



**Baishideng  
Publishing  
Group**

7901 Stoneridge Drive, Suite 501,  
Pleasanton, CA 94588, USA  
**Telephone:** +1-925-223-8242  
**Fax:** +1-925-223-8243  
**E-mail:** bpgoffice@wjgnet.com  
**https://**www.wjgnet.com

## PEER-REVIEW REPORT

**Reviewer's code:** 00503623

### COMMENTS TO AUTHORS

This manuscript presents the literature review of the effectiveness of probiotic mono-therapy on Hp eradication. Based on the data collected from eleven studies, the conclusion is that probiotic-induced reduction rate in Hp eradication varied from 12 to 16%, depending upon the probiotic used. Although the data include the relatively low number of studies, it is apparent that modulation of gastric microbiota by the use of probiotics exerts only limited effect on Hp eradication. The paper is well presented and written in relatively clear language. There are only some minor problems with sentence construction (i.e., Despite several evidences in literature have demonstrated...).

**We thank the reviewer for the positive reception of our article. In the revised version of the manuscript a linguistic revision was performed by a native speaker.**

**Reviewer's code:** 02840182

### COMMENTS TO AUTHORS

Authors performed a systematic review to define probiotic monotherapy effect on H. pylori status. We already know that probiotics alone do not significantly improve the H. pylori eradication rates. Authors evaluated eleven studies. The specified eradication rate is 12% to 16% according to the kinds of probiotics. It is a well written manuscript. I believe that it will make a good contribution to the literature for the effect of probiotics alone on the eradication rates of H. pylori.

**We thank the reviewer for the kind appreciation of our article.**

**Reviewer's code:** 00052339

### COMMENTS TO AUTHORS

PROBIOTIC MONOTHERAPY AND HELICOBACTER PYLORI ERADICATION: A SYSTEMATIC REVIEW WITH POOLED-DATA ANALYSIS Giuseppe Losurdo et al. This manuscript showed the meta-analysis on the utility of probiotics for eradication of HP. The probiotics may be very useful for children with HP infection. The paper

adopted for this analysis is so different, especially on species of probiotics, duration of treatment and time of determination of HP negative. Hence, it is very difficult to obtain the conclusion about the effects of probiotics on HP eradication from these paper.#1 The determination of HP negative after eradication of HP should be performed longer than 8 weeks after finishing the medication such as penicillin, macrolide and proton pump inhibitor. In this paper, the time on determination of HP negative was different from just one day to 8 weeks after finishing the treatment. Thus, the efficacy of probiotics for HP eradication could not be determined.#2 The duration of taking probiotics was also different from 10 days to 12 months. It is so difficult compare the results from these paper. To obtain the conclusion, the author should fix the duration of taking probiotics and the time for HP negative after finishing the treatment at least.

We agree that the criticisms raised by the reviewer may be a problem for the correct reading of our results. Indeed, the different duration time of the therapy and the control of eradication performed at different endpoints could represent the main difficulty in interpreting the data of the present study. On the other hand, we have already highlighted that these aspects were the most important source of heterogeneity and largely discussed about this topic. Additionally, the meta-analytical method allows to quantify the heterogeneity by the application of a specific system (random effect model), which has the aim to minimize this issue and is well supported by the literature on the topic (reference 23). Its use in our analysis is clearly described in the Method section.

**Reviewer's code:** 02444931

## **COMMENTS TO AUTHORS**

1、 The effects of probiotic monotherapy on H. pylori eradication were studied in this paper which evaluating on treatments of only three species of probiotics including Lactobacillus, Bifidobacterium and Saccharomyces in the 11 articles . It may be more completed when adding other more probiotics such us Gram-positive cocci including Streptococcus faecalis and Lactococcus.

After literature search, we did not find any eligible paper including studies investigating Lactococcus or Streptococcus faecalis. However, as reported in Table 1, in an eligible study (Rosania et al), a multistrain formulation with Streptococcus termophilus was used.

2、 The search term ([Helicobacter pylori] AND [probiotic\* OR lactobacilli OR bifidobacteria OR saccharomyces OR treatment OR eradication OR breath test]) may not

be comprehensive enough which taking on only 11 articles that may lead to insufficient results. It will improving the recall rate when adding terms such as Bacillus Acidi Lactici which also expressing Lactobacillus or other acronyms like H. pylori and so on.

We modified the search as follows: ([Helicobacter pylori OR H. pylori] AND [probiotic\* OR lactobacil\* OR bifidobacteria OR saccharomyces OR Bacillus OR treatment OR eradication OR breath test]). Consequently, we modified Figure 1, however, this new search strategy did not allow obtaining further eligible articles.

3、The exclusion criteria “used probiotics in combination to antibiotics, while co-administration of other molecules such as proton pump inhibitors was not considered as an exclusion criterion” can also include more factors such as the combination of surgical and other treatment methods to make the study more targeted and rigorous.

In the revised manuscript we indicated that major digestive surgery was a supplemental exclusion criterion. However, this did not change the list of eligible studies.

4、The factors taken into account when extracting data information may not be comprehensive enough. In Table 1 for instance, factors such as smoking and drinking that affect H. pylori eradication could be added, and further subgroup analysis could be in progress.

We reviewed all the articles included in our meta-analysis and, unfortunately, none of them reported any data about smoking habits neither alcohol assumption. Therefore we were unable to perform a sub-analysis. We would like to underline that most of studies were conducted in pediatric populations, therefore we may assume that in such cases patients did not consume alcohol nor cigarettes.

5、The content of Table 1 may not be good overall because of the difference from sample sizes of each disparate articles taken on, which may result in a greater bias since it weighted. Statistics could be more accuracy to add a "sample size" column for each article.

We should like to highlight that a column reporting sample size for each article was already present in our paper. In detail, this value was reported in the last column entitled “eradication rate”. Indeed, we expressed the eradication rate in n/N form, where the N represents the sample size. Finally, we would like to underline that a “weighting” of the eradication rate according to the sample size was performed by using the inverse variance method. Therefore the imaginable “bias” was minimized.

6、There is a comparisons between subgroups since Figure 2, but the previous heterogeneity analysis might be not convincing that there are no specific statistical

results or graphs that can be supplemented on the analysis of heterogeneity.

The method of sub-analysis and analysis of heterogeneity was made according to the standard method of meta-analysis. Moreover, the paper was co-authored by an internationally known biostatistician (G. Leandro), who accurately revised and confirmed the fairness of the analysis.

7、 All the figures drawing from chart statistics are only Forest plots, which can be added to commonly used Funnel plots and other types of charts to make the results look more abundant.

Funnel plot may not be applied when the inverse variance method is used. On the contrary, we could include a funnel plot for the figure 4 in agreement with the Egger's test. In this case, despite the Egger's test was suggestive of publication bias ( $p=0.02$ ), the low number of included studies and the presence of 0% eradication rates (which are void for the test) imply that the test has a low statistical power, therefore the possibility of bias is questionable.

8、 Some parts of the reference format are not uniform.

We checked the list of references and made appropriate corrections.

9、 English expression may not be appropriate. 1)、 The use of multiple Conjunctions in the full text may be inappropriate. Such that "multistrain" could be amended to "multi-strain", "multicentre" could be amended to "multi-centre". 2)、 Grammatical errors and Single and plural usage errors. For example, the last sentence of paragraph 5 in Page 4 "For these reason, it is hypothesizable that probiotics may exert a direct inhibitory effect on H. pylori growth." should be changed to "For these reasons, it is hypothesized that ..." 3)、 Inappropriate use of prepositions. For example, ① multiple "effects in" could be amended to "effect on" in the whole paper. ② The last sentence of the first paragraphe in Page 4 "Until now, meta-analyses have investigated probiotic effects on H. pylori only in association to antibiotics." could be changed to "..... in association with....." ③ The last sentence of the paragraphe 3 in Page 5 "A third reviewer (GLE) came to a decision about any disagreements." could be amended to ".....decision on....." ④ multiple " details about " could be changed to "details of" in the whole test..

We performed the changes proposed by the reviewer. Moreover, a linguistic correction by an English speaker was performed to improve the quality of the manuscript.