**The Effectiveness of Probiotics on Length of Illness in Healthy Children and Adults who Develop Common Acute Respiratory Infectious Conditions: A Systematic Review and Meta-Analysis**

Sarah King, Julie Glanville, Mary Ellen Sanders, Anita Fitzgerald, Danielle Varley

Supplementary file 3: detailed quality assessment of included studies

| **Reference** | **Was randomisation carried out appropriately?** | **Was the concealment of treatment allocation adequate?** | **Were the care providers, participants and outcome assessors blind to treatment allocation?** | **Groups similar at baseline in terms of prognostic factors?** | **Unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?** | **Authors measured more outcomes than they reported?** | **Did the analysis include an ITT? If so, was this appropriate and were appropriate methods used?** | **Risk of bias of the study [[1]](#footnote-1)** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Bentley 2008 (unpublished) | Yes – computer generated | Yes - assignment of the random numbers to verum or placebo was performed externally; the issued containers comprising the sachets were pre-numbered according to the randomisation code. | Described as double-blind; treatment and placebo sachets were externally identical. | Yes | More drop-outs in the placebo group. | No (i.e. adequate) | Yes – although 6 subjects (3 in each group) could not be accounted for due to missing data | Low risk of bias |
| Berggren 2011 | Yes – computer-generated by a statistician (not involved in the study). | Yes - all test preparations were prepared, packaged in sachets of similar appearance, randomized and labelled with identification numbers from the randomization list by the “Product Development & Production Dept.” | Described as double-blind. The study products were similar in taste and appearance (see test preparations). Both participants and study teams at both centres were blinded to the interventions until the study was completed. | Yes | No | No (i.e. adequate) | No - 46 participants were not included in the analysis. | Low risk of bias |
| Cáceres 2010 | Yes - computer generated random numbers table | Yes - both products were packaged in identical bottles, distinguishable only by a letter code on the label. | Described as double-blind. Packaging was similar for both treatment and placebo. | Yes | Yes - a significantly higher drop-out rate was observed in the treatment group compared to the control group (16.3% vs. 8.21%, p<0.025), but unlikely to be due to treatment as reasons for withdrawal were largely for family reasons. | No (i.e. adequate) | No - 49 participants were not included in the analysis. | Some risk of bias |
| Cazzola 2010 | Yes – computer generated numbers list[[2]](#footnote-2) | Yes - central allocation. | Described as double-blind. The sachets were similar; after dilution, aspect and taste were identical between treatments. | Yes | No | No (i.e. adequate) | Yes | Low risk of bias |
| de Vrese. 2005 | Yes – computer generated numbers table[[3]](#footnote-3) | Yes - central allocation by the supplier. | Described as double-blind. Test preparations were given in tablets with the same appearance, smell and taste. All test preparations were prepared, packaged, and randomised by the supplier (Merck, Consumer Health Care) who labelled the packages with identification numbers in order to fulfil the criteria of a double-blind trial. | Yes | No | No (i.e. adequate) | No - 13 participants in the intervention group and 12 in the placebo group were not included in the analysis | Low risk of bias |
| Guillemard 2010 | Yes – random numbers table[[4]](#footnote-4) | Yes – participants were included sequentially in accordance with the randomisation list. | Described as double blind. The nutritional composition, appearance, taste and packaging were identical in order to maintain blinding. | Yes | No | No (i.e. adequate) | Yes | Low risk of bias |
| Guillemard 2010 | Yes – random numbers table[[5]](#footnote-5) | Yes – participants were included sequentially in accordance with the randomisation list. | Described as double blind. The nutritional composition, appearance, taste and packaging of the fermented product and control were identical throughout the study in order to maintain blinding. | Yes | No | No (i.e. adequate) | Yes | Low risk of bias |
| Hatakka 2001 and 2007 | Yes – Computer generated, randomization list.[[6]](#footnote-6) | Yes – the code was kept in an envelope and kept secure by one person (not the investigators) The milks tasted and smelled the same, and were only distinguishable by a colour code.[[7]](#footnote-7) | Described as double-blind. Researchers, day care staff, parents and children were blinded. | There were more children in the control group who had five or more respiratory infections during the preceding 12 months; the authors adjusted for age in analyses; age distribution also differed between groups. | No. | No (i.e. adequate) | No - 571/594 children randomised were analysed. | Some risk of bias.  Due to colour coding, blinding may not have been maintained. |
| Hojsak 2010 | Yes - computer generated number by an independent person not involved in the clinical trial. | Yes – the study products were prepared centrally in identical packages by independent personnel. [[8]](#footnote-8) | Described as double blind. The L. rhamnosus GG product and placebo were packed in identical bottles; they were of the same colour, weight, smell, and taste. Both the research staff and the patients were unaware of the real nature of the product. | Yes | No | No (i.e. adequate) | Yes | Low risk of bias |
| Hojsak 2010 | Yes - computer generated number by an independent person not involved in the clinical trial. | Yes – the study products were prepared centrally in identical packages by independent personnel.[[9]](#footnote-9) | Described as double blind. L. rhamnosus GG product and placebo were packed in identical bottles; they were of the same colour, weight, smell, and taste (normal taste of fermented milk product, without added flavour). Both the research staff and children were unaware of the real nature of the product. | Yes | No | No (i.e. adequate) | Yes | Low risk of bias |
| Kloster 2008 | Yes – computer generated randomisation list performed by an independent statistician[[10]](#footnote-10) | Partially addressed – each child was allocated a colour code and both products were packaged in identical cartons, distinguishable only by the colour code. | Described as double-blind. Children, parents, day-care staff and operational project staff were blinded. | Yes | No | No (i.e. adequate) | No - 41 children did not have diary data and were excluded from analysis. | Some risk of bias  Due to colour coding, blinding may not have been maintained. |
| Kumpu*.* 2012 | Yes - computer generated randomisation list. | Yes – the code was kept in an envelope and kept secure by one person (not the investigators) The milks tasted and smelled the same, and were only distinguishable by a colour code.[[11]](#footnote-11) | Described as double blind. Researchers, day care staff, parents and children were blinded. | The groups were similar in terms of baseline characteristics except for more atopic eczema diagnosed by a physician in the placebo group (18%) than in the probiotic group (8%) and more adenoidectomies had been performed to children in the probiotic group (14%) than in the placebo group (10%). | Unclear | No (i.e. adequate) | No - 501/523 children randomized were included in the analysis | Some risk of bias  Due to colour coding, blinding may not have been maintained. |
| Leyer 2009 | Yes – computed generated randomization list[[12]](#footnote-12). | Yes – sequentially numbered opaque sealed envelopes were used.[[13]](#footnote-13) | Described as double-blind. No other details reported. | Yes - Although the authors noted the L. acidophilus group tended to weigh more than the placebo and L. acidophilus/B. lactis groups, with mean weights being 18.0, 17.1, and 16.9kg, respectively (P = 0.06). Children assigned to the placebo group were on average older than those assigned to the L. acidophilus group or the L. acidophilus/B. lactis group, by around 4 to 5 months (P<.001). This finding necessitated adjustment for age in subsequent analyses. | No | No (i.e. adequate) | Yes | Low/unclear risk of bias |
| Merenstein 2010 | Yes - computer generated by data managers who had no participant contact. Study identification was generated and a number from 0 to 9 was assigned. | Yes - through masking and use of 10 different number, 0 through 9, it was impossible for research personnel to adjust randomisation or deduce what groups participants were assigned. | Described as double blind. The appearance, taste, nutritional composition and packaging (200g bottles) of the active and control products were identical to ensure that subjects, their parents and, researchers did not know the identity of the study samples. Statisticians and research personnel were masked while examining initial data. Also, an independent data and safety monitoring board reviewed the data. | Yes | No - but there were more participants with major deviation in the control group. | No (i.e. adequate) | Yes | Low risk of bias |
| Niborski 2012 (unpublished) | Yes – random numbers table[[14]](#footnote-14) | Yes – participants were included sequentially in accordance with the randomisation list | Described as double-bind. Participants, care givers, and outcome assessors were blinded. Appearance, packaging and taste were identical | Yes | No | No (i.e. adequate) | Yes | Low risk of bias |
| Prodeus 2008(unpublished) | Yes – random numbers table[[15]](#footnote-15) | Yes – participants were included sequentially in accordance with the randomisation list. | Described as double-bind. Participants, care givers, and outcome assessors were blinded. | Yes - authors stated that they were comparable, but no details were provided. | No - only slightly more withdrawals in the placebo group. | No (i.e. adequate) | Yes | Low risk of bias |
| Smith 2012 | Yes - internet-based random number generator. | Yes - the packaging and contents of the placebo sticks were identical in taste and appearance to the probiotics stick. Chr. Hansen A/S manufactured the probiotics and placebo sticks, and labelled each stick with a 4-digit number code (2930 or 3220) to identify placebo or active. The principal investigator (PI) was blinded as to which 4-digit code represented probiotics or placebo. A person who was not part of the study staff (student health services coordinator at Framingham State University) maintained the randomization list and the codes indicating placebo or probiotics assignment. | Described as double-blind. The packaging and contents of the placebo sticks were identical in taste and appearance to the probiotics stick. The blinding code was provided to the PI after the data cleaning and statistical analysis were completed. | Yes | More students in the placebo group discontinued | No (i.e. adequate) | No - 13/114 randomised to probiotics, did not receive and were not included in the analysis. 20/117 randomised to placebo, did not receive placebo and were not included in the analysis (Smith stated that ITT analysis was conducted on other participants who dropped out) | Some risk of bias |
| Tiollier, 2007 | Yes – random numbers table[[16]](#footnote-16) | Yes - the study intervention and placebo packages were distinguished by letter codes that were not revealed to the investigators. | Described as double-blind. The two treatment drinks had identical packaging, and the same taste and nutrient composition. | Yes | N/A – no dropouts. | No (i.e. adequate) | Yes | Some risk of bias  (due to small sample size, n=47). |
| Tubelius 2007 | Yes - randomisation list generated by a data management company. | Yes - randomisation list generated by a data management company and used for sorting and numbering the packages by another person. A list in a sealed envelope was kept by the sponsor. Randomisation envelopes were also generated by the data management company, and kept for safety by the sponsor. The list of randomisation was kept confidential by the statisticians until all results had been generated and sealed. | Described as double-blind. Packages containing treatment and placebo were identical in appearance. | Yes | No | No (i.e. adequate) | No – 181/262 randomised were included in the analysis. | Low risk of bias |
| Turchet 2003 | Yes – randomization list generated by the sponsor.[[17]](#footnote-17) | Yes –each participant was given a code number plus a letter according to their date of inclusion. | No - open label | Yes – although there was a slight difference in age: mean age was 2 years higher in control group | Yes – 26 (14%) of participants in the treatment group had major deviations compared with 32% in the control group | No (i.e. adequate ) | Yes | Some risk of bias (open label) |

1. To determine whether a study adequately addressed the above criteria (i.e. yes, no or unclear), guidance from the Cochrane Handbook for Systematic Reviews of Interventions was used to apply a judgement.([18](#_ENREF_18)) For the purposes of this review, a study was assumed to have a ‘low risk of bias’ when all of the key quality criteria (i.e. randomisation method, allocation concealment, and blinding) were adequately met as well as most other criteria, an ‘unclear risk’ of bias when most of key criteria were not reported or unclear, and a ‘high risk’ of bias when one or more of the key criteria were not adequately met. We also, included two more categories: the fourth category, ‘some risk of bias’, was applied when all key criteria aspects were adequate, but true intention-to-treat (ITT) was not conducted AND one other criterion was not met, or when two key criteria were adequate, but ITT was not conducted. A fifth category was also created when two key criteria were adequately met, and the rest of the criteria were adequate: ‘unclear/low risk of bias’. These are summarised in Table 2 above. [↑](#footnote-ref-1)
2. Information obtained from study authors. [↑](#footnote-ref-2)
3. Information obtained from study authors. [↑](#footnote-ref-3)
4. Information obtained from study authors. [↑](#footnote-ref-4)
5. Information obtained from study authors. [↑](#footnote-ref-5)
6. Information obtained from study authors/manufacturer. [↑](#footnote-ref-6)
7. Information obtained from study authors/manufacturers. [↑](#footnote-ref-7)
8. Information obtained from study authors/manufacturer. [↑](#footnote-ref-8)
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