

September 30, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5536-edited.doc).

Title: Probiotics for the Prevention of Antibiotic Associated Diarrhea and *Clostridium difficile* Infections: a Meta-analysis and systematic review.

Authors: Lynne V. McFarland and Shan Goh

Name of Journal: *World Journal of Meta-analysis*

ESPS Manuscript NO: 5536

The manuscript has been improved according to the suggestions of reviewers (our responses follow reviewer comments in *italics*:

Reviewer #1.

Comment 1. The submitted manuscript on the meta-analysis of the use of probiotics in AAD and CDI is very well written and I commend the authors for the extensive work they did.

We thank you for your supportive comment!

Comment #2. Only a few minor comments - in the introduction the authors state a 2.7 fold increase in CDI from 2006 to 2009 - but the rates change from 1.2/10,000 to 31.5/10,000 which is more than 2.7 fold increase.

Thank you for catching this! The rate in 2006 should have been 12.8, which results in a 2.5 fold increase. The text has been revised as suggested.

Comment #3. The authors should provide a reference for the time period it takes for the normal bacterial flora to recover after antibiotic intervention.

We added this reference as suggested and please note, further information is given in the Discussion section under the "Suggestions for future research".

Comment #4. Aside from that there are only minor diction and grammar corrections that should be cross-checked by editors or by the authors again (e.g. Cochane instead of Cochrane and Mantel- Haenszel instead of Mantel-Haenazel). A

great paper that is worth publication.

We have corrected these typo errors. Thank you for checking these!

Reviewer #2.

Comment #5. This was a careful work. Thank you very much.

Comment #6. In the introduction : What about other drugs commonly used in Europe like dio- smectite or racecadotril ?

We have added these potential alternatives to the discussion section. To our knowledge, the use of these two medications is typically recommended to treat active disease, not to prevent disease (which is the focus of this paper), but we did add one study that looked at diosmectite for the prevention of radiation induced diarrhea.

Comment #7. In the analysis: -Wasn't it easier to systematically opt for the random effect of the MAL ? fixed effect in this pathology is highly improbable ! –

We used random effect models for all the analyses due to the heterogeneity found in the results. Fixed effects models were not used.

Comment #8. What about a meta-regression for better conclusion on your main results? Was it not a better idea to test the interaction

Thank you for this suggestion. We added a comment about this method to the discussion section. We believe presenting data using meta-analysis models and stratifying on major confounders (like strain type or dose) is more transparent for the readers. We did not adjust for age, as we limited our included trials to just pediatric data. We did look at the results from a meta-regression, but it added no more clarity to the results.

Reviewer #3.

Comment #9. Authors should try to make a better conclusion by considering both sides of probiotics (efficacy and safety).

We have revised the Discussion section as suggested and added more information on the safety of probiotics in general and also results from other types of meta-analyses (using most of the references suggested below).

Comment #10. The same article has been already published;

This is unclear. We are uncertain which article you are referring to being 'already published'. This paper is not a duplicate meta-analysis of pediatric AAD and CD, and presents results from trials not previously published in other meta-analyses.

Comment #11. The authors should use the followings to discuss their results. I hope to see a better discussion considering efficacy and safety. Salari et al. A meta-analysis and systematic review on the effect of probiotics in acute diarrhea. *Inflamm Allergy Drug Targets* 2012; 11: 3-14. Hosseini et al. Probiotics use to treat irritable bowel syndrome. *Expert Opin Biol Ther. Expert Opinion on Biological Therapy* 2012; 12(10): 1323-1334 Nikfar et al. Efficacy of Probiotics in Irritable Bowel Syndrome: A Meta-Analysis of Randomized, Controlled Trials. *Disease of the Colon and Rectum* 2008, 51(12): 1775-1780.

Please see revised Discussion.

Comment #12. Also the limitation of the meta-analysis according to included studies and possible bias should be highlighted.

The Discussion was revised as suggested and more information on bias was added.

We added two of the three references. We substituted a meta-analysis with more trials (n=20) rather than the Nikfar S 2008 meta-analysis for IBS (which only assessed 8 trials). Thank you for pointing out these excellent studies!

Added these references:

- Dinleyid EC, Eren M, Dogan N, Reyhanioglu S, Yargic ZA, Vandenplas Y. Clinical efficacy of *Saccharomyces boulardii* or metronidazole in symptomatic children with *Blastocystis hominis* infection. *Parasitol Res* 2011 Mar;108(3):541-5. doi: 10.1007/s00436-010-2095-4. [PMID: 20922415]
- Faure C. Role of antidiarrhoeal drugs as adjunctive therapies for acute diarrhoea in children. *Int J Pediatr* 2013;2013:612403. doi: 10.1155/2013/612403. Epub 2013 Mar 3. [PMID 16501441]
- Guarner F, Khan AG, Garisch J, Eliakim R, Gangl A, Thomson A, Krabshuis J, Lemair T, Kaufmann P, de Paula JA, Fedorak R, Shanahan F, Sanders ME, Szajewska H, Ramakrishna BS, Karakan T, Kim N; World Gastroenterology Organization. World Gastroenterology Organisation Global Guidelines: probiotics and prebiotics October 2011. *J Clin Gastroenterol* 2012 Jul;46(6):468-81. doi: 10.1097/MCG.0b013e3182549092.[PMID: 22688142]
- Hosseini A, Nikfar S, Abdollahi M. Probiotics use to treat irritable bowel syndrome. *Expert Opin Biol Ther* 2012 Oct;12(10):1323-34. doi: 10.1517/14712598.2012.707179. [PMID:22897430]
- McFarland LV, Dublin S. Meta-analysis of probiotics for the treatment of irritable bowel syndrome. *World J Gastroenterol* 2008 May 7;14(17):2650-61. [PMID: 18461650]
- Salari P, Nikfar S, Abdollahi M. A meta-analysis and systematic review on the effect of probiotics in acute diarrhea. *Inflamm Allergy Drug Targets* 2012 Feb;11(1):3-14. [PMID: 22309079]

Sanders ME, Akkermans LM, Haller D, Hammerman C, Heimbach J, Hi:irmannspurger G, Huys G, Levy DD, Lutgendorff F, Mack D, Phothirath P, Solano-Aguilar G, Vaughan E. Safety assessment of probiotics for human use. *Gut Microbes* 2010 May-Jun;l(3):164- 85. doi: 10.4161/ gm.1.3.12127. [PMID: 21327023]

Santantonio M, Colella M, Fiorica F, Pratissoli S, Stefanelli A, Falchi AM, Venturi A, Balli M. Diosmectite (DIOSMECTAL) in preventive anti-diarrheic therapy in patients subjected to pelvic radiation. *Minerva Gastroenterol Dietol* 2000 Dec;46(4):225-30. [PMID:16501441]

Thank you for your insight comments and suggestions, they have improved our manuscript significantly!

Sincerely,

A handwritten signature in black ink, reading "Lynne V. McFarland", followed by a horizontal line.

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