Table 2. Top 10 Clinical Conditions Identified by Applying PECCS to Administrative Data From 45 US Children's Hospitals[a]

Rank	PECCS category	Encounters, No. (%) (N = 5 041 752)[b]
1	Otitis media	275 418 (5.5)
2	Hypertrophy of tonsils and adenoids	257 996 (5.1)
3	Dental caries	180 472 (3.6)
4	Acute bronchiolitis	143 503 (2.9)
5	Asthma	119 654 (2.4)
6	Chemotherapy	93 296 (1.9)
7	Pneumonia	84 474 (1.7)
8	Respiratory failure, insufficiency, or arrest	80 285 (1.6)
9	Redundant prepuce and phimosis	63 461 (1.3)
10	Seizures with and without intractable epilepsy	62 142 (1.2)

Abbreviation: PECCS, Pediatric Clinical Classification System.

[a] Data are from 45 US hospitals participating in the Pediatric Health Information System between January 1, 2016, and December 31, 2019.

[b] Percentages do not total 100% because only the top 10 conditions are presented.

Table 2 presents the 10 most prevalent conditions at Pediatric Health Information System hospitals identified by using the PECCS. If the HCUP-CCS were used, the categories *bronchiolitis* and *redundant prepuce* and *phimosis* would have been identified as broader, nonpediatric specific categories of *bronchitis* and *other male genital disorders*, respectively.

Discussion | The PECCS builds capacity in child health research by providing an open-source classification system to identify clinically meaningful, pediatric categories in inpatient settings using *ICD-10-CM* administrative data. The HCUP-CCS does not identify several important pediatric conditions owing to its broad categories and adult focus. The PECCS can be used for prioritization of comparative effectiveness research, understanding health services use and trends, and outcomes research. A limitation of the PECCS is that it does not differentiate between acute and chronic conditions. However, it can still be used with different data sources, in different pediatric settings, and by researchers in diverse pediatric fields. The PECCS can be modified for different country-specific *ICD-10* versions to be used internationally. The PECCS will be updated annually to coincide with future *ICD-10-CM* revisions.

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Author Contributions: Dr Hall and Mr Rodean had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Gill, Anwar, Thavam, Hall, Mahant.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Gill, Anwar, Thavam, Hall, Mahant.
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Statistical analysis: Rodean.
Obtained funding: Gill, Mahant.
Administrative, technical, or material support: Gill, Anwar, Thavam, Mahant.
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COMMENT & RESPONSE

Viral Loads of SARS-CoV-2 in Young Children

To the Editor I am writing about the article "Age-Related Differences in Nasopharyngeal Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Levels in Patients With Mild to Moderate Coronavirus Disease 2019 (COVID-19)"[1] published on July 30, 2020, in *JAMA Pediatrics*. I have serious concerns about the validity of their suggestion that individuals younger than 5 years may have more coronavirus disease 2019 (COVID-19) RNA. From a review of the Figure in this article,[1] for children younger than 5 years, the authors plot 3 outliers among a total number of 46 participants. This is 6.5%. Had they included these outliers, I suspect they would not be able to make their suggestion that children younger than 5 years may have more COVID-19 RNA. Good data analysis does not allow scientists to simply discount data as outliers so that a significant outcome can be suggested. I would have preferred to see

a graph with dots for all data points and then indications for the mean and the error bars. Further, the error bars are sufficiently wide and overlapping that I suspect there is not much difference between all the groups. Their suggestion that children younger than 5 years may have more COVID-19 RNA is being cited and amplified as fact over conventional and social media. This can influence important choices about daycare and schools, and I have serious concerns about how the authors analyzed their data.

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To the Editor Reliable data for profiles of viral load are needed and important to guide antiviral treatment, infection control, and vaccination. In their interesting article in *JAMA Pediatrics*, Heald-Sargent and colleagues[1] describe that levels of viral nucleic acid in nasopharyngeal swabs are significantly greater in children younger than 5 years compared with older children. The authors report that children younger than 5 years (n = 46), children aged 5 to 17 years (n = 51), and adults aged 18 to 65 years (n = 48) had median cutoff cycle threshold (Ct) values of 11 for older children and adults and 6.5 for children younger than 5 years.

Ct values reported by Heald-Sargent et al[1] are extremely low and unusual. For example, Wang and collaborators[2] investigated the biodistribution of viral RNA among different types of clinical samples. They evaluated 1070 specimens collected from 205 patients with coronavirus disease 2019 and observed that Ct values of all specimen types were more than 30, except for nasal swabs with a mean Ct value of 24.3 (range, 16.9-38.4).

Already, La Scola et al[3] estimated the correlation between successful isolation of severe acute respiratory syndrome coronavirus 2 in cell culture and Ct values. Among the 183 samples inoculated (9 sputum samples and 174 nasopharyngeal swabs from 155 patients), 129 led to virus isolation. Samples with Ct values of 13 to 17 all led to successful isolation of virus. However, culture positivity rate then decreased progressively according to Ct values reaching 12% at 33 Ct. However, the lowest Ct value reported by these authors was 13, with more than 70% of Ct values between 19 and 29.

Recently, Vivanti and collaborators[4] demonstrate the transplacental transmission of severe acute respiratory syndrome coronavirus 2 in a neonate born to a mother infected in the last trimester and presenting with neurological compromise. In that study, the authors call attention to a very high viral load in the placenta. It is possible to observe in a figure published in this report the amount of amplified RNA and Ct values between 11 to 12 for the placenta and 15 to 16 in the nasopharyngeal swab of the newborn. Magleby et al[5] evaluated 678 patients with coronavirus disease 2019, and a higher viral load was associated with increased age and comorbidities. The lowest Ct values found were 14, and in-hospital mortality was 35% in patients with a high viral load (Ct <25) against 17.6% with a medium viral load (Ct values of 35 to 30). Therefore, the Ct values found by Heald-Sargent et al[1] need to be better understood.

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To the Editor Heald-Sargent et al[1] report significantly higher cycle threshold (Ct) values in children younger than 5 years and conclude that they "can potentially be important drivers of SARS-CoV-2 [severe acute respiratory syndrome coronavirus 2] spread" and raise "concern for SARS-CoV-2 amplification in this population as public health restrictions are eased."[1] In drawing these conclusions, the authors do not account for numerous limitations associated with Ct value determination and fail to place their findings in the context of existing data on transmission in younger children.

Preanalytical factors can significantly affect Ct values and limit the utility of conclusions based on these values.[2] Routine reverse transcriptase–polymerase chain reaction methods do not provide a means to normalize the amount of viral RNA detected to the amount of cells collected, and therefore lower Ct values may simply be because of a collection of more cells rather than higher viral load in vivo. Indeed, the smaller anatomy of younger children may lend itself to more efficient sampling, resulting in collection of more cellular material. Differences in sample handling and delays in testing from diverse collection sites can also affect sample integrity and Ct values.

Additionally, the authors do not report their overall positivity rates by age group, an important metric when concluding which groups are driving community spread. Studies show significantly lower polymerase chain reaction positivity rates in younger children, potentially because of lower gene expression of nasal epithelium angiotensin-converting enzyme 2 receptors, which would argue against this report's conclusions.[3] Another limitation of this study is the exclusion of children with severe infection (and lower Ct values), which biases their findings; it is important to know whether Ct differences between age groups remain if those children are included because it is established that older children are more prone to severe disease than younger children.

Lastly, it is important to place these findings in the context of existing data on SARS-CoV-2 transmission in young children. While initial contact tracing reports and studies demonstrated minimal transmission associated with children,[4] recent data have challenged these findings particularly in older children.[5] However, there have yet to be any studies demonstrating significant transmission in children younger than 5 years, as this study suggests. Therefore, it is premature to draw any conclusions about the likelihood of spread from children younger than 5 years based on this report, particularly given the many factors that can affect Ct values and the current lack of supportive evidence for significant spread from index cases of this age.

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To the Editor I have concerns about the methodology, which influences the results and conclusions, reported in a recent article on coronavirus disease 2019 samples that has garnered attention because of its implications for important public health decisions. In "Age-Related Differences in Nasopharyngeal Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Levels in Patients With Mild to Moderate Coronavirus Disease 2019 (COVID-19)," Heald-Sargent et al[1] compare cycle threshold (Ct) values for different cohorts of patients with coronavirus disease 2019 grouped by age. Most of the data appear to be for Ct values that were less than 11. The median Ct was 6.5 for children younger than 5 years, meaning half of the samples had a Ct value of 6.5 or less. Looking at the range in the plots, it appears some data points may have had a Ct near 3. Yet, Ct values typically are not quantitative in these ranges, and the authors did not include or refer to a standard curve to demonstrate that the values were quantitative in this range. Other related studies[2,3] use Ct values in a range that is typically found to be more quantitative (Ct >14), which can be achieved by diluting the samples prior to testing. Given this problem, the conclusion that the virus is higher in children may not be supported by these data. The article seemingly still demonstrates that the virus can be found at high levels in these samples from these age groups, at least for many of these samples.

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To the Editor Heald-Sargent et al[1] recently reported that preschool- and school-aged children have higher and similar severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA loads than adults, respectively, concluding that children could have an active role in transmission of SARS-CoV-2 to others.[1]

The authors report semiquantitative data on viral loads (VL) using cycle threshold (Ct) values of the Abbott RealTime SARS-CoV-2 Assay (Abbott Laboratories). Ct values are an assay-specific measurement and do not allow comparison with other testing systems nor with studies that report VL expressed as assay-independent viral RNA copy numbers.

Recently, we assessed VL of more than 400 patients with coronavirus disease 2019 in the first 5 days after symptom

onset.[2] We found no statistically significant difference in VL across age, in line with other data.[2,3] However, we saw a tendency towards higher mean SARS-CoV-2 copy numbers in children (aged 0-11 years) vs teenagers (aged 12-19 years) and adults (aged 20-45 years) with 6.13 vs 5.85 and 5.91 $\log_{10}$ copies per milliliter, respectively.[2] Expressed as Ct values obtained by Cobas SARS-CoV-2 test (Roche) and an in-house method, our findings correspond with Ct values ranging between 24.0 and 26.8, compared with 6.5 to 11.1 for the study by Heald-Sargent et al,[1] clearly demonstrating a lack of comparability when using Ct values of different systems.

Furthermore, VL can serve as a surrogate for infectiousness; thresholds of viral RNA copies per millimeter, required for isolation of culture-competent SARS-CoV-2, have been established.[4,5] By giving quantified viral RNA copies, the percentage of patients with VL compatible with infectiousness could be calculated, which is important information when discussing transmission, especially for younger children, for which data are scarce.

Although all patients from the study were diagnosed within 7 days after symptom onset,[1] no information on the mean days after symptom onset of diagnosis is given per age group. Thus, it cannot be excluded that children younger than 5 years were diagnosed earlier compared with older children or adults. In our study, a tendency for earlier testing was seen with 1.75 days after symptom onset in children vs 2.30 and 2.36 in adolescents and adults, respectively. Providing that VL significantly decreases within the first week after symptom onset,[4] an earlier diagnosis might also explain the higher VL in preschool children.[1]

While VL is important to SARS-CoV-2 transmission, other factors likely contribute to the risk of transmission as well. More studies are needed on SARS-CoV-2 in children, and special care should be taken to ensure data comparability. This would enable meta-analyses because single-center data on pediatric coronavirus disease 2019 are limited because of a small overall number of pediatric cases.

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In Reply Thank you for the opportunity to respond to several Letters that facilitate thoughtful discussion of our recently published article.[1] Three Letters raised concerns about our reported cycle threshold (Ct) values. Ct values from different platforms are known to be assay specific, making cross-comparison difficult. The assay used in our study has significantly lower Ct values in comparison with other assays.[2] However, there are abundant data[3] to support use of Ct values as a proxy for level of viral RNA in a sample, including for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The assay used in our study includes an internal control (nonviral) sequence with every sample, and every run included a control sample with 1000 SARS-CoV-2 RNA copies per well. Serial dilutions of samples confirmed an estimate of 3.3 Ct value changes for every logarithm difference in RNA levels, allowing estimation of viral load from Ct data. Thus, a Ct value of 15 or less on our platform correlates with greater than 100 000 copies per milliliter, a viral load associated with culture-competent SARS-CoV-2.[4] While an association between viral load and days from symptom onset would be expected, we did not identify a strong correlation between sample Ct and symptom duration in any of the groups, supporting the validity of our age-based comparisons. We acknowledge that our study demonstrates a wide spectrum of Ct values within and across groups, like many research studies in a diverse population of patients. However, the statistical analyses applied are appropriate and include the full spectrum of collected data (ie, no outliers were discounted from our analyses). Strong statistical significance was demonstrated.

While preanalytical factors, including sample collection, may contribute to variations in measured Ct, we are not familiar with data supporting the assertion that there are age-dependent differences in nasopharyngeal sampling that require application of some correction. Any age-dependent sampling bias would have to be profound to fully account for the 10- to 100-fold difference in viral nucleic acid we identified between younger and older children. Disease severity is a preanalytical factor taken into account a priori, and to limit that potential bias we intentionally omitted children and adults with severe disease.

We appreciate that our article has been widely discussed in the media, sometimes with interpretations beyond those made in the study itself. For example, we did not interpret our findings as evidence that young children are driving community spread and/or are a source of significant transmission. Rather, our data indicate that young children can be infected and replicate SARS-CoV-2, prerequisites for transmission. Our findings run counter to the theory that children may not be

capable of SARS-CoV-2 transmission, which was supported by some earlier in the pandemic. This concept is critical to investigate further as it has important implications for child-focused coronavirus disease 2019 prevention strategies, such as decisions around school reopenings. Epidemiologic data identifying transmission of SARS-CoV-2 from young children have since been reported,[5,6] and we eagerly await larger scale studies to further address this important pediatric public health challenge.

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Estimates From Heterogeneous Studies of Opioid-Related Morbidity

To the Editor We congratulate Quinn et al[1] for their important study demonstrating an association between prescription opioid initiation and increased risk of substance-related morbidity among adolescents and young adults.[1] Their use of multiple rigorous designs to address confounding greatly increases internal validity.

We write to comment on the authors' statement that "the results of this study do not rule out a nontrivial increase in risk of substance-related morbidity due to opioid initiation but suggest that this increase may be smaller than has been estimated in some previous studies."[1] We believe this suggestion is premature.

First, comparing estimates between studies is challenging given differences in data, populations, and methods. Many studies of adolescents and young adults have used US claims data to assess the association between opioid initiation and the 1-year incidence of opioid prescribing patterns suggestive of escalating risk (eg, persistent opioid use).[2,3] In contrast, the authors measure substance-related morbidity over 5 years in Sweden. Although the longer period could bolster the case for overestimation in prior studies, these studies examined outcomes that are not necessarily captured by the authors' outcome, which only represents the most severe consequences of opioid initiation.

Second, the authors likely underestimated the incidence of substance-related morbidity, which was partially defined based on pharmacologic treatment for alcohol use disorder or a visit with an *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* diagnosis code for substance use disorder. Many substance use disorders are never diagnosed or treated, and the sensitivity of *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* diagnosis codes for substance use disorders is unclear.

Finally, this study provides a single data point. As an analogy, if many randomized trials showed a large positive effect of an intervention, a single trial showing a smaller positive effect would not constitute evidence of systematic overestimation.

An additional key point is that adolescents and young adults frequently sell, share, or trade opioids prescribed to them.[4,5] Thus, the risk of substance-related morbidity associated with opioid initiation does not accrue only to the patient.

We offer our interpretation of this well-done study. The authors provide strong observational evidence that initiation of prescription opioid use is associated with increased risk of substance-related morbidity among adolescents and young adults. If estimates are unbiased, the absolute magnitude of this risk (1-2 percentage points) translates to substantial excess morbidity given the frequency of opioid prescribing to this population. Accordingly, clinicians should only prescribe opioids when absolutely necessary, providing the least amount that feasibly could control pain.

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