Reviewer’s report

Title: A practical guide for probiotics applied to the case of antibiotic-associated diarrhea in The Netherlands

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Reviewer: Lynne Vernice McFarland

Reviewer's report:

A paper on this subject is much needed, as there exists a great deal of confusion for clinicians and patients on how to choose an appropriate probiotic for their specific disease condition. The authors have put in a great deal of work into this paper, but it fails currently to meet its goal of providing any practical advice.

Major comments:

1. Main Outcome. The data is poorly presented, often incorrect and the outcomes that should have been presented in the main paper are buried in supplementary excel spreadsheets, which are so poorly formatted, the text is often hidden and illegible. The main outcome (efficacy for preventing AAD by different types of probiotics) in theory is given in Figure 3, but the figure is so blurry, you can't read what the probiotics are. In addition the labelling is poor (for example, what does "et alia (1)" refer to?-this does not do justice to a complete description of either the strains contained in the probiotic products and does not describe all the studies within one probiotic group. What does (1) refer to? It's not the reference #1, so the readers will not understand what this refers to. Indeed some of the classifications are wrong. For example, Gao 2010 is described as a dietary supplement, but the same product is also described as a 'dairy product' (Beasoleil 2007 and Sampalis 2010). This product [Bio-K+] is actually a mixture of three Lactobacilli strains, not just two and the strain designations for the L. casei is not given. A better analysis would be to have the first column as the subgroup of specific probiotics, then give all the studies under that one type of probiotic, along with a pooled RR for that probiotic. Then you can easily see which probiotics are effective and which are not. The current Figure 3 does not help at all. Pooling by 'dairy product' vs 'food supplement' does not provide any useful clinical summary.

2. Methods. The methods are poorly described. It is not apparent from the abstract if this is just a systematic review or a meta-analysis or what ? The methods section is lacking any description of recommended methods for meta-analysis or reviews (no PRISMA statements or descriptions), exclusion criteria are not described, inclusion criteria are poorly presented. The authors present their methods as "a 4 step work-flow" which is not helpful and is not
very applicable to how they really did the paper. EVERY review should start with prevent vs treatment, reviewing articles, etc. Were the exclusion criteria stated a priori, etc. were the reasons 96 studies were excluded in the protocol? The first time they appear to be described is in the figure 2 (and not in the Methods section). There is no description of the methods they used for their meta-analyses in the Methods section (for example, heterogeneity measurements, risk of bias, etc).

3. Introduction. The introduction reads like a paper all about AAD by itself (with 61 references, even before we get into the review itself!). Re-focus this and shorten dramatically. Three short paragraphs should do it.

4. Results are incorrect. The three main RRs reported in the text (page 13, lines 1-24) do not match the pooled RR in Figure 3. Why is this?

5. The true value of this paper is to give a practical guide to probiotic products, but the most glaring result is that not all probiotic types pooled within Figure 3 are equally effective. Also, the authors consistently use the term "shows an effect" when 'an effect' could be either a significant reduction in efficacy for AAD' or 'a non-significant finding of efficacy' or 'reduction in adverse reactions'. Please be more precise.

6. One of the big problems I found with this paper is that the authors state in the text that some studies 'showed an effect', (assuming once again they mean a significant effect of AAD efficacy) but do not present of how many studies were reviewed in total? For example, for L. rhamnosus GG, (page 13, line 39-41), they state 'there is an effect in at least three... studies' and provide citations for (Arvola 1999, Szajewsak 2009 and Vanderhoof 1999), but how many other studies with non-significant efficacy findings were reviewed? I know there are more studies than these three! It is impossible to find this out from Figure 3 (those references/studies not given) and the studies may be buried in the supplementary data (assuming you can decipher those spreadsheets), but this data is not given in the text, where it is sorely needed. In addition, in the Discussion (page 14, line 19) where this is discussed, the authors quote the incorrect references (#39,60,63) do not refer to Lactobacillus rhamnosus GG studies at all!

7. The authors do not seem to follow their own 'star' recommendation scheme. In the results under Recommendations (page 13, lines 43-50), the state that "A number of multi-strain formulations led to a two-star recommendation, including those with an effect in only selected study". But in their Methods sections, they stated that in order to achieve a 'two-star' recommendation rating, there had to be at least two studies with a [significant I assume] effect.
8. The authors also state that Saccharomyces boulardii achieved only a trend from 5 studies, but where is the data for this? A frustrating search through the long supplementary data tables appears to have included five studies with this probiotic (Kotowska 2005, Lewis 1998, McFarland 1995, Pozzoni 2012 and Surawicz 1989). However, how can they explain that other meta-analyses looking at this same probiotic continually finds a significant reduction in AAD risk? Goldenberg JA 2013 had 9 trials and found significant efficacy for S. boulardii and well as Szajewska H 2015 with 21 RCTs! Why does their review differ so dramatically from others?

9. There are too many numerous other errors in the text to list here (for example, page 4, line 24) "Nevertheless, in the past decade (2004-2009)…" It's 2017! The past decade would be 2007-2017!

10. Where was the data on the doses and duration of probiotic therapy given? This might help to provide some guidance. Little of this was covered in the Discussion section also.

11. Table 1. Need to clearly describe the Table so that it can stand alone and be understandable. For example, what does "category" refer to? Isn't this "Recommendation level"? Also, column labeled "Product" should be "Brand name" and the column labeled "Brand name" should be the manufacturer! Define all abbreviations.

12. Figure 1 is interesting, but could as easily be described in the Introductory section of the paper.

13. Figure 3. This is horrible. Can't read it, sub-groups are inappropriate, same type of products are included as dairy products and food supplement. Do not use 'et alia'-list the studies! List of species/strains! what do the numbers in the () refer to? Not references, but what? Very hard to evaluate this figure, as even when it is on zoom, the text is blurry and incomplete.

14. Supplement Tables are even worse. Excel spreadsheets are not appropriate, especially when the cells have hidden text and when published, they will be not able to be uncovered. Take the time to do presentable Tables. In addition, the value of supplement table 1 (side effects of antibiotics) is not worth the space. Tables in file 2 and 3 are valuable, but need to be legible. Re-do. Additional file 4 (Figure of probiotics for AAD from 32 studies listed in chronological order). Why? The lack of sub-groups by type of probiotic is needed, not by the year they were published. No valuable conclusion or inference was made from this figure, so why is it here? File 5 (products available in The Netherlands) is interesting and almost understandable but not well formatted—use wrap text for cells.

Although it would be valuable to have a practical guide, this paper completely fails to provide one. I do appreciate the thoroughness of the search and presenting the types of probiotic products
available in The Netherlands is a valuable. This papers needs to be refocused, trimmed and checked for accuracy. Consider the types of what types of Figures need to be presented, the data that your readers will actually need to see in a paper of this type, etc.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

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No

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