Reviewer's report

Title: Probiotics for infantile colic: A Systematic Review

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Reviewer: H. Szajewska

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The review by Anabrees et al. evaluated the efficacy of probiotic supplementation in the reduction of crying time and successful treatment of infantile colic. The Authors concluded that the use of Lactobacillus reuteri may be effective as a treatment strategy for crying in exclusively breastfed infants with colic.

MAJOR COMPULSORY REVISION

This review was generally well-conducted. However, data entry for one of the outcomes (overall response rate) was incorrect. Re-analysis is needed. For details, see comment #17.

ABSTRACT

1. Background. In the objective, please define the population of interest (infants).
2. Results. Please provide the strain identification.
3. Results. Please add that all infant were breastfed.
4. Results. Mean difference. Please do not show more than one decimal place.
5. Results. The authors stated that 'successful treatment of infantile colic was significantly increased with a relative risk (RR) of 0.06; 95% CI (0.01, 0.25)'. First, this result is not correct due to inadequate data entry (see my comment under the Results). Second, even if it is correct, an RR of less than 1 shows the number of times LESS likely an event (in this case successful treatment) is likely to happen in one group compared with another. Thus, it should have been interpreted as the reduced efficacy, not increased efficacy....
6. Conclusions. Lactobacillus reuteri. Please specify the strain (here and throughout the manuscript).
7. Conclusions. The statement 'the evidence supporting use for the PREVENTION of infant colic or crying in formula-fed infants remains unresolved' is true, but it does not come from the Results. It is redundant. If the authors want to leave it, please consider changing 'PREVENTION' to 'TREATMENT'.
8. Conclusions. Last but not least, the conclusions have to be rewritten when the data are re-analyzed.

METHODS

9. Search strategy. As suggested in PRISMA, please present full electronic search strategy for at least one database (perhaps as the supplementary
10. Search strategy. Did the authors search the registries of clinical trials? There are some on-going studies on the use of probiotics and it would be useful for the readers to be aware of them.

11. Data extraction. The authors stated that the principal investigator of the primary study was contacted for further information and clarification. Please provide reference and whether the contact was successful.

12. Primary and secondary outcomes. Please clearly state what were the predefined outcomes for this systematic review.

13. Data synthesis. Please provide the rational for using a fixed effect model.

14. Data synthesis. Review Manager 5.0 software. Please provide the proper citation (as recommended at the RevMan website).

RESULTS

15. Please provide the strain characteristics (identification). The readers might not be aware that one of the strains used in the included trials (L. reuteri ATCC 55730) was found to carry resistance traits for some antibiotics and was replaced by L. reuteri DSM 17938. This needs to be clarified and discussed in the Discussion.

16. Effect of probiotics on crying time. This analysis is based on pooling data from 2 RCTs which used different interventions in the control groups (i.e. placebo or simethicone). In my opinion, the studies that compared L. reuteri with placebo and the studies that compared L. reuteri with simethicone should be evaluated separately.

17. Effect of probiotics on overall response rate. Figure 4. I have re-checked the original studies by Savino (2010) and Szajewska (2013). In the Savino et al. study, responders (50% reduction in crying time from baseline) were significantly higher in the L. reuteri group versus placebo group on days 7 [20 vs 8; (not 5 vs 13)], on day 14 [24 vs 13; (not 1 versus 8)], and on day 21 [24 vs 15; (not 1 versus 6)]. In the study by Szajewska et al. study, the treatment success on day 7 (6 vs 0; not 34 vs 40), on day 14 (30 vs 7; not 10 vs 33), on day 21 (39 vs 15; not 1 vs 25), etc. Please re-analyse the data.

DISCUSSION

18. First paragraph. Instead of 'probiotics' please clearly define the strain.

19. The authors stated that none of the include studies reported any adverse side effects; however, side effects have not been described in the Results. Please clarify.

20. 24. As this is the reference, the parenthesis is needed.

21. Discussion. The results of the study by Song et al. (reference 32) have been presented at some meetings. As the results are negative perhaps it is worth to wait until the study is published, and only then to perform this systematic review. Please consider.
TABLE 1.
22. Please provide the definition of infantile colic used in the included trials.
23. Information on the study type (randomized, double or open) is redundant as it is included in Table 2 (The quality and risk of bias).
24. Please provide the duration of intervention in the study by Savino et al. 2007.
25. Please provide the dose of L reuteri in the study by Savino 2010 and Szajewska 2013.
26. In principle, the authors aimed to include trials in infants less than 4 months of age (as per the Methods section). One of the study included infants less than 5 months. It is not a major problem, but should be discussed somewhere.

TABLE 2 AND FIGURE 2.
28. Both provide the same information on the risk of bias. One is redundant.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I have participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for Arla, Biogaia, Biocodex, Danone, Dicofarm, Nestle, Nestle Nutrition Institute, Nutricia, and Mead Johnson.