APPENDIX FIGURES AND TABLES

Appendix figure S1: Risk of bias graph: review authors' judgements about each risk of bias item, presented in A) as percentages across all included studies, and in B) separately for each included study.

 

Appendix figure S2: Classis pair-wise forest plots on placebo versus the specified probiotic strain or combinations to reduce mortality.



Appendix figure S3: Funnel plot of studies on mortality.



Appendix figure S4: Classis pair-wise forest plots on placebo versus the specified probiotic strain or combinations to reduce NEC grade 2 or 3.

Appendix figure S5: Node-splitting consistency model. There were no inconsistencies detected between direct and indirect evidence for reducing NEC grades 2 or 3.



Appendix figure S6: Funnel plot of studies on NEC grades 2 or 3.



Appendix figure S7: Classis pair-wise forest plots on placebo versus the specified probiotic strain or combinations to reduce sepsis.



Appendix figure S8: Node-splitting consistency model. There were no inconsistencies detected between direct and indirect evidence for reducing LOS.



Appendix figure S9: Funnel plot of studies on LOS.



Appendix figure S10: Classis pair-wise forest plots on placebo versus the specified probiotic strain or combinations to reduce time until full enteral feeding (d).



Appendix figure S11: Node-splitting consistency model.



Appendix figure 12: Funnel plot of studies on time to reach full enteral feeding.



Table S1: Overview of all identified strains that were used in the RCTs. Name of the first author and manufacturer are displayed between brackets. If multiple strains were administered in a product or study arm together, a number denotes to the total number of strains in that arm.

|  |  |
| --- | --- |
| **Bacillus:** |  |
| *Ba. clausii* 4 strains: O/C, N/R84, T84, Sin8 | Tewari (Enterogermina) |
| *Ba. coagulans* (previously L. sporogenes) | Sari (DMG Italia) |
| *Ba. subtilis* R0179 (CNCM I-3471) | Zhang 2 (Medilac-Vita) |
|  |  |
| **Bifidobacterium:** |  |
| *B. bifidum* | Roy 4 (Prowel, Alkem); Samanta 4; Underwood 4 (ProBioPlus DDS, UAS) |
| *B. bifidum* NCDO 1453 | Lin 2008 2 (Infloran Berna); Saengtawesin 2 (Infloran Berna) |
| *B. bifidum* OLB6378 | Totsu (Meiji) |
| *B. breve* | Braga 2 (Yakult LB) |
| *B. breve* BBG-001 (YIT4010) | Costeloe (Yakult Honsha) |
| *B. breve* M-16V | Fujii; Hikaru (Morinaga); Patole (Morinaga); Wang (Morinaga) |
| *B. infantis* | Fernández-Carrocera 6 (Italmex); Samanta 4; Underwood 4 (ProBioPlus DDS, UAS) |
| *B. infantis* ATCC 15697 (DSM 20088; S12) | Lin 2005 2 (Infloran) |
| *B. infantis* Bb-02 (DSM 96579) | Jacobs 3 (ABC Dophilus); Bin-Nun 3 (ABC Dophilus) |
| *B. infantis* PTA-5843 | Kanic 3 (Linex) |
| *B. lactis* | Roy 4 (Prowel, Alkem) |
| *B. lactis* B94 (Lafti) | Dilli (Maflor) |
| *B. lactis* Bb-12 (DSM 15954; Chr Hansen; BL 818; NCC 2818)\* | Bin-Nun 3 (ABC Dophilus); Jacobs 3 (ABC Dophilus); Mihatsch (Nestlé); Mohan (Nestlé); Hays 1&2 (Nestlé); Stratiki (Nestlé) |
| *B. longum* | Roy 4 (Prowel, Alkem); Samanta 4; Underwood 4 (ProBioPlus DDS, UAS) |
| *B. longum* 35624 (NCIMB 41003; Bifantis) \*\* | Al Hosni 2 (Align); Havranek 2 (Align); Van Niekerk 2 (ProB2, C Pharm) |
| *B. longum* BB536 (ATCC BAA-999; BL 999; NCC3001) | Hays 1&2 (Nestlé); Rougé 2 (Morinaga) |
| *B. longum* R00175 (CNCM I-3470) | Arora 4 (Darolac, Aristo); Dutta 4 (Darolac, Aristo); Shashidhar 4 (Darolac, Aristo)  |
|  |  |
| **Enterococcus:** |  |
| *E. faecium* PTA-5844 | Kanic 3 (Linex) |
| *E. faecium* R0026 | Zhang 2 (Medilac-Vita) |
|  |  |
| **Lactobacillus:** |  |
| *L. acidophilus* | Fernández-Carrocera 6 (Italmex); Roy 4 (Prowel, Alkem); Samanta 4; Underwood 4 (ProBioPlus DDS, UAS) |
| *L. acidophilus* ATCC 4356 | Lin 2005 2 (Infloran) |
| *L. acidophilus* LA-5 (DSM 13241; Chr Hansen) | Reuman |
| *L. acidophilus* Lb | Awad (Lacteol fort) |
| *L. acidophilus* NCDO 1748 | Lin 2008 2 (Infloran Berna); Saengtawesin 2 (Infloran Berna) |
| *L. casei* | Braga 2 (Yakult LB); Fernández-Carrocera 6 (Italmex) |
| *L. gasseri* PTA-5845 | Kanic 3 (Linex) |
| *L. helveticus* R0052 (CNCM I-1722) \*\*\* | Arora 4 (Darolac, Aristo); Dutta 4 (Darolac, Aristo); Shashidhar 4 (Darolac, Aristo) |
| *L. plantarum* | Fernández-Carrocera 6 (Italmex) |
| *L. reuteri* ATCC 55730 (SD2112) | Romeo |
| *L. reuteri* DSM 17938 | Indrio (BioGaia); Oncel (BioGaia); Rojas (BioGaia); Shadkam (BioGaia) |
| *L. rhamnosus* | Fernández-Carrocera 6 (Italmex) |
| *L. rhamnosus* GG (ATCC 53103; NCC4007; Chr Hansen) | Al Hosni 2 (Culturelle); Chrzanowska- Liszewska (Vitis); Dani (Dicoflor); Havranek 2 (Culturelle); Manzoni 2006 (Dicoflor); Manzoni 2009 (Dicoflor); Manzoni 2014 (Dicoflor); Millar (Valio); Pärtty (Mead Johnson); Romeo; Rougé 2 (Valio); Underwood (Culturelle); Van Niekerk 2 (ProB2, C Pharm) |
| *L. rhamnosus* R0011 (CNCM I-1720) | Arora 4 (Darolac, Aristo); Dutta 4 (Darolac, Aristo); Shashidhar 4 (Darolac, Aristo) |
|  |  |
| **Sacharomyces:** |  |
| *Sa. boulardii* CNCM I-745 | Costalos; Demirel (Reflor); Serce (Reflor); Xu (Bioflor); Zhang (Bioflor) |
| *Sa. boulardii* CNCM I-1079 | Arora 4 (Darolac, Aristo); Dutta 4 (Darolac, Aristo); Shashidhar 4 (Darolac, Aristo) |
| *Sa. boulardii* CNCM I-3799 | Zeber-Lubecka (Dierol; Sequoia) |
|  |  |
| **Streptococcus:** |  |
| *S. thermophilus* | Fernández-Carrocera 6 (Italmex) |
| *S. thermophilus* TH-4 (DSM 15957; Chr Hansen) | Jacobs 3 (ABC Dophilus); Bin-Nun 3 (ABC Dophilus) |

\* Previously also known as *B. bifidum* Bb-12

\*\* Previously also known as *B. infantis* 35624

\*\*\* Previously also known as *L. acidophilus* R0052

Table S2: All included studies in which data on mortality were available. n/N denotes number of affected infants (n) and number of included infants (N).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Placebo | Ba. clausii (4 strains) | Ba. coagulans (L sporogenes) | B. bifidum OLB6378 | B. bifidum NCDO 1453 +L. acidophilus NCDO 1748 | B. bifidum + B. infantis + B. longum +L. acidophilus | B. bifidum + B. lactis + B. longum +L. acidophilus | B. breve BBG-001 | B. breve M-16V | B. breve + L. casei | B. infantis Bb-02 + B. lactis Bb-12 +S. thermophilus TH-4 | B. infantis ATCC 15697 +L. acidophilus ATCC 4356 | B. infantis + L. acidoph + L. casei +L. plantarum + L. rhamnos + S. thermoph | B. infantis PTA-5843 + E. faecium PTA-5844 + L. gasseri PTA-5845 | B. lactis Bb-12 *OR* B. lactis B94 | B. lactis Bb-12 + B. longum BB536 | B. longum BB536 | B. longum BB536 + L. rhamnosus GG | B. longum 35624 + L. rhamnosus GG | B. longum R00175 + L. helveticus R0052 +L. rhamn R0011 + Sa. boul CNCM I-1079 | L. acidophilus Lb | L. acidophilus LA-5 (DSM 13241) | L. reuteri ATCC 55730 *OR* L. reuteri DSM 17938 | L. rhamnosus GG ATCC 53103 | Sa. boulardii CNCM I-745 | Sa. boulardii CNCM I-3799 |
| Al-Hosni, 2012 | 4/51 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 3/50 |  |  |  |  |  |  |  |
| Arora, 2017 | 2/75 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 0/75 |  |  |  |  |  |  |
| Awad, 2010 | 5/16 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 4/36 |  |  |  |  |  |
| Bin-Nun, 2005 | 8/73 |  |  |  |  |  |  |  |  |  | 3/72 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Braga, 2011 | 27/112 |  |  |  |  |  |  |  |  | 26/119 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Costeloe, 2016 | 56/660 |  |  |  |  |  |  | 54/650 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Demirel, 2013 | 5/136 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 5/135 |  |
| Dilli, 2015 | 14/200 |  |  |  |  |  |  |  |  |  |  |  |  |  | 6/200 |  |  |  |  |  |  |  |  |  |  |  |
| Dutta, 2015 | 2/35 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 8/114 |  |  |  |  |  |  |
| Fernández-Carrocera, 2013 | 7/75 |  |  |  |  |  |  |  |  |  |  |  | 1/75 |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Hays, 2016 | 1/52 |  |  |  |  |  |  |  |  |  |  |  |  |  | 1/50 | 1/47 | 3/48 |  |  |  |  |  |  |  |  |  |
| Hikaru, 2010 | 4/100 |  |  |  |  |  |  |  | 0/108 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Jacobs, 2013 | 28/551 |  |  |  |  |  |  |  |  |  | 27/548 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Kanic, 2015 | 3/40 |  |  |  |  |  |  |  |  |  |  |  |  | 2/40 |  |  |  |  |  |  |  |  |  |  |  |  |
| Lin, 2005 | 20/187 |  |  |  |  |  |  |  |  |  |  | 7/180 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lin, 2008 | 9/217 |  |  |  | 2/217 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Manzoni, 2006 | 6/41 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 5/39 |  |  |
| Manzoni, 2009 | 4/153 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 6/151 |  |  |
| Mihatsch, 2010 | 1/89 |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 2/91 |  |  |  |  |  |  |  |  |  |  |
| Oncel, 2014 | 20/200 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 15/200 |  |  |  |
| Patole, 2014 | 0/76 |  |  |  |  |  |  |  | 0/76 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Reuman, 1986 | 3/15 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1/15 |  |  |  |  |
| Rojas, 2012 | 28/378 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 22/372 |  |  |  |
| Romeo, 2011 | 0/83 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 0/83 | 0/83 |  |  |
| Rougé, 2009 | 4/49 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 2/45 |  |  |  |  |  |  |  |  |
| Roy, 2014 | 8/56 |  |  |  |  |  | 7/56 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Saengtawesin, 2014 | 0/29 |  |  |  | 0/31 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Samanta, 2009 | 14/95 |  |  |  |  | 4/91 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Sari, 2011 | 4/111 |  | 3/110 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Serce, 2013 | 4/104 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 5/104 |  |
| Shadkam, 2015 | 2/30 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1/30 |  |  |  |
| Shashidhar, 2017 | 3/52 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1/52 |  |  |  |  |  |  |
| Tewari, 2015 | 14/121 | 12/123 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Totsu, 2014 | 0/130 |  |  | 2/153 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Van Niekerk, 2015 | 6/93 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 5/91 |  |  |  |  |  |  |  |
| Zeber-Lubecka, 2016 | 0/27 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 0/28 |
| Total infants (n/N) | 316/4512 | 12/123 | 3/110 | 2/153 | 2/248 | 4/91 | 7/56 | 54/650 | 0/184 | 26/119 | 30/620 | 7/180 | 1/75 | 2/40 | 7/250 | 3/138 | 3/48 | 2/45 | 8/141 | 9/241 | 4/36 | 1/15 | 38/685 | 11/273 | 10/239 | 0/28 |
| Total studies | 36 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 2 | 1 | 2 | 1 | 1 | 1 | 2 | 2 | 1 | 1 | 2 | 3 | 1 | 1 | 4 | 3 | 2 | 1 |

Table S3: All included studies in which data on NEC grades 2 or 3 were available. n/N denotes number of affected infants (n) and number of included infants (N).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Placebo | Ba. clausii (4 strains)  | Ba. coagulans (L sporogenes) | Ba. subtilis R0179 + E. faecium R0026 | B. bifidum OLB6378 | B. bifidum NCDO 1453 +L. acidophilus NCDO 1748 | B. bifidum + B. infantis + B. longum +L. acidophilus | B. bifidum + B. lactis + B. longum +L. acidophilus | B. breve BBG-001 | B. breve M-16V | B. breve + L. casei | B. infantis Bb-02 + B. lactis Bb-12 +S. thermophilus TH-4 | B. infantis ATCC 15697 +L. acidophilus ATCC 4356 | B. infantis + L. acidoph + L. casei +L. plantarum + L. rhamnos + S. thermoph | B. infantis PTA-5843 + E. faecium PTA-5844 + L. gasseri PTA-5845 | B. lactis Bb-12 *OR* B. lactis B94 | B. lactis Bb-12 + B. longum BB536 | B. longum BB536 | B. longum BB536 + L. rhamnosus GG | B. longum 35624 + L. rhamnosus GG | B. longum R00175 + L. helveticus R0052 +L. rhamn R0011 + Sa. boul CNCM I-1079 | L. acidophilus Lb | L. reuteri ATCC 55730 *OR* L. reuteri DSM 17938 | L. rhamnosus GG ATCC 53103 | Sa. boulardii CNCM I-745 | Sa. boulardii CNCM I-3799 |
| Al-Hosni, 2012 | 2/51 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 2/50 |  |  |  |  |  |  |
| Arora, 2017 | 4/75 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 0/75 |  |  |  |  |  |
| Awad, 2010 | 5/16 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 0/36 |  |  |  |  |
| Bin-Nun, 2005 | 10/73 |  |  |  |  |  |  |  |  |  |  | 1/72 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Braga, 2011 | 4/112 |  |  |  |  |  |  |  |  |  | 0/119 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Chrzanowska-Liszewska, 2012 | 0/26 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 0/21 |  |  |
| Costalos, 2003 | 6/36 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 5/51 |  |
| Costeloe, 2016 | 66/660 |  |  |  |  |  |  |  | 61/650 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dani, 2002 | 8/290 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 4/295 |  |  |
| Demirel, 2013 | 7/136 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 6/135 |  |
| Dilli, 2015 | 30/200 |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 6/200 |  |  |  |  |  |  |  |  |  |  |
| Dutta, 2015 | 0/35 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 6/114 |  |  |  |  |  |
| Fernández-Carrocera, 2013 | 12/75 |  |  |  |  |  |  |  |  |  |  |  |  | 6/75 |  |  |  |  |  |  |  |  |  |  |  |  |
| Fujii, 2006 | 0/8 |  |  |  |  |  |  |  |  | 0/11 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Hays, 2016 | 3/52 |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 2/50 | 5/47 | 1/48 |  |  |  |  |  |  |  |  |
| Hikaru, 2010 | 0/100 |  |  |  |  |  |  |  |  | 0/108 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Jacobs, 2013 | 24/551 |  |  |  |  |  |  |  |  |  |  | 11/548 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Kanic, 2015 | 5/40 |  |  |  |  |  |  |  |  |  |  |  |  |  | 0/40 |  |  |  |  |  |  |  |  |  |  |  |
| Lin, 2005 | 10/187 |  |  |  |  |  |  |  |  |  |  |  | 2/180 |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lin, 2008 | 14/217 |  |  |  |  | 4/217 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Manzoni, 2006 | 3/41 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1/39 |  |  |
| Manzoni, 2014 | 5/247 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 0/238 |  |  |
| Mihatsch, 2010 | 4/89 |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 2/91 |  |  |  |  |  |  |  |  |  |  |
| Mohan, 2006 | 1/32 |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 2/37 |  |  |  |  |  |  |  |  |  |  |
| Oncel, 2014 | 10/200 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 8/200 |  |  |  |
| Patole, 2014 | 1/76 |  |  |  |  |  |  |  |  | 0/77 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Rojas, 2012 | 15/378 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 9/372 |  |  |  |
| Romeo, 2011 | 0/83 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 0/83 | 0/83 |  |  |
| Rougé, 2009 | 1/49 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 2/45 |  |  |  |  |  |  |  |
| Roy, 2014 | 2/56 |  |  |  |  |  |  | 1/56 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Saengtawesin, 2014 | 1/29 |  |  |  |  | 1/31 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Samanta, 2009 | 15/95 |  |  |  |  |  | 5/91 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Sari, 2011 | 10/111 |  | 6/110 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Serce, 2013 | 7/104 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 7/104 |  |
| Shadkam, 2015 | 11/30 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 2/30 |  |  |  |
| Shashidhar, 2017 | 6/52 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 2/52 |  |  |  |  |  |
| Stratiki, 2007 | 3/36 |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 0/41 |  |  |  |  |  |  |  |  |  |  |
| Tewari, 2015 | 0/121 | 0/123 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Totsu, 2014 | 0/130 |  |  |  | 0/153 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Underwood, 2009 |  |  |  |  |  |  | 1/31 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1/30 |  |  |
| Van Niekerk, 2015 | 4/93 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 0/91 |  |  |  |  |  |  |
| Wang 2007 | 0/33 |  |  |  |  |  |  |  |  | 0/33 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Xu, 2016 | 0/49 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 0/51 |  |
| Zeber-Lubecka, 2016 | 0/27 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 0/28 |
| Zhang, 2017 |  |  |  | 3/80 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 4/80 |  |
| Total infants (n/N) | 309/5101 | 0/123 | 6/110 | 3/80 | 0/153 | 5/248 | 6/122 | 1/56 | 61/650 | 0/229 | 0/119 | 12/620 | 2/180 | 6/75 | 0/40 | 12/419 | 5/47 | 1/48 | 2/45 | 2/141 | 8/241 | 0/36 | 19/685 | 6/706 | 22/421 | 0/28 |
| Total studies | 43 | 1 | 1 | 1 | 1 | 2 | 2 | 1 | 1 | 4 | 1 | 2 | 1 | 1 | 1 | 5 | 1 | 1 | 1 | 2 | 3 | 1 | 4 | 6 | 5 | 1 |

Table S4: All included studies in which data on LOS were available. n/N denotes number of affected infants (n) and number of included infants (N).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|   | Placebo | Ba. clausii (4 strains)  | Ba. coagulans (L sporogenes) | Ba. subtilis R0179 + E. faecium R0026 | B. bifidum OLB6378 | B. bifidum NCDO 1453 +L. acidophilus NCDO 1748 | B. bifidum + B. infantis + B. longum +L. acidophilus | B. bifidum + B. lactis + B. longum +L. acidophilus | B. breve BBG-001 | B. breve M-16V | B. breve + L. casei | B. infantis Bb-02 + B. lactis Bb-12 +S. thermophilus TH-4 | B. infantis ATCC 15697 +L. acidophilus ATCC 4356 | B. infantis + L. acidoph + L. casei +L. plantarum + L. rhamnos + S. thermoph | B. infantis PTA-5843 + E. faecium PTA-5844 + L. gasseri PTA-5845 | B. lactis Bb-12 OR B. lactis B94 | B. lactis Bb-12 + B. longum BB536 | B. longum BB536 | B. longum BB536 + L. rhamnosus GG | B. longum 35624 + L. rhamnosus GG | B. longum R00175 + L. helveticus R0052 +L. rham R0011 + Sa. boul CNCM I-1079 | L. acidophilus Lb | L. reuteri ATCC 55730 *OR* L. reuteri DSM 17938 | L. rhamnosus GG ATCC 53103 | Sa. boulardii CNCM I-745 | Sa. boulardii CNCM I-3799 |
| Al-Hosni, 2012 | 16/51 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 13/50 |  |  |  |  |  |  |
| Arora, 2017 | 21/75 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 2/75 |  |  |  |  |  |
| Awad, 2010 | 12/16 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 18/36 |  |  |  |  |
| Bin-Nun, 2005 | 24/73 |  |  |  |  |  |  |  |  |  |  | 31/72 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Braga, 2011 | 42/112 |  |  |  |  |  |  |  |  |  | 40/119 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Chrzanowska-Liszewska, 2012 | 3/26 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 2/21 |  |  |
| Costalos, 2003 | 3/36 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 3/51 |  |
| Costeloe, 2016 | 206/660 |  |  |  |  |  |  |  | 186/650 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Dani, 2002 | 12/290 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 14/295 |  |  |
| Demirel, 2013 | 21/136 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 20/135 |  |
| Dilli, 2015 | 23/200 |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 16/200 |  |  |  |  |  |  |  |  |  |  |
| Dutta, 2015 | 6/35 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 10/114 |  |  |  |  |  |
| Fernández-Carrocera, 2013 | 44/75 |  |  |  |  |  |  |  |  |  |  |  |  | 42/75 |  |  |  |  |  |  |  |  |  |  |  |  |
| Fujii, 2006 | 1/8 |  |  |  |  |  |  |  |  | 1/11 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Hays, 2016 | 10/52 |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 9/50 | 8/47 | 8/48 |  |  |  |  |  |  |  |  |
| Hikaru, 2010 | 22/100 |  |  |  |  |  |  |  |  | 10/108 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Jacobs, 2013 | 89/551 |  |  |  |  |  |  |  |  |  |  | 72/548 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Kanic, 2015 | 29/40 |  |  |  |  |  |  |  |  |  |  |  |  |  | 16/40 |  |  |  |  |  |  |  |  |  |  |  |
| Lin, 2005 | 36/187 |  |  |  |  |  |  |  |  |  |  |  | 22/180 |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lin, 2008 | 24/217 |  |  |  |  | 40/217 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Manzoni, 2006 | 22/41 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 19/39 |  |  |
| Manzoni, 2009 | 9/153 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 7/151 |  |  |
| Mihatsch, 2010 | 29/89 |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 28/91 |  |  |  |  |  |  |  |  |  |  |
| Millar, 1993 | 0/10 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 0/10 |  |  |
| Mohan, 2006 | 1/32 |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 3/37 |  |  |  |  |  |  |  |  |  |  |
| Oncel, 2014 | 25/200 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 13/200 |  |  |  |
| Pärtty, 2013 | 0/32 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 0/31 |  |  |
| Patole, 2014 | 12/76 |  |  |  |  |  |  |  |  | 17/77 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Rojas, 2012 | 17/378 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 24/372 |  |  |  |
| Romeo, 2011 | 4/83 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 0/83 | 1/83 |  |  |
| Rougé, 2009 | 13/49 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 15/45 |  |  |  |  |  |  |  |
| Roy, 2014 | 42/56 |  |  |  |  |  |  | 31/56 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Saengtawesin, 2014 | 1/29 |  |  |  |  | 2/31 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Samanta, 2009 | 28/95 |  |  |  |  |  | 13/91 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Sari, 2011 | 26/111 |  | 29/110 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Serce, 2013 | 25/104 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 19/104 |  |
| Shadkam, 2015 | 10/30 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 4/30 |  |  |  |
| Shashidhar, 2017 | 7/52 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 6/52 |  |  |  |  |  |
| Stratiki, 2007 | 3/36 |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 0/41 |  |  |  |  |  |  |  |  |  |  |
| Tewari, 2015 | 11/121 | 8/123 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Totsu, 2014 | 13/130 |  |  |  | 6/153 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Underwood, 2009 |  |  |  |  |  |  | 2/31 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 4/30 |  |  |
| Van Niekerk, 2015 | 10/93 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 15/91 |  |  |  |  |  |  |
| Wang 2007 | 0/33 |  |  |  |  |  |  |  |  | 0/33 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Xu, 2016 | 6/49 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 4/51 |  |
| Zeber-Lubecka, 2016 | 0/27 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 0/28 |
| Zhang, 2017 |  |  |  | 5/80 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1/80 |  |
| Total infants (n/N) | 1255/5049 | 8/123 | 29/110 | 5/80 | 6/153 | 42/248 | 15/122 | 31/56 | 186/650 | 28/229 | 40/119 | 103/620 | 22/180 | 42/75 | 16/40 | 56/419 | 8/47 | 8/48 | 15/45 | 28/141 | 18/241 | 18/36 | 41/685 | 47/660 | 47/421 | 0/28 |
| Total studies | 45 | 1 | 1 | 1 | 1 | 2 | 2 | 1 | 1 | 4 | 1 | 2 | 1 | 1 | 1 | 5 | 1 | 1 | 1 | 2 | 3 | 1 | 4 | 8 | 5 | 1 |

Table S5: All included studies in which data on time to reach full enteral feeding were available. Data presented as mean ± SD (N), where N denotes number of included infants.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Placebo | Ba. coagulans (L sporogenes) | B. bifidum + B. infantis +B. longum + L. acidophilus | B. breve BBG-001 (YIT4010) | B. breve M-16V | B. breve + L. casei | B. infantis Bb-02 + B. lactis Bb-12 + S. thermophilus TH-4 | B. lactis Bb-12 OR B. lactis B94 | B. longum BB536 +L. rhamnosus GG | B. longum 35624 +L. rhamnosus GG | B. longum R00175 + L. helveticus R0052 +L. rhamnosus R0011 +Sa. boulardii CNCM I-1079 | L. reuteri ATCC 55730 *OR* L. reuteri DSM 17938 | L. rhamnosus GG ATCC 53103 | Sa. boulardii CNCM I-745 |
| Arora, 2017 | 10.7 ± 3.3(75) |  |  |  |  |  |  |  |  |  | 8.5 ± 2.1(75) |  |  |  |
| Braga, 2011 | 17.4 ± 5.7(112) |  |  |  |  | 15.2 ± 5.2 (119) |  |  |  |  |  |  |  |  |
| Costalos, 2003 | 9.9 ± 4.5(36) |  |  |  |  |  |  |  |  |  |  |  |  | 9.3 ± 2.7(51) |
| Costeloe, 2016 | 14 ± 8.9(660) |  |  | 14 ± 8.9(650) |  |  |  |  |  |  |  |  |  |  |
| Demirel, 2013 | 13.2 ± 12.8(136) |  |  |  |  |  |  |  |  |  |  |  |  | 11.7 ± 4.7(135) |
| Dilli, 2015 | 21 ± 13.7(200) |  |  |  |  |  |  | 19 ± 9.7(200) |  |  |  |  |  |  |
| Havranek, 2013 | 22.1 ± 8.5(16) |  |  |  |  |  |  |  |  | 23.9 ± 8.3(15) |  |  |  |  |
| Indrio, 2017 | 7.5 ± 3.2(30) |  |  |  |  |  |  |  |  |  |  | 4.2 ± 1.1(30) |  |  |
| Jacobs, 2013 | 12 ± 5.2(551) |  |  |  |  |  | 12 ± 5.2(548) |  |  |  |  |  |  |  |
| Manzoni, 2006 | 17 ± 9(41) |  |  |  |  |  |  |  |  |  |  |  | 15 ± 8(39) |  |
| Manzoni, 2014 | 12.3 ± 4.3(247) |  |  |  |  |  |  |  |  |  |  |  | 13.2 ± 5.0(238) |  |
| Mihatsch, 2010 | 18 ± 7.4(89) |  |  |  |  |  |  | 17.9 ± 6.8 (91) |  |  |  |  |  |  |
| Oncel, 2014 | 10.1 ± 4.3(200) |  |  |  |  |  |  |  |  |  |  | 9.1 ± 3.2(200) |  |  |
| Patole, 2014 | 12 ± 13(76) |  |  |  | 12 ± 10.8(77) |  |  |  |  |  |  |  |  |  |
| Romeo, 2011 | 17.3 ± 9.7(83) |  |  |  |  |  |  |  |  |  |  | 10.7 ± 7.2(83) | 15.2 ± 6.8(83) |  |
| Rougé, 2009 | 26 ± 11.1(49) |  |  |  |  |  |  |  | 16 ± 8.9(45) |  |  |  |  |  |
| Samanta, 2009 | 19.2 ± 2.0(95) |  | 13.8 ± 2.3(91) |  |  |  |  |  |  |  |  |  |  |  |
| Sari, 2011 | 18.3 ± 9.8 (111) | 17.3 ± 8.7(110) |  |  |  |  |  |  |  |  |  |  |  |  |
| Shashidhar, 2017 | 12.7 ± 8.9(52) |  |  |  |  |  |  |  |  |  | 11.2 ± 8.3(52) |  |  |  |
| Stratiki, 2007 | 10 ± 7.5(36) |  |  |  |  |  |  | 10 ± 13(41) |  |  |  |  |  |  |
| Underwood, 2009 |  |  | 9 ± 5.2(30) |  |  |  |  |  |  |  |  |  | 12 ± 6.7(28) |  |
| Van Niekerk, 2015 | 10.5 ± 4.0(93) |  |  |  |  |  |  |  |  | 9.8 ± 3.2(91) |  |  |  |  |
| Total infants (N) | 2988 | 110 | 121 | 650 | 77 | 119 | 548 | 332 | 45 | 106 | 127 | 313 | 388 | 186 |
| Total studies | 21 | 1 | 2 | 1 | 1 | 1 | 1 | 3 | 1 | 2 | 2 | 3 | 4 | 2 |