Nasopharyngeal Expression of Angiotensin-Converting Enzyme-2 and Transmembrane Serine Protease-2 in Children Within SARS-CoV-2 Infected Family Clusters

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Sincerely,

Clinton Jones
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Reviewer comments:

Reviewer #1 (Comments for the Author):

The paper write by Hasan and colleagues is well-constructed. It will be valuable to understand why children are more susceptible to COVID-19 infection.
Some elements need to be corrected.

Details:
The first sentence in the abstract section is little bit confusing. "accumulating evidences...may be related"
If we have all evidences? Rephrase it please
In line 38 "the odds of Covid-19 positivity increased" authors mean in children group? Please clarify this sentence.
Please for the reference 6 and its related sentence in the line 63 authors could add other references.
In line 74 theories or hypotheses?
Hasan and colleagues report that the ACE2 mRNA expression in NPS (as a surrogate for ACE2 expression in upper respiratory tract epithelium) was lower in children who were SARS-CoV-2 negative in exposed family (with at least one adult family member who were SARS-CoV-2 positive). Their family cohort design involving 105 families with 129 adults and 105 children, though using convenient leftover samples collected for precautionary testing from visitors to their medical unit, adds to the weight of ACE2 in SARS-CoV-2 pathogenesis. It should be noted that all subjects are asymptomatic or pre-symptomatic at the time of sample collection and the laboratory status of these initially SARS-CoV-2 negative cases could not be prospectively evaluated and confirmed.

The manuscript is easy to follow and data is well-presented. It could be improved by attention to the following points:

1. As the authors attempted to use the family cohort with SARS-CoV-2 exposure to illustrate that lower ACE2 expression in children was associated with lower chance of infection, the viral load of the infected adult family members was clearly one important confounding factor to the risk of virus transmission in household that was unfortunately not evaluated in the current study. It would be very helpful to include viral load data in their multivariate analysis if such information is available. This could substantially enhance their claim that SARS-CoV-2 infection status is ACE2 level dependent.

2. ACE2 mRNA level could not be determined from 58% (135/234) of samples. How many of them were ACE2 negative but SARS-CoV-2 positive? This large proportion appears to be problematic. Suggest adding a subgroup analysis of using samples with detectable ACE2 only to confirm their major observations.

3. The study was conducted between June 2020 and December 2020. It is presumed that all subjects were unvaccinated, and results are thus not confounded by vaccination status. This point should be mentioned in the Discussion.

4. Table 1: Indicate the unit of age.

5. Line 161 states that "the children and adults included in this study are asymptomatic at the time of NPS collection.". Therefore, it is a bit confusing that the term COVID-19 was used throughout the study (e.g., title, main text, tables and figures). Would it be more appropriate to use the term "SARS-CoV-2 infection" instead?
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Thank you for submitting your paper to Microbiology Spectrum.
October 9, 2021

Dr. Mohammad Rubayet Hasan
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Doha
Qatar

Re: Spectrum00783-21R1 (Nasopharyngeal Expression of Angiotensin-Converting Enzyme-2 and Transmembrane Serine Protease-2 in Children Within SARS-CoV-2 Infected Family Clusters)

Dear Dr. Mohammad Rubayet Hasan:

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Supplemental Material: Accept