ROUND 1

We thank the Editor and the Reviewers for the time spent in reviewing our manuscript and for the opportunity to resubmit it after appropriate revision. Changes made have been highlighted in yellow in the revised version of the text.

Reviewer #1: The review summarizes the current knowledge about gut microbiota and COVID-19 in children. Accumulating data have pointed out that gut dysbiosis might have a potential impact on the severity of the disease. Based on the increased risk of inflammatory diseases in children with COVID-19, a potential correlation between gut microbiota dysfunction and COVID-19 is assumed. The inter-organ crosstalk is essential addressed. The topic is of high relevance.

Comments 1. ACE2 is introduced to the reader at least three times (Abstract, page 4, page 7).

Answer: We corrected typos in the revised text. Please see lines 130,131,160

2. The terms ACE2 and ACE2 receptor should be used more precisely. In Figure 2 the ACE2 receptor is addressed, but in the body of the manuscript ACE2 is always discussed.

Answer: we used more precisely these terms in the revised version of the text. Please see lines 33, 160 of the revised text.

3. Figure/ Table: there is need for a scheme demonstrating the (putative) COVID-19 effects on the different microbiome species in lung versus gut.

Answer: thank you for your insightful suggestion. We added a table on the putative COVID-19 effects on the different lung and gut microbiome species. Please see the new Table 1 in the revised version of the text.

Reviewer #2: INTRODUCTION - Overall, it provides an appropriate background with the main introductory concepts.

Answer: thank you for your appreciation.

THE PLEIOTROPIC EFFECT OF GUT MICROBIOTA IN PEDIATRIC DISEASES - “More, the gut microbiota has been linked to the spectrum of metabolic diseases [14] including obesity, metabolic syndrome, type 2 diabetes, and Non Alcoholic fatty liver disease (NAFLD) both in adults and children [15-18] (Figure 1).” Here, I think the authors should expand a little this concept and, importantly, the potential role of microbiome is not limited to “metabolic diseases”, but in general a spectrum of non-communicable diseases, including autoimmune disorders, such as rheumatic diseases (see: Clin Rheumatol. 2020 Sep;39(9):2523-2528. doi: 10.1007/s10067-020-05170-9) or celiac disease (refer to: Front Pediatr. 2021 Apr 22;9:652208. doi: 10.3389/fped.2021.652208), for instance, even if a clear microbiome signature is not evident yet. This observation may be useful to introduce some aspects of COVID19-related disorders, since for instance immune-mediated mechanisms are definitely implicated in some aspects of long COVID.

Answer: thank you for your insightful suggestion. As supported by several scientific data, gut microbiome has been linked to different non-communicable diseases such as metabolic condition (e.g. obesity, metabolic syndrome, T2D, and NAFLD), celiac disease, rheumatic disease, and

cardiovascular disease. Therefore, we discussing this aspect by including also all the suggested references in the revised version of the text. Given that, we also updated the figure 1. Please see lines 98-103 of the revised manuscript and the new figure 1 of the revised text. More, certain pathogenic elements linking COVID-19 infection to these diseases might explain some aspects of COVID-19 –related disorders such as long COVID. Please see lines 103-109 of the revised text.

THE GUT-LUNG AXIS IN COVID-19 INFECTION - I think this section introduces several and important concepts and mechanisms, which should be discussed deeper. It sounds too general.

Answer: thank you for your comment. We more focused on the relationship of COVID-19 infection with the gut-lung axis and we also added a table summarizing the main aspects in this intriguing field. Please see lines 114-116 and the new Table 1 in the revised version of the manuscript.

INFANT MICROBIOTA AND COVID-19 INFECTION - "Compared to the colonization of Lactobacillus after a vaginal delivery,…a lower risk for multiple sclerosis in two case-control studies [35,36]". All this part sounds too general. I would suggest the authors to focus more on the COVID19- related dysbiosis in infants. A table summarizing the main aspects of the available studies so far is helpful.

Answer: thank you for your valuable comment. Following this, we focused in a more specific manner on the COVID19- related dysbiosis in infants by adding a table summarizing the current evidence at this age. Please see lines 214 and the new Table 3 in the revised text.

GUT MICROBIOTA CHANGES COVID-19 INDUCED: EVIDENCE FROM ADULTHOOD TO CHILDHOOD - Considering this specific section, the authors may place this section before the previous one, which may be then dedicated to discuss the potential mechanisms by which the virus may directly or indirectly affect the gut microbiota.

Answer: thank you for your suggestion. In the revised text, we replaced this section accordingly. Please see lines 139-209 of the revised text.

GUT MICROBIOTA, IMMUNE RESPONSE, AND VACCINE RESPONSE: IS THERE A LINK? - It is not clear if there are any available studies addressing this issue in children, since this mini-review aims at providing a pediatric perspective.

Answer: thank you for your comment. As observed in adults, pediatric data confirmed the influence of gut microbiota on the response to oral and parental vaccines. However, no studies examining this aspect in children receiving COVID-19 vaccine are currently available. As an insightful perspective, previous robust data on the modulation of gut microbiota on different vaccines in childhood might suggest a similar effect for COVID-19 vaccine. On this ground, further pediatric studies evaluating this tangled relationship are needed. Please see lines 297-302 of the revised text.

CONCLUSIONS - correct "occurence". Double check the manuscript for other grammar inconsistencies. - I would suggest avoiding the use of references in the conclusion: indeed, this section should briefly summarize authors' conclusions.

Answer: we corrected the previous typo and the other grammar inconsistencies throughout the entire manuscript. We also deleted references in the conclusions section. Please see lines 305-311 of the revised text.

REFERENCES - to be updated and revised according to the comments FIGURES - the resolution should be improved - please, confirm there are no copyright issues related to the use of images included in these figures.

Answer: we updated and revised accordingly. More, we improved the resolution of the figures. We confirm that there are no copyright issued for the images of both figures.

Reviewer #3: 1. Grammatical errors in the abstract and throughout the text. Please correct. This reviewer will strongly suggest to get the manuscript reviewed for grammatical errors before submitting to the journal. 2. “Of note, these findings have been supported by additional studies demonstrating remarkably low rates of vertical virus transmission and self-limited symptoms in most cases of horizontal transmission”. It would be good to explain vertical and horizontal virus transmission concept in the text. Overall, non-coherent and poorly written article. There are few factual errors too in the article. The text does not justify the title as well. This article cannot be accepted for publication at this current form.

Answer: we corrected grammatical errors throughout the entire text and explained vertical and horizontal virus transmission concept in the revised version of the text. Please see lines 75-76 of the revised text.

2 Editorial Office's comments

1) **Science Editor:** Please consider the reviewers' comment and careful revise the manuscript.
   Language Quality: Grade B (Minor language polishing)
   Scientific Quality: Grade C (Good)

   Answer: thank you for this valuable opportunity. We revised the manuscript according to reviewers’ comment and polished the English language throughout the manuscript.

2) **Company Editor-in-Chief:** I recommend the manuscript to be published in the World Journal of Clinical Cases. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/.

Answer: thank you for this valuable opportunity. We revised the manuscript accordingly.

ROUND 2

-In general, I think the authors addressed most of my previous comments in an acceptable way. - However, I think that table 1 should be further improved as regards the graphical aspects (too much test) and each schematic message should be precisely linked to a specific reference, in my opinion.

Answer: Thank you for your comment. We improved the table 1 accordingly. Specific references were also added to each schematic message. Please see the revised version of the Table 1.

- In terms of gut microbiome alterations/changes, I think the authors should include a subsection or actually discuss somewhere the potential effect of antibiotic therapies administered during the COVID-19 clinical course (see e.g. "SARS-CoV-2 and Prevotella spp.: friend or foe? A systematic literature review"; "Impact of azithromycin mass drug administration on the antibiotic-resistant gut microbiome in children: a randomized, controlled trial"; others), with particular consideration about the use (more or less appropriate and evidence-based supported) of macrolides, perhaps (see "Clinical evidence on the antiviral properties of macrolide antibiotics in the COVID-19 era and beyond")

Answer: thank you for your valuable suggestion. Based on the suggested references, we further improved evidence in this field and discussed this interesting aspect in the revised version of the manuscript. Please see lines 270-293 of the revised version of the manuscript.

- "Given the potential influence of microbiota composition on vaccine responses especially in children and its changes in different age groups [58], it could be also supposed a similar role in modulating immune responses to viral infections." This sentence is not clear enough.

Answer: following your comment, we clarified this sentence in the revised version of the text. Please see lines of the revised version of the manuscript. Please see lines 297-300 of the revised version of the text.