Table S1. Summary of methods

Criteria for considering studies	
Research question	For each condition, the clinical question was "*Should any specific probiotic vs. placebo or no probiotic be used for children with [GI disease]?"*
Type of document	ESPGHAN Position Paper
Type of studies	Systematic reviews and/or meta-analyses, as well as subsequently published peer-reviewed RCTs. Previously published ESPGHAN/Working Group/Committee on Nutrition documents related to probiotics. Search date: from [date of the last search to December 2021. Not more than 15 years back - or update from a previous systematic review.
Type of participants	Children up to age 18 years, preferably living in geographic Europe.
Type of interventions	Active (e.g., live or viable) forms of probiotics (single or in combination) in all delivery vehicles (and formulations).
Type of outcomes	The following diseases were included: acute gastroenteritis (AGE); antibiotic-associated diarrhea (AAD); nosocomial diarrhea; necrotizing enterocolitis (NEC); *H pylori* infection; inflammatory bowel disease (IBD); functional GI disorders, particularly infantile colic, functional abdominal pain disorders (FAPD), functional constipation; celiac disease; small intestinal bacterial overgrowth (SIBO); pancreatitis. Some of the conditions were previously evaluated by the ESPGHAN Working Group on Probiotics and Prebiotics (e.g., acute gastroenteritis, AAD, NEC). If so, the document provides updated recommendations. The final list of the conditions to be included is the result of voting by the members of the ESPGHAN Working Group prior to the start of the project.
Search methods of identification of studies	
Electronic searches	For systematic reviews/meta-analyses: • The *Cochrane Database of Systematic Reviews* • The DARE (*Database of Abstracts of Reviews of Effects)* For systematic reviews/meta-analyses and subsequently published trials (starting from the date of the most recent search in the included reviews). • CENTRAL *(Cochrane Central Register of Controlled Trials).* • PubMed *(National Library of Medicine, includes MEDLINE®).* • EMBASE *(Biomedical and pharmacological bibliographic database).* The search was carried out independently by at least two reviewers. Language: English.
Searching other resources	The reference lists from identified studies and key review articles, including previously published meta-analyses.
Search terms	Depends on the topic. For updates, the same search terms as used earlier.
Data collection and analysis	
Selection of studies	An initial screening of the title, abstract, and keywords of every record identified was performed. The next step was the retrieval of the full text of potentially relevant publications. At least two reviewers independently assessed the eligibility of each potentially relevant trial with the use of inclusion criteria. If they were different opinions, these were resolved by discussion with at least one other member of the Working Group.
Data extraction	The data extracted included baseline characteristics, inclusion criteria, experimental and control treatments, setting, dose, outcomes of interest (with definitions, if available), and funding.

Assessment of risk of bias in included trials	RCT: The Cochrane Collaboration's tool for assessing risk of bias was used, which includes the following criteria: adequacy of sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; and incomplete outcome data were addressed. RCTs included in published systematic reviews/meta-analyses: the reviewers' assessment was considered.
Measures of treatment effect	If feasible, for dichotomous outcomes, the results for individual studies, and pooled statistics were reported as the risk ratio (RR) between the experimental and control groups with 95% confidence intervals (CI). For continuous outcomes, the results were reported as the mean difference (MD) with 95% CI.
Certainty of evidence	The certainty of evidence (also called quality of the evidence) was categorized as high, moderate, low, or very low based on consideration of the risk of bias, the directness of evidence, consistency, and precision of the estimates. *Low* and *very low-certainty of evidence* indicates that the estimated effects of interventions are very uncertain, and further research is very likely to influence the resulting recommendations.
Strength of recommendations	The strength of each recommendation is expressed as either • *strong* [when the evidence showed that the benefit of the intervention clearly outweighs the undesirable effects] or • *weak (conditional)* [when the trade-offs were less certain (either because of the low quality of evidence or because the evidence suggests that desirable and undesirable effects are closely balanced)].
Wording of statements	Strong recommendation *for*: Healthcare professionals should recommend X to Y. Weak recommendation *for*: Healthcare professionals may recommend X to Y. No recommendation: There is no recommendation *for* or *against* X to Y. Weak recommendation *against:* Healthcare professionals may *not* recommend X to Y. Strong recommendation *against* (i.e., Healthcare professionals should *not* recommend X to Y") *[X is the probiotic intervention and Y is the population]*
Formulation of the statements The modified Delphi process to establish consensus on the statements	The modified Delphi process was used to establish consensus on the statements. Round 1 • The draft document containing the list of statements formulated by the core group was circulated by email to all group members. • Each member was asked to vote by marking "agree" or "disagree" beside each statement. • Each member was given the opportunity to provide comments and suggest different wording. • Anonymity was retained. • Eighty percent agreement from the group was required in order to accept or omit a statement during development of the final document. • Statements not meeting 80% agreement were modified according to feedback provided by the group members and sent to the group for round 2. Round 2 • The list of statements that did not meet consensus from round 1 was emailed to all the members. • In round 2, the group used the same voting method as described for round 1, but with the knowledge of the group scores and comments. • Thus, everyone could reflect upon the group results and change their mind, while preserving the anonymity of their responses. • Final responses were analyzed as described for round 1, and statements not meeting agreement were retained for discussion in round 3. Round 3 • Round 3 was a [virtual] face-to-face meeting.

	• Eighty percent agreement was used to determine acceptance or rejection of a statement. • Anonymity was not retained. • The discussion continued until agreement was reached to retain, modify, or eliminate the statement from the final document. Once full consensus was reached, the statements were included in the final document.
Public consultation	The prefinal draft of this document was submitted for public consultation on X via the ESPGHAN website. ESPGHAN members and all interested parties were invited to submit written comments within 10 days.

Table S2.
The list of probiotics used in studies on *H pylori* infection and functional gastrointestinal disorders (infant colic and functional constipation).

Note: The genus of *Lactobacillus* has been recently reclassified into 25 genera, which include 23 novel genera (1). For example, the new name for *Lactobacillus rhamnosus* is *Lacticaseibacillus rhamnosus.* However, the abbreviations of microorganisms remained the same *(*i.e., *L rhamnosus).* Species names and strain designations did not change (1). Throughout the manuscript and in the supplementary materials, the strain names were used as in the original publications. However, when formulating the recommendation, the new strain names were used.

***Helicobacter pylori* Infection**

The following probiotics (in alphabetical order) were included in the reviews (2-5).

- *Bacillus cereus, Bifidobacterium infantis, Enterococcus faecalis* and *Lactobacillus acidophilus* (6)
- *Bacillus mesentericus, Clostridium butyricum and Streptococcus faecalis* (7)
- *Bifidobacterium animalis* and *Lactobacillus casei* (in yoghurt)(8)
- *Bifidobacterium bifidum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus bulgaricus, Lactobacillus casei, Lactobacillus reuteri and Streptococcus* (9)
- *Bifidobacterium infantis and Clostridium butyricum* (10) (11)
- *Bifidobacterium longum, Enterococcus faecalis* and *Lactobacillus acidophilus* (12) (13)
- *Bifidobacterium longum, Lactobacillus bulgaricus* and *Streptococcus thermophilus* (no strain specification) (14, 15)
- *Bifidobacterium longum, Lactobacillus bulgaricus* and *Streptococcus thermophilus* (16) (17)
- *Lactobacillus* (14)
- *Lactobacillus acidophilus* (15, 18-20)
- *Lactobacillus acidophilus & B bifidum* (21)
- *Lactobacillus acidophilus* R0052 & *L rhamnosus* R0011 (22)
- *Lactobacillus acidophilus, L rhamnosus, L bulgaricus, L casei, Streptococcus thermophilus, B infantis* and *B breve*](23)
- *Lactobacillus casei* 2401, *L. acidophilus* 2027, and *B. lactis* 2211 (24)
- *Lactobacillus casei* DN 114 001 (25)
- *Lactobacillus delbrueckii, Lactobacillus acidophilus and Lactococcus lactis* (26)
- *Lactobacillus plantarum, L reuteri, L casei subsp. rhamnosus, B infantis, B longum, L salivarius, L acidophilus, Streptococcus thermophilus, L sporogenes* (27)
- *Lactobacillus reuteri* ATCC 55730 (currently replaced by *L reuteri* DSM 17938) (28)
- *Lactobacillus reuteri* DSM 17938 (29)
- *Lactobacillus rhamnosus* GG (30)
- *Saccharomyces boulardii* (31, 32) (33), (34), including one trial clearly stating the strain *S boulardii* CNCM I-745 (35)

For this document, four systematic reviews with meta-analyses, some additionally with network meta-analyses, were identified (2-5). Information about the single probiotic strain (*S boulardii)* for which recommendations were made is presented in the main text. While additional probiotics were evaluated in these reviews, none of the probiotics was evaluated in more than one trial, thus, none met our inclusion criteria. Information about use of these various probiotic stains for *H pylori* eradication and treatment of therapy-related adverse effects is presented below.

Eradication

A 2017 traditional and network meta-analysis evaluated the effects of probiotics (17 various regimens: strains not always well defined) on *H pylori* eradication rates in children (2)(Feng et al., 2017). A traditional meta-analysis found that, compared with placebo, probiotics (as a group) increased the eradication rate of triple therapy (29 trials, n=3122, RR 1.19, 95% 1.13-1.25). A network meta-analysis found *L casei* [DN-114 001] as the best probiotic to increase *H pylori* eradication rates in children (P score = 0.84; P-scores with a higher value indicate greater effect)(2)(Feng et al., 2017). However, this was based on a single trial only.

A 2019 meta-analysis by Fang et al. focused on the efficacy of *Lactobacillus*-supplementation given along with triple *H pylori* therapy in children (36). The strains were *L acidophilus* and *L rhamnosus*, *L reuteri*, *L casei*, *Lactobacillus* GG, or not specified. Overall, in the *Lactobacillus*-supplemented groups compared to the control groups, the eradication rate was significantly higher (84% vs. 71.4%, respectively, RR 1.19, 95% CI 1.07 to 1.33, I^2=0%). The eradication rate was increased significantly in the high-dose *Lactobacillus* group (2 RCTs, n=146, 91.3% vs. 64.9%, respectively, RR 1.36, 95% CI 1.15 to 1.60, I^2=0%) and in the long-term (>4 weeks) supplementation group (2 RCTs, n=110, RR 1.24, 95% CI 1.06 to 1.46, I^2=0%). However, in all subgroup analyses, various lactobacilli strains were pooled together. None of the strains was evaluated in more than one trial.

For use of S boulardii for eradication, see main text.

Treatment of therapy-related adverse effects

In the 2017 meta-analysis, Feng et al. (2) found that, compared with placebo or no intervention, probiotics (as a group) reduced the risk of overall *H-pylori* therapy-related adverse effects (18 RCTs, n=2154, RR 0.49, 95% CI 0.38 to 0.65, I^2=61.7%). A difference was observed regarding which probiotic and which side effect was evaluated. A subgroup analysis based on strains found a reduced risk of total side (adverse) effects when *S boulardii* was used (3 trials, n=366, RR 0.37, 95% CI 0.24 to 0.60). Regarding the type of adverse effects, probiotics given along with triple therapy particularly reduced the risk of diarrhea (20 RCTs, n= 2360, RR 0.46 [0.37 to 0.58] and nausea/vomiting (20 RCTs, n=2199, RR 60 [0.48 to 0.75]). There was no effect of probiotic supplementation on headache (3 RCTs, n=510. RR 0.47 [0.16-1.39]) and abdominal pain (6 RCTs, n= 601, RR 0.65 [0.38–1.11]).

The 2019 meta-analysis by Fang et al. (36) also investigated the effect of the probiotic *Lactobacillus* strains on *H pylori* therapy-related adverse effects. Overall, lactobacilli compared with controls decreased adverse effects; however, the difference between groups was not significant (17.9% vs. 35.6%, respectively, RR 0.47, 95% CI 0.19–1.17, I^2 = 83%). For specific side effects, *Lactobacillus* strains reduced significantly the incidence of diarrhea (3 RCTs, n = 348, 2.2% vs. 9.5%, respectively, RR 0.30, 95% CI 0.10–0.85, I^2 = 0%), but not abdominal distention (2 RCTs, n = 288, 4.0% vs. 3.6%, RR 1.07, 95% CI 0.31 – 3.64, I^2 = 0%) or taste disturbance (3 RCTs, n = 348, 3.9% vs. 9.5%, RR 0.46, 95% CI 0.19–1.14, I^2 = 0%) (Fang, Zhang, Cheng, & Li, 2019).

In adults and children evaluated jointly, Zhou et al. (4) reported overall reduced risk of total side effects (11 RCTs, n=2464, RR 0.47, 95% CI 0.36 to 0.61), specifically diarrhea (14 RCTs, n=3002, RR 0.33, 95% CI 0.23 to 0.47), nausea (10 RCTs, n=2115, RR 0.67, 95% CI 0.53 to 0.84), constipation (4 RCTs, n=763, RR 0.37, 95% CI 0.23 to 0.57), abdominal distention (5 RCTs, n=807, RR 0.48, 95% CI 0.29 to 0.81), and improved stomatitis (2 RCTs, n=629, RR 0.24, 95% CI 0.09 to 0.66). It also reduced vomiting (5 RCTs, n=863, RR 0.69, 95% CI 0.48 to 1.00); however, the latter finding was of borderline significance.

For use of S boulardii for treatment of therapy-related adverse effects, see main text.

Functional Gastrointestinal Disorders

Infantile colic

For this document, 10 systematic reviews and/or meta-analyses (37-46) focusing on infant colic were identified. The following probiotics (in alphabetical order) were investigated:

- *B breve* BR03 (DSM 16604) and *B breve* B632 (DSM 24706) (47, 48) – PREVENTION
- *Bifidobacterium animalis* subsp. *lactis* BB-12 (49, 50)
- *L reuteri* (not clear: breastfed but received infant formula) (Ashraf, MW, Ayaz, SB)
- *L reuteri* DSM 17938
    - *treatment* (51-59)
    - *prevention (60)*
- *L rhamnosus* 19070-2, *L reuteri* 12246 (61)
- *L rhamnosus* GG (62)
- *L rhamnosus* GG, *L rhamnosus* LC705, *B breve* Bbi99, *P freudenreichii* ssp. *shermanii* JS (63)
- *L paracasei* DSM 24733, *L plantarum* DSM 24730, *L acidophilus* DSM 24735, *L delbrueckii subsp. bulgaricus* DSM 24734), three strains of bifidobacteria (*B longum* DSM 24736, *B breve* DSM 24732, and *B infantis* DSM 24737), and one strain of *Streptococcus thermophilus* DSM 24731 (64)

Functional constipation

For this document, three systematic reviews were analyzed (65-67), which evaluated the following probiotics (in alphabetical order):

- *B lactis* DN-173 010 (and yogurt starter cultures: *L delbrueckii* ssp. *bulgaricus* [CNCM I-1632 and I-1519], *Str thermophilus* CNCM I-1630, and *Lactococcus cremoris* [CNCM I-1631]) (68)
- *B longum* (plus yogurt starters *L delbrueckii* subsp. *bulgaricus* and *Str thermophilus*) (69)
- *Bifidobacteria breve* M-16 V®, *infantis* M-63®, and *longum* BB536® (70)
- *Bifidobacterium, Bifidobacterium infantis Bifidobacterium bifidum, Lactobacillus, Bifidobacterium longum, Lactobacillus plantarum, Lactobacillus casei, Lactobacillus rhamnosus* (71).
- *L casei* PXN 37, *L rhamnosus* PXN 54, *Str thermophilus* PXN 66, *B breve* PXN 25, *L acidophilus* PXN 35, *B infantis* PXN 27, and *L bulgaricus* PXN 39)(72)
- *L reuteri* DSM 17938 (5 RCTs) (73-77)
- *L rhamnosus* GG (78)
- *L casei rhamnosus* Lcr35 (79, 80)

The only probiotics which were evaluated in more than 2 RCTs were *L casei rhamnosus* Lcr35 and *L reuteri* DSM 17938.

REFERENCES

1. Zheng J, Wittouck S, Salvetti E, Franz C, Harris HMB, Mattarelli P, et al. A taxonomic note on the genus Lactobacillus: Description of 23 novel genera, emended description of the genus Lactobacillus Beijerinck 1901, and union of Lactobacillaceae and Leuconostocaceae. Int J Syst Evol Microbiol. 2020;70(4):2782-858.
2. Feng JR, Wang F, Qiu X, McFarland LV, Chen PF, Zhou R, et al. Efficacy and safety of probiotic-supplemented triple therapy for eradication of Helicobacter pylori in children: a systematic review and network meta-analysis. Eur J Clin Pharmacol. 2017;73(10):1199-208.
3. Wen J, Peng P, Chen P, Zeng L, Pan Q, Wei W, et al. Probiotics in 14-day triple therapy for Asian pediatric patients with Helicobacter pylori infection: a network meta-analysis. Oncotarget. 2017;8(56):96409-18.
4. Zhou BG, Chen LX, Li B, Wan LY, Ai YW. Saccharomyces boulardii as an adjuvant therapy for Helicobacter pylori eradication: A systematic review and meta-analysis with trial sequential analysis. Helicobacter. 2019;24(5):e12651.
5. Szajewska H, Horvath A, Kolodziej M. Systematic review with meta-analysis: Saccharomyces boulardii supplementation and eradication of Helicobacter pylori infection. Aliment Pharmacol Ther. 2015;41(12):1237-45.
6. Zhou Y. Clinical observation of the effect of Helicobacter pylori eradication in children with Helicobacter pylori infection. Chin J Integr Trad West Med Dig. 2012;10:458-9.
7. Peng HM MH, Wang B (2015) Efficacy of quadruple therapy containing probiotics on Helicobacter pylori. . J Chin Physician. 2015;17(8):1249–51.
8. Goldman CG, Barrado DA, Balcarce N, Rua EC, Oshiro M, Calcagno ML, et al. Effect of a probiotic food as an adjuvant to triple therapy for eradication of Helicobacter pylori infection in children. Nutrition. 2006;22(10):984-8.
9. Saneeyan H LS, Rahimi H. Effectivness of probiotic on treatment of Helicobacter pylori infection in children. . J Isfahan Med Sch. 2011;29(146):882-9.
10. Xu LF YX, Guo J Randomized controlled trial of Clostridium butyricum in eradication treatment of Helicobacter pylori infection in children. . Chin J Microecol. 2016;28(4):413-6.
11. XL Y. The clinical trial on the eradication of Helicobacter

pylori using probiotics with standard triple therapy on children.
. China Medical University, Dissertation. 2014.
12. Li Z. Efficacy of sequential triple therapy combined with probiotics in the treatment of Helicobacter pylori infection in children.
. Chin Prev Med 2009;10(8):728–9.
13. Yang Y HJ, Shao S Efficacy of probiotics combined with triple therapy in treatment of Helicobacter pylori infection in children. . Chin J Nosocomiol. 2013;23(23):5757-8.
14. Zhu XL, Liu Z, Wu ZQ, Li D, Jiang AP, Yu GX. [Clinical effects of different therapeutic regimens for Helicobacter pylori infection in children]. Zhongguo Dang Dai Er Ke Za Zhi. 2017;19(6):672-6.
15. AZ H. Efficacy of probiotics combined with triple therapy in treatment of Helicobacter pylori infection in children. . World Health Dig. 2014;14(19):122.
16. Wang WJ LH, Wei J Effect of probiotics on Helicobacter pylori eradication in children with abdominal pain. . Chin J Microecol. 2011;23(10):916-7.
17. Zhong H, Ye Y, Lv B. Clinical observation of the application of probiotics combined with triple therapy in the treatment of Helicobacter pylori infection in children. . Chin Med Engineering. 2015;23(11):144-6.
18. Pan TT ZH, Lu H Clinical observation on the effect of probiotics in the treatment of Helicobacter pylori infection in children. Strait Pharma J 2010;22(2):109-10.
19. BB S. Clinical effect of probiotics combined with triple therapy on Helicobacter pylori infection in children.
. Chin Med Herald. 2015;12(20):122-5.
20. Wang HJ FD. The effect of multi-drug combination in treatment of children with active gastric ulcer. . Chin Med Herald. 2014;11(26):58-61.
21. Wang YH, Huang Y. Effect of Lactobacillus acidophilus and Bifidobacterium bifidum supplementation to standard triple therapy on Helicobacter pylori eradication and dynamic changes in intestinal flora. World J Microbiol Biotechnol. 2014;30(3):847-53.
22. Plewinska EM P-MI, Bak-Romaniszyn L,, Czkwianlanc E M-PE. Probiotics in the treatment of Helicobacter pylori infection in children. . Gastroenterol Pol
. 2006;13(4):315–9.

23. Ahmad K, Fatemeh F, Mehri N, Maryam S. Probiotics for the treatment of pediatric helicobacter pylori infection: a randomized double blind clinical trial. Iran J Pediatr. 2013;23(1):79-84.
24. Akcam M, Koca T, Salman H, Karahan N. The effects of probiotics on treatment of Helicobacter pylori eradication in children. Saudi Med J. 2015;36(3):286-90.
25. Sykora J, Valeckova K, Amlerova J, Siala K, Dedek P, Watkins S, et al. Effects of a specially designed fermented milk product containing probiotic Lactobacillus casei DN-114 001 and the eradication of H. pylori in children: a prospective randomized double-blind study. J Clin Gastroenterol. 2005;39(8):692-8.
26. Pan X. Effect of probiotics combined with triple therapy clinical value in treatment of Helicobacter pylori associated chronic gastritis. . J Qiqihar University Med 2015;36(24):3627-9.
27. Tolone S, Pellino V, Vitaliti G, Lanzafame A, Tolone C. Evaluation of Helicobacter Pylori eradication in pediatric patients by triple therapy plus lactoferrin and probiotics compared to triple therapy alone. Ital J Pediatr. 2012;38:63.
28. Francavilla R, Lionetti E, Castellaneta SP, Magista AM, Maurogiovanni G, Bucci N, et al. Inhibition of Helicobacter pylori infection in humans by Lactobacillus reuteri ATCC 55730 and effect on eradication therapy: a pilot study. Helicobacter. 2008;13(2):127-34.
29. Shahraki T SM, Shahri ES, Mohammadi M. No Significant Impact of Lactobacillus reuteri on Eradication of Helicobacter pylori in Children (Double-Blind Randomized Clinical Trial). Iran Red Crescent Med J 2017;19:e42101.
30. Szajewska H, Albrecht P, Topczewska-Cabanek A. Randomized, double-blind, placebo-controlled trial: effect of lactobacillus GG supplementation on Helicobacter pylori eradication rates and side effects during treatment in children. J Pediatr Gastroenterol Nutr. 2009;48(4):431-6.
31. Hurduc V, Plesca D, Dragomir D, Sajin M, Vandenplas Y. A randomized, open trial evaluating the effect of Saccharomyces boulardii on the eradication rate of Helicobacter pylori infection in children. Acta Paediatr. 2009;98(1):127-31.
32. Zhao HM, Ou-Yang HJ, Duan BP, Xu B, Chen ZY, Tang J, et al. [Clinical effect of triple therapy combined with Saccharomyces boulardii in the treatment of Helicobacter pylori infection in children]. Zhongguo Dang Dai Er Ke Za Zhi. 2014;16(3):230-3.
33. Zhang H. Clinical effect about Boulardii powder combined

triple therapy treating Helicobacter pylori infection in children.
. Medical J Chin People Health. 2013;25(1):38-40.
34. Zhang Y, Li J. Effect of Saccharomyces boulardii on treatment of Helicobacter pylori infection in children of triple therapy. J Clin Pediatr. 2012;30(10):928-31.
35. Bin Z, Ya-Zheng X, Zhao-Hui D, Bo C, Li-Rong J, Vandenplas Y. The Efficacy of Saccharomyces boulardii CNCM I-745 in Addition to Standard Helicobacter pylori Eradication Treatment in Children. Pediatr Gastroenterol Hepatol Nutr. 2015;18(1):17-22.
36. Fang HR, Zhang GQ, Cheng JY, Li ZY. Efficacy of Lactobacillus-supplemented triple therapy for Helicobacter pylori infection in children: a meta-analysis of randomized controlled trials. Eur J Pediatr. 2019;178(1):7-16.
37. Sung V, D'Amico F, Cabana MD, Chau K, Koren G, Savino F, et al. Lactobacillus reuteri to Treat Infant Colic: A Meta-analysis. Pediatrics. 2018;141(1).
38. Skonieczna-Żydecka K, Janda K, Kaczmarczyk M, Marlicz W, Łoniewski I, Łoniewska B. The Effect of Probiotics on Symptoms, Gut Microbiota and Inflammatory Markers in Infantile Colic: A Systematic Review, Meta-Analysis and Meta-Regression of Randomized Controlled Trials. J Clin Med. 2020;9(4).
39. Ong TG, Gordon M, Banks SS, Thomas MR, Akobeng AK. Probiotics to prevent infantile colic. Cochrane Database Syst Rev. 2019;3(3):Cd012473.
40. Dryl R, Szajewska H. Probiotics for management of infantile colic: a systematic review of randomized controlled trials. Archives of medical science : AMS. 2018;14(5):1137-43.
41. Gutiérrez-Castrellón P, Indrio F, Bolio-Galvis A, Jiménez-Gutiérrez C, Jimenez-Escobar I, López-Velázquez G. Efficacy of Lactobacillus reuteri DSM 17938 for infantile colic: Systematic review with network meta-analysis. Medicine (Baltimore). 2017;96(51):e9375.
42. Schreck Bird A, Gregory PJ, Jalloh MA, Risoldi Cochrane Z, Hein DJ. Probiotics for the Treatment of Infantile Colic: A Systematic Review. J Pharm Pract. 2017;30(3):366-74.
43. Harb T, Matsuyama M, David M, Hill RJ. Infant Colic-What works: A Systematic Review of Interventions for Breast-fed Infants. J Pediatr Gastroenterol Nutr. 2016;62(5):668-86.
44. Xu M, Wang J, Wang N, Sun F, Wang L, Liu XH. The Efficacy and Safety of the Probiotic Bacterium Lactobacillus reuteri

DSM 17938 for Infantile Colic: A Meta-Analysis of Randomized Controlled Trials. PLoS One. 2015;10(10):e0141445.
45. Anabrees J, Indrio F, Paes B, AlFaleh K. Probiotics for infantile colic: a systematic review. BMC Pediatr. 2013;13:186.
46. Simonson J, Haglund K, Weber E, Fial A, Hanson L. Probiotics for the Management of Infantile Colic: A Systematic Review. MCN Am J Matern Child Nurs. 2021;46(2):88-96.
47. Aloisio I, Prodam F, Giglione E, Bozzi Cionci N, Solito A, Bellone S, et al. Three-Month Feeding Integration With Bifidobacterium Strains Prevents Gastrointestinal Symptoms in Healthy Newborns. Front Nutr. 2018;5:39.
48. Giglione E, Prodam F, Bellone S, Monticone S, Beux S, Marolda A, et al. The Association of Bifidobacterium breve BR03 and B632 is Effective to Prevent Colics in Bottle-fed Infants: A Pilot, Controlled, Randomized, and Double-Blind Study. J Clin Gastroenterol. 2016;50 Suppl 2, Proceedings from the 8th Probiotics, Prebiotics & New Foods for Microbiota and Human Health meeting held in Rome, Italy on September 13-15, 2015:S164-s7.
49. Nocerino R, De Filippis F, Cecere G, Marino A, Micillo M, Di Scala C, et al. The therapeutic efficacy of Bifidobacterium animalis subsp. lactis BB-12(®) in infant colic: A randomised, double blind, placebo-controlled trial. Aliment Pharmacol Ther. 2020;51(1):110-20.
50. Chen K, Zhang G, Xie H, You L, Li H, Zhang Y, et al. Efficacy of Bifidobacterium animalis subsp. lactis, BB-12(®) on infant colic - a randomised, double-blinded, placebo-controlled study. Benef Microbes. 2021;12(6):531-40.
51. Savino F, Cordisco L, Tarasco V, Palumeri E, Calabrese R, Oggero R, et al. Lactobacillus reuteri DSM 17938 in infantile colic: a randomized, double-blind, placebo-controlled trial. Pediatrics. 2010;126(3):e526-33.
52. Savino F, Garro M, Montanari P, Galliano I, Bergallo M. Crying Time and RORγ/FOXP3 Expression in Lactobacillus reuteri DSM17938-Treated Infants with Colic: A Randomized Trial. J Pediatr. 2018;192:171-7.e1.
53. Savino F, Galliano I, Savino A, Daprà V, Montanari P, Calvi C, et al. Lactobacillus reuteri DSM 17938 Probiotics May Increase CC-Chemokine Receptor 7 Expression in Infants Treated With for Colic. Front Pediatr. 2019;7:292.

54. Szajewska H, Gyrczuk E, Horvath A. Lactobacillus reuteri DSM 17938 for the management of infantile colic in breastfed infants: a randomized, double-blind, placebo-controlled trial. J Pediatr. 2013;162(2):257-62.
55. Sung V, Hiscock H, Tang ML, Mensah FK, Nation ML, Satzke C, et al. Treating infant colic with the probiotic Lactobacillus reuteri: double blind, placebo controlled randomised trial. Bmj. 2014;348:g2107.
56. Chau K, Lau E, Greenberg S, Jacobson S, Yazdani-Brojeni P, Verma N, et al. Probiotics for infantile colic: a randomized, double-blind, placebo-controlled trial investigating Lactobacillus reuteri DSM 17938. J Pediatr. 2015;166(1):74-8.
57. Mi GL, Zhao L, Qiao DD, Kang WQ, Tang MQ, Xu JK. Effectiveness of Lactobacillus reuteri in infantile colic and colicky induced maternal depression: a prospective single blind randomized trial. Antonie Van Leeuwenhoek. 2015;107(6):1547-53.
58. Fatheree NY, Liu Y, Taylor CM, Hoang TK, Cai C, Rahbar MH, et al. Lactobacillus reuteri for Infants with Colic: A Double-Blind, Placebo-Controlled, Randomized Clinical Trial. J Pediatr. 2017;191:170-8.e2.
59. Nation ML, Dunne EM, Joseph SJ, Mensah FK, Sung V, Satzke C, et al. Impact of Lactobacillus reuteri colonization on gut microbiota, inflammation, and crying time in infant colic. Sci Rep. 2017;7(1):15047.
60. Indrio F, Di Mauro A, Riezzo G, Civardi E, Intini C, Corvaglia L, et al. Prophylactic use of a probiotic in the prevention of colic, regurgitation, and functional constipation: a randomized clinical trial. JAMA Pediatr. 2014;168(3):228-33.
61. Gerasimov S, Gantzel J, Dementieva N, Schevchenko O, Tsitsura O, Guta N, et al. Role of Lactobacillus rhamnosus (FloraActive™) 19070-2 and Lactobacillus reuteri (FloraActive™) 12246 in Infant Colic: A Randomized Dietary Study. Nutrients. 2018;10(12).
62. Pärtty A, Lehtonen L, Kalliomäki M, Salminen S, Isolauri E. Probiotic Lactobacillus rhamnosus GG therapy and microbiological programming in infantile colic: a randomized, controlled trial. Pediatr Res. 2015;78(4):470-5.
63. Mentula S, Tuure T, Koskenala R, Korpela R, Könönen E. Microbial composition and fecal fermentation end products from colicky infants – a probiotic supplementation pilot. Microbial Ecology in Health and Disease. 2008;20(1):37-47.

64. Baldassarre ME, Di Mauro A, Tafuri S, Rizzo V, Gallone MS, Mastromarino P, et al. Effectiveness and Safety of a Probiotic-Mixture for the Treatment of Infantile Colic: A Double-Blind, Randomized, Placebo-Controlled Clinical Trial with Fecal Real-Time PCR and NMR-Based Metabolomics Analysis. Nutrients. 2018;10(2).
65. Wojtyniak K, Szajewska H. Systematic review: probiotics for functional constipation in children. Eur J Pediatr. 2017;176(9):1155-62.
66. Wegh CAM BD, Tabbers MM, Smidt H, Benninga MA. Non-pharmacological Treatment for Children With Functional Constipation: A Systematic Review and Meta-analysis
. Journal of Pediatrics. 2021;in press(in press
).
67. Wegh CAM, Benninga MA, Tabbers MM. Effectiveness of Probiotics in Children With Functional Abdominal Pain Disorders and Functional Constipation: A Systematic Review. J Clin Gastroenterol. 2018;52 Suppl 1, Proceedings from the 9th Probiotics, Prebiotics and New Foods, Nutraceuticals and Botanicals for Nutrition & Human and Microbiota Health Meeting, held in Rome, Italy from September 10 to 12, 2017:S10-s26.
68. Tabbers MM, Chmielewska A, Roseboom MG, Crastes N, Perrin C, Reitsma JB, et al. Fermented milk containing Bifidobacterium lactis DN-173 010 in childhood constipation: a randomized, double-blind, controlled trial. Pediatrics. 2011;127(6):e1392-9.
69. Guerra PV, Lima LN, Souza TC, Mazochi V, Penna FJ, Silva AM, et al. Pediatric functional constipation treatment with Bifidobacterium-containing yogurt: a crossover, double-blind, controlled trial. World J Gastroenterol. 2011;17(34):3916-21.
70. Russo M, Giugliano FP, Quitadamo P, Mancusi V, Miele E, Staiano A. Efficacy of a mixture of probiotic agents as complementary therapy for chronic functional constipation in childhood. Ital J Pediatr. 2017;43(1):24.
71. Abediny M AP, Afkhamzadeh A, Seifmanesh M, Sedaghat B. The effect of probiotics on the treatment of functional constipation in children of 4-12 years of age. Journal of Isfahan Medical School. 2016;33(368):2448-54.
72. Sadeghzadeh M, Rabieefar A, Khoshnevisasl P, Mousavinasab N, Eftekhari K. The effect of probiotics on childhood

constipation: a randomized controlled double blind clinical trial. Int J Pediatr. 2014;2014:937212.
73. Coccorullo P, Strisciuglio C, Martinelli M, Miele E, Greco L, Staiano A. Lactobacillus reuteri (DSM 17938) in infants with functional chronic constipation: a double-blind, randomized, placebo-controlled study. J Pediatr. 2010;157(4):598-602.
74. Jadresin O, Sila S, Trivic I, Misak Z, Hojsak I, Kolacek S. Lack of Benefit of Lactobacillus reuteri DSM 17938 as an Addition to the Treatment of Functional Constipation. J Pediatr Gastroenterol Nutr. 2018;67(6):763-6.
75. Wegner A, Banaszkiewicz A, Kierkus J, Landowski P, Korlatowicz-Bilar A, Wiecek S, et al. The effectiveness of Lactobacillus reuteri DSM 17938 as an adjunct to macrogol in the treatment of functional constipation in children. A randomized, double-blind, placebo-controlled, multicentre trial. Clin Res Hepatol Gastroenterol. 2018;42(5):494-500.
76. Kubota M, Ito K, Tomimoto K, Kanazaki M, Tsukiyama K, Kubota A, et al. Lactobacillus reuteri DSM 17938 and Magnesium Oxide in Children with Functional Chronic Constipation: A Double-Blind and Randomized Clinical Trial. Nutrients. 2020;12(1).
77. Asburce OB, Sezer OB, Ozcay F. Comparison of probiotic and lactulose treatments in children with functional constipation and determination of the effects of constipation treatment on quality of life. [Turkish]. Cocuk Sagligi ve Hastaliklari Dergisi. 2013;56(1):1-7.
78. Banaszkiewicz A, Szajewska H. Ineffectiveness of Lactobacillus GG as an adjunct to lactulose for the treatment of constipation in children: a double-blind, placebo-controlled randomized trial. J Pediatr. 2005;146(3):364-9.
79. Bu LN, Chang MH, Ni YH, Chen HL, Cheng CC. Lactobacillus casei rhamnosus Lcr35 in children with chronic constipation. Pediatr Int. 2007;49(4):485-90.
80. Wojtyniak K, Horvath A, Dziechciarz P, Szajewska H. Lactobacillus casei rhamnosus Lcr35 in the Management of Functional Constipation in Children: A Randomized Trial. J Pediatr. 2017;184:101-5 e1.

Probiotics for the management of pediatric gastrointestinal disorders: position paper of the ESPGHAN Special Interest Group on Gut Microbiota and Modifications

SUMMARY OF RECOMMENDATIONS

Acute Gastroenteritis

- Healthcare professionals (HCPs) may recommend *Lacticaseibacillus rhamnosus (L rhamnosus)* GG [at a dose of $\geq 10^{10}$ CFU/day, typically 5–7 days] for the management of acute gastroenteritis in children, since there is evidence of reduced duration of diarrhea, length of hospitalization, and stool output (certainty of evidence: low; grade of recommendation: weak).
- HCPs may recommend *Saccharomyces (S) boulardii** (at a dose of 250–750 mg/day, for 5–7 days) for the management of acute gastroenteritis in children, since there is evidence of reduced duration of diarrhea (certainty of evidence: low; grade of recommendation: weak).
- HCPs may recommend *Limosilactobacillus reuteri (L reuteri)* DSM 17938 (at daily doses $1x10^8$ to $4x10^8$ CFU, for 5 days) for the management of acute gastroenteritis in children, since there is evidence of reduced duration of diarrhea (certainty of evidence: very low; grade of recommendation: weak).
- HCPs may recommend the combination of *L rhamnosus* 19070-2 and *L reuteri* DSM 12246 (at a dose of $2x10^{10}$ CFU for each strain, for 5 days) for the management of acute gastroenteritis in children, since there is evidence of reduced duration of diarrhea (certainty of evidence: very low; grade of recommendation: weak).
- HCPs should *not* recommend the combination of *Lactobacillus helveticus* R0052 and *L rhamnosus* R0011 for the management of acute gastroenteritis due to the lack of efficacy (certainty of evidence: moderate; grade of recommendation: strong).
- HCPs may *not* recommend *Bacillus clausii* strains O/C, SIN, N/R, and T for the management of acute gastroenteritis in children due to the lack of efficacy (certainty of evidence: very low; grade of recommendation: weak).

Prevention of Antibiotic-Associated Diarrhea (AAD)

- If the use of probiotics for preventing AAD is considered because of the existence of risk factors such as class of antibiotic(s), duration of antibiotic treatment, age, need for hospitalization, comorbidities, or previous episodes of AAD, HCPs may recommend high doses (≥5 billion CFU per day) of *S boulardii** or *L rhamnosus* GG started simultaneously with antibiotic treatment to prevent AAD in outpatients and hospitalized children (certainty of evidence: moderate; grade of recommendation: moderate).

Prevention of Nosocomial Diarrhea

- HCPs may recommend *L rhamnosus* GG (at least 10^9 CFU/day) for the duration of the hospital stay for the prevention of nosocomial diarrhea in children (certainty of evidence: moderate; grade of recommendation: weak).
- HCPs should *not* recommend *L reuteri* DSM 17938 for the prevention of nosocomial diarrhea in children due to the lack of efficacy (certainty of evidence: high; grade of recommendation: strong).

Prevention of Necrotizing Enterocolitis (NEC)

- For reducing the risk of NEC in preterm infants, provided all safety issues are met, HCPs may recommend *L rhamnosus* GG (at a dose ranging from $1x10^9$ CFU to $6x10^9$ CFU) (certainty of evidence: low; grade of recommendation: weak) **or** the combination of *Bifidobacterium (B) infantis* BB-02, *B lactis* BB-12, and *Streptococcus thermophilus* TH-4 at 3.0 to 3.5×10^8 CFU (of each strain) (certainty of evidence: low; grade of recommendation: weak).
- Due to insufficient evidence, no recommendation can be made *for* or *against L reuteri* DSM 17938 **or** the combination of *B bifidum* NCDO 1453 *&* *Lactobacillus acidophilus* NCDO 1748 (certainty of evidence: for both, very low to moderate).
- Due to the lack of efficacy, HCPs may *not* recommend *B breve* BBG-001 (certainty of evidence: low to moderate; grade of recommendation: weak) or *S boulardii* (certainty of evidence: very low to moderate; grade of recommendation: weak).

***Helicobacter pylori (H pylori)* infection**

- In children with *H pylori* infection, HCPs may recommend, along with *H pylori* therapy, *S boulardii** for increasing the eradication rates and decreasing gastrointestinal adverse effects (certainty of evidence: very low; grade of recommendation: weak).

Inflammatory Bowel Disease

- No recommendation can be made *for* or *against* the use of probiotics studied so far in the management of children with ulcerative colitis due to insufficient evidence.
- No recommendation can be made *for* or *against* the use of probiotics studied so far in the treatment of children with Crohn's disease due to insufficient evidence.

Infant Colic

- HCPs may recommend *L reuteri* DSM 17938 (at least 10^8 CFU/day for at least 21 days) for the management of infant colic in breastfed infants (certainty of evidence: moderate; grade of recommendation: weak).
- No recommendation can be made *for* or *against* the use of *L reuteri* DSM 17938 in formula-fed infants due to insufficient evidence.
- HCPs may recommend *B lactis* BB-12 (at least 10^8 CFU/day, for 21-28 days) for the management of infant colic in breastfed infants (certainty of evidence: moderate; grade of recommendation: weak).
- No recommendation can be made *for* or *against* the use of any of the probiotics studied so far for preventing infant colic due to insufficient evidence.

Functional Abdominal Pain Disorders (FAPD)

- HCPs may recommend *L reuteri* DSM 17938 (at a dose of 10^8 CFU to 2×10^8 CFU/day) for pain intensity reduction in children with FAPD (certainty of evidence: moderate; grade of recommendation: weak).
- HCPs may recommend *L rhamnosus GG* (at a dose of 10^9 CFU to 3×10^9 CFU twice daily) for the reduction of pain frequency and intensity in children with irritable bowel syndrome (certainty of evidence: moderate; grade of recommendation: weak).

Functional Constipation

- HCPs may *not* recommend the use of probiotics as a single or adjuvant therapy for treatment of functional constipation in children due to the lack of efficacy (certainty of evidence: moderate; grade of recommendation: weak).

Celiac Disease

- No recommendation can be made *for* or *against* the use of probiotics in children with celiac disease due to insufficient evidence.

Small Intestinal Bacterial Overgrowth (SIBO)

- No recommendation can be made *for* or *against* the use of probiotics in the treatment or prevention of SIBO due to insufficient evidence.

Pancreatitis

- As no randomized controlled trial on the use of probiotics for pancreatitis in children was identified, no recommendation can be made *for* or *against* the use of probiotics for the management of pancreatitis.

* Note: In many of the trials, the strain designation of *S boulardii* was not available. However, if available, or assessed retrospectively, most used was that recently designated as *S boulardii* CNCM I-745.

Probiotics for the management of pediatric gastrointestinal disorders: position paper of the ESPGHAN Special Interest Group on Gut Microbiota and Modifications

SUMMARY OF RECOMMENDATIONS

* Note: In many of the trials, the strain designation of *S boulardii* was not available. However, if available, or assessed retrospectively, most used was that recently designated as *S boulardii* CNCM I-745.

ESPGHAN Special Interest Group on Gut Microbiota and Modifications
Probiotics for the Management of Pediatric Gastrointestinal Disorders

	RECOMMENDED	NOT RECOMMENDED	NO RECOMMENDATION *FOR* or *AGAINST*
Acute Gastroenteritis	• *S oulardii** • *L rhamnosus* GG • *L reuteri* DSM 17938 • *L rhamnosus* 19070-2 & *L reuteri* DSM 12246	• *L helveticus* R0052 & *L rhamnosus* R0011 • *B clausii* strains O/C, SIN, N/R & T	
Prevention of AAD	• *L rhamnosus* GG • *S boulardii**		
Prevention of Nosocomial Diarrhea	• *L rhamnosus* GG	• *L reuteri* DSM 17938	
Crohn Disease			Insufficient evidence
Ulcerative Colitis			Insufficient evidence
Management Infant Colic	• *L reuteri* DSM 17938 (BF) • *B lactis* BB-12 (BF)		• *L reuteri* DSM 17938 (FF)
Functional Abdominal Pain Disorders	• *L reuteri* DSM 17938 • *L rhamnosus* GG		
Functional Constipation		Not effective	
***H pylori* Eradication**	• *S boulardii**		
Prevention of NEC	• *L rhamnosus* GG • *B infantis* BB-02, *B lactis* BB-12 & *Str thermophilus* TH-4	• *B breve* BBG-001; • *S boulardii*	• *L reuteri* DSM 17938; • *B bifidum* NCDO 1453 &*L acidophilus* NCDO 1748
Celiac Disease			Insufficient evidence
Small Intestinal Bacterial Overgrowth			Insufficient evidence
Pancreatitis			No RCT data

* Note: In many of the trials, the strain designation of *S boulardii* was not available. However, if available, or assessed retrospectively, most used was that recently designated as *S boulardii* CNCM I-745.
BF, breastfed; FF, formula-fed; RCT, randomized controlled trial.