

## PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Probiotics for the prevention of surgical necrotizing enterocolitis: systematic review and meta-analysis
<b>AUTHORS</b>	Eaton, Simon; Rees, Clare; Hall, Nigel; Fleming, Paul

### VERSION 1 - REVIEW

<b>REVIEWER</b>	McGuire, William University of York, UK Competing interests None
<b>REVIEW RETURNED</b>	22-May-2017

<b>GENERAL COMMENTS</b>	<p>In general, this is a well-conducted and presented study and I have only a few methodological comments for the editors and authors to consider:</p> <ol style="list-style-type: none"><li>1. Was a protocol prepared, and was the review registered on Prospero?</li><li>2. Please complete a PRISMA form.</li><li>3. The first mention of "surgical NEC" could describe, for the non-specialist, what this means- why is it different to "non-surgical NEC", is the difference due to specific findings (e.g. perforation) or to clinical preference (e.g. some clinicians favour surgery rather than medical management).</li><li>4. The electronic search is very limited (only one database, very few search terms, English only) and could be improved by consultation with an information specialist.</li><li>5. How was small study or other publication bias assessed?</li></ol> <p>Bottom line- this is interesting and important, but methodologically falls short of e.g. standards expected by the Cochrane collaboration.</p>
-------------------------	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

<b>REVIEWER</b>	Mihatsch, Walter A. Helios Hospital Pforzheim - Dept. of Pediatrics Pforzheim and Ulm University - Dept. of Pediatrics Ulm Germany Competing interests: None
<b>REVIEW RETURNED</b>	24-May-2017

<b>GENERAL COMMENTS</b>	<p>the present systematic review on the effect of probiotics in preterm infants on prevention of surgical NEC is a very important paper.</p> <p>Prevention of surgical NEC is the important issue in neonatology. The paper is very well written.</p> <p>The reviewer would like to add a few comments.</p> <ol style="list-style-type: none"><li>1. The paper should focus on bacterial probiotics only. It has not been shown that <i>S. boulardii</i> has any effect on NEC (4 RCTs).</li></ol>
-------------------------	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

	<p>Meta-analyzing bifidobacteria and lactobacilli together is certainly a point of discussion. People argue about infant stool microbiota. However, fungi should be excluded or analyzed separately.</p> <p>2. The reader will not accept the reason for exclusion of ref 43.</p> <p>3. Please use “no significant heterogeneity” instead of “homogeneous”.</p> <p>4. With regard to the discussion: In addition, please comment on the difficulties defining NEC stage 2. Frequently it may be difficult to exactly define “pneumatosis intestinalis” and some of the RCTs did not have independent radiologists.</p> <p>5. Conclusion / last sentence: Please add: “reporting of surgical NEC, SIP, and any abdominal surgery”</p> <p>6. Conclusion / end of last sentence: The reviewer would suggest to finish the final sentence with “ ..... assess the benefits of probiotic interventions.” -</p>
--	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

## VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1. Was a protocol prepared, and was the review registered on Prospero?

The study was initiated and the literature review commenced without writing a formal protocol, with the basic methodology agreed by e-mail between the authors. The initial aim was to complete the review and present to the British Association of Paediatric Surgeons meeting in 2016, with a deadline for abstract submission of Jan 2016. The senior author went to register the review with PROSPERO after this deadline, but read the guidance and decided that to retrospectively register after data extraction was complete would be dishonest. We have added a statement to the methods regarding the fact that that a protocol was not prepared.

2. Please complete a PRISMA form.

A PRISMA Form is now included.

3. The first mention of "surgical NEC" could describe, for the non-specialist, what this means- why is it different to "non-surgical NEC", is the difference due to specific findings (e.g. perforation) or to clinical preference (e.g. some clinicians favour surgery rather than medical management).

We have now added more information on this aspect to the introduction.

4. The electronic search is very limited (only one database, very few search terms, English only).

We have expanded the electronic search (databases, search terms, language) and one further paper was included, and several more screened or excluded at the full text level, as a result.

5. How was small study or other publication bias assessed?

We have now included funnel plots in Figure 3, and risk of bias in individual studies is indicated in supplementary Table 1.

Reviewer: 2

1. The paper should focus on bacterial probiotics only. It has not been shown that *S. boulardii* has any effect on NEC (4 RCTs). Meta-analyzing bifidobacteria and lactobacilli together is certainly a point of

discussion. People argue about infant stool microbiota. However, fungi should be excluded or analyzed separately.

We have repeated the meta-analyses excluding the *Saccharomyces*, and added a section to the results on this, and expanded the discussion on different products.

2. The reader will not accept the reason for exclusion of ref 43.

We have now formally included reference 43 and a further reference identified from the extended literature search, in which there was also a zero incidence of NEC. This has not changed the results of the meta-analysis, as there was a zero incidence of NEC in either arm on both studies so neither study contributes to the overall relative risk.

3. Please use “no significant heterogeneity” instead of “homogeneous”.

We agree with the reviewer that this wording is better and have changed the descriptions in the results to the wording ‘no evidence for significant heterogeneity’.

4. With regard to the discussion: In addition, please comment on the difficulties defining NEC stage 2. Frequently it may be difficult to exactly define “pneumatosis intestinalis” and some of the RCTs did not have independent radiologists.

We completely agree with the reviewer and have added a sentence to the discussion on this point.

5. Conclusion / last sentence: Please add: “reporting of surgical NEC, SIP, and any abdominal surgery”

We agree with the reviewer that reporting of any abdominal surgery is important and have amended this sentence.

6. Conclusion / end of last sentence: The reviewer would suggest to finish the final sentence with “..... assess the benefits of probiotic interventions.” –

We have made the suggested change.