**Appendix Methods**

**Appendix Methods 1. Search strategy**

*Electronic searches*

On April 11, 2016, we performed a comprehensive search using the following electronic databases:  PubMed (1966 to 2016), EMBASE (1966 to 2016), CENTRAL (2016, Issue 1), CINAHL (1982 to 2016), AMED (1985 to 2016), and ISI Web of Science (the first 500 citations of ISI’s large retrieval set were pre-screened).  Searches included both controlled vocabulary (e.g. Probiotics, Cultured Milk Products) and text words (e.g. “fermented foods”, gastroenteritis). No language, publication status, or date limits were applied. Each search strategy was adapted for the particular database. See Appendix Table 1 and 2 for the Medline and EMBASE search strategy.

*Searching other resources*

In addition, reference lists for relevant studies and systematic reviews were checked to make sure all cited RCTs had been identified in the electronic searches. BIOSIS (Thomson Reuters; 1969 to 2013) was searched specifically for conference proceedings as well as the British Society of Gastroenterology Annual General Meeting abstracts (years: 2006 to 2013) and Digestive Disease Week (years: 2009 to 2013). Authors of pertinent presentations were contacted for further information. The following sources were also reviewed:  Canadian Agency for Drugs and Technologies in Health; McGill University Health Centre, Technology Assessment Unit; trial registers, e.g. the Inflammatory Bowel Disease and Functional Bowel Disorders Review Group’s specialized trials register, and the metaRegister of Controlled Trials, dissertations abstracts (Proquest’s Theses and Dissertations Full Text); TRIP Database; Highwire Press; and Google Scholar. To complete the search process, companies that manufacture probiotic agents (Metagenics; Seroyal/Pharmax; Yeo Valley Organics; Biocodex Inc.; Sanofi-Aventis; Probugs/Lifeway Foods Inc.; IBSS Biomed S.A.) were contacted to identify any unpublished, ongoing, randomised trials.

*References:*

Goldenberg JZ, Ma SSY, Saxton JD, Martzen MR, Vandvik PO, Thorlund K, Guyatt GH, Johnston BC. Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. Cochrane Database of Systematic Reviews 2013, Issue 5. Art. No.: CD006095. DOI: 10.1002/14651858.CD006095.pub3.

**Appendix Methods 2. Risk of bias assessment: Modifications to previous Cochrane systematic review (2013).**

First, the previous review considered all adverse events, whereas we only considered SAEs. Thus, for SAEs, risk of bias due to inadequate blinding was considered low, as it was considered an objective outcome for which lack of blinding was unlikely to have an effect1. Second, for studies where new outcomes (i.e. CDI, SAE) became available after IPD requests, judgements for those outcome-specific domains were added. Third, if there were considerably less data between published outcome data and IPD that was not resolved with study authors, we considered this high risk of bias for incomplete outcome data. For example, one abstract reported 16 CDI cases, however in their IPD there were only two test-confirmed cases2. We did not exclude studies if their IPD was not consistent with their published data, however these two studies were not included in our adjusted analysis2. Fourth, in addition to participants lost to follow up, we considered participants who had diarrhea but were not tested for CDI as missing participant outcome data: If under 10% of participants, we considered this an unclear risk of bias, and high risk of bias if over 10%3. Fifth, if a study published data on outcomes (e.g. SAEs) or variables (e.g. antibiotics) but it was not available in the IPD, we considered this a high risk of bias for selective outcome reporting4. Last, one published interim analysis from the previous review had been completed and published, thus risk of bias judgements were re-assessed based on the published article.

*References:*

1. Wood L, Egger M, Gluud LL, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *Bmj.* 2008;336(7644):601-605.

2. Miller M. Results of 2 prospective randomized studies of Lactobacillus GG to prevent C. difficileinfection in hospitalized adults receiving antibiotics. 2008.

3. Bennett DA. How can I deal with missing data in my study? *Australian and New Zealand Journal of Public Health.* 2001;25(5):464-469.

4. Higgins J, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. *BMJ.* 2011;343.

**Appendix Tables**

**Appendix Table 1. Example search strategy in Medline (April 11 2016).**

**# Searches**

**1** ’probiotic agent’/exp OR ’probiotic agent’ OR probio\* OR ’dairy product’:de OR ’yoghurt’/exp OR yoghurt OR ’yogurt’/exp OR yogurt OR ’kefir’/exp OR kefir OR ’fermented product’/exp OR ’fermented product’

**2** ’lactobacillus’/exp OR lactobacillus OR lactobacill\* OR l AND acidophilus OR l AND casei OR l AND delbrueckii OR l AND helveticus OR l AND johnsonii OR l AND paracasei OR l AND plantarum OR l AND reuteri OR l AND rhamnosus OR l AND salivarius

**3** saccharomyce\*OR’streptococcus’/expORstreptococcus

ANDthermophilusOR’clostridium’/ exp OR clostridiumANDbutyricum OR

’enterococcus’/exp OR enterococcus AND faecium OR ’antibiosis’/exp OR

antibiosis OR biotherapeutic AND agent\*

**4** ’bifidobacterium’/exp OR bifidobacterium OR bifidobacter\* OR b AND animalis OR b AND bifidum OR b AND breve OR b AND infantis OR b AND lactis OR b AND longum

**5** #1 OR #2 OR #3 OR #4

**6** ’anti-bacterial agents’:de OR antimicrobial\* OR antibiotic\* OR

’antimicrobial’/exp OR antimicrobial OR ’anti microbial’ OR antimycobacteri\*

OR antibacteri\* OR bacteriocid\* NEAR/1 agent\*

**7** ’*Clostridium difficile* infection’:de OR ’clostridium’/exp OR clostridium AND difficile OR c AND diff OR ’*Clostridium difficile* associated’ NEXT/1 diarrhea OR ’disease’/exp OR disease OR ’colitis’/exp OR colitis OR infections OR

’*Clostridium difficile* toxin a’/ exp OR ’*Clostridium difficile* toxin a’ OR

’*Clostridium difficile* toxin b’/exp OR ’*Clostridium difficile* toxin b’ OR

’diarrhea’/exp OR diarrhea OR diarrhea\* OR diarrhoe\* OR diarhe\* OR diarhoe\* OR dysenter\* OR gastroenteritis\* OR ’gastro’/exp OR gastro AND enteritis\*

**8** random\* OR factorial\* OR crossover\* OR cross AND over\* OR placebo\* OR

doubl\* OR singl\* NEXT/1 blind\* OR assign\* OR allocate\* OR volunteer\* OR

’crossover procedure’/exp OR ’crossover procedure’ OR ’double blind procedure’/exp OR ’double blind procedure’ OR ’randomized controlled trial’/exp OR ’randomized controlled trial’ OR ’single blind procedure’/exp OR

’single blind procedure’

**9** #9 #5 AND #6 AND #7 AND #8

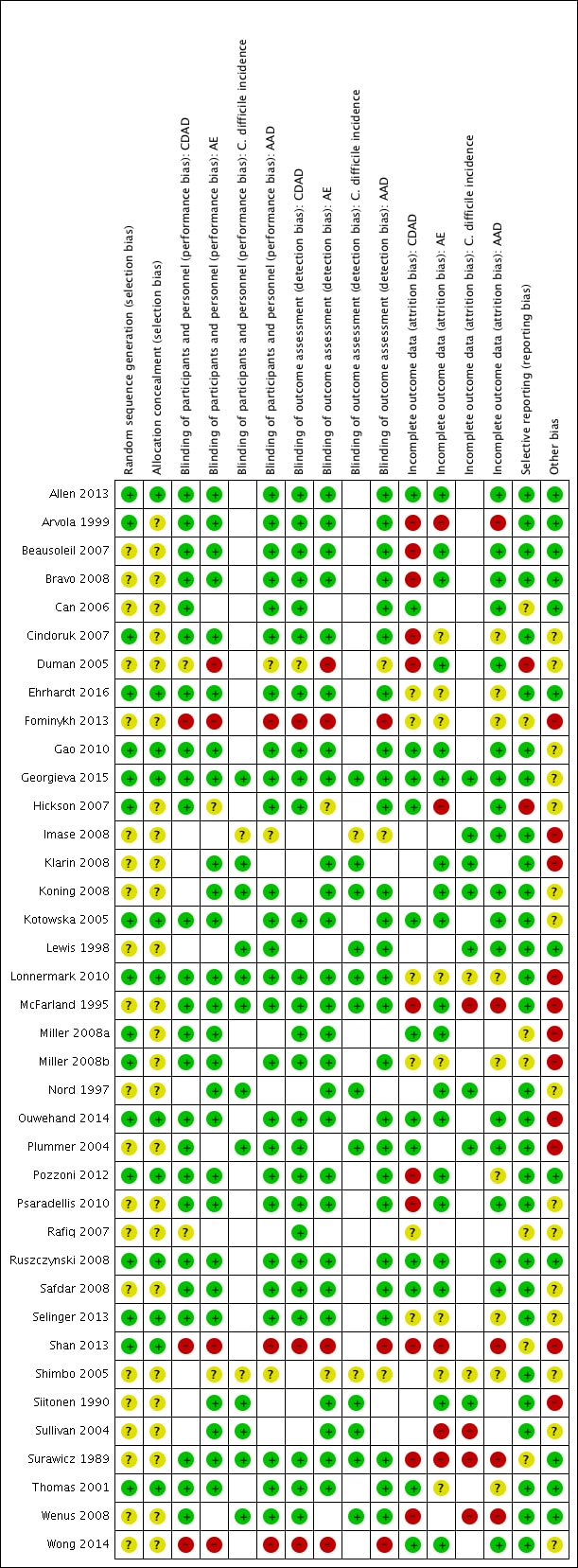
|  |  |
| --- | --- |
| **Appendix Table 2. Example search strategy in EMBASE (April 11 2016).** | |
| **#** | **Searches** |
| **1** | random$.mp. |
| **2** | factorial$.mp. |
| **3** | (crossover$ or cross over$ or cross-over$).mp. |
| **4** | placebo$.mp. |
| **5** | single blind.mp. |
| **6** | double blind.mp. |
| **7** | triple blind.mp. |
| **8** | (singl$ adj blind$).mp. |
| **9** | (double$ adj blind$).mp. |
| **10** | (tripl$ adj blind$).mp. |
| **11** | assign$.mp. |
| **12** | allocat$.mp. |
| **13** | crossover procedure/ |
| **14** | double blind procedure/ |
| **15** | single blind procedure/ |
| **16** | triple blind procedure/ |
| **17** | randomized controlled trial/ |
| **18** | or/1-17 |
| **19** | (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or  (human or humans).ti. |
| **20** | 18 not 19 |
| **21** | exp Probiotics/ |
| **22** | exp Synbiotics/ |
| **23** | probiotic\*.mp. |
| **24** | synbiotic\*.mp. |
| **25** | exp Lactobacillus/ |
| **26** | lactobacill\*.mp. |
| **27** | exp Bifidobacterium/ |
| **28** | (bifidus or bifidobacter\*).mp. |
| **29** | exp Streptococcus thermophilus/ |
| **30** | streptococcus thermophilus.mp. |
| **31** | streptococc\*.mp. |
| **32** | exp Lactococcus/ |
| **33** | lactococc\*.mp. |
| **34** | Bacillus subtilis/ |
| **35** | bacillus subtilis.mp. |
| **36** | exp Enterococcus/ |
| **37** | enterococcus faec\*.mp. |
| **38** | exp Saccharomyces/ |
| **39** | saccharomyc\*.mp. |
| **40** | leuconostoc.mp. |
| **41** | pediococc\*.mp. |
| **42** | bulgarian bacillus.mp. |
| **43** | (beneficial adj3 bacter\*).mp. |
| **44** | dairy.mp. |
| **45** | yog?urt.mp. |
| **46** | kefir.mp. |
| **47** | clostridium.mp. |
| **48** | or/21-47 |
| **49** | clostridium difficile.mp. |
| **50** | c diff.mp. |
| **51** | 49 or 50 |
| **52** | (diarrhea or diarrhoe or diarhe or diarhoe or dystener\* or gastroenteritis).mp. |
| **53** | 48 and 51 and 52 |
| **54** | 53 and 20 |

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| **Appendix Table 3. Characteristics of individual participants in primary adjusted analysis of CDI (complete case, n = 13 studies).** † | | |
|  | **Probiotics group**  **(n=2581)** | **Control group**  **(n=2493)** |
| **Age (mean, SD) years** | 64.2 (24.3) | 64.0 (25.1) |
| <1 | 34 | 35 |
| 1 to <18 | 208 | 215 |
| 18 to <65 | 541 | 482 |
| 65+ | 1798 | 1761 |
| **Sex (Male, %)** | 1369 (53.0) | 1216 (48.8) |
| **Hospitalized (yes, %)** | 2189 (84.8) | 2113 (84.8) |
| **High risk antibiotic\* at any time** | 456 (17.7) | 415 (16.6) |
| ***C. difficile* infection** | 31 (1.2) | 67 (2.7) |
| **Multiple antibiotic users (%)** | 1590 (61.6) | 1590 (63.8) |

\*High risk antibiotics; 3rd and 4th generation cephalosporins, lincosamides, and fluoroquinolones. †Miller 2008a, Miller 2008b and Georgieva 2015 excluded for not reporting age; Plummer 2004 and Psaradellis 2012 excluded for lack of antibiotics data; Georgieva 2015 also did not report patient sex.

|  |  |  |
| --- | --- | --- |
| **Appendix Table 4. Characteristics of individual participants in primary adjusted analysis of SAEs (complete case; n = 11 studies).** † | | |
|  | **Probiotics group**  **(n=2410)** | **Control group**  **(n=2308)** |
| **Age (mean, SD) years** | 64.4 (24.6) | 64.4 (25.4) |
| <1 | 34 | 35 |
| 1 to <18 | 210 | 215 |
| 18 to <65 | 454 | 383 |
| 65+ | 1712 | 1675 |
| **Sex (Male, %)** | 1264 (52.4) | 1100 (47.7) |
| **Hospitalized (yes, %)** | 2016 (83.7) | 1928 (83.5) |
| **High risk antibiotic\* at any time** | 396 (16.4) | 360 (15.6) |
| **Multiple antibiotic users (%)** | 1506 (62.5) | 1499 (64.9) |
| **Serious adverse events** | 297 (12.3) | 281 (12.2) |

\*High risk antibiotics; 3rd and 4th generation cephalosporins, lincosamides, and fluoroquinolones. †Miller 2008a, Miller 2008b and Georgieva 2015 excluded for not reporting age and IPD on SAEs (Georgieva 2015 also did not report patient sex); Plummer 2004 and Psaradellis 2012 excluded for lack of antibiotics data; Wong and Hickson 2007 excluded for not reporting IPD on SAEs.

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**Appendix Figure 1.** Risk of bias for studies included in individual participant data meta-analysis: (+) Low risk of bias; (?) Unclear risk of bias; (-) High risk of bias.



**Appendix Figure 2.** Funnel plot for studies, with effect estimates, that reported

*Clostridium difficile* infection, both for studies obtained for the individual participant data

meta-analysis and not obtained. IPD, Individual Participant Data. OR, Odds Ratio. SE,

Standard Error.



**Appendix Figure 3.** Pooled random effects meta-analysis for probiotics versus control on *Clostridium difficile* Infection, comparing studies obtained for the individual participant data (IPD) meta-analysis and not obtained (Non-IPD). CI, Confidence Interval. M-H, Mantel-Haenszel. OR, Odds Ratio.