Peer-Review comments and authors responses

Reviewer 1

Recommendation: *Revisions Required*

This manuscript by Langenegger and co-authors describes a systematic review on the effects of probiotics on the prevention of respiratory tract infections in children and adolescents.

I appreciate the authors' efforts and dedication to address a topic that is interesting and relevant to the field. Nevertheless, I would like to suggest that they explain the gap in the literature more clearly and provide more context to show the novelty of their study.

Here are some constructive comments that I believe the authors could consider to help improve the quality of the paper, detailed section by section:

ABSTRACT: *It is well structured, but I would like to suggest the following:*

- *Make the gap in the literature more clear in the text (final part of Introduction subsection)*
- *Separate the Methods from the Results section;*
- *Include all the elements of the PICOS and the eligibility criteria in the Methods subsection;*
- *The conclusion is the take-home message, so I believe there is no need to repeat that 78% of the studies showed a decrease in the incidence of respiratory infections.*

***Response**:* As requested, the abstract and introduction was modified and gaps were added. The gap and issues with current research on this topic has been made more clear, as also the aim of the review. As requested, we have separated the Methods and Results sections, with the Results section reformulated for clarity. Additionally, the Methods section now includes a concise mention of the PICOS elements and eligibility criteria to provide a clearer overview of the study scope and selection process. We revised the conclusion to focus on the main take-home message, avoiding redundancy with the 78% mentioned in the results section.

INTRODUCTION: *Overall, the authors provided important general information regarding the burden of the disease (respiratory infections) and the rationale for the use of probiotics.*

Nevertheless, I suggest considering the following comments to improve this section:

- *In the first paragraph, I suggest adding more information and details on the burden of the condition (respiratory infections) in children, such as epidemiological data.*

Response: We consider this as a good point. Maybe we can include more epidemiological data such as “Worldwide, about 85–88 % of ARI episodes are Acute Upper Respiratory

Infections (AURI) while the remaining are Acute Lower Respiratory Infections (ALRI)". (1,2)

- *In the second paragraph, I suggest mentioning whether there are previous systematic reviews on the same topic. If that is the case, mention the summarized results and state how yours is different and is going to add to this body of evidence. If there are no previous systematic reviews, adding a sentence clarifying that would be important to show the novelty.*

Response: This is a very good observation because it is important to compare the results from other systematic reviews to our version. In this case, we suggest adding this information:

Recent research has demonstrated that the administration of probiotics can reduce the incidence and severity of RTIs in children. Ahrén et al. (2020) evaluated the effectiveness of L. plantarum HEAL9 and L. paracasei 8700:2, showing a significant reduction in the duration and severity of respiratory infections in children attending daycare centers. A study by Andaloro et al. (2019) reported that the use of S. salivarius 24SMB and S. oralis 89a reduced the recurrence of streptococcal pharyngotonsillitis in children. Also, a previous systematic review found that probiotics were better than placebo or no treatment in preventing acute URTIs. Zhao et al. (2022). However, this systematic review included people of all ages and excluded studies that did not specify Acute Respiratory Infections as "Upper".

Response: This evidence also contributes to our present review which suggests that probiotics may be useful for reducing the incidence of RTIs in healthy children and adolescents when compared to placebo or no intervention.

- *In the second paragraph, the sentence "Furthermore, the exact mechanisms by which probiotics exert their preventive effects on RTIs are not yet completely understood (Lei et al., 2020; Santamaria et al., 2019)" seems a little out of place here. My understanding is that the mini review is not trying to establish the mechanisms by which the probiotics work, but rather its effects in preventing RTIs. Therefore, I believe this sentence would be more suited for the first paragraph, where the authors provide general information about the probiotics.*

Response: Thanks for your great suggestion, but we consider that including this evidence at the beginning of the paragraph might also seem a little out of place because we initiate talking about Respiratory tract infections and then we introduce the evidence about probiotics.
After taking into consideration your comment and analyzing the fittest place for this comments, we consider that changing the sentence for the updated one could be better:

"Despite probiotics are live microorganisms that, when administered in adequate amounts, provide health benefits to the host, mainly through modulating the immune system and improving intestinal health (Hill et al., 2014), the exact mechanisms by which probiotics exert their preventive effects on RTIs are not yet completely understood (Lei et al., 2020; Santamaria et al., 2019)."

- *In the sentence " The aim of this mini-review is to investigate the effects of probiotic supplementation in preventing RTI in this specific population to reduce its occurrence", I suggest the authors describe what "this population" means, because it is not mentioned in this paragraph.*

Response: As requested, "this" was replaced with "pediatric and adolescents"

- *Since the presence of any severe chronic comorbidity was part of the exclusion criteria, I suggest considering further specifying the population as "healthy" children and adolescents.*

Response: Great comment. In this case, we should specify healthy pediatric and adolescents populations instead of healthy pediatric populations.

METHODS: *I suggest considering the following comments to improve this section:*

- *Please review the punctuation in "To automate this process, we utilized Covidence systematic review online tool, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org."*

  Response: As requested, a small adjustment which improves clarity has been made.
- *In "The study selection relies on the well-defined PICOS structured by the authors as well as the defined inclusion and exclusion criteria, mentioned above", consider changing for the past tense (relied).*
  Response: As requested, the verb "rely" was changed into past tense.

- *Define PICOS abbreviation at the first time it is mentioned (subsection Selection of studies and data extraction).*
  Response: As requested, PICOS abbreviation defined.

- *Have you applied any specific definitions for probiotics (intervention) and respiratory infection (outcome)?*
  Response: As requested, we added the definition of probiotics and respiratory tract infections with epidemiological data in the introduction section.
- *Has the group collected data on the setting of the participants (community? hospital? school? private practice?)*
  Response: We included population setting collection into the methods section as suggested.

- *In the eligibility criteria (Table 1), it would be important to outline all the types of upper and lower RTI considered to be included in the study.*

Response: As requested, the types of upper and lower RTI have been added to the eligibility criteria. They were based on a classification by Hothan et al. (2022).

- *Also, in the eligibility criteria (Table 1), there was no mention of the component "intervention" from the PICOS. Which was the definition of a probiotic?*
  Response: As requested the use of probiotics in the trial was included as eligibility criteria. Probiotics were defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" (Hill et al, 2014)

- *In the subsection Risk of bias assessment, Figures 2 and 3 are first mentioned, without Figure 1 being mentioned at that point. Usually, the Figures are numbered in order of appearance. I suggest you consider referencing Figures 2 and 3 only in Results.*

  Response: As requested, the changes were made in the text and the order of the figures. Figure 1 is now the PRISMA flowchart of the included studies in the systematic review. Figure 2 corresponds to the "traffic-light plot" of the Risk of bias assessment. Figure 3 is the weighted bar plot risk of bias assessment.

RESULTS: *This section could be improved in the following ways:*

- *In the subsection "Population", in the sentence "The mean age varied largely because different studies used different age ranges for the intervention (from 18 months to 16-year-olds)", I could not find a study in the table which included participants above 15 years of age. Were there any?*

  Response: Participants above the age of 15 years old were not included in our study. This sentence referred to articles whose age range used was broader. Nevertheless, to avoid inconsistencies with our tables and further confusion, this sentence was removed. Thank you for raising this concern.
- *In the subsection "Probiotic strains" review grammar and punctuation in the sentence: "Followed by Bifidobacterium.."*
  Response: As requested, the grammar and punctuation have been reviewed and corrected.
- *In the sentence "No safety reporting and consequently no adverse events were reported" (last paragraph of the subsection "Outcomes"), it is not clear if the papers did not assess safety issues at all, or if they assessed and there were no safety concerns.*
  Response: Thank you for your remark. As requested, a clear distinction was made between the studies that did not assess safety at all, and the ones that did assess it and their findings. For the 25 studies that did evaluate safety, no serious adverse events were reported. Consequently, no serious safety concerns were present with the treatments.
- *In the subsection "Main results", first paragraph, review punctuation in the sentence ", a summary can be found in Table 4."*
  Response: As requested, punctuation on the sentence was corrected.

- *In the subsection "Main results", first paragraph, please clarify the sentence "The rate of infections varied significantly among the included studies due to differences in the length of follow-up within the same treatment group". Does it mean that the follow up varied among participants in the same group in the same study?*
  Response: As requested, the sentence was clarified. "The rate of infections varied significantly among the included studies due to differences in the length of follow-up."
- *What were the results regarding the main settings of the population?*
  Response: We reviewed the data and added the settings to the paper.
- *In the subsection "Assessment of risk of bias in individual studies", in the sentence "Overall, the studies exhibited significant heterogeneity in terms of quality and the strains of probiotics used", there is no need to mention the variability in the strains of probiotics here, since it is not related to the methodological quality. Also, it may be worth mentioning here that less than half of the studies displayed a less risk of bias.*

  Response: We have revised the sentence and removed the reference to the variability in probiotic strains, as it does not belong to methodologic quality indeed. As it was suggested, we also have added a statement indicating that less than half of the studies displayed a lower risk of bias.

DISCUSSION: *I believe this section could be improved in the following ways:*

- *In the first paragraph, the sentence "Many studies evaluated the efficacy of various probiotics on the immune system, particularly on gastrointestinal and respiratory systems, with promising effects" does not seem important here.*

  Response: As requested, the sentence has been removed
- *In the last paragraph, consider changing the following sentence to past tense: "This study examines probiotics and RTIs in healthy children, particularly infants and preschool-aged ones".*
  Response: This sentence has been changed to past tense.
- *In the fifth paragraph, it is stated "The settings in which the children were observed were diverse, including daycare facilities, outpatient clinics, and home environments". Nevertheless, the setting of the participants was not mentioned in the Results section.*
  Response: Children's settings were put in results section.
- In the seventh paragraph, the text says "There were only 6 high-quality studies", but in Figure 2 there are 11 studies with low risk of bias. I suggest you review the text here.
  Response: Sentence was continued to include that only six studies obtained a low-risk bias across all domains.

- Also, in the seventh paragraph, in "Additionally, variations in study designs, strains, treatment plans, and the number of participants limited the evidence of effectiveness in this particular group", to what "in this particular group" refer to?

Response: This has been further specified as the “particular group” refers to the children population that was studied.

- I also suggest adding in the end of the seventh paragraph that, aside from adolescents, the results may not be generalizable to the population of children with comorbidities, who were excluded from the review.

Response: This suggestion was added to complement the end of the 9th paragraph.

CONCLUSION: *In this paragraph, I suggest changing the word reliability for validity.*

Response: As requested, this wording choice was updated to validity.

Reviewer 2

Recommendation: *Revisions Required*

This systematic review explores the effects of probiotic supplementation in preventing respiratory tract infections (RTIs) in children. The paper identifies the potential benefits of probiotics in reducing the incidence and severity of RTIs, as demonstrated by various studies. However, it also highlights the variability in study results, driven by differences in probiotic strains, doses, and populations. The review follows PRISMA guidelines, incorporating data from 32 studies, most of which are randomized controlled trials (RCTs). The results suggest that probiotics can be beneficial, though the evidence is not entirely consistent.

Areas for Improvement

INTRODUCTION: *The introduction briefly mentions that the mechanisms by which probiotics prevent RTIs are not well understood. A more detailed discussion of potential mechanisms, even speculative, would strengthen the paper.*

Response: This is indeed an excellent observation, which is why we decided to conduct this study. As we have seen in the literature, the use of probiotics has been suggested as a protective factor against respiratory tract infections, but the optimal strain and dose, as well as the mechanism by which they impact children's respiratory health, are not yet well described. This systematic review used only randomized controlled trials to assess the impact of probiotic supplementation on preventing respiratory tract infections in children. Of the 32 studies included, the strains used were identified, as well as the recommended dose in each study and its duration of use. This information was categorized to assume the effect size in comparison with each of them. Each study follows its specific design, which is why we need to consider the variability in the results.

METHODS:

- ***Study Selection Justification.*** *The rationale for selecting specific studies over others should be more explicit. For example, why were certain studies excluded at the full-text screening stage? This would enhance the transparency of your review process.*

  Response: As suggested, in this review of 32 articles, the article selection criteria were randomized clinical trials involving children aged 2 to 11 years without previously diagnosed chronic respiratory diseases, as established in the study. The article selection criteria were therefore to meet these criteria.

- **Heterogeneity of Studies:** *The variability among studies in terms of age groups, probiotic strains, and outcome measures is a significant limitation. Consider performing a subgroup analysis or meta-regression to explore these sources of heterogeneity.*

  Response: Once the study selection criteria were met, we analyzed the population in the age range indicated as pediatric. The use of probiotic strains was found to be most frequent and their dosage was determined. As suggested, we comment on the possibility of evaluating the subgroups in a secondary analysis to better define the impact of the intervention with probiotics in each of them.

DISCUSSION:

- *While you assessed the risk of bias, the results of this assessment are not fully integrated into the discussion. How did the risk of bias influence your findings? Highlighting this could provide a more nuanced interpretation of your results.*
  Response: As mentioned previously, regarding the heterogeneity of the studies and the wide range of the population analyzed, these factors may contribute to different measures of the impact of our intervention. Again, analyzing more homogeneous groups may make this impact more pronounced.
- ***Reporting of Safety Data:*** *The absence of safety reporting and adverse events in the included studies is concerning. If no adverse events were reported, it is crucial to discuss whether this reflects a true absence of risk or a gap in reporting*.
  Response: Thank you for highlighting the issue of adverse event reporting. The absence of safety data in the included studies is indeed concerning, as it raises the question of whether this reflects a true lack of risk or an underreporting of adverse events. As requested, We will add a discussion on this aspect, emphasizing that a lack of adverse event reports does not inherently confirm safety.

- ***Clarity in Outcome Reporting:*** *The outcome measures are diverse across studies, which makes direct comparisons challenging. Consider categorizing outcomes more systematically to facilitate comparison.*
  Response: As requested, the categories were presented more clearly in the outcomes section.

- ***Language and Style:*** *There are minor language and stylistic issues that need attention, such as the consistency in terminology (e.g., RTIs vs. respiratory infections) and clarity in some sections of the results.*

  Response: Thank you for highlighting these language and stylistic issues. We have reviewed and standardized the terminology to ensure consistency. Additionally, we have revised specific sections in the results to improve clarity.

Reviewer 3
Recommendation: *Revisions Required*

Dear Dr. Sandes and Group 12,

Congratulations on your work titled "The Effect of Probiotics on Prevention of Respiratory Tract Infections in Children and Adolescents: A Systematic Review". It was a pleasure to read your manuscript and contribute to improving it.

Response: Thank you so much for the comment, we really appreciate it.

Your manuscript is scientifically interesting and well-written. In my point of view, it can be considered with some adjustments for publication in the PPCR journal.

The only major issue I would mention is that you need to clearly address what is new in your paper and how it is different from previous studies. In a quick look at Pubmed, we can find other reviews about probiotics for the prevention of respiratory infections in children, some of them with metanalysis: https://pubmed.ncbi.nlm.nih.gov/?term=probiotics+respiratory+infections&filter=pubt.meta-analysis&filter=age.allchild You should present what is innovative in your work for the readers, maybe you included more databases, maybe you are the only one looking to randomized controlled trials, for example. Please, check the previous reviews and mention on your introduction what differentiate your work from them.

Response: Our review was solely based on randomized controlled trials, to obtain high-quality results, with the aim of being able to define guidelines and recommendations for the future, which do not exist until now. This strategy was added in the 'Introduction' section.

TITLE: *Please, check on lines 102-103 the study type. You called your review a "systematic review" in your title, and here it is called a "mini-review". Check it and choose which denomination is more appropriate for your work, based on your methods.*

Response: We have addressed the terminology regarding "systematic review" versus "mini-review." Given that we followed systematic review protocols, we believe "systematic review" is more accurate indeed.

ABSTRACT: *Your abstract is well-structured and clean. As Prof. Fregni has already mentioned, I missed some information on your results about better strain or dosage schedules for the prevention of RTI recurrence.*

Response: As requested, the most frequent genus and doses were added in the abstract section.

INTRODUCTION: *The Introduction section structure is adequate. You pointed out the background and what is known about this topic, clearly mentioned the existent gap, and how you would address it.*

Response: Thank you for the comment.

METHODS: *Your Methods section is well-written and presents how your study was done. There are some points that I would like to mention that you could improve it:*

- *Although it is about writing style, eligibility criteria should be presented as text, nor in a table format. I would do the same for your PICOS.*

  Response: Thank you for the suggestion. We have revised the presentation of the eligibility criteria and the PICOS breakdown, now integrating them within the text rather than in table format, as recommended. The PICOS and eligibility criteria tables are still available as supplemental materials.

- *You should mention why you chose January 1st, 2000, as the initial date for this review. Do you think including previous results could have changed your results? It would be to discuss it in your Discussion section.*
  Response: There was no initial date limit for the review, we removed this information.

- *Usually, Methods should mention who was responsible for each step of the review process (screening and data extraction), citing the initials of the author's names. If all the authors were involved in this process, cite it properly.*
  Response: We included the information that all authors were involved in the screening and data extraction
- *Figures 2 and 3 were cited in the text before Figure 1. Maybe you forgot to cite Figure 1 in the line 110 context. Please check it or rename the Figures in the order it is cited.*

  Response: We have revised the manuscript and corrected the order of the figures, now citing Figure 1 in the subsection “Description of the studies” in the results, before referring to Figures 2 and 3. This ensures consistency in the flow of the text

RESULTS: *The results section is complete and accurate, but some points could improve it even more:*

- *You should include a table summarizing the studies you included. This table is Table is Table 4, but it should be presented before Table 3 (summary of the strains). In this new table, you should include information about the study design (such as RCT or cluster RCT, blinding), details on type of probiotic used and its dose etc. This information was presented in the text, but as a table would be better. This table should include which outcome was assessed in each study, but not the result of the outcome itself.*
  Response: Thank you for your valuable suggestion. Given our current deadline, it's challenging to construct a detailed summary table with all study design elements and specific details. As we mentioned to another reviewer, we are likely to conduct a meta-analysis in the future, which will certainly include all of this information.

- *In your Abstract you mention that these 32 studies included 8,938 participants. However, I could not find this information about the sample included in the review in your Results.*
  Response: We included the information in the results section, as suggested, and corrected the value.
- *Another table is missing, summarizing the results of the intervention that you found in each study. In Table 4 you cited the results in a categorical way (positive or negative study on RTI recurrence), but it does not allow us to understand the effect size of the intervention. For example, reducing RTI by 5% is totally different from 40%, although both results could be statistically significant.*
  Response: As mentioned in our previous response, due to the timeline, it's not possible to include this table at this stage. However, this excellent suggestion will certainly be incorporated into our future meta-analysis.
- *In the line 280, Figure 2 should be cited together with Figure 3 about bias assessment.*

  Response: We have updated the manuscript to cite Figure 2 together with Figure 3 in the context of the bias assessment, as recommended. This ensures that both figures are appropriately referenced in relation to the bias assessment discussion.

DISCUSSION: *The Discussion section is well-written and structured. You cited some previous reviews here (a major point I cited above), but it is not clear for me what is different in your paper. You discussed and pointed out the limitations of your review, mainly related to the heterogeneity and quality of the studies you included. However, at the end of this section, where generally we talk about future studies that are needed, you mention that "The large sample size of the study provides valuable guidance to healthcare providers in establishing standards, contributing to policy discussions, and assisting in cost-effectiveness analyses." Please, think about if there is sufficient evidence to change the standard of care and introduce probiotics for the prevention of RTI – primarily about its efficacy but also about the cost-effectiveness of this intervention. Maybe, you could rephrase this sentence and mention what type of studies you think should be done in the future.*

Response: Thank you for your comment. We revised and removed this sentence. Additionally we provided a clearer emphasis on the limitations posed by heterogeneity in outcome measurements.

CONCLUSION: *Your Conclusion section is longer than it should be in my opinion. It clearly presented that the intervention "may be useful" in the outcome, but the sentences in the sequence could be summarized more shortly and objectively. The sentence "Further research should aim…" does not belong to the conclusion and should be presented in the Discussion (as I mentioned above). Again, in the Conclusion it is called "systematic review".*

Response: Thank you for your comment, the conclusion was modified to fit those essential key points.

You did a great job in this paper summarizing the findings of 32 studies of probiotics on RTI recurrence. I recognize your efforts and congratulate your group for this work. The points I mention above aim to improve your work and make it even more interesting for readers. As a final comment, I would like to suggest that you should consider doing a metanalysis of these findings. It would be interesting to understand the effect of this intervention on the sample you reviewed, although we can anticipate higher heterogeneity. I would also suggest including a sensitivity analysis with only high-quality studies.

If you can address these points, in my opinion, your work will be ready for publication in the PPCR Journal.

All the best,

The reviewer.

Response: Currently we will keep this paper as a descriptive systematic review, because due to the heterogeneity we are not sure we are able to perform a correct meta-analysis. However, we agree on the importance of meta-analysis and we will keep the suggestion in mind, to possibly perform a meta-analysis in the future. Thank you for your suggestion.

Reviewer 4
Recommendation: Resubmit for Review

The subject is very interesting. The introduction and methods are clear and well written. However, there are some issues that should be addressed particularly in the Results and Discussion sections.

Major issues

The study involves a systematic review on the effect of various probiotic strains and administration schedules on RTIs in children and adolescents. However, previous systematic reviews and meta-analysis with the same topic have been published, so it is important to emphasize what are the differences between this study and the previous ones, in other words, what makes this study original to justify the publication.

Response: We addressed this comments in blue, previously requested by Reviewer 3

RESULTS:

- The authors state that: "Identifying optimal strains and doses of probiotics could further improve the impact on RTIs.", which is true, however the results do not report which are the most effective strains and regimens in the RCT. Table 4 should include the information on the strain, so we could understand which ones showed favorable results or not.
  Response: We have revised Table 4 to include specific probiotic strains and their dosages, along with their effectiveness in reducing RTIs, directly addressing your concerns about identifying the most effective treatments.

- Previous studies and systematic reviews compare the results using measures of association such as RR. The description of the outcome with no measure of association, frequency or other statistic, only defining that there was a decrease or not in RTIs is not robust enough to "guide to healthcare providers in establishing standards, contributing to policy discussions" as stated in the last paragraph of the discussion.
  Response: We revised this statement and deleted it from the text. The limitations section was reinforced regarding this outcomes' measurement heterogeneity.

DISCUSSION:

- The discussion should include comparison of the findings of the present study with previous ones. Many paragraphs in the discussion are just literature review with no comparison with the present study.

Response: We added several paragraphs comparing our results to findings from other systematic reviews.

- The authors conclude that: “Our results had a large total sample size, evaluated different strains and presentations of probiotics, recruited children from different settings and age ranges, and evaluated both upper and lower RTIs.”, however the results and discussion do not include an analysis of the outcome according to the different strains and presentations.

  Response: Thank you for pointing out the omission. We acknowledge that our initial analysis did not sufficiently differentiate the outcomes by probiotic strains and presentations. We did some modifications in the discussion and results section to include these details.

Minor issues

METHODS:

- *In the section of Intervention Duration and follow-up period: Instead of mean and median it would be better to choose 1 of them and report a variability statistic, such as SD or IQR, as appropriate.*
  Response: Thank you for your suggestion. The corresponding IQR was added and the mean was deleted.
- *In the section Administration route and formulas: remove the apostrophe of “probiotics’ administration” and substitute for probiotic administration.*
  Response: As requested, the apostrophe was reviewed and corrected.
- *In probiotic dose “change “the hundred thousands” for “a hundred thousand”.*
  Response: The sentence was revised and changed to a slightly different version: “ranged from hundreds of thousands (10^5) to over tens of billions (10^{10})”
- *In outcomes : « **Five** (15.63%) studies used questionnaires completed by proxies (...), **two** (6.25%) studies relied solely on proxy reports (...), and **seven** (21.8%) studies employed a combination of these methods (...) ». The number os studies completed by proxies does not match. Which combination of methods ? Please revise.*
  Response: We have reviewed the data and revised the section to ensure accurate reporting of the number of studies using proxies and combination of methods.

RESULTS: *“Italy being the country with the most number of studies”, Substitute “most” for “greatest”.*

Response: As requested, the term has been replaced for “greatest”.

- *In Population section: “Population included individuals aged from 1 month **to 15** years old. The mean age varied largely because different studies used different age ranges for the intervention (from 18 months **to 16-year-olds**)”. Please use the same age as inclusion criteria: 15 or 16?.*

Response: We addressed these comments in red, previously requested by Reviewer 1

- *In Population section: "Among other demographic characteristics, a balanced distribution was also identified regarding ethnicity and weight" it is not clear if this sentence refers to a specific study or to the population included in this review. If this is the case, how did you assess it as there are no tables/information in the text to support?*
  Response: Thanks for pointing out this issue, we really did not have enough information from the studies to make that statement. It was removed from the text.
- In main results : « studies with a shorter duration of 12 weeks ". Does the author mean: "a duration of 12 weeks or less"?
  Response: The sentence was revised and adjusted to: "Most studies lasting 12 weeks or less"

DISCUSSION: *"significant reduction in URTI". URTI was not abbreviated before: upper RTIs?*

Response: Thank you for this comment. The text has been amended to explain and include this abbreviation. URTI was used for "upper respiratory tract infection"

CONCLUSION: *"Our systematic review suggests that probiotics may be useful for reducing the incidence of RTIs". Be more specific regarding the best strains and dosing in the studies.*

Response: We added the most frequently used strains and doses, which might serve as a base for further research, in the conclusion.

Reviewer 5
Comment:

Thank you for considering me again as a reviewer for the PPCR Journal. It was my pleasure to read and comment on "The Effect of Probiotics on Prevention of Respiratory Tract Infections in Children and Adolescents: A Systematic Review".
Langenegger et al. performed a systematic review of the literature about the effect of probiotics use and the prevention of respiratory tract infections in children. This is an interesting topic of study because the efficacy of this intervention is not established yet. The manuscript is well-written and structured, and I recommend it for publication after some adjustments.
Response: Thank You for the comment.

- *My major concern is related to its innovation. In a quick look at PubMed, you will find other reviews on the same topic, some of them with metanalysis of the results. I recognize the students' efforts and maybe it can be an update of previous reviews, or it can have a different study question, for example only including RCTs. I asked the authors to check it and properly discuss it in the manuscript.*

Response: We addressed these comments in blue, previously requested by Reviewer 3

RESULTS: *In my comments for the authors, I pointed out other issues that I believe can improve their work. For example, they could better organize the results section in a table format and summarize their text. As this section is long, some important information is missing, such as the total sample included in the review (cited in the Abstract) and the effect size of the intervention – they only cite each study as positive or negative.*
Response: Thank you for your necessary comment. We modified the text and included the total sample number correctly mentioned in the results section. Articles from the systematic review are organized in our reviewed version of table 4.

METHODS: *As a final comment, I suggested them to consider doing a metanalysis of these results. It would be a way to differentiate this work from previous studies, especially if they perform some sensitivity analysis including only high-quality studies they reviewed.*

Response: Currently we will keep this paper as a descriptive systematic review, because due to the heterogeneity we are not sure we are able to perform a correct meta-analysis. However, we agree on the importance of meta-analysis, and we will keep the suggestion in mind, to possibly perform a meta-analysis in the future. Thank you for your suggestion.