



PEER-REVIEW REPORT

Name of journal: *World Journal of Clinical Cases*

Manuscript NO: 76550

Title: Gut microbiota and COVID-19: An intriguing pediatric perspective

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05398051

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: India

Author's Country/Territory: Italy

Manuscript submission date: 2022-03-20

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-03-21 05:18

Reviewer performed review: 2022-03-21 05:48

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input checked="" type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input checked="" type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input checked="" type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



**Baishideng
Publishing
Group**

7041 Koll Center Parkway, Suite
160, Pleasanton, CA 94566, USA
Telephone: +1-925-399-1568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

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.



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Reviewer’s code: 03307766

Position: Editorial Board

Academic degree: MD, MSc, PhD

Professional title: Associate Professor, Director, Doctor

Reviewer’s Country/Territory: Kazakhstan

Author’s Country/Territory: Italy

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Reviewer chosen by: AI Technique

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Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
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SPECIFIC COMMENTS TO AUTHORS

INTRODUCTION - Overall, it provides an appropriate background with the main introductory concepts. 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. 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. 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. GUT MICROBIOTA CHANGES COVID-19 INDUCED: EVIDENCE FROM ADULTHOOD TO CHILDHOOD - Considering this specific section, the authors may place this section



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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.

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. CONCLUSIONS - correct "occurrence". 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. 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.



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Reviewer's code: 02440884

Position: Editorial Board

Academic degree: MD

Professional title: Chief Doctor, Full Professor, Professor, Senior Lecturer

Reviewer's Country/Territory: Germany

Author's Country/Territory: Italy

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
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Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

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



RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Reviewer's code: 03307766

Position: Editorial Board

Academic degree: MD, MSc, PhD

Professional title: Associate Professor, Director, Doctor

Reviewer's Country/Territory: Kazakhstan

Author's Country/Territory: Italy

Manuscript submission date: 2022-03-20

Reviewer chosen by: Jia-Ru Fan

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Reviewer performed review: 2022-06-15 14:57

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

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 text) and each schematic message should be precisely linked to a specific reference, in my opinion. - 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") - "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.