nature research

Peer Review Information

Journal: Nature Immunology
Manuscript Title: Distinct antibody responses to SARS-CoV-2 in children and adults across the COVID-19 clinical spectrum
Corresponding author name(s): Donna L. Farber, Matteo Porotto

Editorial Notes:

Transferred manuscripts This manuscript has been previously reviewed at another journal that is not operating a transparent peer review scheme. This document only contains reviewer comments, rebuttal and decision letters for versions considered at Nature Immunology.

Reviewer Comments & Decisions:

Decision Letter, initial version:

Subject: Decision on Nature Immunology submission NI-LE30732-T
Message: 2nd Oct 2020

Dear Donna,

Thank you for supplying a point-by-point response to the referees' comment on your manuscript entitled, "Distinct antibody responses to SARS-CoV-2 infection in children and adults across the COVID-19 clinical spectrum". As noted previously, while they find your work of interest, some important points are raised. It appears from your response that you and your colleagues can provide clarifications to address most of these concerns, as well as a reanalysis of data that are already in-hand. We are very interested in the possibility of publishing your study in Nature Immunology, but would like you to revise the manuscript along the lines proposed in your response letter.

We therefore invite you to revise your manuscript taking into account all reviewer and editor comments. Please highlight all changes in the manuscript text file in Microsoft Word format.

We are committed to providing a fair and constructive peer-review process. Do not hesitate to contact us if there are specific requests from the reviewers that you believe are technically impossible or unlikely to yield a meaningful outcome.

When revising your manuscript:

* Include a "Response to referees" document detailing, point-by-point, how you addressed each referee comment. If no action was taken to address a point, you must provide a compelling argument. This response will be sent back to the referees along with the revised manuscript.

* If you have not done so already please begin to revise your manuscript so that it conforms to our Letter format instructions at http://www.nature.com/ni/authors/index.html. Refer also to any guidelines provided in this letter.

* Please include a revised version of any required reporting checklist. It will be available to referees to aid in their evaluation of the manuscript goes back for peer review. They are available here:

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Note: This URL links to your confidential home page and associated information about manuscripts you may have submitted, or that you are reviewing for us. If you wish to forward this email to co-authors, please delete the link to your homepage.

We hope to receive your revised manuscript within two weeks. If you cannot send it within this time, please let us know. We will be happy to consider your revision so long as nothing similar has been accepted for publication at Nature Immunology or published elsewhere.

Please do not hesitate to contact me if you have any questions or would like to discuss these revisions further.

Nature Immunology is committed to improving transparency in authorship. As part of our efforts in this direction, we are now requesting that all authors identified as 'corresponding author' on published papers create and link their Open Researcher and Contributor Identifier (ORCID) with their account on the Manuscript Tracking System

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We look forward to seeing the revised manuscript and thank you for the opportunity to review your work.

Kind regards,

Laurie

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Nature Immunology
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Referee expertise:

Referee #1:

Referee #2:

Referee #3:

Reviewers' Comments:

Reviewer #1:
Remarks to the Author:
Weisberg et al make a point that the IgG response is narrower in children and focused on Spike, while adults make broader responses. Could this be due to a more efficient innate response in children, leading to less pronounced adaptive immune activation in children?

Also, the conclusion that children respond differently from adults to SARS-CoV-2 infection, how does this differ from other infections? I think a more careful discussion on the novelty offered by this study would be useful.

The differences between MIS-C and non-MIS-C children are complicated by the fact that the MIS-C children were likely infected 1-2 months prior to symptom onset and hospital admission. How can the qualitative differences between MIS-C and non-MIS-C be distinguished from possible differences in kinetics and phase of the disease?

The authors speculate about ADE as a possible mechanism of MIS-C. Wouldn't that suggest that all MIS-C patients would be positive for the virus by PCR? This is typically not the case, but instead many patients are only anti-SARS-CoV-2 IgG+ and PCR-. Can the authors discuss this point?

Several recent papers investigating the immune response in MIS-C have not been cited and should be mentioned and discussed in relation to the results herein. In particular the papers looking into serological responses in MIS-C and non-MIS-C children (ex Consiglio et al, Cell, 2020 and Pierce et al, Science Translational Medicine, 2020) should be discussed.

Reviewer #2:
Remarks to the Author:
The authors have responded to all prior comments of the reviewers. Most importantly, the addition of the non-MISC pediatric cohort identified an interesting new feature of pediatric cases (both MIS-C and non-MIS-C), which was the reduced presence of anti-N antibodies. Various other concerns raised, particularly about the interpretation of the data, have also been addressed.

I do have one significant request if possible: all the statistical analyses corelating with infection-related or demographic features are done as pairwise correlations. Given the possibility that some of these features tested might themselves be related (e.g. time after symptom sampling and age, given the differences in how the cohorts were collected), it would seem like putting all of the data into a linear, multivariate model and asking what factors remain significant could be very informative. The authors could attempt both a combined model and one still splitting pediatrics and adults.

Reviewer #3:
Remarks to the Author:
Weisberg and colleagues studied antibody responses in adults and children with COVID-19, with a subset of the children having MIS-C. In their cohort, they found that adults, particularly those with severe disease, had higher binding and neutralizing Ab response than children, whether or not they had MIS-C. This is a useful addition to the pediatric literature however much of the data is largely as expected.

Comments

It is well established that more severe illness results in higher levels of binding and neutralizing antibodies. Children tend to have milder illnesses and thus could be expected to have lower levels. It would be helpful to match severity of illness (and duration, see below) with the adult and pediatric groups to determine if their findings are governed by severity rather than age.

The severity of the illness in the convalescent plasma donors would therefore be helpful. Presumably it was less severe although some centres recruit more severe subjects as they have higher AB levesl. If the clinical severity cannot be obtained, perhaps testing and matching the plasma for biomarkers of severity would be helpful. In their response the authors state "Importantly, both pediatric cohorts had comparable anti-S IgG but reduced anti- S IgM, anti-N and anti-S neutralizing activity compared to the adult COVID cohorts with mild and serve disease." The "mild disease" I assume is referring to the convalescent plasma samples but they do not show disease severity for this group as far as I could find.

Duration of illness is an important factor in the generation of an antibody response particularly for IgM. The limited information on duration of illness, or time since exposure, or PCR+ samples in the 2 pediatric cohorts makes it inherently difficult to compare them with the adult cohorts.

There were treatments of some adult and pediatric subjects with convalescent plasma and monoclonal antibodies – was this prior to the sampling? If not, it may influence the data?

Author Rebuttal to Initial comments

Point-by Point Response

"Distinct antibody responses to SARS-CoV-2 infection in children and adults across the COVID-19 clinical spectrum"

NI-LE30732-T

Corresponding Author: Donna L. Farber

We appreciate the helpful and insightful comments from each Reviewer about our revised manuscript. Please see below our itemized response describing how we revised our manuscript to address each comment.

Reviewer #1:

1. *Weisberg et al make a point that the IgG response is narrower in children and focused on Spike, while adults make broader responses. Could this be due to a more efficient innate response in children, leading to less pronounced adaptive immune activation in children?*

Response: In the revised manuscript (p. 9) we have discussed the potential role of innate immunity in protection to SARS-CoV-2 in children, in providing early control of viral load, resulting in a less robust and extensive adaptive response. Recent studies show high levels of multiple pro-inflammatory mediators in the serum of MIS-C patients indicative of a robust innate responses[1,2], although the innate immune response of non-MIS-C children to acute SARS-CoV-2 infection is not clear.

2. Also, the conclusion that children respond differently from adults to SARS-CoV-2 infection, how does this differ from other infections? I think a more careful discussion on the novelty offered by this study would be useful.

Response: The novelty of this study is that it measures the primary antibody response to a new infection in children and adults. Most endemic viral respiratory tract infections are initially encountered during infancy and childhood with repeated exposures throughout life. As a result, adult responses to viruses are invariably secondary (memory) responses, while those in children are primary, and it is generally not feasible to compare responses to newly encountered viruses in adults and children. The sudden and widespread emergence of a novel pathogen such as SARS-CoV-2 provides an unprecedented opportunity to assess primary immune responses across all ages. We have included discussion on this point in the revised manuscript (p. 8).

3. The differences between MIS-C and non-MIS-C children are complicated by the fact that the MIS-C children were likely infected 1-2 months prior to symptom onset and hospital admission. How can the qualitative differences between MIS-C and non-MIS-C be distinguished from possible differences in kinetics and phase of the disease?

Response: It is important to note that all the subjects studied in this manuscript were infected and samples were collected during the same 60-day window of time during the peak pandemic in New York City. We have assessed the timing post-symptom onset in the hospitalized adult and pediatric patients (MIS-C and non-MIS-C) by review of each and every chart, and from the convalescent plasma donors (CPD) based on the questionnaire. As a result, we have accurate assessments of days post-symptom onset for all 32 adults and 32/47 children (16/16 MIS-C and 16/31 non-MIS-C) (Table 1). For MIS-C subjects, the time post-symptom onset in the chart referred to the MIS-C symptoms; however, we can infer the timing of primary infection based on their admission date relative to the singular sharp peak of infections from mid-March to mid-May; we also have 3 week follow up on the MIS-C patients. From these data, we conclude that the children presented with MIS-C 2 weeks-2 months after infection consistent with estimates by others[3], and that children in the MIS-C and non-MIS-C groups were infected during the same time window. In the revised manuscript we discuss this point on p 8.

Regarding the differences between MIS-C and non-MIS-C - for the pediatric groups, the antibody results for both groups are similar, while the main differences in antibody responses

are between pediatric and adult groups. In the manuscript, we analyzed antibody levels and neutralizing activity based on the timing of SARS-CoV-2 exposure or symptoms for both adult and pediatric cohorts, including follow-up of 8 MIS-C patients 3 weeks after hospital discharge. For this revision, we also performed multivariate analysis to account for potential confounding factors including the time post symptom onset (Table S3 and p 8). Together, these results indicate that the differences identified between pediatric and adult cohorts are independent of the timing post-symptom onset. We have included these data as main figures (Figures 2 and 4) and a supplemental table (Table S3), and discuss these results in detail on page 8.

4. The authors speculate about ADE as a possible mechanism of MIS-C. Wouldn't that suggest that all MIS-C patients would be positive for the virus by PCR? This is typically not the case, but instead many patients are only anti-SARS-CoV-2 IgG+ and PCR-. Can the authors discuss this point?

Response: We propose ADE as one potential mechanism for how a low-level, non-neutralizing antibody response may potentially exacerbate a virus-associated systemic inflammatory response. Determining whether this mechanism is contributing to MIS-C would require testing of multiple sites within an individual for virus, and it is not clear whether testing using nasopharyngeal swab sampling exclusively would enable one to make any conclusions on the systemic spread of the virus. In the revised manuscript, we include additional discussion regarding the possibilities for the pathogenesis of MIS-C (p. 9-10), citing recent studies that were published while our manuscript was under review. Additionally, we discuss and reference evidence of prolonged fecal shedding of SARS-CoV-2 in children who presented without significant respiratory symptoms[4] to support the possibility of the virus persisting outside the respiratory tract.

5. Several recent papers investigating the immune response in MIS-C have not been cited and should be mentioned and discussed in relation to the results herein. In particular the papers looking into serological responses in MIS-C and non-MIS-C children (ex Consiglio et al, Cell, 2020 and Pierce et al, Science Translational Medicine, 2020) should be discussed.

Response: We have updated our manuscript throughout to cite studies on MIS-C and the pediatric immune response to SARS-CoV-2 that were published while our manuscript was under review, including the ones mentioned by this reviewer.

Reviewer #2

1. The authors have responded to all prior comments of the reviewers. Most importantly, the addition of the non-MISC pediatric cohort identified an interesting new feature of pediatric cases (both MIS-C and non-MIS-C), which was the reduced presence of anti-N antibodies. Various other concerns raised, particularly about the interpretation of the data, have also been addressed.

I do have one significant request if possible: all the statistical analyses corelating with infection-related or demographic features are done as pairwise correlations. Given the possibility that some of these features tested might themselves be related (e.g. time after symptom sampling and age, given the differences in how the cohorts were collected), it would seem like putting all of the data into a linear, multivariate model and asking what factors remain significant could be very informative. The authors could attempt both a combined model and one still splitting pediatrics and adults.

Response: To control for the effects of covariates, we have performed a multivariable analysis using the following predictor variables: age group, time after symptom sampling, sex, and clinical syndrome for both the combined dataset (n=79) and separately for the pediatric (n=47) and adult cohorts (n=32). We find that, in a model incorporating all subjects, pediatric age group was a significant independent predictor of lower neutralizing activity, anti-S IgM and anti-N IgG. In addition, ARDS was independently associated with increased neutralizing activity and anti-S antibody levels for both combined and adult dataset. We have included these results in Table S3 and described this analysis in the revised text (pp.7-8). In our analysis of the combined adult and pediatric data we used the categorical 'pediatric age group' variable rather than age as a continuous variable because it better reflects the grouped analysis presented in Fig.1a-d and Fig. 3b.

Reviewer #3

1. Weisberg and colleagues studied antibody responses in adults and children with COVID-19, with a subset of the children having MIS-C. In their cohort, they found that adults, particularly those with severe disease, had higher binding and neutralizing Ab response than children, whether or not they had MIS-C. This is a useful addition to the pediatric literature however much of the data is largely as expected.

It is well established that more severe illness results in higher levels of binding and neutralizing antibodies. Children tend to have milder illnesses and thus could be expected to have lower levels. It would be helpful to match severity of illness (and duration, see below) with the adult and pediatric groups to determine if their findings are governed by severity rather than age.

Response: The relationship between the immune response to SARS-CoV-2 and disease severity remains unresolved. For example, a very recent report integrating different aspects of the virus-specific adaptive immune response found a more coordinated and robust adaptive immune response that was associated with mild disease, while those with severe disease or older age lacked certain aspects of the virus-specific adaptive response[5]. While severe disease in adults is largely associated with acute respiratory distress syndrome (ARDS), in children severe disease is manifested differently, by MIS-C. Our results show similar antibody levels and neutralizing activity in children with and without MIS-C, and therefore that disease severity does not correlate with the magnitude of the antibody response in children. We have included additional discussions on these points in the revised manuscript (pp.9-10).

2. The severity of the illness in the convalescent plasma donors would therefore be helpful. Presumably it was less severe although some centres recruit more severe subjects as they have higher AB levels. If the clinical severity cannot be obtained, perhaps testing and matching the plasma for biomarkers of severity would be helpful. In their response the authors state "Importantly, both pediatric cohorts had comparable anti-S IgG but reduced anti- S IgM, anti-N and anti-S neutralizing activity compared to the adult COVID cohorts with mild and serve disease." The "mild disease" I assume is referring to the convalescent plasma samples but they do not show disease severity for this group as far as I could find.

Response: At our institution, convalescent plasma donors were recruited from the general population (including a number of health care workers) following self-reported symptoms consistent with acute infection Based on responses to the donor questionnaire, none of the donors sampled for this study had been hospitalized for COVID-19. We have provided additional clarification regarding our subject groups in the revised manuscript (p. 4).

3. Duration of illness is an important factor in the generation of an antibody response particularly for IgM. The limited information on duration of illness, or time since exposure, or PCR+ samples in the 2 pediatric cohorts makes it inherently difficult to compare them with the adult cohorts.

Response: Please see response to Reviewer 1 pt. #3 above. We have included the time post symptom onset for all subjects (Table 1) and analysis of the time post symptom onset vs antibody response (Figures 2 and 4). The pediatric Non-MIS-C cohort had a similar time post symptom onset to sample collection as our adult CPD group (Table 1; Non-MIS-C 29 days vs CPD 24 days). Importantly, we were able to obtain samples from multiple MIS-C subjects at their follow-up appointments 3-4 weeks after their initial presentation and found no difference in antibodies when compared to their acute presentation (Figure 4) suggesting that changes in antibody levels or function did not vary much over short periods of time. Moreover, in a multivariable analysis adjusting for the time post symptom onset and other infection-related clinical and demographic variables (Table S3) ARDS was a significant predictor of increased anti-S IgM and pediatric age group was a significant predictor of lower anti-S IgM. In the revised manuscript, we provide the multivariate analysis results in a supplemental table (Table S3) which provides additional statistical analysis that shows no direct association of antibody levels with time post-symptom onset.

4. There were treatments of some adult and pediatric subjects with convalescent plasma and monoclonal antibodies – was this prior to the sampling? If not, it may influence the data?

Response: We have included information on treatments with convalescent plasma and monoclonal antibodies for the hospitalized cohorts (COVID-ARDS and MIS-C groups) in Supplemental Table 1. It is important to note that the pediatric samples in our study were largely obtained prior to therapeutic interventions, which contrasts with recently published reports[1] where immune responses during MIS-C were reported following application of monoclonal antibodies. Samples from adults were likewise obtained within 24-36hrs of their intubation. We have provided an additional footnote to Supplement Table 1 denoting how many subjects received a particular therapy prior to obtaining the sample for this study.

References

1. Gruber, C.N., *et al.* Mapping Systemic Inflammation and Antibody Responses in Multisystem Inflammatory Syndrome in Children (MIS-C). *Cell* (2020).
2. Consiglio, C.R., *et al.* The Immunology of Multisystem Inflammatory Syndrome in Children with COVID-19. *Cell* (2020).
3. Levin, M. Childhood Multisystem Inflammatory Syndrome - A New Challenge in the Pandemic. *N Engl J Med* **383**, 393-395 (2020).

4. Xu, Y., *et al.* Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. *Nat Med* **26**, 502-505 (2020).
5. Moderbacher, C.R., *et al.* Antigen-specific adaptive immunity to SARS-CoV-2 in acute COVID-19 and associations with age and disease severity. *Cell* **https://www.cell.com/cell/fulltext/S0092-8674(20)31235-6**(2020).

Decision Letter, first revision:

Subject: Nature Immunology - NI-LE30732A pre-edit

Message: Our ref: NI-LE30732A

16th Oct 2020

Dear Donna,

Thank you for your patience as we've prepared the guidelines for final submission of your Nature Immunology manuscript, "Distinct antibody responses to SARS-CoV-2 infection in children and adults across the COVID-19 clinical spectrum" (NI-LE30732A).

Please follow the instructions provided here and in the attached files, as the formal acceptance of your manuscript will be delayed if these issues are not addressed.

When you upload your final materials, please include a point-by-point response to the points below. We won't be able to proceed further without this detailed response.

General formatting:

Given that this will be a Letter type of content, the current formatting of the Introduction and Main body is fine, but for the remaining sections, please assemble in order as noted in the formatting guide sheet.

Please include a separate "Data availability" subsection at the end of your Online Methods. This section should inform our readers about the availability of the data used to support the conclusions of your study and should include references to source data, accession codes to public repositories, URLs to data repository entries, dataset DOIs, and any other statement about data availability. We strongly encourage submission of source data (see below) for all your figures. At a minimum, you should include the following statement: "The data that support the findings of this study are available from the corresponding author upon request", mentioning any restrictions on availability. If DOIs are provided, these should be included in the Reference list (authors, title, publisher (repository name), identifier, year). For more guidance on how to write this section please see: http://www.nature.com/authors/policies/data/data-availability-statements-data-citations.pdf.

The title should provide a clear and compelling summary of the main findings in fewer than 100 characters including spaces and without punctuation.

As a guideline, Articles allow up to 50 references in the main text. An additional 20 references can be included in the Online Methods. Only papers that have been published or accepted by a named publication or recognized preprint server should be in the numbered list. Published conference abstracts, numbered patents and research data sets that have been assigned a digital object identifier may be included in the reference list.

All references must be cited in numerical order. Place Methods-only references after the Methods section and continue the numbering of the main reference list (i.e., do not start at 1).

Figures and Tables:

All figures and tables, including Extended Data, must be cited in the text in numerical order.

Figure legends should be concise. Begin with a brief title and then describe what is presented in the figure and detail all relevant statistical information, avoiding inappropriate methodological detail.

All relevant figures must have defined error bars.

When submitting the revised version of your manuscript, please pay close attention to our href="https://www.nature.com/nature-research/editorial-policies/image-integrity">Digital Image Integrity Guidelines. .

Finally, please ensure that you retain unprocessed data and metadata files after publication, ideally archiving data in perpetuity, as these may be requested during the peer review and production process or after publication if any issues arise.

Statistics and Reproducibility:

The Methods must include a statistics section where you describe the statistical tests used. For all statistics (including error bars), provide the EXACT n values used to calculate the statistics (reporting individual values rather than a range if n varied among experiments) AND define type of replicates (e.g., cell cultures, technical replicates). Please avoid use of the ambiguous term “biological replicates”; instead state what constituted the replicates (e.g., cell cultures, independent experiments, etc.). For all representative results, indicate number of times experiments were repeated, number of images collected, etc. Indicate statistical tests used, whether the test was one- or two-tailed, exact values for both significant and non-significant P values where relevant, F values and degrees of freedom for all ANOVAs and t-values and degrees of freedom for t-tests.

Reporting Guidelines– Attached you will find an annotated version of the Reporting Summary you submitted, along with a Word document indicating revisions that need to be made in compliance with our reproducibility requirements. These documents detail any changes that will need to be made to the text, and particularly the main and supplementary figure legends, including (but not limited to) details regarding sample sizes, replication, scale and error bars, and statistics. Please use these documents as a

guide when preparing your revision and submit an updated Reporting Summary with your revised manuscript. The Reporting Summary will be published as supplementary material when your manuscript is published.

Please provide an updated version of the Reporting Summary and Editorial Policy Checklist with your final files and include the following statement in the Methods section to indicate where this information can be found: "Further information on research design is available in the Nature Research Reporting Summary linked to this article."

The Reporting Summary and Editorial Policy Checklist can be found here:
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https://www.nature.com/documents/nr-editorial-policy-checklist.pdf

Note that these forms are smart "dynamic" PDFs which cannot be opened by most web browsers. Download them or right-click and choose "save as" in order to save them to your computer desktop and fill them in using Adobe Acrobat.

Supplementary Information:
All Supplementary Information must be submitted in accordance with the instructions in the attached Inventory of Supporting Information, and should fit into one of three categories:

EXTENDED DATA: Extended Data are an integral part of the paper and only data that directly contribute to the main message should be presented. These figures will be integrated into the full-text HTML version of your paper and will be appended to the online PDF. There is a limit of 10 Extended Data figures, and each must be referred to in the main text. Each Extended Data figure should be of the same quality as the main figures, and should be supplied at a size that will allow both the figure and legend to be presented on a single legal-sized page. Each figure should be submitted as an individual .jpg, .tif or .eps file with a maximum size of 10 MB each. All Extended Data figure legends must be provided in the attached Inventory of Accessory Information, not in the figure files themselves.

SUPPLEMENTARY INFORMATION: Supplementary Information is material that is essential background to the study but which is not practical to include in the printed version of the paper (for example, video files, large data sets and calculations). Each item must be referred to in the main manuscript and detailed in the attached Inventory of Accessory Information. Tables containing large data sets should be in Excel format, with the table number and title included within the body of the table. All textual information and any additional Supplementary Figures (which should be presented with the legends directly below each figure) should be provided as a single, combined PDF. Please note that we cannot accept resupplies of Supplementary Information after the paper has been formally accepted unless there has been a critical scientific error.

All Extended Data must be called you in your manuscript and cited as Extended Data 1, Extended Data 2, etc. Additional Supplementary Figures (if permitted) and other items are not required to be called out in your manuscript text, but should be numerically numbered, starting at one, as Supplementary Figure 1, not SI1, etc.

SOURCE DATA: We encourage you to provide source data for your figures whenever possible. Full-length, unprocessed gels and blots must be provided as source data for any

relevant figures, and should be provided as individual PDF files for each figure containing all supporting blots and/or gels with the linked figure noted directly in the file. Statistics source data should be provided in Excel format, one file for each relevant figure, with the linked figure noted directly in the file. For imaging source data, we encourage deposition to a relevant repository, such as figshare (https://figshare.com/) or the Image Data Resource (https://idr.openmicroscopy.org).

Other
As mentioned in our previous letter, all corresponding authors on a manuscript should have an ORCID – please visit your account in our manuscript system to link your ORCID to your profile, or to create one if necessary. For more information please see our previous letter or visit www.springernature.com/orcid.

Nature Research journals encourage authors to share their step-by-step experimental protocols on a protocol sharing platform of their choice. Nature Research's Protocol Exchange is a free-to-use and open resource for protocols; protocols deposited in Protocol Exchange are citable and can be linked from the published article. More details can found at www.nature.com/protocolexchange/about.

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In addition to addressing these points, please refer to the attached policy and rights worksheet, which contains information on how to comply with our legal guidelines for publication and describes the files that you will need to upload prior to final acceptance. You must initial the relevant portions of this checklist, sign it and return it with your final files. I have also attached a formatting guide for you to consult as you prepare the revised manuscript. Careful attention to this guide will ensure that the production process for your paper is more efficient.

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Please use the following link for uploading these materials: [REDACTED]

We ask that you aim to return your revised paper within 7 days. If you have any further questions, please feel free to contact me.

Best regards,

Laurie

Laurie A. Dempsey, Ph.D.
Senior Editor
Nature Immunology
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ORCID: 0000-0002-3304-796X

Final Decision Letter:

Subject: Decision on Nature Immunology submission NI-LE30732B

Message: In reply please quote: NI-LE30732B

Dear Donna,

I am delighted to accept your manuscript entitled "Distinct antibody responses to SARS-CoV-2 in children and adults across the COVID-19 clinical spectrum" for publication in an upcoming issue of Nature Immunology.

The manuscript will now be copy-edited and prepared for the printer. Please check your calendar: if you will be unavailable to check the galley for some portion of the next 10 days, we need the contact information of whom will be making corrections in your stead. When you receive your galleys, please examine them carefully to ensure that we have not inadvertently altered the sense of your text.

Acceptance is conditional on the data in the manuscript not being published elsewhere, or

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