August 31, 2020

COVID-19 – Reducing Transmission in Children, Reduced Vitamin K in Severe Cases, Saliva vs. NP PCR Detection of Virus

Good morning-I hope everyone had a relaxing weekend

Today I have included 2 articles on the "little people". The first article is a report from RI's childcare centers. The study demonstrated very little secondary spread among young children and is reassuring and suggests that the mitigation steps outlined by the CDC/AAP for infection prevention can play a role in reducing transmission in day care and schools. The second article from JAMA Pediatrics confirms that children in fact can be infected with SARS-CoV-2. 22% of positive children never developed symptoms highlighting infected patients could be missed using a testing strategy focused on testing of symptomatic patients alone. Both studies support universal masking and other mitigation strategies needed to significantly reduce transmission in children. Moving on I found the next article of interest on the potential role of reduced vitamin K in the pathogenesis of severe COVID-19. The last two articles look at saliva versus traditional NP PCR in detection of SARS-CoV-2. For hospitalized patients saliva appeared more sensitive than NP PCR, however, for outpatient(most asymptomatic) use NP PCR appeared more sensitive than saliva.

Have a wonderful day and week

Ed

Limited Secondary Transmission of SARS-CoV-2 in Child Care Programs — Rhode Island, June 1–July 31, 2020 MMWR August 28, 2020 69: 1170-1172

The Rhode Island Department of Public Health investigated all COVID-19 cases associated with licensed home- and center-based childcare programs approved to reopen on June 1. Centers reopened with mandated reduced enrollment, cohorting of children and staff, symptom tracking, universal masking by staff, and enhanced cleaning procedures. High compliance with recommended infection practices was observed during 127 unannounced program monitoring visits. Below are the key findings:

- From June 1 to July 31, 52 cases (33 confirmed, 19 probable) were identified at the 666 centers, which had capacity for roughly 19,000 children.
- 58% of cases were in children and 42% in adults; of the 22 adults, 20 were teachers and only 2 were parents.
- Cases occurred in 29 childcare programs, and in 20 of these, a single case was reported, with no evidence of secondary transmission.
- Possible secondary transmission was detected in 4 centers (17 cases in children and adults) between July 15 and 31, leading to center closures and quarantining.

Comment: Transmission of SARS CoV-2 in children remains unclear. Studies to date have created challenges for school and childcare center reopening. This study, demonstrating very little secondary spread among young children in one state, is reassuring and suggests that the mitigation steps outlined by the CDC/AAP for infection prevention can play a role in significantly reducing transmission. The study provides clinicians with concrete data to share with families when considering return to school. Since there was not universal screening for asymptomatic carriage among the children and staff, it is not possible to fully understand transmission that may have occurred; however, the robust contact tracing and adherence to infection control measures lends support for reopening schools in communities with declining prevalence of infections.

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Clinical Characteristics and Viral RNA Detection in Children with Coronavirus Disease 2019 in the Republic of Korea JAMA Pediatrics published online August 28, 2020

This case series of children with COVID-19 was conducted in 20 hospitals and 2 nonhospital isolation facilities across the country from February 18, 2020, to March 31, 2020. Children younger than 19 years who had COVID-19 were included. Confirmed COVID-19, detected via SARS-CoV-2 RNA in a combined nasopharyngeal and oropharyngeal swab or sputum detected by PCR.

A total of 91 children with COVID-19 were included (median [range] age, 11 [0-18] years; 53 boys [58%]). Twenty children (22%) were asymptomatic during the entire observation period. Among 71 symptomatic cases, 47 children (66%) had unrecognized symptoms before diagnosis, 18 (25%) developed symptoms after diagnosis, and only 6 (9%) were diagnosed at the time of symptom onset. Presymptomatic children remained symptom free for a median of 2.5 days before developing symptoms. Twenty-two children (24%) had lower respiratory tract infections. The mean (SD) duration of the presence of SARS-CoV-2 RNA in upper respiratory samples was 17.6 (6.7) days. Virus RNA was detected for a mean (SD) of 14.1 (7.7) days in asymptomatic individuals. There was no difference in the duration of virus RNA detection between children with upper respiratory tract infections and lower respiratory tract infections (mean [SD], 18.7 [5.8] days vs 19.9 [5.6] days; *P* = .54).

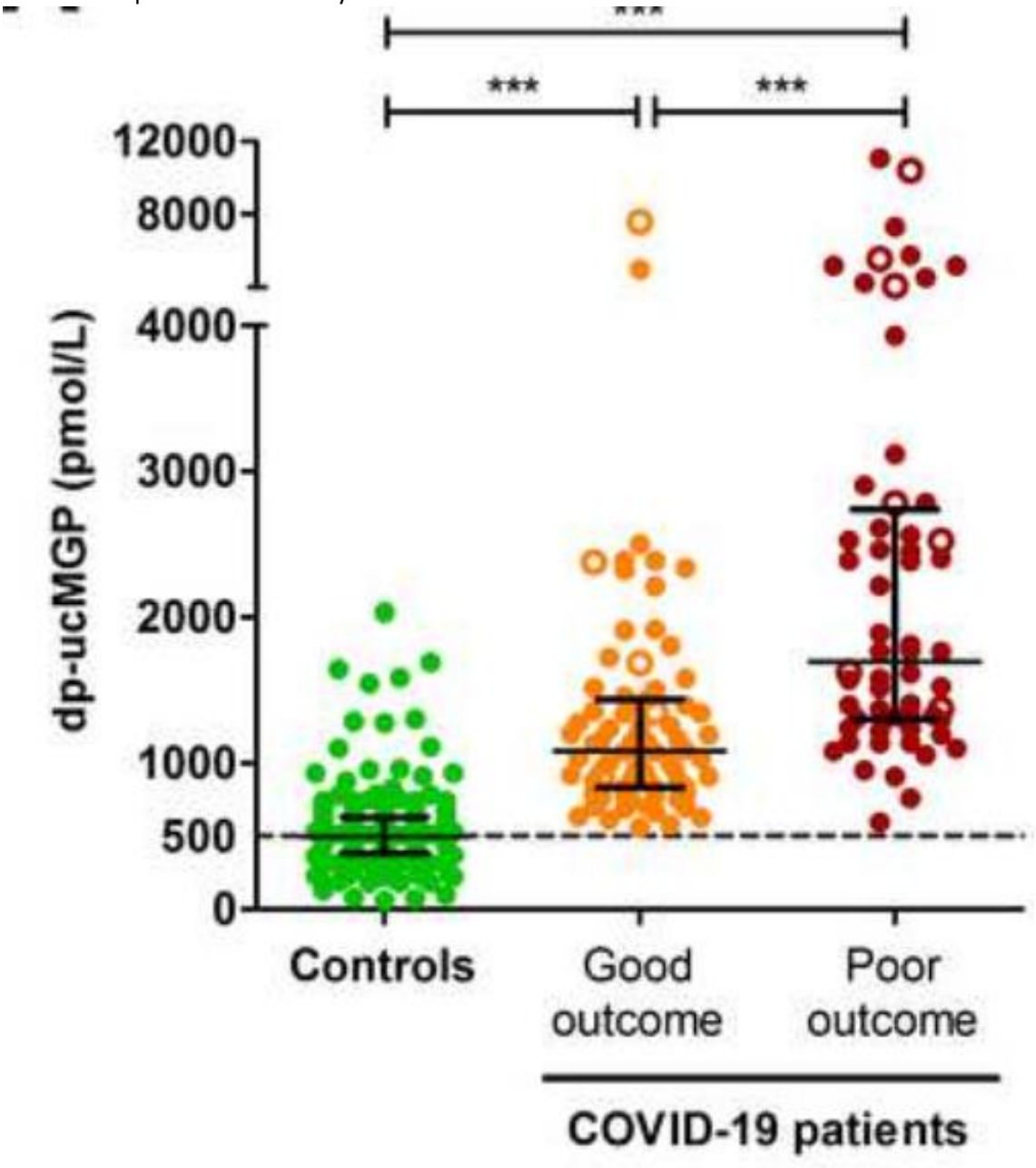
Comment: In this study, the authors estimate that 85 infected children (93%) would have been missed using a testing strategy focused on testing of symptomatic patients alone. A major limitation of this study and studies like this is due to qualitative molecular detection methods, which are the standard clinical approach for testing of nasopharyngeal swab specimens. Qualitative positive or negative findings for molecular detection of virus may not necessarily correlate with infectivity. Sensitive molecular detection methods may detect viable, infective virus but also nonviable or fragments of RNA with no capability for transmission. Additionally, even if viable virus is present, transmissibility is related to the quantity of virus present in the respiratory tract and duration of exposure. A qualitative molecular test at a single point in time in each of these scenarios cannot be assumed to be equal; the degree of viral load or kinetics of shedding is very likely to be different in each of these, and formal studies to dissect this are needed to fill this knowledge gap. In regions where use of face masks is not widely accepted or used by the general public, asymptomatic carriers may serve as an important reservoir that may facilitate silent spread through a community. This is why universal masking is so vital to reduce community spread including schools. We see in the study above that following recommended mitigation strategies can significantly reduce risk of spread of SARS-CoV-2 in schools and daycare centers.

Reduced vitamin K status as a potentially modifiable risk factor of severe COVID-19 Clin Infect Dis published online August 28, 2020

Vitamin K activates both hepatic coagulation factors and extrahepatic endothelial anticoagulant protein S, required for thrombosis prevention. In times of vitamin K insufficiency, hepatic procoagulant factors are preferentially activated over extrahepatic proteins. Vitamin K also activates Vitamin K also activates matrix Gla protein (MGP), which protects against pulmonary and vascular elastic fiber damage. The investigators hypothesized that vitamin K may be implicated in coronavirus disease 2019 (COVID-19), linking pulmonary and thromboembolic disease.

135 hospitalized COVID-19 patients were compared with 184 historical controls. Poor outcome was defined as invasive ventilation and/or death. Inactive vitamin K-dependent MGP (dpucMGP) and prothrombin (PIVKA-II) were measured, inversely related to extrahepatic and hepatic vitamin K status, respectively. Desmosine was measured to quantify the rate of elastic fiber degradation. Arterial calcification severity was assessed by computed tomography.

Dp-ucMGP was elevated in COVID-19 patients compared to controls (p<0.001), with even higher dp-ucMGP in patients with poor outcomes (p<0.001). PIVKA-II was normal in 82.1% of patients. Dp-ucMGP also correlated with desmosine (p<0.001), and coronary artery (p=0.002) and thoracic aortic (p<0.001) calcification scores. Dp-ucMGP was severely increased in COVID-19 patients, indicating extrahepatic vitamin K insufficiency, which was related to poor outcome while hepatic procoagulant factor II remained unaffected. They did not find a significant correlation between dp-ucMGP and pneumonia severity.



Comment: These data suggest a mechanism of pneumonia-induced extrahepatic vitamin K depletion leading to accelerated elastic fiber damage and thrombosis in severe COVID-19 due to

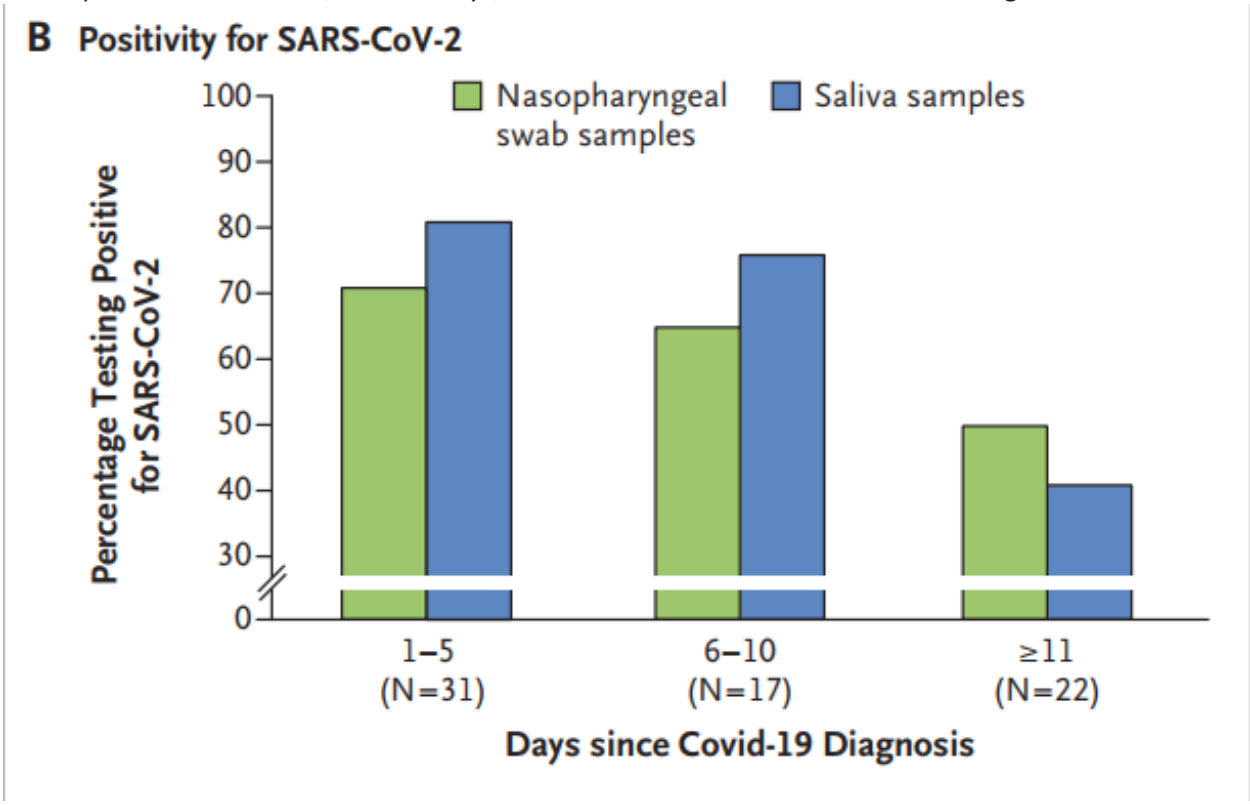
impaired activation of MGP and endothelial protein S, respectively. The findings, however, are limited by the fact that it is impossible to determine which proportion of circulating ducMGP and DES levels originated from the lungs, as both biomarkers are not tissue specific. As low vitamin K levels are found in comorbidities that are related to poor outcome of COVID-19 , they were unable to determine whether vitamin K insufficiency truly predisposes patients to the development of severe COVID-19 or whether it is merely an epiphenomenon. A clinical trial is needed to determine whether vitamin K administration improves COVID-19 outcomes.

Saliva or Nasopharyngeal Swab Specimens for Detection of SARS-CoV-2 N Engl J Med published online August 29, 2020

A total of 70 inpatients with Covid-19 provided written informed consent to participate in this study. After Covid-19 was confirmed with a positive nasopharyngeal swab specimen at hospital admission, we obtained additional samples from the patients during hospitalization. We tested saliva specimens collected by the patients themselves and nasopharyngeal swabs collected from the patients at the same
time point by health care workers.

The investigators detected more SARS-CoV-2 RNA copies in the saliva specimens than in the nasopharyngeal swab specimens. In addition, a higher percentage of saliva samples than nasopharyngeal(NP) swab samples were positive up to 10 days after the Covid-19 diagnosis.

At 1 to 5 days after diagnosis, 81% of the saliva samples were positive, as compared with 71% of the NP swab specimens. However, after 11 days, NP swabs were more sensitive in detecting SARS-CoV-2.



Comment: These findings suggest that saliva specimens and nasopharyngeal swab specimens have at least similar if not higher sensitivity in the detection of SARS-CoV-2 during the course of

hospitalization. Of interest even by day 1-5 only 80% of confirmed cases were still positive for SARS-CoV-2 highlighting concern over false-negative results. Collection of saliva samples by patients themselves negates the need for direct interaction between health care workers and patients. It would also reduce need for supplies of swabs and HCW PPE. See below on another study with opposite results.

Salivary Detection of COVID-19 Ann Intern Med published online August 28, 2020

The investigators prospectively enrolled consecutive, asymptomatic, high-risk persons and those with mild symptoms suggestive of COVID-19 at a centralized testing center in Canada. Eligible adults provided 1 saliva specimen using a self-collection kit and were paired with NP swabs. Of the 1939 paired swab and saliva samples analyzed, SARS-CoV-2 E gene was detected in 70 samples, 80.0% with swabs and 68.6% with saliva. Thirty-four participants (48.6%) tested positive for SARS-CoV-2 on both swab and saliva samples. Discordant test results were seen in 22 participants (31.4%) who tested positive with swab alone and in 14 (20%) who tested positive with saliva alone.

Comment: Unlike study above, this study found that standard diagnostic methods of nasopharyngeal and oropharyngeal swabs detected more COVID-19 cases than saliva testing among patients who were asymptomatic but at high risk or who were mildly symptomatic. Previous studies including the one above, have focused on salivary tests of symptomatic or hospitalized patients have suggested that saliva tests may be more sensitive. By design, these investigators included asymptomatic and mildly symptomatic persons to simulate mass screening for COVID-19 (e.g. schools). As stated above saliva testing presents potential advantages: Collection does not require trained staff or personal protective equipment, can be done outside testing centers, and may be better tolerated in challenging or pediatric populations. RNA can be unstable, so use of raw saliva necessitates rapid transportation to a laboratory for extraction of viral material and PCR analysis. This study is unique in that it used a novel collection kit containing a preservative and viricidal fluid, allowing for safe and stable storage and transport of the samples. Of interest, more than half of eligible patients declined participation.