Author's response to reviews

Title: A Systematic Review and Meta-Analysis: Probiotics in the treatment of Irritable Bowel Syndrome

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Version: 3 Date: 2 October 2008

Author's response to reviews: see over
Reviewer's report
Title: A Systematic Review and Meta-Analysis: Probiotics in the treatment of Irritable Bowel Syndrome
Version: 2 Date: 21 June 2008
Reviewer: Sue Wilson

Reviewer's report:
This is a well conducted systematic review which is topical and will be of wide interest. The limitations are appropriately acknowledged.

Major point:
Page 5: “Non English language publications were excluded” – why was this done? Are there relevant publications in other languages? What potential bias has the exclusion of these studies generated?

We discussed this in the limitations. The reason is the resources and the practicality of undertaking such a review with no restrictions. We have added to the discussion this may be lead to an over representation of positive results.

‘One of the limitations of this review is exclusion of non-English language publications which may lead to an over-representation of positive studies.’

Minor points:
Page 4: “where possible, lead researchers were contacted for further details” – does this mean all were contacted but only some responded?

We contacted all authors by e-mail when additional information was required. We did not highlight those that did not respond as it is not normal practice in the conduct of a systematic review. Highlighting those that did not respond could have implications in how these trials were viewed. This difference has not been shown to produce a major bias in terms of the results.

Page 7: It would be useful if the reasons for the 8 exclusions was added
We agree with the reviewer and have added to the text page 6 and start of 7:

‘On further analysis of retrieved articles, 8 trials were excluded for being non-controlled studies. Therefore, a total of 14 articles met the inclusion criteria (17-30) (fig. 1).’

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
Competing interests: have recently completed a trial of probiotics for IBS
Reviewer's report

Title: A Systematic Review and Meta-Analysis: Probiotics in the treatment of Irritable Bowel Syndrome
Version: 2 Date: 12 June 2008
Reviewer: Lisa Conboy

Reviewer's report:
This article is important and well-accomplished. I have only a few minor comments.
1-In the abstract, "Longer terms trials are recommended" the "L" should not be a capital letter.
   Changed now read as: intermittent longer term trials are recommended.

2-In Literature search section please tell the reader when the searching was done; months and year.
   We have added the following part to the sentence at the start of the Literature search section:

3-Page 5 first paragraph offers Bittner as the example of an excluded study. Please tell the reader an example of how studies may have not treated the groups equally and then end sentence with Bittner citation.
   We have added the following sentence: For example in Bittner’s study (15) a two week randomised placebo control trial patients in the intervention group received a pro-biotic plus a pre-biotic.

4-In the limitations mention why the readers were not blinded to the citation information and what bias might be introduced because of this.
   The practicalities of blinding the people doing the data-extraction means that this is very difficult, is not done very often and has not shown to produce a bias in the estimates.

Level of interest: An article of outstanding merit and interest in its field
Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:
I declare that I have no competing interests.
Reviewer's report
Title: A Systematic Review and Meta-Analysis: Probiotics in the treatment of Irritable Bowel Syndrome
Version: 2 Date: 5 July 2008
Reviewer: Eamonn M M Quigley
Reviewer's report:
Major Compulsory Revisions
1. Page 5 and elsewhere. "Flatulence" is NOT a primary or secondary symptom of IBS and is not included in any of the definitions of IBS for the very good reason that bloating (which is an IBS symptom) and flatulence are very different in pathophysiology. The inclusion of flatulence in this discussion of IBS is misleading and symptom scores that incorporate flatulence should be discounted. In contrast, symptoms related to difficulty with bowel movements (urgency, difficult defecation) which ARE major IBS symptoms are not discussed or included in the analysis (page 8).

We disagree with the reviewer for the following reasons: in Gade’s study (18) published in 1989, the IBS definition of constipation and/or diarrhoea, abdominal pain, meteorism, borborygmus and flatulence was used. Five studies also report flatulence and also recent studies suggest treatments such as non-systemic antibiotics (e.g. rifaximin) are effective for flatulence giving credibility to the role of bacterial overgrowth in some patients with IBS.
However we agree urgency and difficult defecation are important but were not reported independently. We have added these to the limitations of the study. In some trials, we could not include data as they were incomplete or missing despite writing to authors. Specifically, trials should report individual outcomes for IBS. These should include important symptoms such as urgency and difficult defecation.

2. Page 12. Incorrectly refer to the O'Mahony study as a cross-over study which it is not.
Agree, we have deleted the sentence with the error.

3. Page 12. Here refer to the studies referred to as refs 20 and 30 as non-significant yet go on on page 14 to detail the issues related to ref 30 (Whorwell et al) and the fact that one dose in ref 30 was significant. Specifically, this meta-analysis does not take account of the fact that this particular study was a dose-ranging study and would have been deliberately designed to include a lower dose that would not work!
The study by Whorwell does not specify in the methods that this was a dose-ranging study in terms of one of the doses not being effective. We have taken a conservative approach when combining the different studies. This is the correct approach to answer the question “do pro-biotics work?”. A second systematic review should address the dose-response issue and we have flagged this issue in our conclusions.

4. Table 2. I am surprised by the low scores for Kim (from the Mayo clinic) and Whorwell (the largest study). What issues did these studies have with randomization and concealment of allocation?

The issues with these studies were due to lack of reporting of the actual methods of randomization in the published paper. This is a good example of why we contacted authors; however we could not clarify the actual methods of allocation. Therefore, they are scored as methods unclear (standard review practice) and receive no mark in the quality assessment.

5. Figure 3. Which dose from the Whorwell study was included here?

The reviewers will note in the methods section we included the following ‘For studies with more than one intervention arm a conservative estimate (i.e. the intervention with the least effect) was used.’ Therefore the trial used the Bifido 1X10^{10}. This is the correct approach to take so any estimation we have made is a conservative one.

We then go on to discuss what we did i in the discussion

Whorwell et al (30) studied a probiotic (B.infantis 35624) at three different strengths of 10^6, 10^8, 10^10 against placebo. The study found B.infantis 35624 at a dosage level of 10^8 cfu is effective in reducing the symptoms of IBS at four weeks. They suggested that this may be because the highest dose formulation 1X10^{10} cfu, “coagulated” into a firm glue like mass. As Whorwell’s study had more than one intervention arm, in our meta-analysis a conservative estimate (i.e. the intervention with the least effect) was used.’

This is the correct approach in determining overall effects for the question of interest.

6. Figs 4-6. Why were all studies not included here?

All studies were included when they reported the outcomes. We state the number of studies in the text that report each outcome. Where the outcomes are not reported in the paper it would not be helpful to include them in the figure.

Minor Essential Revisions
O’Mahony is mis-spelt in a number of locations.

Checked and corrected O’Mahoney name

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
I have received honoraria and research support from Procter and Gamble, the manufacturers of Align and am President of the World Gastroenterology Organisation which has received unrestricted support from Danone.