**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 2: details of the included studies

**Table 1: Study participants, condition investigated, details of the intervention and comparator and numbers randomised**

|  | | | **Intervention** | | **Comparator** | |
| --- | --- | --- | --- | --- | --- | --- |
| **Study and country of study** | **Population group** | **Condition** | **Detail(s)** | **Number randomised (included in the analysis)** | **Details** | **Number randomised (included in the analysis)** |
| Bentley 2008 (unpublished)  Germany | Adults at increased risk of infection (at least 2 episodes in the previous 6 months) | Common cold | L. plantarum HEAL9, L. paracasei 8700:2 in maltodextrin | 155 (146) | Placebo: sachet containing maltodextrin without living cultures | 155 (138) |
| Berggren 2011  Sweden | Healthy adults aged 18–65 years | Common cold | L. plantarum HEAL9, L. paracasei 8700:2 in maltodextrin | 159 (137) | Placebo: sachet containing maltodextrin without living cultures | 159 (135) |
| Cáceres 2010  Chile | Children (1 to 5 years of age) attending day care centres | Acute respiratory tract infections | L. rhamnosus HN001 | 203 (170) | Placebo: milk product with no probiotic | 195 (179) |
| Cazzola 2010  France | Children (3-7 years) attending school | Common winter diseases (URTI, LRTI, and gastrointestinal tract infections) | L. helveticus R0052, B. infantis R0033, B. bifidum R0071 bacteria | 52 (62) | Placebo: contained only common excipients | 73 (50) |
| de Vrese 2005  Germany | Healthy adults (aged 18–67) | Common cold | L. gasseri PA 16/8, B. longum SP 07/3, B. bifidum MF 20/5 | 238 (225) | Placebo: vitamin mineral preparation without probiotic | 241 (229) |
| Guillemard, Tanguy *et al.* 2010  Germany | Healthy shift workers | Common infectious diseases (URTI, LRTI, and gastrointestinal tract infections) | Actimel, L. paracasei subsp. casei DN- 114 001 combined with S. thermophilus + L. delbrueckii subsp. Bulgaricus | 500 (500) | Placebo: dairy drink without active components | 500 (500) |
| Guillemard, Tondu *et al.* 2010  France | Elderly (not living in an institution) | Upper respiratory tract infection | Actimel, L. paracasei subsp. casei DN- 114 001 combined with S. thermophilus + L. delbrueckii subsp. Bulgaricus | 537 (535) | Placebo: dairy drink without the active components | 535 (535) |
| Hatakka 2001 and 2007  Finland | Children (1-6 years) attending day care centres | Gastrointestinal and respiratory infections | L. rhamnosus GG | Unclear (282) | Placebo: milk without probiotic | Unclear (289) |
| Hojsak, Abdovic *et al.* 2010  Croatia | Hospitalised children aged over 12 months | Respiratory symptoms | L. rhamnosus GG | 376 (376) | Placebo: fermented milk product without L. rhamnosus GG | 366 (366) |
| Hojsak, Snovak *et al.* 2010  Croatia | Children attending day care centres | Respiratory symptoms | L. rhamnosus GG | 139 (139) | Placebo: fermented milk product without L. rhamnosus GG | 142 (142) |
| Kloster 2008  Norway | Children (12-36 months) attending day care centres | Gastrointestinal and respiratory symptoms | Biola with L. rhamnosus GG, L. acidophilus LA-5 and B. lactis BB-12 | 117 (97) | Placebo: fermented milk drink without probiotic bacteria | 123 (102) |
| Kumpu 2012  Finland | Children (2-6 years) attending day care centres | Respiratory symptoms | L. rhamnosus GG | 261 (251) | Placebo: fresh milk without L. rhamnosus | 262 (250) |
| Leyer2009  China | Children (3-5 years of age) | Cold and influenza-like symptoms | (Two interventions)  L. acidophilus NCFM (ATCC 700396)  L. acidophilus NCFM and B. animalis subsp. lactis Bi-07 (ATCC PTA-4802) | 110 (110)  112 (112) | Placebo: sucrose added to 1% fat milk | 104 (104) |
| Merenstein 2010  USA | Healthy children (3 to 6 years) attending day care/school | Common infectious diseases[[1]](#footnote-1) | DanActive, L. paracasei subsp. casei DN-114 001 with S. thermophilus and L. bulgaricus | 314 (250 households) | Placebo: non-fermented acidified dairy drink | 324 (250 households) |
| Niborski 2008 (unpublished)  France | Healthy adults (mostly men); recruited from a fireman training course | Common infectious diseases[[2]](#footnote-2) | L. paracasei subsp. casei DN- 114 001 with S. thermophilus + L. delbrueckii subsp. bulgaricus. | 118 (118) | Placebo: acidified milk (no bacteria) | 121 (121) |
| Prodeus 2008 (unpublished)  Russia | Children (3-5 years) attending day care centres | Upper respiratory infection | L. paracasei subsp. casei DN- 114 001 with S. thermophilus + L. delbrueckii subsp. bulgaricus | 300 (300) | Placebo: acidified milk (no bacteria) | 299 (299) |
| Smith 2012  USA | Apparently healthy college students | Upper respiratory infections (RI) | L. rhamnosus GG and B. lactis BB-12 | 114 (101) | Placebo: powder without probiotic | 117 (97) |
| Tiollier 2007  France | Male cadets undergoing commando training | Respiratory tract infections (RTI) | L. paracasei subsp. casei DN 114 001 | 24 (24) | Placebo: non-fermented milk | 23 (23) |
| Tubelius 2005  Sweden | Healthy employees working at TetraPak. | Respiratory and/or gastrointestinal tract infections | Probiotic drinking straw with L. reuteri protectis, | 132 (94) | Placebo: drinking straw without probiotic | 130 (87) |
| Turchet2003  Italy | Free-living elderly people over 60 years of age | Common infectious diseases[[3]](#footnote-3) | L. casei DN-114 001 | 180 (180) | No treatment | 180 (180) |

**Table 2: Results of studies in children**

| **Study** | **Condition** | **Duration of treatment**  **(months)** | **Treatments** | Mean age (years, standard deviation) | **Number randomised (included in the analysis)** | % female | **Number (%) of participants with at least one illness** | **Number of illness episodes** | **Mean (SD) duration of episodes (days)** | **Mean (SD) number of days ill** | **Mean (SD) duration of days absent** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Cáceres 2010 | Acute RTI | 3 | L. rhamnosus HN001 | 3.1 (1.1) | 203 (170) | 52.7 | NR | 172[[4]](#footnote-4) | 20.4 (14.4) | NR | 4.70 (5.5) |
| Placebo | 3.2 (1.0) | 195 (179) | 50.8 | NR | 181 | 19.4 (14.8) | NR | 4.05 (5.6) |
| Cazzola 2010 | Common winter diseases | 3 | L. helveticus R0052, B. infantis R0033, B. bifidum R0071 + 750mg FOS[[5]](#footnote-5) | 4.1 (1.0) | 62 (62) | 46.8 | 29[[6]](#footnote-6) (47%) | 64[[7]](#footnote-7) | NR | NR | 2.11 (2.1) |
| Placebo | 4.2 (1.1) | 73 (50) | 46.6 | 43 (86%) | 87[[8]](#footnote-8) | 2.88 (2.8) |
| Hatakka 2001 and 2007 | GI and RI | 7 | L. rhamnosus GG | 4.6 (1.5) | Unclear (282) | 46 | 97 (34%) | NR | NR | NR[[9]](#footnote-9) | 4.9 (SD NR)[[10]](#footnote-10) |
| Placebo | 4.4 (1.5) | Unclear (289) | 52 | 123 (43%) | 5.8 (SD NR) |
| Hojsak, 2010 | Respiratory symptoms | Median: 5 days | L. rhamnosus GG | 9.9 (5.1) | 376 (376) | 49.2 | 8 (2%) | NR | NR r | 8 (2.1%)[[11]](#footnote-11) | NR |
| Placebo | 10.6 (5.0) | 366 (366) | 44.3 | 20 (6%) | 19 (5.2%)[[12]](#footnote-12) |
| Hojsak, Snovak 2010 | Respiratory symptoms | 3 | L. rhamnosus GG | 51.9 months (13-86) | 139 (139) | 43.9 | 60 (43%) | NR | NR | 39 (28.1%)[[13]](#footnote-13) | 3.1 (3.6)[[14]](#footnote-14) |
| Placebo | 53.6 months (13-83) | 142 (142) | 44.4 | 96 (68%) | 70 (49.3%)[[15]](#footnote-15) | 5.1 (3.6) |
| Kloster 2008 | Gastrointestinal and respiratory symptoms | 7 | Biola (L. rhamnosus GG with L. acidophilus LA-5 and B. lactis BB-12) | Over both groups: 18 months | 117 (97) | NR | 92[[16]](#footnote-16) (95%) | 492 | 5.39 (7.89)[[17]](#footnote-17) | 5.35 (3.97)[[18]](#footnote-18) | 7.5 (5.0)[[19]](#footnote-19) |
| Placebo | 123 (102) | 95 (93%) | 564 | 4.69 (5.19) | 5.94 (3.77) | 8.5 (5.0) |
| Kumpu 2012 | Respiratory symptoms | 28 weeks | L. rhamnosus GG | 4.0 (1.3) | 261 (251) | 47 | 239 (95%) | NR | Median 8 days (IQR 5,12) | 5.03[[20]](#footnote-20) (0.88) | NR |
| Placebo | 4.0 (1.4) | 262 (250) | 47 | 236 (94%) | NR | Median 8 days (IQR 5, 12) | 5.17 (0.96) |
| Leyer 2009 | Cold and influenza-like symptoms | 6 | L. acidophilus NCFM | 3.7 (0.7) | 110 (110) | 57 | NR | NR | NR | 4.5 (4.7) | 3.6 (3.7)[[21]](#footnote-21) |
| L. acidophilus NCFM and B. animalis subsp. lactis Bi-07 | 3.8 (0.6) | 112 (112) | 52.7 | 3.4 (3.7) | 3.8 (3.9) |
| Placebo | 4.1 (0.54) | 104 (104) | 57.7 | 6.5 (7.3) | 5.2 (5.7) |
| Merenstein 2010 | Common infectious diseases[[22]](#footnote-22) | 90 days | DanActive (L. paracasei subsp. casei DN-114 001 with S. thermophilus and L. bulgaricus) | 4.86 (1.12) | 314 (250 households) | 50 | NR | NR | NR | NR | 421.5[[23]](#footnote-23) days absent (1.69 days/  household |
| Placebo | 4.94 (1.13) | 324 (250 households) | 46.9 | 463.0 days absent (1.85 days/  household |
| Prodeus 2008 (unpublished) | Upper RI | 3 | L. paracasei subsp. casei DN- 114 001 with S. thermophilus + L. delbrueckii subsp. bulgaricus. | Over both groups: 4 | 300 (300) | Overall 45.7 | 66 (22%) | 98[[24]](#footnote-24) | NR | NR | 5.68 (4.01)[[25]](#footnote-25) |
| Placebo | 299 (299) | 73 (24%) | 93[[26]](#footnote-26) | 5.64 (3.67) |

CID – common infectious diseases; GI – gastrointestinal infections; NR - not reported; RI – respiratory infections; RTI – respiratory tract infections

**Table 3a: Results for studies in adults**

| **Study** | **Condition** | **Duration of treatment**  **(weeks)** | **Treatments** | Mean age (years, standard deviation) | **Number randomised (included in the analysis)** | % female | **Number (%) of participants with at least one illness** | **Number of illness episodes** | **Mean (SD) duration of episodes (days)** | **Mean (SD) number of days ill** | **Mean (SD) duration of days absent** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Bentley 2008 | Common cold | 12 | L. plantarum HEAL9 (DSM 15312) and L. paracasei 8700:2 (DSM 13434) | 155 (146) | 45.3 (17.1) | Overall 66.5 | 72 (49%) | 87 | 5.6 (1.3) | NR | NR |
| Placebo | 155 (138) | 46.6 (17.2) | 76 (55%) | 98 | 6.7 (0.8) | NR | NR |
| Berggren, 2011 | Common cold | 12 | L. plantarum HEAL9 (DSM 15312), L. paracasei 8700:2 (DSM 13434) i | 159 (137) | 46.5 | 65.7 | 76 (55%) | 121 | 7.0 (NR)[[27]](#footnote-27) | 6.2 (9.27)[[28]](#footnote-28) | NR |
| Placebo | 159 (135) | 43.7 | 66.7 | 91 (67%) | 170 | 7.0 (NR)[[29]](#footnote-29) | 8.6 (10.45) | NR |
| de Vrese  2005 | Common cold | 3 to 5.5 months | L. gasseri PA 16/8, B. longum SP 07/3, B. bifidum MF 20/5 with Tribion harmonis | 238 (225) | 37 (12) | 63.9 | NR | 158 | 7.0 (SEM 0.5)[[30]](#footnote-30) | NR | NR |
| Placebo | 241 (229) | 38 (14) | 58.9 | NR | 153 | 8.9 (SEM 1.0) |
| Guillemard  2010 | Common infectious diseases | 3 months | Actimel (L. paracasei subsp. casei DN- 114 001 +S. thermophilus + L. delbrueckii subsp. Bulgaricus) | 500 (500) | 31.8 (8.9) | 57 | 213 (43%) | Unclear | 6.9 (4.5) | NR | 2.0 (4.3)[[31]](#footnote-31) |
| Placebo | 500 (500) | 32.5 (8.9) | 56 | 256 (51%) | Unclear | 6.5 (4.5) | NR | 1.6 (4.0) |
| Niborski, 2008 (unpublished) | Common infectious diseases[[32]](#footnote-32) | 7 | L. paracasei subsp. casei DN- 114 001 + S. thermophilus + L. delbrueckii subsp. bulgaricus. | 118 (118) | Overall median 21 (range 18-29) | Overall 1.3 | 28 (24%) | 32 | 3 (2.04)[[33]](#footnote-33) | 3 (2.29) [[34]](#footnote-34) | 0.18 (0.61)[[35]](#footnote-35) |
| Placebo | 121 (121) | 34 (28%) | 38 | 4 (2.04) | 4 (2.29) | 0.24 (0.61) |
| Smith2012 | Upper RTI | 12  s | L. rhamnosus GG and B. lactis BB-12 | 114 (101) | Overall median 19 (range 18-24 years) | 80.2 | Not clear | 83 ‘cases’ | NR | 5.58 (4.41) | 23 days missed work and school (0.27/‘case’) |
| Placebo | 117 (97) | 72.2 | Not clear | 84 ‘cases’ | NR | 7.11 (5.07) | 45 days missed work and school  (0.54/‘case’) |
| Tiollier2007 | RTI | 4 | L. paracasei subsp. casei DN 114 001 | 24 (24) | 21.3 (0.2) | 100% male | 11 (46%) | 17 | NR | 5.5 (1.6) | NR |
| Placebo | 23 (23) | 21.3 (0.4) | 13 (57%) | 30 | NR | 6.1 (1.7) | NR |
| Tubelius 2005 | RTI and GI | 80 days | L. reuteri protectis | 132 (94) | 44 | 35% | NR | NR | NR | NR | Median 3 days |
| Placebo | 130 (87) | 44 | 29% | Median 3 days |

**Table 3b: Results for studies in elderly people**

| **Study** | **Condition** | **Duration of treatment**  **(months)** | **Treatments** | Mean age (years, standard deviation) | **Number randomised (included in the analysis)** | % female | **Number (%) of participants with at least one illness** | **Number of illness episodes** | **Mean (SD) duration of episodes (days)** | **Mean (SD) number of days ill** | **Mean (SD) duration of days absent** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Guillemard  2010 | Upper RTI | 3 | Actimel (L. paracasei subsp. casei DN- 114 001 + S. thermophilus + L. delbrueckii subsp. bulgaricus | 537 (535) | median 76.0 | 63.1 | 61 (11%) | 120 | 7.7 (7.2) | 8.5 (7.2) | NR |
| Placebo | 535 (535) | median 76.0 | 62.2 | 66 (12%) | 135 | 11.0 (7.7) | 11.6 (7.9) |
| Turchet*.* 2003 | Common infectious diseases[[36]](#footnote-36) | 3 | Milk fermented yogurt culture and L. casei DN-114 001 | 180 (180) | 67.1 (SD 6.0) | Overall 67 | 52 (29%) | NR | 7.0 (3.2) | NR | NR |
| No treatment | 180 (180) | 69.3 (SD 5.6) | 50 (28%) | 8.7 (3.7) |

1. Common infectious disease (CID) included upper respiratory tract infections, lower respiratory tract infections, and gastrointestinal tract infections. [↑](#footnote-ref-1)
2. Common infectious disease (CID) included upper respiratory tract infections, lower respiratory tract infections, and gastrointestinal tract infections. [↑](#footnote-ref-2)
3. Common infectious disease (CID) included upper respiratory tract infections, lower respiratory tract infections, and gastrointestinal tract infections. [↑](#footnote-ref-3)
4. The total number of episodes was calculated from the total number of episodes per child (included in the analysis). [↑](#footnote-ref-4)
5. Although this study uses FOS along with probiotic, and does not use it in the control, the level of FOS is only 750 mg, which is considered to be below an active dose (Bouhnik Y, Raskine L, Simoneau G, Paineau D, Bornet F. The capacity of short-chain fructo-oligosaccharides to stimulate faecal bifidobacteria: a dose-response relationship study in healthy humans. *Nutrition Journal* 2006, 5:8; Sabater-Molina M, Larqué E, Torrella F, Zamora S. Dietary fructooligosaccharides and potential benefits on health. J Physiol Biochem. 2009 Sep;65(3):315-28.) [↑](#footnote-ref-5)
6. Data obtained from study authors. [↑](#footnote-ref-6)
7. ‘health events’ [↑](#footnote-ref-7)
8. ‘health events’ [↑](#footnote-ref-8)
9. The authors stated that the number of days with symptoms was lower in the treatment group, but the difference was not significant. [↑](#footnote-ref-9)
10. To calculate mean difference and 95% CIs, standard deviation was calculated from the confidence intervals. [↑](#footnote-ref-10)
11. Children with a RT that lasted > 3 days [↑](#footnote-ref-11)
12. Children with a RT that lasted > 3 days [↑](#footnote-ref-12)
13. Children with a RT that lasted > 3 days [↑](#footnote-ref-13)
14. Standard deviation was calculated from the p value. [↑](#footnote-ref-14)
15. Children with a RT that lasted > 3 days [↑](#footnote-ref-15)
16. Data obtained from study authors. [↑](#footnote-ref-16)
17. Data obtained from study authors. [↑](#footnote-ref-17)
18. Data obtained from study authors. [↑](#footnote-ref-18)
19. Standard deviation was calculated from the p value. [↑](#footnote-ref-19)
20. Number of days with at least one respiratory symptom per subject per month. [↑](#footnote-ref-20)
21. Data obtained from study authors. [↑](#footnote-ref-21)
22. Common infectious disease (CID) included upper respiratory tract infections, lower respiratory tract infections, and gastrointestinal tract infections. [↑](#footnote-ref-22)
23. Data obtained from study authors. [↑](#footnote-ref-23)
24. Number of CIDs [↑](#footnote-ref-24)
25. Data obtained from study authors. [↑](#footnote-ref-25)
26. Number of CIDs [↑](#footnote-ref-26)
27. To calculate mean difference with 95% CIs, standard deviations were imputed based on de Vrese 2005. [↑](#footnote-ref-27)
28. SDs were obtained from the study authors. [↑](#footnote-ref-28)
29. no p value reported [↑](#footnote-ref-29)
30. To calculate mean difference with 95% CIs, standard deviation was calculated from the standard error of the mean (SEM). [↑](#footnote-ref-30)
31. Data obtained from study authors. [↑](#footnote-ref-31)
32. Common infectious disease (CID) included upper respiratory tract infections, lower respiratory tract infections, and gastrointestinal tract infections. [↑](#footnote-ref-32)
33. Standard deviation was calculated from the p value. [↑](#footnote-ref-33)
34. Standard deviation was calculated from the p value. [↑](#footnote-ref-34)
35. Data obtained from study authors. [↑](#footnote-ref-35)
36. Common infectious disease (CID) included upper respiratory tract infections, lower respiratory tract infections, and gastrointestinal tract infections. [↑](#footnote-ref-36)