**Appendix**

Appendix to ‘Probiotics for celiac disease: a systematic review and meta-analysis of randomized controlled trials.’

This appendix provides supplemental information on this systematic review. It is divided into four appendices (Appendix 1 – 12).

**Table of Contents**

|  |  |
| --- | --- |
| Appendix 1 | MEDLINE search strategy for article selection (from 1 Jan 1970 to 5 February 2019). |
| Appendix 2 | Excluded studies and reasons for exclusion. |
| Appendix 3 | Summary of studies evaluating the effects of probiotics in CD. |
| Appendix 4 | Effect of probiotics vs. placebo on GI symptoms, sub-grouped by presence of IBS diagnosis. |
| Appendix 5 | Effect of probiotics vs. placebo on GI symptoms, sub-grouped by GFD adherence. |
| Appendix 6 | Effect of probiotics vs. placebo on faecal *Bifidobacterium* counts, sub-grouped by geographical location. |
| Appendix 7 | Effect of probiotics vs. placebo on faecal *Lactobacillus* counts, sub-grouped by probiotic type, length of GFD adherence, and age group. |
| Appendix 8 | Effect of probiotics vs. placebo on faecal *Lactobacillus* counts, sub-grouped by geographical location. |
| Appendix 9 | Effect of probiotics vs. placebo on number of adverse events, sub-grouped by age group. |
| Appendix 10 | Effect of probiotics vs. placebo on number of adverse events, sub-grouped by GFD adherence. |
| Appendix 11 | Effect of probiotics vs. placebo on number of adverse events, sub-grouped by probiotic type. |
| Appendix 12 | Effect of probiotics vs. placebo on number of adverse events, sub-grouped by geographical location. |

**Appendix 1. MEDLINE search strategy for article selection (from 1 Jan 1970 to 5 February 2019).**

|  |  |
| --- | --- |
| 1 | Celiac Disease/ |
| 2 | c?eliac.mp. |
| 3 | (gluten adj2 enteropath\*).mp. |
| 4 | nontropical sprue.mp. |
| 5 | gluten enteropathy.mp. |
| 6 | gluten enteropathies.mp. |
| 7 | (gluten adj2 sensitive).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] |
| 8 | gluten sensitive enteropathy.mp. |
| 9 | gluten sensitive enteropathies.mp. |
| 10 | (Celiac adj3 sprue).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] |
| 11 | (nontropical adj3 sprue).mp. |
| 12 | exp Diet, Gluten-Free/ |
| 13 | gluten free diet.mp. |
| 14 | Gliadin\*.mp. |
| 15 | exp Glutens/ |
| 16 | gluten\*.mp. |
| 17 | or/1-16 |
| 18 | exp Probiotics/ |
| 19 | probiotic\*.mp. |
| 20 | exp symbiosis/ or exp microbiota/ or exp GI microbiome/ or exp microbial consortia/ or exp mycobiome/ |
| 21 | microbiome.mp. |
| 22 | bacterial microbiome.mp. |
| 23 | microbiota.mp. |
| 24 | mycobiome.mp. |
| 25 | symbiosis.mp. |
| 26 | endosymbiosis.mp. |
| 27 | microbial consortium.mp. |
| 28 | microflora.mp. |
| 29 | bacterial flora.mp. |
| 30 | intestine flora.mp. |
| 31 | (probiotic\* adj3 commensal).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] |
| 32 | (probiotic\* adj3 complimentary).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] |
| 33 | (probiotic\* adj2 commensal).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] |
| 34 | (probiotic\* adj2 complimentary).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] |
| 35 | exp Lactobacillus/ |
| 36 | Lactobacillus.mp. |
| 37 | exp Bifidobacterium/ |
| 38 | Bifidobacteri\*.mp. |
| 39 | Nissle Yeast.mp. |
| 40 | exp Saccharomyces/ |
| 41 | Saccharomyces.mp. |
| 42 | boulardii.mp. |
| 43 | VSL$.mp. |
| 44 | exp Streptococcus/ |
| 45 | Streptococcus.mp. |
| 46 | or/18-45 |
| 47 | 17 and 46 |

**Appendix 2. Excluded studies and reasons for exclusion.**

|  |  |
| --- | --- |
| **Author, yr** | **Reason for Exclusion** |
| Afifi 20171 | Study population does not include CD patients |
| Coqueiro 20172 | Review article. Not a study |
| Cristofori 20183 | Review article. Not a study |
| Darby 19464 | Not a randomised controlled trial and the intervention is not probiotics. |
| Kim 20065 | Study population does not include CD patients |
| Klemenak 20166 | Duplicate of Klemenak 201528 |
| Martinello 20177 | Not a randomised controlled trial |
| NCT012576208 | Duplicate of Smecuol 201317 |
| NCT016991919 | Duplicate of Smecuol 201317 |
| NCT0281030110 | Study population does not include CD patients |
| NCT0317609511 | Study population does not include CD patients |
| NCT0340338712 | Study population does not include CD patients |
| NCT0348380513 | Intervention is not solely probiotics |
| NCT0377549914 | Study intervention too short (<2 weeks) |
| Novik 201615 | Not a randomised controlled trial |
| Pinto-Sánchez 201716 | Not a randomized controlled trial |
| Pisarello 201517 | Not a randomised controlled trial |
| Rall 201018 | Not a randomised controlled trial |
| Respondek 201319 | Study population does not include CD patients |
| Savilahti 201820 | Study population does not include CD patients |
| Serena 201921 | Review article. Not a study |
| Smecuol 201222 | Duplicate of Smecuol 201317 |
| Smecuol 2013 (2)23 | Duplicate of Smecuol 201317 |
| Smecuol 201524 | Not a randomised controlled trial |
| Tavakkoli 201325 | Review article. Not a study |
| Tjellstrom 201626 | Not a randomised controlled trial |
| Uspenskaia 199127 | Probiotics in both intervention and placebo groups |
| Wilms 201628 | Study population does not include CD patients |

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11- ClinicalTrials.gov. Celiac Disease Prevention With Probiotics (CiPP). Bethesda (MD): National Library of Medicine (US). https://clinicaltrials.gov/ct2/show/NCT03176095. Published 2017.

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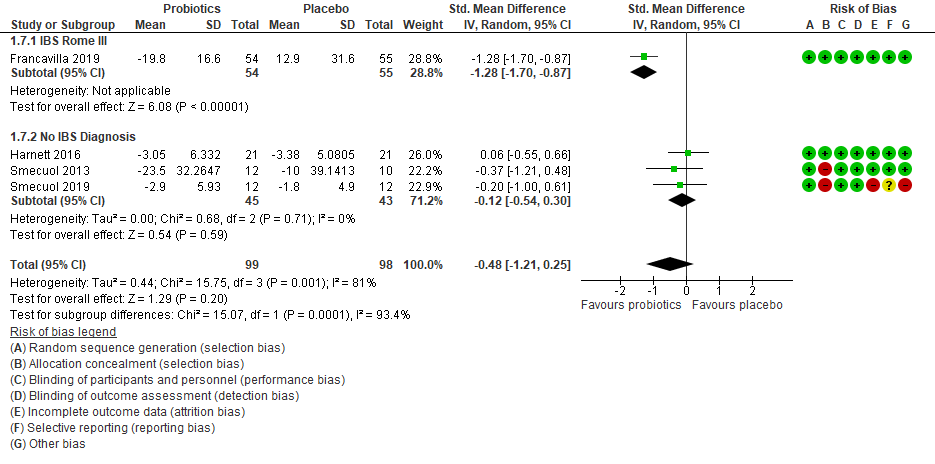
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**Appendix 3. Summary of studies evaluating the effects of probiotics in CD.**

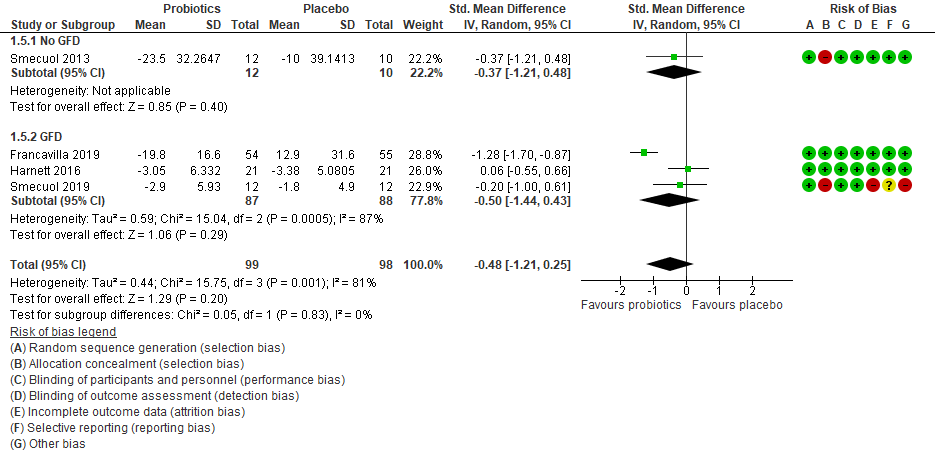
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Year | Country | Age category | N | Funding | Outcomes | | | | | | |
| GI | QOL | AE | TNF-α | IP | Bifido | Lacto |
| Francavilla9 | 2019 | Italy | Adults | 109 | NR | ↓ |  |  |  |  | ↑ | ↑ |
| Harnett11 | 2016 | Australia | Adults | 45 | NR |  |  |  |  |  |  |  |
| Klemenak20 | 2015 | Slovenia | Children | 49 | G & I |  |  |  | ↓ |  |  |  |
| Olivares19 | 2014 | Spain | Children | 36 | G |  |  |  |  |  |  |  |
| Primec22 | 2018 | Slovenia | Children | 40 | G & I |  |  |  |  |  |  |  |
| Quagliariello21 | 2016 | Slovenia | Children | 40 | G & I |  |  |  |  |  |  | ↑ |
| Smecuol10 | 2013 | Argentina | Adults | 22 | G |  |  |  |  |  |  |  |
| Smecuol26 | 2019 | Argentina | Adults | 12 | NR | ↓ |  |  |  |  |  |  |

NOTE: Study design: all RCTs; Green: Significant benefit in probiotics vs placebo; Yellow: no difference probiotic vs placebo; white: outcome not assessed. Abbreviations: Bifido = Bifidobacteria; GI = gastrointestinal symptoms; G = peer-reviewed grant; I = industry; IP = intestinal permeability; Lacto = Lactobacilli; NR = not reported; QOL= quality of life; AE = adverse events; TNF-α = change in serum TNF-α. Symbols: ↑=increase; ↓=decrease.

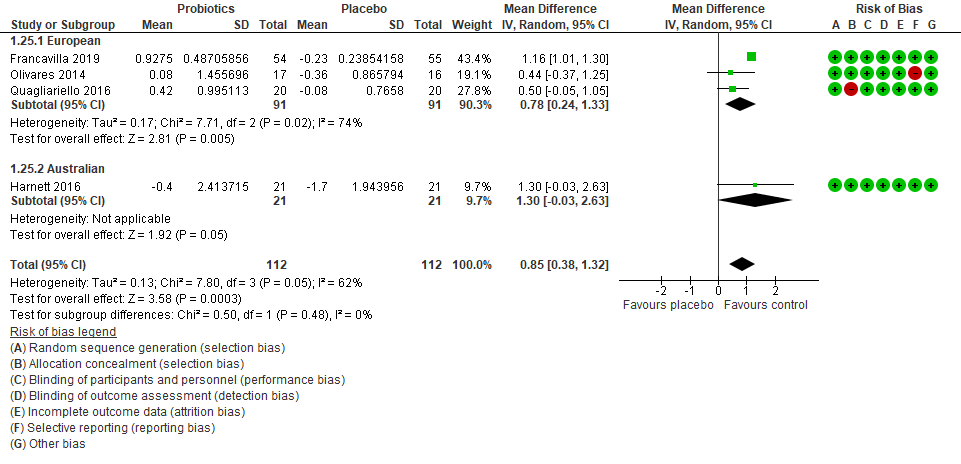
**Appendix 4. Effect of probiotics vs. placebo on GI symptoms, sub-grouped by presence of IBS diagnosis.**



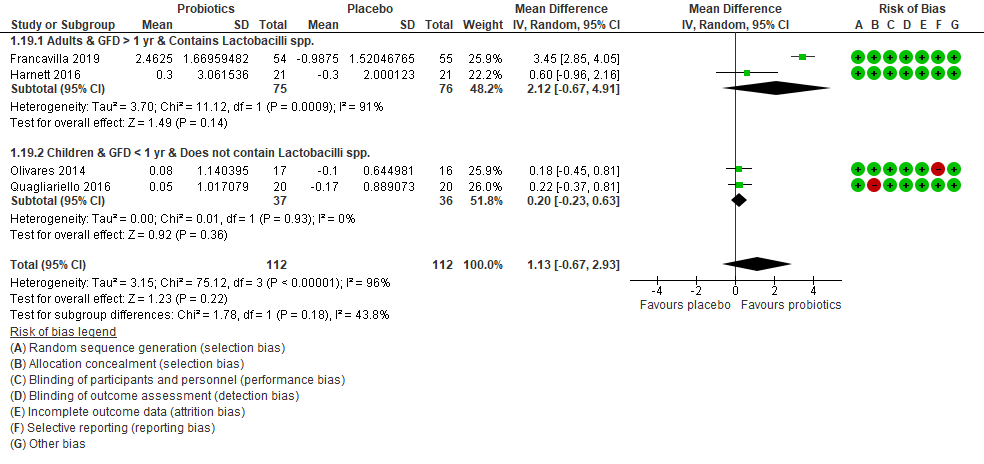
**Appendix 5. Effect of probiotics vs. placebo on GI symptoms, sub-grouped by GFD adherence.**



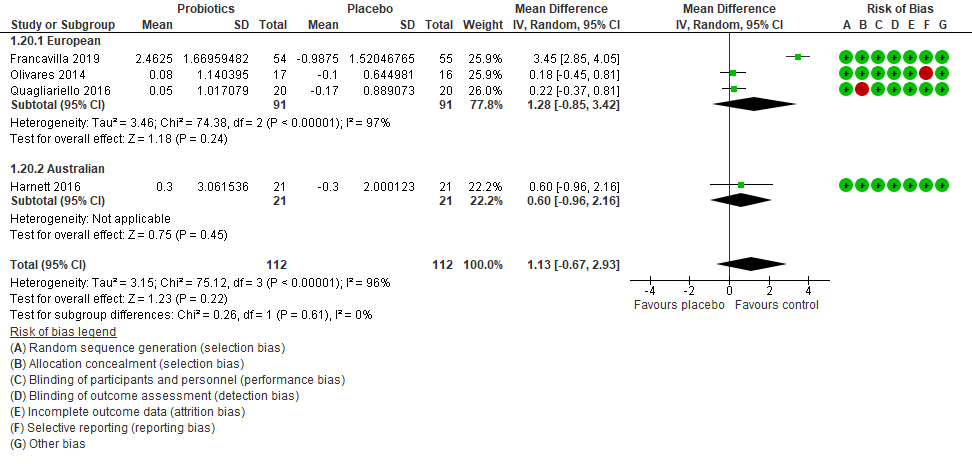
**Appendix 6. Effect of probiotics vs. placebo on faecal *Bifidobacterium* counts, sub-grouped by geographical location.**

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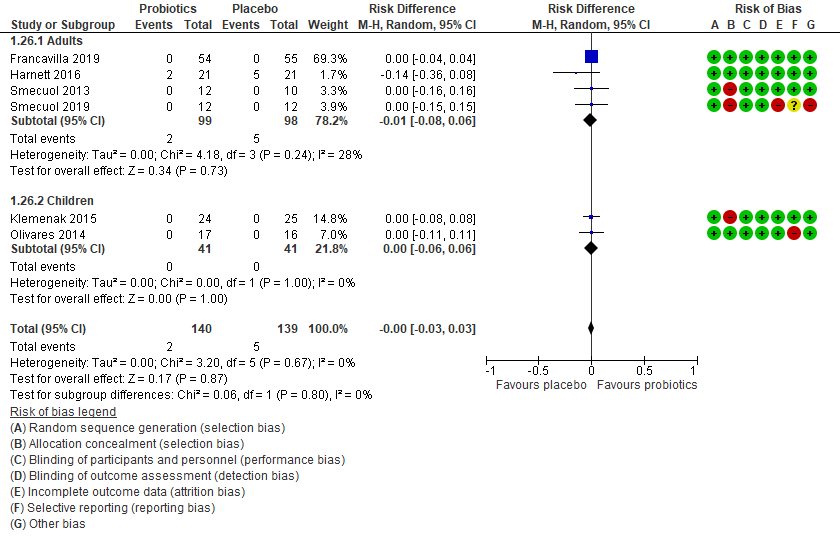
**Appendix 7. Effect of probiotics vs. placebo on faecal *Lactobacillus* counts, sub-grouped by probiotic type, length of GFD adherence, and age group.**



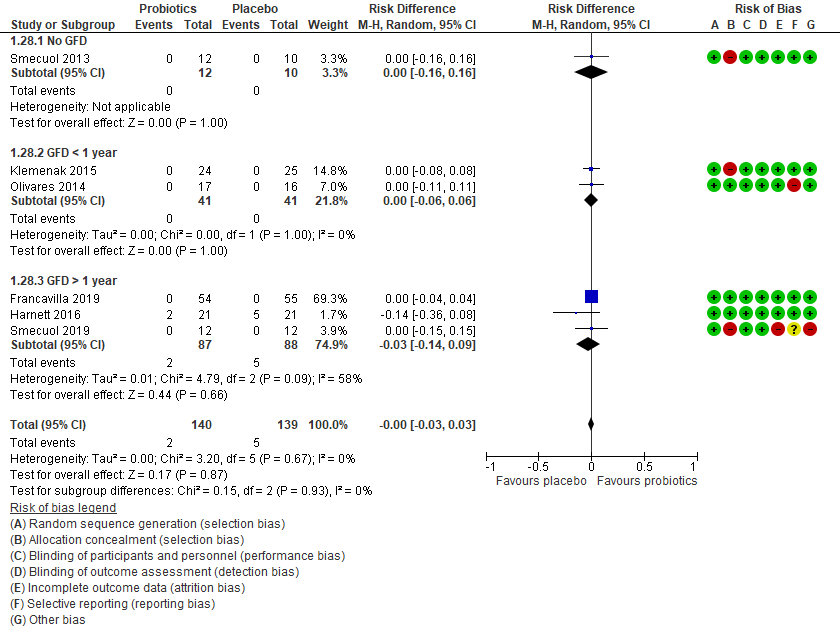
**Appendix 8. Effect of probiotics vs. placebo on faecal *Lactobacillus* counts, sub-grouped by geographical location.**



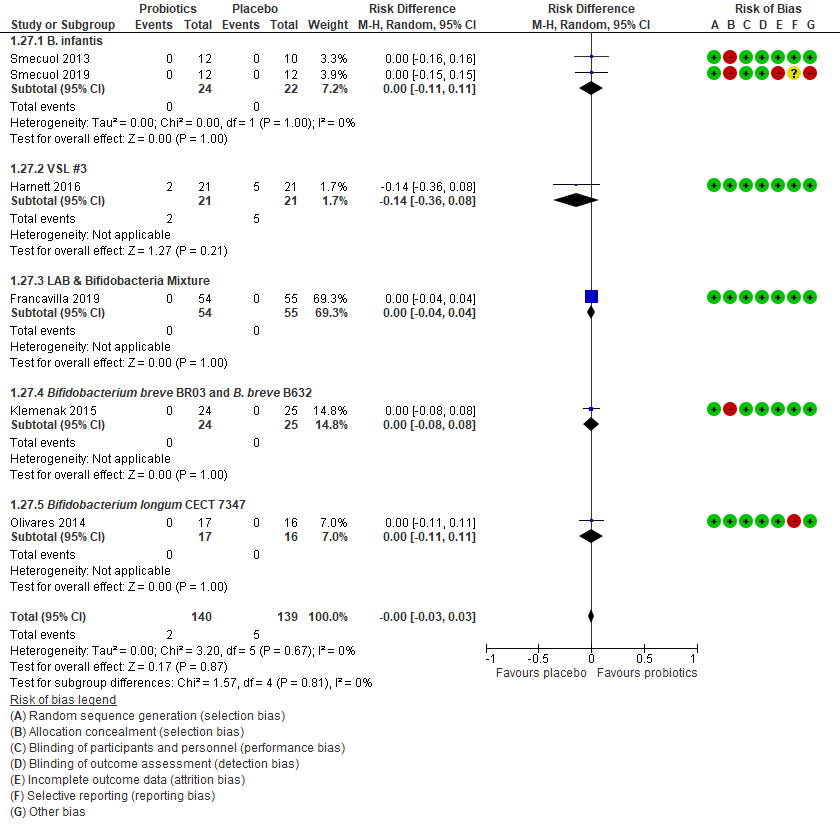
**Appendix 9. Effect of probiotics vs. placebo on number of adverse events, sub-grouped by age group.**

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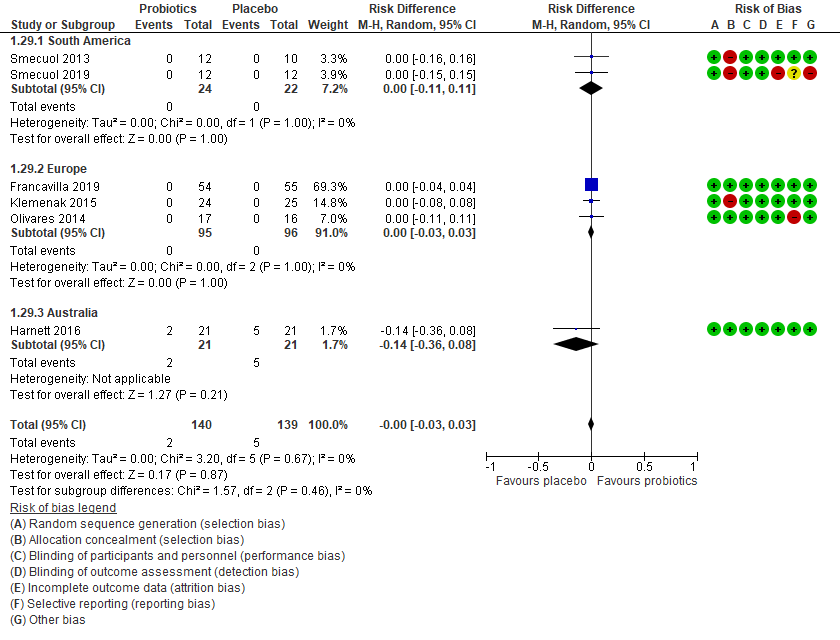
**Appendix 10. Effect of probiotics vs. placebo on number of adverse events, sub-grouped by GFD adherence.**

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**Appendix 11. Effect of probiotics vs. placebo on number of adverse events, sub-grouped by probiotic type.**

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**Appendix 12. Effect of probiotics vs. placebo on number of adverse events, sub-grouped by geographical location.**

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