Differential infectivity of original and Delta variants of SARS-CoV-2 in children compared to adults

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Reviewer(s): Disclosure of reviewer identity is with reference to reviewer comments included in decision letter(s). The following individuals involved in review of your submission have agreed to reveal their identity: ASAAD MOHAMMED ATAA (Reviewer #3)

Transaction Report:

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Dear Dr. James Eric Strong:

Thank you for submitting your manuscript to Microbiology Spectrum.

As Editor I agree with the reviewers' comments, and I would welcome a revised manuscript that addresses all of these.

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Sincerely,

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Reviewer comments:

Reviewer #1 (Comments for the Author):

I appreciate the opportunity to review this interesting manuscript by Garnett et al which aimed to examine differences in both viral RNA and viable virus levels from children infected with Delta compared to original variants and to same measurements in adults. They compared Ct values and infectivity of VOCs in different age demographics. The study showed that children infected with Delta are 2.7 times more likely to produce viable SARS-CoV-2 with higher TCID50/mL titers, regardless of viral RNA levels
than those infected with original variants.
This manuscript has both epidemiological and virological importance but the manuscript requires some corrections before considering its publication.
Areas for revision and correction:
Please delete subheadings labelling numbers in the manuscript e.g. 1.0. Introduction
Abstract:
The abstract is concise and explains the study well. However to be in line with the journal style, replace the heading "Interpretation" with "Importance".
Methods:
SARS-CoV-2 RT-PCR
For the variant mutations, they were mentioned "N501Y, 484K and 452R", please write them consistently. E.g E484K etc
Statistical analysis:
Page 6, line 180 -184: There should be citation of your previous work on this subject and citation of other studies where you mentioned about the delta variant infectious rate. In addition, what method was used to calculate the sample size, please elaborate on this "In our previous work, we found that adults had a culture positivity rate of 28.9%. Based on published data that the Delta variant may be 40-60% more infectious than wild type SARS-CoV-2, and assuming that this value would be related to culture positivity, we would require 116 pediatric samples to detect a 40% increase in culture positive rates, with a power of 0.8 and α of 0.05 among children."
Figures
Write a figure legend page and the next pages put the figures without captions
In page 1, line 377: Figure 1 please explain what does these numbers mean? "(24, [18-30] vs. 23, [20] P 0.97)."
In page 14, line 382: Figure 2 please write p-value as p= 0.68
In page 14, line 384: explain what these numbers are?
"Figure 2: Comparison of Tissue Culture Infective dose 50% (TCID50) per mL by variant of concern (VOC) vs. age group. There was no difference in TCID50/ml between the different age categories with respect to the Delta variant specifically (P 0.68 Kruskal-Wallis ANOVA). In the pediatric age groups, the TCID50/ml was significantly higher for the Delta variant in the 11-17 age category than for OV (5620 [1780-17800] vs. 316 [178-2125], P <0.001), but there was no difference in the 0-10 age category."

Reviewer #3 (Comments for the Author):
I would like to thank you for this wonderful work, which will be a qualitative addition to understanding important molecules of the COVID-19 pandemic, but there are some comments that should be reviewed.
In lines (118-120), You need updated statistical data for Coronavirus disease (COVID-19) pandemic.
In lines (239-243) It is preferable to delete this sentence. We still do not know what the side effects of vaccines are. Also, some studies have confirmed that there are side effects to the vaccine, and there are many opponents to the vaccine. Also, there are many voices that have not agreed to give vaccinations to children. The results of this study will tell us important things about how new mutations spread and how to stop them, and you don't need to mention the vaccine at the moment to children.
In References, You need to standardize the format for all references (style). There are some errors in the year of publication, as well as the contents of some references.

Staff Comments:

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Research: Observational Study

Differential infectivity of original and Delta variants of SARS-CoV-2 in children compared to adults

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Short title: Delta VOC SARS-CoV-2 infectivity in children vs adults

Conflict of Interest Disclosures (includes financial disclosures): The authors have no conflicts of interest to disclose.

Funding/Support: No funding was secured for this study.

Abbreviations: Severe acute respiratory syndrome coronavirus (SARS-CoV-2), coronavirus disease 2019 (COVID-19), variants of concern (VOC), reverse transcriptase polymerase chain reaction (RT-PCR), cycle threshold (Ct), 50% tissue culture infective dose (TCID\textsubscript{50}/mL)

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Contribution's Statement Page

Drs Bullard, Dust, Funk, Strong and Poliquin conceptualized and designed the study, analyzed the data, and reviewed and revised the manuscript.

Dr Tse and Ms Garnett drafted the initial manuscript and performed revisions.

Mr. Hedley collected, analyzed by RT-PCR, stored, and transported respiratory samples. He also reviewed and revised the manuscript.

Ms. Tran and Garnett and Dr Strong collected, stored, and transported specimens in addition to performing cell culture experiments. They also reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.
Abstract

Background: Although children of all ages are susceptible to SARS-CoV-2 infection, they have not been implicated as major drivers of transmission thus far. However, it is still unknown if this finding holds true with new Variants of Concern (VOC), such as Delta (B.1.617.2). This study aimed to examine differences in both viral RNA (as measured by cycle threshold [Ct]) and viable virus levels from children infected with Delta compared to original variants (OV). Furthermore, we aimed to compare the pediatric population infection trends to adults.

Methods: We obtained 690 SARS-CoV-2 RT-PCR positive nasopharyngeal swabs from across Manitoba, Canada which were further screened for mutations characteristic of VOCs. Aliquots of sample were then provided for TCID\textsubscript{50} assays to determine infectious titre. Using a variety of statistical analyses we compared Ct and infectivity of VOCs in different age demographics.

Findings: Comparing 122 Delta to 175 OV positive nasopharyngeal swab samples from children, we found that those infected with Delta are 2.7 times more likely to produce viable SARS-CoV-2 with higher TCID\textsubscript{50}/mL titres, regardless of viral RNA levels. Moreover, comparing the pediatric samples to 130 OV and 263 Delta positive samples from adults, we found only that the Delta pediatric culture positive samples had TCID\textsubscript{50}/mL titres similar to culture positive adult samples.

Interpretation: These important findings show that children may play a larger role in viral transmission of Delta than for previously circulating SARS-CoV-2 variants. Additionally, it may suggest a mechanism for why Delta has evolved to be the predominant circulating variant.
Introduction

Severe acute respiratory syndrome 2 (SARS-CoV-2), the etiological agent of COVID-19, has caused over 265 million cases and 5.2 million deaths globally as of December 2021 (WHO Dashboard). It has been previously reported that children of all ages are susceptible to SARS-CoV-2 infection, however, unlike other respiratory viruses, they seem to account for fewer cases and deaths, milder symptoms and a reduced role in viral transmission relative to adults (1–7).

Nevertheless, with new SARS-CoV-2 Variants of Concern (VOC) rapidly appearing, it is important to understand and monitor how children contribute to ongoing infection and transmission trends. This is particularly imperative with reduced vaccine eligibility and the return of in-person learning at school and early care settings, as their proximity between themselves, educators, household contacts and the wider community could lead to rapid transmission (8).

The SARS-CoV-2 Delta (B.1.617.2) variant first appeared with devastating effects in India and was quickly detected around the globe causing surges in case numbers subsequently becoming the predominant circulating strain by June 2021 (9). Delta was determined to be a VOC by the World Health Organization due to evidence of higher transmissibility, worsened clinical implications, and decreased vaccine efficacy (10–13). Specifically, early data showed that Delta has a 60% increase in transmissibility in adults over previous VOCs including alpha (B.1.1.7) (14).

Coinciding with the circulation of Delta, pediatric cases, hospitalizations, COVID-19 related complications and deaths have also increased (15). This was evident by the Centre for Disease Control and Prevention work reporting up to a 10-fold increase in COVID-19 associated
hospitalizations rates (16). However, no studies have been completed specifically evaluating the infectivity of children infected with Delta. Therefore, the aim of this study was to investigate if there are any significant differences in cycle threshold (Ct) or viable infectious virus levels obtained from swab samples from children and adults infected with Delta and compare these rates to previously circulating original variants (OV).

2.0. Methods

2.1. Sampling Collection

690 nasopharyngeal swab samples from unvaccinated cases across Manitoba, Canada (Population 1.4 million) from March to December 2020 and July to September 2021 were provided to Cadham Provincial Laboratory, the public health reference laboratory for Manitoba, as part of routine clinical care and contact tracing. The study was performed in accordance with protocol HS23906 (H2020:211) as approved by the University of Manitoba Research Ethics Board.

2.2. SARS-CoV-2 RT-PCR

Samples positive for SARS-CoV-2 Envelope (E) gene by real time polymerase chain reaction (RT-PCR) were further screened for mutations characteristic of VOCs. The screening targets included spike region deletions in amino acids 69 and 70, and single nucleotide polymorphisms (SNP) including N150IY, 484K and 452R. If quality and quantity of sample allowed, lineages were further confirmed by whole genome sequencing using the Freed primer scheme (17). In addition, beta globin (BGB) levels, a standard housekeeping gene, were used to test the quality of the swab sample and as an nucleic acid integrity control as measured by RT-PCR (18).
2.3. Tissue Culture Infectious Dose 50%

Aliquots of patient samples were provided to the National Microbiology Laboratory for tissue culture infective dose 50% (TCID$_{50}$) determination. For TCID$_{50}$ evaluation, nasopharyngeal samples were diluted 10-fold and incubated on VERO cells (ATCC: CCL-81) maintained in modified Eagle’s medium (MEM) supplemented with 2% fetal bovine serum (FBS), 1% penicillin/streptomycin, and 1% L-glutamine at 37°C with 5% carbon dioxide for 96 hours. Following incubation, cytopathic effect was evaluated under a microscope and recorded. TCID$_{50}$ and TCID$_{50}$/mL were calculated using the Reed and Muench method previously described (19).

2.4. Statistical Analysis

Statistical analysis were as previously described (20). Briefly, here we present normally distributed data with means and standard deviations, and present non-normally distributed data with medians and interquartile ranges (IQRs). We assessed normality using the Kolmogorov–Smirnov test. We performed between-group comparisons using the Student t test or the Mann–Whitney test, and used the Fisher exact test for categorical data. We compared nonparametric group medians using Kruskal–Wallis analysis of variance. We considered two-tailed p values less than 0.05 as significant. We performed statistical analysis with Stata version 16.1 and GraphPad Prism 9. In our previous work, we found that adults had a culture positivity rate of 28.9%. Based on published data that the Delta variant may be 40-60% more infectious than wild type SARS-CoV-2, and assuming that this value would be related to culture positivity, we would require 116 pediatric samples to detect a 40% increase in culture positive rates, with a power of 0.8 and α of 0.05 among children.

3.0. Results
A total of 130 OV and 263 Delta positive samples from adults were compared to 175 OV and 122 Delta positives samples from children. In children, there was no difference in median cycle threshold (Ct) between OV and Delta samples (24 [18-30], vs. 23 [20-28], P 0.97, Figure 1). However, the odds of cell culture positivity were significantly higher for pediatric Delta samples than for OV (OR 2.7, 95% CI 1.6-4.5, P <0.001). We found viable virus in 41.0% (95% CI 32.1-50.2%) of Delta samples compared to 20.5% (95% CI 14.8-27.3%) of OV samples. In samples that were culture positive, the quantity of viable virus, measured by TCID<sub>50</sub>/mL, was also significantly higher for Delta than for OV (5.62E+03 TCID<sub>50</sub>/mL [5.62E+2 - 1.78E+04] vs. 5.62E+02 TCID<sub>50</sub>/mL [3.16E+02-3.16E+03], P 0.001, Figure 2).

When comparing the pediatric samples to the adult samples, children had a significantly higher mean Ct, denoting less viral RNA, for the Delta VOC (23.3 [19.8-27.6] vs 20.9 ([18.0-24.1] P <0.001, Figure 1). Comparably, children also had a 0.55 reduction in the odds ratio of a positive culture (95% CI 0.36-0.85, P 0.008) compared to adults. However, pediatric Delta samples that were culture positive resulted in similar TCID<sub>50</sub>/ml titres compared to adult samples (5.62E+03 [5.62E+2 - 1.78E+04] vs. 5.62E+03 [5.62E+02 – 3.16E+04], P 0.62, Figure 2).

BGB Ct levels show no statistical difference between samples by age (Figure 3), thereby signifying that the quality of the samples is comparable between age groups. This also confirms that there are no differential PCR inhibitors within the samples as tested and that all reagents and protocols are working appropriately.

**4.0. Discussion**

**4.1. Interpretation**
Within the pediatric population, we found that individuals infected with Delta are 2.7 times more likely to produce viable SARS-CoV-2 and at higher titres, compared to age matched individuals infected with OVs. This important finding shows that children may play a larger role in viral transmission of Delta than previously circulating SARS-CoV-2 variants. Children and youth contributing to increased viral transmission of Delta may help explain one mechanism of how Delta became the predominant circulating variant (9). However, in agreeance with our previous study, children infected with Delta still have a 45% reduction in the odds of having a culture positive sample compared to adults (20).

Children have borne a significant burden from disruptions in developmental, social, and educational aspects from the SARS-CoV-2 pandemic, all while their role in the spread of disease has been continuously scrutinized. Although earlier studies suggested that the spread of disease from and amongst children is low, more recent evidence suggests that this may be changing (15,21). As highly transmissible VOCs, such as Delta, arise globally, there is a renewed concern regarding the pediatric populations role in seeding outbreaks and an increasing importance to understanding the infection dynamics in this population (2,22). In the absence of epidemiological evidence of the spread of the various variants of SARS-CoV-2 amongst and from children, we investigated differences in both Ct and viable virus levels in children infected with Delta compared to OVs. We then further compared the pediatric population infection trends to the adult population.

The physiological mechanism for age discrepancies for SARS-CoV-2 infection is still widely under investigation due to the potentially large number of biological, host and environmental factors (23). These factors may include differences in the dynamics of shedding
from children as compared to adults and/or reflect differences in maturity of their respective immune systems (24).

While it has been generally accepted that higher secondary attack rates are associated with higher viral loads as measured by quantitative nucleic acid amplification methods (i.e. RT-PCR), others have shown that nucleic acid detection does not necessarily coincide with the presence of infectious virus (20,25). This latter point is apparent in the results shown here finding similar Ct levels in children infected with Delta and OV, however, Delta positive samples produced much higher culture positivity compared to previous variants. Here culture positivity was evaluated using TCID$_{50}$/mL titres on cells as a surrogate for transmissibility, a much more specific test of infectivity than RT-PCR. This difference between Delta and OV culture positivity in children may reveal one aspect of its transmissibility advantage (26).

Parents are encouraged to vaccinate as well as implement other non-pharmaceutical public health interventions such as social distancing, staying home when sick, hand hygiene and mask use. Some resistance to these measures has come from the fact that, on balance, children generally do well following infection. The virological data showing increased infectious potential of Delta VOC in pediatric individuals reiterates the importance of vaccination, especially with the recent approval of the BioNTech COVID-19 vaccine for children 5-11 (26). Recognizing this, it reinforces the need for a whole-of-society approach to vaccination and other interventions, since the protection against severe outcome involves all.

4.2. Limitations

There are limitations of this study that should be considered. This includes the lack of clinical and epidemiological data linked to samples from this study. Incorporation of this data is an important next step in establishing SARS-CoV2 Delta VOC transmission dynamics in
children. Additionally, without longitudinal sampling any difference in onset and duration of viral shedding between Delta and OVs in children cannot be determined. The duration of infectivity likely plays a major role in increased viral transmission of Delta compared to OVs and should be further investigated. It is also possible that differences in RT-PCR and culturable virus between children and adults are accounted for by the nature or quality of the swab sampling differences between these demographics. However, the fact that the quantification of the housekeeping gene (BGB) from adults and children are comparable make this less likely (Figure 3). Furthermore, the same samples are used for PCR testing and culturable virus and so if this is an accepted critique, we should not consider similar Ct cut-offs in adults and children.

4.3. Conclusion

The relationship between age, SARS-CoV-2 viral load, and transmission has not been comprehensively explored and requires further investigation. Continuation of this work also involves monitoring of viral dynamics for new emerging SARS-CoV-2 VOCs, such as Omicron (B.1.1.529) in different age populations. However, the results presented, showing Delta variant grows more often and to higher levels from nasopharyngeal swabs taken from children compared to previous variants of SARS-CoV-2, may have revealed changing infection trends within the pediatric demographic with novel VOCs.

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Figure 1: Comparison of SARS-CoV-2 E gene RT-PCR cycle threshold (Ct) value by variant of concern vs. age group. Median Ct was higher for the Delta variant in pediatric age groups than for adults (P <0.001 Kruskal-Wallis ANOVA) implying lower viral RNA levels. Median [IQR] Ct was similar for children ages 0-17 between OV and Delta variants (24, [18-30] vs. 23, [20-28], P 0.97).
Figure 2: Comparison of Tissue Culture Infective dose 50% (TCID$_{50}$) per mL by variant of concern (VOC) vs. age group. There was no difference in TCID$_{50}$/ml between the different age categories with respect to the Delta variant specifically ($P = 0.68$ Kruskal-Wallis ANOVA). In the pediatric age groups, the TCID$_{50}$/ml was significantly higher for the Delta variant in the 11-17 age category than for OV (5620 [1780-17800] vs. 316 [178-2125], $P < 0.001$), but there was no difference in the 0-10 age category.
Figure 3: Linear regression analysis of swab beta globin (BGB) Ct vs age shows no statistical difference between BGB Ct level and age at which the sample was obtained.
Fig. 2
Responses to Reviewers

Reviewer 1:

Please delete subheadings labelling numbers in the manuscript e.g. 1.0. Introduction
All numbering format for subheadings has been removed.

Abstract:
The abstract is concise and explains the study well. However to be in line with the journal style, replace the heading "Interpretation" with "Importance".
The heading titled interpretation has been changed to Importance.

Methods:
SARS-CoV-2 RT-PCR
For the variant mutations, they were mentioned "N501Y, 484K and 452R", please write them consistently. E.g E484K etc
Thank you for pointing out this inconsistency, the single nucleotide polymorphism nomenclature has been updated on line 159 “N501Y, E484K and L452R”

Statistical analysis:
Page 6, line 180 -184: There should be citation of your previous work on this subject and citation of other studies where you mentioned about the delta variant infectious rate. In addition, what method was used to calculate the sample size, please elaborate on this "In our previous work, we found that adults had a culture positivity rate of 28.9%. Based on published data that the Delta variant may be 40-60% more infectious than wild type SARS-CoV-2, and assuming that this value would be related to culture positivity, we would require 116 pediatric samples to detect a 40% increase in culture positive rates, with a power of 0.8 and α of 0.05 among children."

We apologize for missing these references beforehand, the following references have been added as suggested:
21. Bullard J, Dust K, Funk D, Strong JE, Alexander D, Garnett L, Boodman C, Bello A, Hedley A, Schiffman Z, Doan K, Bastien N, Li Y, van Caeseele PG, Poliquin G. 2020. Predicting infectious severe acute respiratory syndrome coronavirus 2 from diagnostic samples. Clin Infect Dis 71:2663–2666.
22. Yang W, Shaman J. 2022. COVID-19 pandemic dynamics in India, the SARS-CoV-2 Delta variant and implications for vaccination. J R Soc Interface 19.
23. Liu Y, Rocklöv J. 2021. The reproductive number of the Delta variant of SARS-CoV-2 is far higher compared to the ancestral SARS-CoV-2 virus. J Travel Med 28.

Figures
Write a figure legend page and the next pages put the figures without captions
A figure legend page has been added on page 13 with the figures following without the respective figure legends.

In page 1, line 377: Figure 1 please explain what does these numbers mean? "(24, [18-30] vs. 23, [20377 28], P 0.97)."
Thanks for pointing this out as it was not clear in the original. This is in response to the Figure 1 legend (now line 419-423) comparing the SARS-CoV-2 positive cycle threshold values by variant in children. The numbers in question represent the median cycle threshold and its associated interquartile range “(24, [18-30] vs. 23, [20-28], P=0.97)” for children aged 0-17 infected with the original variant and delta variant respectively.

To help clarify this we have added a sentence to the methods section under statistical analysis on line 184 showing a representation of how the statistical results are presented “Statistical results are reported as (Median [Interquartile range], P value).”. Similarly a simplified version “Median [IQR]” precedes the statement in question on Line 421.

In page 14, line 382: Figure 2 please write p-value as p= 0.68
This grammatical error has been corrected, thank you.

In page 14, line 384: explain what these numbers are?
"Figure 2: Comparison of Tissue Culture Infective dose 50% (TCID50) per mL by variant of concern (VOC) vs. age group. There was no difference in TCID50/ml between the different age categories with respect to the Delta variant specifically (P 0.68 Kruskal-Wallis ANOVA). In the pediatric age groups, the TCID50/ml was significantly higher for the Delta variant in the 11-17 age category than for OV (5620 [1780-17800] vs. 316 [178-2125], P <0.001), but there was no difference in the 0-10 age category."

The numbers in figure 2 caption are the median TCID50/mL and the associated interquartile range for children (aged 11-17) infected with delta variant (5620[1780-17800]) and the original variant (316[178-2125]). As these numbers showed a significant difference we have also included the P value.

For clarity we have added a sentence to the statistical methods section Line 184 depicting how the statistical results are presented throughout the paper. “Statistical results are reported as (Median [Interquartile range], P value).”

Reviewer 3:

In lines (118-120), You need updated statistical data for Coronavirus disease (COVID-19) pandemic.

The statistics on case and deaths has been updated as of July 15, 2022 on line 120.
“Severe acute respiratory syndrome 2 (SARS-CoV-2), the etiological agent of COVID-19, has caused over 556 million cases and 6.3 million deaths globally as of July 15, 2022 (WHO Dashboard).”

In lines (239-243) It is preferable to delete this sentence. We still do not know what the side effects of vaccines are. Also, some studies have confirmed that there are side effects to the vaccine, and there are many opponents to the vaccine. Also, there are many voices that have not agreed to give vaccinations to children. The results of this study will tell us important things about how new mutations spread and how to stop them, and you don't need to mention the vaccine at the moment to children.

The sentence has been deleted as suggested.
In References, You need to standardize the format for all references (style). There are some errors in the year of publication, as well as the contents of some references.

Thank you for pointing this out. We have gone through the references and made it a consistent format as well as corrected the mistakes as follows:

1. Dawood FS, Porucznik CA, Veguilla V, Stanford JB, Duque J, Rolfes MA, Dixon A, Thind P, Hacker E, Castro MJE, Jedy Z, Daugherty M, Altunkaynak K, Hunt DR, Kattel U, Meece J, Stockwell MS. 2022. Incidence Rates, Household Infection Risk, and Clinical Characteristics of SARS-CoV-2 Infection among Children and Adults in Utah and New York City, New York. JAMA Pediatr 30329:1–9.

*changed to 2022

10. Luo CH, Morris CP, Sachithanandham J, Amadi A, Gaston DC, Li M, Swanson NJ, Schwartz M, Klein EY, Pekosz A, Mostafa HH. 2021. Infection with the SARS-CoV-2 Delta Variant is Associated with Higher Recovery of Infectious Virus Compared to the Alpha Variant in both Unvaccinated and Vaccinated Individuals. Clin Infect Dis. 2021 Dec 18;ciab986.c doi: 10.1093/cid/ciab986.

*No longer a preprint- now published in Clinical Infectious Diseases

24. Allen H, Vusirikala A, Flannagan J, Twohig KA, Zaidi A, Chudasama D, Lamagni T, Groves N, Turner C, Rawlinson C, Lopez-Bernal J, Harris R, Charlett A, Dabrera G, Kall M. 2021. Household transmission of COVID-19 cases associated with SARS-CoV-2 delta variant (B.1.617.2): national case-control study. Lancet Reg Heal - Eur 12:100252.

*changed to 2021

29. Walter EB, Talaat KR, Sabharwal C, Gurtman A, Lockhart S, Paulsen GC, Barnett ED, Muñoz FM, Maldonado Y, Pahud BA, Domachowske JB, Simões EAF, Sarwar UN, Kitchin N, Cunliffe L, Rojo P, Kuchar E, Rämet M, Munjal I, Perez JL, Frenck RW, Lagkadinou E, Swanson KA, Ma H, Xu X, Koury K, Mather S, Belanger TJ, Cooper D, Türeci Ö, Dormitzer PR, Şahin U, Jansen KU, Gruber WC. 2022. Evaluation of the BNT162b2 Covid-19 Vaccine in Children 5 to 11 Years of Age. N Engl J Med 35–46.

*changed to 2022
August 1, 2022

Dr. James Eric Strong  
Public Health Agency of Canada  
Division of Special Pathogens  
1015 Arlington Street  
Winnipeg, Manitoba R3E 3P6  
Canada

Re: Spectrum00395-22R1 (Differential infectivity of original and Delta variants of SARS-CoV-2 in children compared to adults)

Dear Dr. James Eric Strong:

Thank you for responding to the reviewers comments.

Your manuscript has been accepted, and I am forwarding it to the ASM Journals Department for publication. You will be notified when your proofs are ready to be viewed.

The ASM Journals program strives for constant improvement in our submission and publication process. Please tell us how we can improve your experience by taking this quick Author Survey.

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