased for around $15 (30 cents per mask), we should preferentially encourage the use of these if patients can afford them.

Which face masks are best for health care providers caring for patients with COVID-19?

This is a different question than the above, as it assumes that the health care provider is not infected. In this setting, the function of the mask is the prevention of acquisition of infection during patient care. A study in *JAMA Internal Medicine* looked at a variety of N-95 and three-layer surgical masks routinely used in care settings and asked "Which mask is best at blocking transmission of droplets from the environment through the mask?" This is the reverse of the above study, which looked at droplets generated during normal speech moving from the lungs into the environment. This study used a custom-built exposure chamber at the EPA. A particle generator in the chamber produced saline particles and particle counts were sampled just outside the mask and from beneath the mask. In this study, once again, the approved N-95 masks, with or without valves, provided filtration efficiencies of >95%, even up to 11 years past their expiration data and post a variety of sterilizing techniques. In this study, however, surgical masks significantly underperformed the N-95 masks and the performance was related to the fit of the mask. Surgical masks with ties and therefore tighter fits performed better than the ear loop masks, with filtration efficiencies averaging 71%. Surgical masks with ear loops averaged 38% filtration efficiency due to looser fitting with leakage around the edges of the mask. This study suggests that the N-95 mask should be used by health care providers for all patient contacts when risk of acquisition is above minimal. Surgical masks with ties are recommended over those with ear loops in the health care setting, as the fit was shown to be better with increased filtration efficiency.[6] One could also argue based upon these results that an N-95 mask should be the preferred mask in every setting, including community use by the general population. Unfortunately, supply limits, cost, knowledge of proper fitting and comfort are all meaningful barriers to making this a practical reality.

Hydroxychloroquine does not prevent illness after moderate- or high-risk COVID-19 exposure

Researchers conducted a randomized, double-blind, placebo-controlled clinical trial of hydroxychloroquine prophylaxis following exposure to SARS-CoV-2.[7] Exposure was defined as proximity to one or more persons with laboratory-confirmed COVID-19, at less than six feet distance for more than 10 minutes. If the individual was not wearing a face mask or eye shield, the exposure was considered high risk. If the individual was wearing a face mask but no eye shield, the exposure was considered moderate risk. Patients were assigned hydroxychloroquine (800 mg once, followed by 600 mg in six to eight hours, then 600 mg daily for four additional days) or placebo within four days after exposure and then were followed for 14 days to determine illness status, which included laboratory-confirmed COVID-19 or illness compatible with COVID-19.

Among the 821 asymptomatic individuals enrolled, 719 (87.6%) reported high-risk exposure. Rates of illness following exposure did not statistically differ between groups. Forty-nine of 414 (11.8%) participants who received hydroxychloroquine and 58 of 407 (14.3%) participants who received placebo developed illness. The absolute difference was -2.4% (95% confidence interval, -7.0 to 2.2, p=0.35). Over 40% participants in the hydroxychloroquine group reported side effects by day five. Nausea, loose stools and abdominal discomfort were reported most commonly. In contrast, only 16% of participants in the placebo group reported side effects.

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Among hospitalized patients, hydroxychloroquine (with or without azithromycin) does not appear to decrease intubation rates, cardiac arrest or death.[8,9] The current study suggests that it is not effective as post-exposure prophylaxis. The effectiveness of pre-exposure prophylaxis was not addressed. Research about pre-exposure prophylaxis is ongoing.

Characteristics of multisystem inflammatory syndrome: A Kawasaki-like illness following COVID-19

The rate of COVID-19 cases among children in the United States increased by 40% in the last two weeks of July, corresponding to an overall rate of 447 per 100,000 children.[10] Among children who become ill, the manifestations of COVID-19 appear similar to COVID-19 in adults with the exception of the multisystem inflammatory syndrome. Multisystem inflammatory syndrome in children (MIS-C) is a rare condition that can develop two to four weeks after the onset of COVID-19. Signs and symptoms tend to be severe, often including features of shock, cardiac involvement, gastrointestinal involvement and substantial elevation of markers of inflammation. The Centers for Disease Control and Prevention established a reporting system for MIS-C that included demographics, clinical findings and laboratory results. From March 2 to July 29, 2020, 570 MIS-C patients had been reported from 40 state health departments and the District of Columbia. The analysis of those cases was recently published.[11]

All 565 patients (99.1%) who had SARS-CoV-2 testing had positive results. At least four organ systems were involved in 490 (86%) patients. Table 2 lists common signs and symptoms by report frequency. Table 3 lists common laboratory abnormalities by report frequency.

Latent class analysis was performed to explore potential groupings of patients based on similarities across reported features. Three groups were distinguished.

- Class 1 patients had involvement of six or more organ systems with higher frequencies of abdominal pain, shock, myocarditis and certain laboratory abnormalities compared to patients grouped in classes 2 and 3.
- Class 2 patients had more severe respiratory symptoms and the highest case fatality rate (5.1%) compared to the other two classes.
- Class 3 patients were the youngest at a median age of five years, had the highest prevalence of rash and mucocutaneous, and were most likely to fit diagnostic criteria for complete Kawasaki disease (6.6%), compared to class 1 (4.9%) and class 2 (3%).

Table 2. Common signs and symptoms among children and adolescents with MIS-C

Signs and symptoms	Frequency
Abdominal pain	61.9%
Vomiting	61.8%
Rash	55.3%
Diarrhea	53.2%
Hypotension	49.5%
Conjunctival injection	48.4%
Cardiac dysfunction	40.6%
Mucocutaneous lesions	35.5%
Shock	35.4%
Headache	32.6%
Cough	28.6%
Shortness of breath	26.1%
Pleural effusion	23.9%
Myocarditis	22.8%
Pneumonia	19.3%
Coronary artery dilatation	18.6%
Acute kidney disease	18.4%
Chest pain or tightness	11.6%
Congestive heart failure	7.0%
ARDS	6.0%

Table 3. Common laboratory abnormalities among children and adolescents with MIS-C

Laboratory results	Frequency
Elevated D-dimer	60.4%
Elevated BNP or NT–proBNP	43.2%
Lymphopenia	35.4%
Elevated troponin	30.9%
Thrombocytopenia	30.9%

Treatments varied across patients. Among all 570 patients, 527 (92.5%) received at least one treatment; 424 (80.5%) received intravenous immunoglobulin (IVIG); 331 (52.8%) received steroids; 309 (58.6%) received antiplatelet medication; 233 (44.2%) received anticoagulation; and 221 (41.9%) received a vasoactive medicine.

Controlling COVID-19

Two countries — New Zealand and Vietnam — have been remarkably successful at controlling COVID-19, both recently achieving 99 days or more without documented community spread.

Vietnam has achieved this with very early imposition of stringent control measures, including travel restrictions, border closures, mandatory monitored quarantine upon entry, health checks, school closures and the quick ramp-up of a functional contact tracing system. Local outbreaks have been cordoned off early with temporary travel and business restrictions until they burned out, and as a result, the country has not relied on extensive national testing or widespread and prolonged business closures.[12]

The New Zealand story is similar, with an emphasis on speed — speed to detecting cases, isolating cases and contact tracing. In both countries, apart from temporary and isolated closures of non-essential businesses, the economy has largely been allowed to function at a level of normalcy not enjoyed in most of the world. The differences in population density, climate, culture and economic development between these two countries highlight that none of these characteristics occur by chance, and satisfactory results can be achieved by almost any country that takes the right steps.[13]

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Kenneth Roy Cohen, MD, FACP | *Chief Medical Officer*

Dr. Kenneth Cohen is an experienced physician leader, practicing internist, and researcher who has attained national recognition for health care quality improvement. He has successfully developed and reported numerous clinical quality studies in primary care, including tobacco cessation, osteoporosis, asthma, diabetes, hypertension, and ischemic vascular disease. He was one of the founding physicians of New West Physicians, which is the largest primary care group practice in Colorado and now part of OptumCare. He has served as Chief Medical Officer since 1995. Dr. Cohen has received awards of recognition and distinction for teaching, including the Lutheran Medical Center Physician of the Year award in 2011. Under his stewardship New West Physicians was awarded the AMGA Acclaim award in 2015 and the Million Hearts Hypertension Champion Award in 2017. He is a Clinical Associate Professor of Medicine and Pharmacy at the University of Colorado School of Medicine. Dr. Cohen holds degrees from Dickinson College and Hahnemann University. He is a Fellow of the American College of Physicians and a member of the Phi Beta Kappa and Alpha Omega Alpha honor societies.

John Hitt, MD, MBA | *Senior Medical Director*

Dr. Hitt has been a physician executive for more than 25 years. Most recently he was the CMO of Ativa Medical a medical device startup company and an independent health care consultant. Previously, he was CMO at Maricopa Integrated Health System (MIHS) and a key member of the senior leadership team having responsibility for Medical Staff Services, Grants and Research, Academic Affairs, Risk Management, physician contracted services and the activity of Residency Program Directors, Clinical Department Chairs, and Medical Staff.

Dr. Hitt has over 25 years of experience in quality and performance improvement, clinical integration, academic and medical staff affairs. He served as the Chief Medical Quality Officer for Hennepin Health System, a premier Level 1 Adult and Pediatric Trauma Center. He was a physician leader for VHA (now Vizient). He was the national Medical Director for Disease Management at Caremark International and the VP of Medical Affairs at the University of Minnesota Hospital.

Dr. Hitt is a graduate of the University of Virginia where he played Division 1 soccer. He received his Medical Doctorate from the Medical College of Georgia in 1984 (AOA honors) and completed his Internal Medicine and Infectious Disease Fellowship training at the University of Minnesota Hospital and Clinics. Dr. Hitt completed his MBA at the Carlson School of Management at the University of Minnesota in 2003. He is the proud father of seven children.

Geoffrey Heyer, MD | *Senior Clinical Practice Performance Consultant*

Dr. Heyer is board certified in neurology with special certification in child neurology and in headache medicine. Prior to joining our team, Dr. Heyer was an associate professor of neurology and pediatrics at The Ohio State University and Columbia University Medical Center, specializing in autonomic disorders, headache, and pain management. He has published over 50 peer-reviewed research papers and numerous editorials, clinical reviews, and textbook chapters. He also co-authored a textbook on childhood stroke and cerebrovascular disorders.

Dr. Heyer received his medical degree from Columbia University, College of Physicians and Surgeons. He completed his neurology and child neurology residencies at Columbia-Presbyterian Medical Center. He has additional research training from the Mailman School of Public Health, Columbia University.

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