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SUMMARY WITH CRITICAL APPRAISAL

Probiotics for Antibiotic-Associated Diarrhea in Pediatrics: A Review of Clinical Effectiveness and Guidelines

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Authors: Casey Gray, Camille Dulong, Charlene Argáez

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Abbreviations

AAD	Antibiotic-associated diarrhea
AE	Adverse Event
ARR	Absolute risk reduction
CDAD	Clostridium difficile-associated diarrhea
CFU	colony forming units
CI	Confidence interval
CPS	Canadian Paediatric Society
HpSA	*H. pylori* stool antigen
H.	*Helicobacter*
LGG	*Lactobacillus rhamnosus GG*
L.	*Lactobacillus*
mg	milligram
NNT	Number needed to treat
OR	Odds Ratio
PICO	Population, Intervention, Comparator, Outcome
PIs	Principal Investigators
PPI	Proton Pump Inhibitor
RCT	randomized controlled trial
RoB	Risk of Bias
RR	Relative risk
RUT	Rapid urease test
SD	Standard deviation
S.	*Saccharomyces*
UBT	Urea breath test

Context and Policy Issues

Diarrhea is a common side-effect associated with use of many antibiotics prescribed for children.[1] Antibiotic-associated diarrhea (AAD) has been defined according to the World Health Organization's definition of diarrhea of three or more loose stools per day,[1] which take place up to two weeks following initiation of antibiotics.[2] AAD has also been defined as "diarrhea that occurs in relation to antibiotic treatment with the exclusion of other etiologies.[3]"

Between 11% and 40% of children treated with broad spectrum antibiotics experience AAD.[4] There are several potential reasons AAD occurs. Generally, it is thought that antibiotic treatment disrupts the colonization resistance of gastrointestinal flora and associated overgrowth of enteropathogens.[1] Infection with the *Clostridium difficile* (*C. difficile*) pathogen is most commonly associated with AAD.[1]

Probiotics are a potential option for the prevention and treatment of AAD.[4] Probiotics are live non-pathogenic bacteria and there are various preparations of probiotics with various degrees of effectiveness for the prevention of AAD.[4]

The purpose of this report is to review the clinical effectiveness and evidence-based guidelines on the use of probiotics for preventing and treating AAD in the pediatric population.

Research Questions

1. What is the clinical effectiveness of probiotics (with or without concurrent antibiotics) for preventing and treating antibiotic-associated diarrhea in the pediatric population?
2. What are the evidence-based guidelines regarding the use of probiotics (with or without concurrent antibiotics) for the prevention and treatment of antibiotic-associated diarrhea in the pediatric population?

Key Findings

Evidence of limited quality from nine systematic reviews suggested favourable effects of probiotics on antibiotic-associated diarrhea (AAD) relative to placebo, no additional treatment, or other non-probiotic treatment comparators. However, clinical evidence regarding the conditions under which probiotics were effective (e.g., specific dosing regimens, other outcomes, and indications) was sparse.

Two evidence-based guidelines recommended the use of probiotics for the treatment of AAD and one guideline recommended probiotics for the treatment of *Clostridium difficile*-associated diarrhea

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD), Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and February 26, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1. Randomized and non-randomized primary studies were not extracted due to the large volume of data in included systematic reviews.

Table 1: Selection Criteria

Population	Pediatric patients (less than 18 years old) in all settings diagnosed with, or at risk for, antibiotic-associated diarrhea
Intervention	Probiotics (mixed strains, individual strains [*e.g., Saccharomyces boulardii, Lactobacillus acidophilus, Lactobacillus rhamnosus*], and Kefir) taken with or without concurrent antibiotics
Comparator	Q1: No treatment (i.e., no probiotics) Q2: No comparator
Outcomes	Q1: Clinical effectiveness (e.g., *Clostridium difficile* infection prevention, preventing antibiotic-associated diarrhea, shortening length of stay); safety (e.g., side effects, adverse reactions) Q2: Evidence-based guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, if they were duplicate publications, if they were primary studies also captured in an included systematic review, or if they were published prior to 2014. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using AMSTAR 2[5] and guidelines were assessed with the AGREE II instrument.[6] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 346 citations were identified in the literature search. Following screening of titles and abstracts, 310 citations were excluded and 36 potentially relevant reports from the electronic search were retrieved for full-text review. Three potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 25 publications were excluded for various reasons, and fourteen publications met the inclusion criteria and were included in this report. These comprised nine systematic reviews,[4,7-14] three RCTs,[15-17] two evidence-based guidelines,[3,18] and no observational studies. Appendix 1 presents the PRISMA[19] flowchart of the study selection.

Due to the high volume of available data from systematic reviews, data from the three eligible RCTs[15-17] were not extracted.

Summary of Study Characteristics

Complete details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

Nine systematic reviews published between 2014 and 2019 are included in this report.[4,7-14] Dates covered by database searches were database inception up to June 2018. There was substantial overlap in the primary studies included in the systematic reviews, as described in Appendix 5. In total, data from 66 primary studies are synthesized in this report.

Two evidence-based guidelines were identified for inclusion in this report.[3,18] The Nutrition and Gastroenterology Committee of the Canadian Paediatric Society developed their position statement based on findings from a literature review of RCTs and meta-analyses.[18] The Working Group of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHN) developed their guideline based on findings from a systematic review of systematic reviews and RCTs published subsequent to the most recent systematic review identified.[3] Risk of bias in included studies was not assessed in the CPS position statement,[18] and was assessed in the ESPGHN guideline[3] using the Cochrane Collaboration's tool.[20] The quality of evidence and strength of each recommendation were not rated in the CPS position statement,[18] and were rated using the Grading Recommendations Assessment, Development, and Evaluations (GRADE) system in the ESPGHN guideline.[21] Table 4 provides a detailed description of the GRADE system. Recommendations included in the CPS position statement were developed over email and discussion. It is unclear if or how consensus was achieved.[18] The ESPGHN guideline recommendations were developed based on a systematic process of voting, discussion, and consensus.[3]

Country of Origin

Systematic reviews were conducted by authors in China (3 studies),[7,9,14] the US (4 studies),[4,8,10,11] and Poland (2 studies).[12,13] The guideline is applicable to the European context.[3]

Patient Population

Included systematic reviews presented data on a total of 21,649 children up to 18 years of age.[4,7-14] Given the substantial overlap in the included primary studies between systematic reviews, double counting of participants has occurred and the actual number of included children is likely to be much smaller. Where reported, age ranges across studies spanned ages 1 month up to 14 years.[9] Children were in-patients and outpatients who were receiving antibiotic therapy for *Helicobacter pylori* (*H. pylori*) eradication,[7,11-14] or for the treatment of various other infections.[4,8-10]

The CPS guideline was relevant to pediatric patients in general, while the specific recommendation of interest was relevant to those at risk of developing AAD.[18] The ESPGHN guideline was relevant to pediatric patients who were prescribed antibiotics and were therefore at risk of AAD or *Clostridium difficile*-associated diarrhea (CDAD).[3]

Interventions and Comparators

Systematic reviews examined the clinical effectiveness of probiotics of various strains and dosage regimens. Two reviews examined a specific strain of probiotic; one review examined Lactobacillus rhamnosus GG,[12] and the other examined Saccharomyces boulardii.[13] 3 reviews examined categories of probiotic strains, including Lactobacillus strains,[7] Bifidobacterium-based probiotics,[9] and one review examined *Lactobacillus* GG, *Saccharomyces boulardii (S. boulardii)*, or *Lactobacillus rhamnosus* (*L. rhamnosus*)

probiotics.[10] Four reviews examined any strain of probiotic.[4,8,11,14] Where reported, duration of probiotic treatment ranged from three days[4] to 30 days.[4,7,11,14] Eligible comparators were placebo,[4,7,8,10-14] no additional treatment,[4,7-14] alternative prophylaxis.[4,8], or standard practice.[11]

Both sets of recommendations addressed the use of probiotics generally.[3,18] The ESPGHN guideline also provided recommendations regarding two specific probiotic strains: *L. rhamnosus* and *S. boulardii*.[3] Detailed recommendations are presented in Appendix 4.

Outcomes

Measurement properties of outcome assessment measures and the minimum clinically important difference in study outcomes were not reported for any review.[4,7-14]

Diarrhea

AAD (identified specifically as AAD[8,9,11-13] or generally as diarrhea[4,7,14]) was assessed in eight reviews. Diarrhea was not defined,[7,14] was defined in the review based on the definition provided by authors of included RCTs,[4,8,9,12,13] or defined as more than two to three loose or watery stools/day for more than two consecutive days.[11] CDAD was assessed in three reviews.[8,10,13] Two reviews used the definitions provided by included study authors,[8,13] and the third review defined CDAD as diarrhea with a positive stool culture or cytotoxin assay.[10] The included guideline provided recommendations on the use of probiotics for the prevention of AAD and CDAD.[3]

C. difficile Infection Prevention

The presence of *C. difficile* infection was assessed in one study based on unspecified method of identification in a stool sample. [8]

Adverse Effects

Adverse effects or events were reported in two reviews using the definition provided in each included study [4,8] A third review included diarrhea as an adverse side-effect in addition to incidence of constipation and incidence of nausea and/or vomiting, also using the definitions provided by the included study authors.[14] Number of events were reported.[4,8,14]

Summary of Critical Appraisal

Critical appraisal of the included systematic reviews is presented here. Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Systematic Reviews

The nine systematic reviews[4,7-14] were assessed using AMSTAR 2[5] and several strengths and limitations were identified. Common strengths included clear inclusion criteria for all reviews, the use of a comprehensive literature search strategy, appropriate methods of statistical combination of results, and use of visual plots or statistical analyses to investigate the potential for publication bias. [4,7-14] One minor limitation was common across all reviews, namely, the absence of an explanation for limiting the type of study design eligible for inclusion. [4,7-14] Critical limitations include the failure to assess risk of bias associated with included studies in two reviews[10,14] and unclear methods of study selection in five reviews.[10-14]

Guidelines

Strengths and weaknesses of the evidence-based guidelines[3,18] were identified through the use of the AGREE II instrument.[6] Common strengths included clearly defined target users, a systematic literature search using multiple databases, and clearly presented recommendations.[3,18] Common limitations were related to stakeholder involvement and applicability. Regarding stakeholder involvement, it is unclear whether members of the target population or intended users were involved in the guideline development process, as the composition of the Working Group was not sufficiently described and a separate process of stakeholder engagement was not reported.[3,18] Regarding applicability, it does not appear that barriers or facilitators to implementation or resource implications were considered in the formulation of recommendations for either guideline.[3,18] In addition, important limitations of the CPS position statement included a lack of transparent reporting of the literature review process, such that it is not clear if studies were selected or extracted in duplicate, or if a new search was conducted when the position statement was reaffirmed in 2019.[18] Furthermore, the quality of the included evidence was not critically appraised and the recommendations were not graded.[18]

Summary of Findings

Appendix 4 presents a table of the main study findings and authors' conclusions.

Clinical Effectiveness of Probiotics

Diarrhea

Antibiotic-associated diarrhea was examined in eight systematic reviews.[4] In the three reviews where evidence on various strains of probiotics were pooled, relative risk of AAD ranged from 0.16 to 0.38 favouring intervention with probiotics versus no probiotic comparators.[7,8,14] The remaining reviews examined individual strains or categories of strains of probiotics in isolation. The effectiveness of treatment with *L. rhamnosus* was inconsistent across three systematic reviews.[4,11,12] Specifically, Goldenberg found a favourable effect of *L. rhamnosus* on the incidence of AAD relative to comparators.[4] Similarly, in one review by Szajewska[12] there was an overall risk reduction in the incidence of AAD with *L. rhamnosus*, however results were no longer significant when data were analyzed by the reasons for taking antibiotics (i.e., common infections and *H. pylori* eradication).[12] After removing a large study driving the favourable results, McFarland showed no difference in the effect of *L. rhamnosus* and comparators on AAD.[11] Effectiveness of treatment with *S. boulardii* was consistently shown to have favourable results relative to comparator groups.[4,11,13] In the review by Szajewska, the difference in relative risk favouring *S. boulardii* remained significant when the reasons for taking antibiotics (i.e., common infections and *H. pylori* eradication) were examined separately.[13]

Finally, treatment with Bifidobacterium was associated with lower odds of developing AAD, and better odds of successfully treating AAD, as well as an overall lower incidence of AAD in one review.[9]

CDAD was assessed in three reviews.[10] There was a relative risk reduction in the incidence of CDAD with pooled probiotics in one review,[10] with *S. boulardii* in a second review,[13] and no difference between probiotics and comparators in the third review.[8]

C. difficile Infection Prevention

One review showed no significant difference between the effect of probiotic supplementation or comparator on the incidence of *C. difficile* infection following treatment with antibiotics.[8]

Adverse Effects

Adverse effects in general were assessed in two systematic reviews and showed no significant differences in the number of reported adverse events between probiotic and comparator groups.[4,8] Specific side effects were reported in a third review, which also showed no differences between probiotics and comparator groups with regard to incidence of constipation or nausea and vomiting.[14] None of the adverse effects reported were described as serious.[14]

Length of Hospital Stay

No relevant evidence regarding the effect of probiotics on the length of hospital stay in pediatric populations was identified; therefore, no summary can be provided.

Guidelines

Two guidelines recommend the use of probiotics for the prevention of AAD in children.[3,18] The CPS[18] recommends probiotics in general for the prevention of AAD, and the ESPGHN specifically recommends the use of *L. rhamnosus* GG (strong recommendation; moderate quality evidence) and *S. boulardii* (strong recommendation; moderate quality evidence) for the prevention of AAD in children.[3] For the prevention of CDAD, the ESPGHN suggests the use of *S. boulardii* (conditional recommendation; low quality evidence).[3]

Limitations

There are a number of key limitations to note with respect to the current report. Regarding the clinical-effectiveness evidence, although several systematic reviews were identified, there was considerable heterogeneity in the included RCTs. For example, data on various strains, doses, and durations of probiotic treatments were combined in meta-analyses. The appropriateness of pooling data on different probiotics has been repeatedly called into question.[3] Additional sources of heterogeneity included the conditions for which patients were being treated, types of antibiotics being used to treat patients, durations of antibiotic treatment, definitions of study outcomes, and follow-up periods. In the few reviews where sub-analyses were performed, significant results were only observed for certain strains, doses, and types of infection, calling into question those findings for which more precise intervention and population characteristics were not examined.

There was limited or no information available on some outcomes of interest. No studies examined length of hospital stay. One review reported on *C. difficile* infection based on two RCTs.[8] Three reviews[4,8,14] reported adverse effects however the types of adverse effects were not specified in the two largest reviews[4,8] Regarding evidence based guidelines, the recommendations developed in Canada only considered clinical effectiveness and therefore the possibility of barriers to implementation of the recommendations in the identified guideline cannot be ruled out.

Conclusions and Implications for Decision or Policy Making

Evidence from nine systematic reviews[4,7-14] and two evidence-based guidelines regarding the use of probiotics for the prevention and treatment of AAD[3,18] are summarized in this report. For the most part, the findings in this report suggest that probiotics reduce the risk of developing AAD and CDAD compared with controls and no evidence of an increased risk of AAD or CDAD with probiotics was identified.[4,7-14] *S. boulardii* was shown to be better at preventing AAD relative to comparators groups in three reviews.[4,11,13] It should be noted that there was substantial overlap in the included RCTs, and the findings regarding *S. boulardii* were based on syntheses of a total of seven unique RCTs.[4,11,13] The effectiveness of treatment with *L. rhamnosus* was less clear in the included systematic reviews, with one review reporting favourable effects,[4] and two reporting null findings.[11,12] However, the authors of one study postulated null findings were likely due to methodological flaws of included studies rather than the probiotic strain.[11] Future well-conducted RCTs examining different doses, treatment durations, and patients with different types of infection may eliminate this uncertainty.

There were no reported differences in adverse effects between probiotics and comparators, and none of the side effects reported were considered serious.[4,8,14] This is consistent with previous studies conducted with healthy children.[4] Evidence from neonates or severely immunocompromised children regarding the safety of probiotics is divided.[4] Further research is needed to provided clarity on the safety of probiotics in these populations.

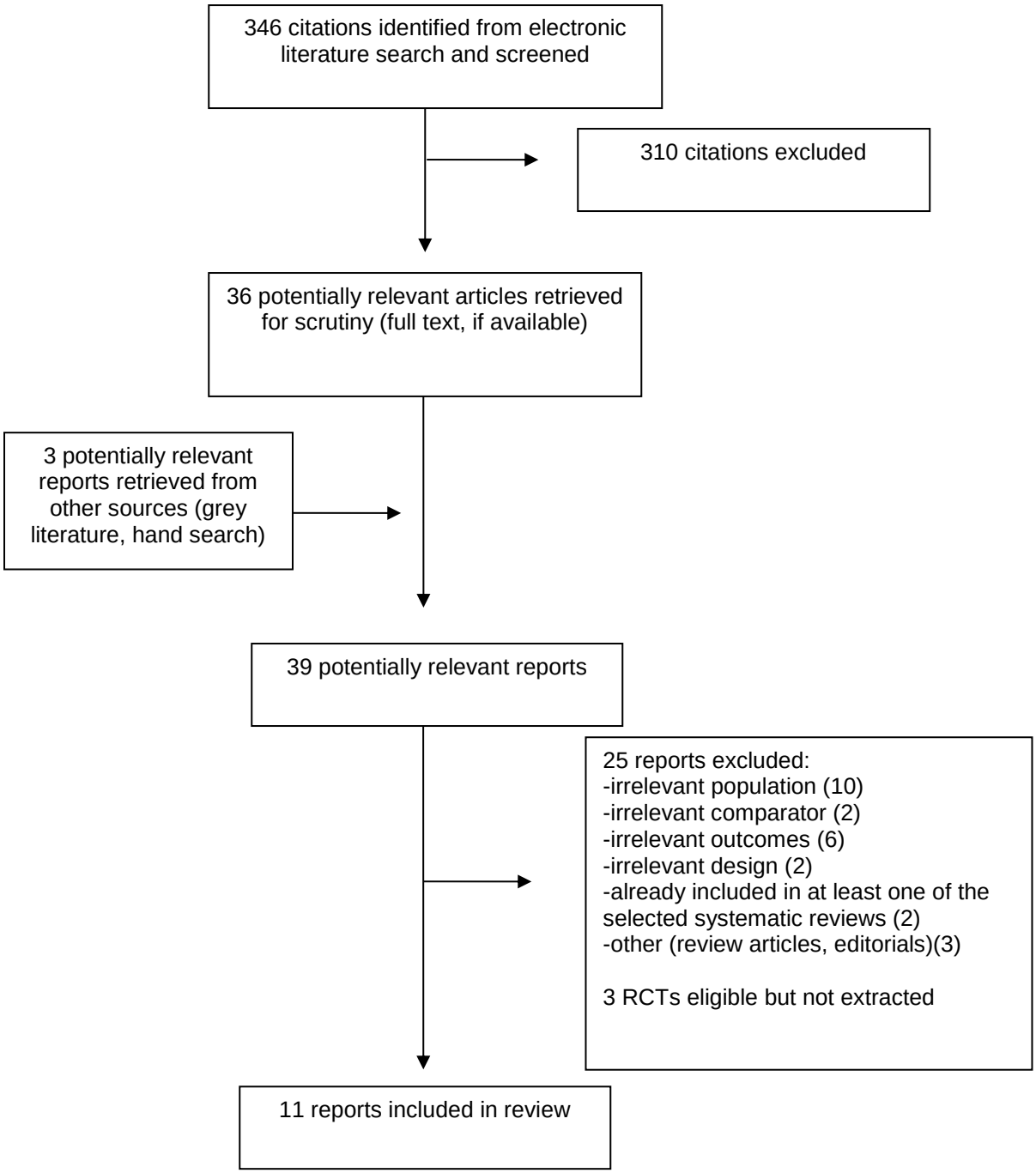
Two evidence-based guidelines were identified for inclusion in this report.[3,18] In their position statement, the CPS encouraged physicians to recommend probiotics to children to prevent AAD.[18] Specific probiotics or dosing recommendations were not provided, although a list of available products licensed in Canada is referred to. Given that the evidence upon which the recommendations were based was not critically appraised and the strength of the recommendations was not assessed, it is difficult to have confidence in the recommended course of action. One relevant guideline developed for the European context included recommendations regarding the use of probiotics for the prevention of AAD in children.[3] The recommendations support the use of *L. rhamnosus* for AAD, and *S. boulardii* for prevention of AAD and CDAD,[3] preparations of which are available in Canada.[18] The guideline development working group considered the recommendations regarding AAD to be strong recommendations based on high quality evidence,[3] which increases confidence in the recommended course of action. the ESPGHAN recommendation regarding CDAD was based on low quality evidence and considered to be a conditional recommendation, indicating the benefits of the intervention may not outweigh the potential undesirable effects [3] With an apparent lack of patient perspectives or resource implications taken into consideration in the development of either guideline, it is unclear if children or their caregivers would choose to use probiotics for the prevention of AAD.

Previous CADTH Rapid Response reports were recently published regarding the clinical-effectiveness and guidelines on the use of probiotics for the prevention of AAD and *C.difficile* infection in adults.[22,23] The findings in this report are similar to those of the previous clinical effectiveness report, in that probiotics appear to be effective in the prevention of AAD, although the conditions under probiotics are most effective are not entirely clear.[23] As with the current report, the previous guideline report recommends *L. rhamnosus* GG for the prevention of AAD, and provides a lower strength recommendation for the use of *S.boulardii*, among a list of other probiotics.[22]

References

1. Fleisher GR. Approach to diarrhea in children in resource-rich countries. In: Post TW, ed. *UpToDate*. Waltham (MA): UpToDate; 2018 Mar: www.uptodate.com. Accessed 2019 Mar 25.
2. Cai J. Comparative efficacy and tolerability of probiotics for antibiotic-associated diarrhea: systematic review with network meta-analysis. . *United European Gastroenterol J* 2018;6(2).
3. Szajewska H, Canani RB, Guarino A, et al. Probiotics for the prevention of antibiotic-associated diarrhea in children. *J Pediatr Gastroenterol Nutr.* 2016;62(3):495-506.
4. Goldenberg JZ, Lytvyn L, Steurich J, Parkin P, Mahant S, Johnston BC. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. *Cochrane Database Syst Rev.* 2015(12):Cd004827.
5. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008. http://www.bmj.com/content/bmj/358/bmj.j4008.full.pdf. Accessed 2019 Mar 25.
6. Consortium ANS. The AGREE II Instrument. [Hamilton, ON]: AGREE Enterprise; 2017: https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf. Accessed 2019 Mar 25.
7. 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.
8. Goldenberg JZ, Yap C, Lytvyn L, et al. Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. *Cochrane Database Syst Rev.* 2017;12:Cd006095.
9. Xu HB, Jiang RH, Sheng HB. Meta-analysis of the effects of Bifidobacterium preparations for the prevention and treatment of pediatric antibiotic-associated diarrhea in China. *Complement Ther Med.* 2017;33:105-113.
10. Lau CS, Chamberlain RS. Probiotics are effective at preventing Clostridium difficile-associated diarrhea: a systematic review and meta-analysis. *Int J Gen Med.* 2016;9:27-37.
11. McFarland LV. Deciphering meta-analytic results: a mini-review of probiotics for the prevention of paediatric antibiotic-associated diarrhoea and Clostridium difficile infections. *Benef Microbes.* 2015;6(2):189-194.
12. Szajewska H, Kolodziej M. Systematic review with meta-analysis: Lactobacillus rhamnosus GG in the prevention of antibiotic-associated diarrhoea in children and adults. *Aliment Pharmacol Ther.* 2015;42(10):1149-1157.
13. Szajewska H, Kolodziej M. Systematic review with meta-analysis: Saccharomyces boulardii in the prevention of antibiotic-associated diarrhoea. *Aliment Pharmacol Ther.* 2015;42(7):793-801.
14. Li S, Huang XL, Sui JZ, et al. Meta-analysis of randomized controlled trials on the efficacy of probiotics in Helicobacter pylori eradication therapy in children. *Eur J Pediatr.* 2014;173(2):153-161.
15. Esposito C, Roberti A, Turra F, et al. Frequency of antibiotic-associated diarrhea and related complications in pediatric patients who underwent hypospadias repair: a comparative study using probiotics vs placebo. *Probiotics Antimicrob Prot.* 2018;10(2):323-328.
16. Kolodziej M, Szajewska H. Lactobacillus reuteri DSM 17938 in the prevention of antibiotic-associated diarrhoea in children: a randomized clinical trial. *Clin Microbiol Infect.* 2018.
17. Olek A, Woynarowski M, Ahren IL, et al. Efficacy and safety of Lactobacillus plantarum DSM 9843 (LP299V) in the prevention of antibiotic-associated gastrointestinal symptoms in children-randomized, double-blind, placebo-controlled study. *J Pediatr.* 2017;186:82-86.
18. Marchand V. Position statement: using probiotics in the paediatric population. *Canadian Paediatric Society* 2019 Feb: https://www.cps.ca/en/documents/position/probiotics-in-the-paediatric-population Accessed 2019 Mar 25.
19. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.
20. Higgins JPT. ssessing risk of bias in included studies. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0. 2011.
21. Guyatt GH, A.D. O, Vist GEK, R., Falck-Ytter Y, Alonso-Coello P, Schünemann HJ. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* 2008;336:924-926.
22. Banerjee S, Adcock L. Probiotics for antibiotic-associated diarrhea and Clostridium difficile infection: a review of guidelines. Ottawa (ON): CADTH; 2018 Sep: https://www.cadth.ca/sites/default/files/pdf/htis/2018/RC1013-Probiotics%20forAAD%20and%20C.pdf Accessed 2019 Mar 25.
23. Williams D, Adcock L. Probiotics for antibiotic-associated diarrhea and Clostridium difficile infection: a review of clinical effectiveness. Ottawa (ON): CADTH; 2018 Sep: https://cadth.ca/sites/default/files/pdf/htis/2018/RC1022-Probiotics%20for%20AAD%20and%20C.pdf. Accessed 2019 Mar 25.
24. McFarland LV. Preventing pediatric antibiotic-associated diarrhea and Clostridium difficile infections with probiotics: a meta-analysis. *World J Meta Anal.* 2013;1(3):102-120.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Fang, 2019[7] China	5 RCTs published between 2005 and 2017 Databases were searched from inception to June 2018	N = 484 children with *H. pylori* infection undergoing triple therapy (PPI and 2 antibiotics) Duration of antibiotic treatment; range: 10 days to 1 month Age range: 3 years to 18 years	Intervention *Lactobacillus* (i.e., *L. acidophilus, L. rhamnosus, L. reuteri, L. casei*) Doses ranged from 1 x 10^9 CFU / day to 10 x 10^9 CFU / day Duration of treatment with probiotic ranged from 2 weeks to 30 days Comparator C1: placebo C2: no additional treatment	Outcomes **Incidence of diarrhea** Not described Follow-up Range: 4 to 6 weeks
Goldenberg, 2017[8] US	31 RCTs [6 studies in children published between 1999 and 2013 Databases were searched from inception to March 2017	N = 1141 children given antibiotics for any reason Age range: 6 months to 14 years among studies that reported it	Intervention Probiotics (any strain, any dose, any duration) Comparator Placebo, alternative prophylaxis, or no additional treatment	Outcome **AAD** As defined in each included study ***C. difficile* infection** Confirmed by detection in stool **Incidence of CDAD** As defined in each included study **AE** As defined in each included study Follow-up Range: no post-treatment follow-up to 3 months after initiation of antibiotics
Xu, 2017[9] China	30 RCTs published between 2004 and 2013	N = 7225 Chinese children given antibiotics for any	Intervention Bifidobacterium-based probiotics (5 strains	Outcomes **Diarrhea** As defined in each

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	Databases were searched up to December 2016	reason Age range: 1 month to 168 months	were included: *Lactobacillus, Enterococcus, Bacillus, Streptococcus*, or *Clostridium*) Comparator No additional treatment Treatment dose and duration were largely unreported in included studies	included study; incidence Follow-up Not reported
Lau, 2016[10] US	26 RCTs [4 studies in children published between 1999 and 2013] Databases were searched from 1966 to 2015	N = 888 Children taking antibiotics for any reason in in-patient and outpatient settings Age range: Mean ages of pediatric subsample ranged from 18.6 months to 48.7 months	Intervention *Lactobacillus* GG, *Saccharomyces boulardi*, or *Lactobacillus rhamnosus* Comparator C1: placebo C2: no additional treatment Treatments initiated within 3 days of starting antibiotics and continued for at least the entire duration of antibiotic treatment	Outcomes **Incidence of CDAD** Defined as diarrhea and positive stool cytotoxin assay or culture Follow-up: Not reported for pediatric subsample
Goldenberg, 2015[4] US	23 parallel RCTs published between 1990 and 2013 or unpublished Databases were searched from inception to November 2014	N = 3938 children receiving antibiotics for any reason Eligible age range: 1 month to 18 years	Intervention Single or multiple strain of probiotics (i.e., 2 to 10); specific, identified probiotic in any form Total dose ranged from 200 million CFU / day to 40 billion CFU / day Duration of treatment ranged from 3 to 30 days of antibiotic therapy Comparator Placebo, active, or no additional treatment	Outcomes: **Incidence of Diarrhea** As defined in each study **AE** As defined in each included study; Number and type of AE Follow-up: Range: no post-treatment follow-up to 21 days following end of treatment

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
			control	
McFarland, 2015[11] US	22 RCTs published between 1990 and 2013 Databases were searched from 1960 to 2013	N = 5366 pediatric outpatients or inpatients receiving antibiotics for "a variety of diseases, including respiratory tract infections, *H. pylori* eradication, otitis media, skin infections, urinary tract infections, etc." (*p190*)[24] Eligible age range: 1 month to 18 years[24] Mean duration of antibiotic use during the trial ranged from 3 to 30 days[24]	Intervention Single or multiple (i.e., 2 to 9) strain of probiotic Dose ranged from 10^7 CFU/day to 10^{10} CFU / day Frequency of doses ranged from 1 to 8 doses per day Duration of treatment ranged from 5 to 30 days based on duration of antibiotic co-intervention[24] Comparator Placebo, standard practice, or no treatment control	Outcomes: **Incidence of AAD** Defined as >2 to 3 loose or watery stools/day for >2 consecutive days Follow up: Range: no post-treatment follow-up to 12 weeks[24]
Szajewska, 2015[12] Poland	12 RCTs [5 studies specific to children published between 1998 to 2010] Databases were searched up to July 2015	N = 445 children who received antibiotics for common infections or *H. pylori* eradication Ages not reported for pediatric subsample	Intervention *Lactobacillus rhamnosus* GG Comparator Placebo or no additional treatment comparator Other details not provided for pediatric studies	**AAD** Defined by study authors Follow-up: Not reported for pediatric subsample
Szajewska, 2015[13] Poland	21 RCTs [7 studies specific to children published between 2004 to 2015] Databases were searched up to May 2015	N = 1,653 children who received antibiotics for common infections or *H. pylori* eradication Ages not reported for pediatric subsample	Intervention *Saccharomyces boulardii* Comparator Placebo or no additional treatment comparator Other details not provided for pediatric studies	**Incidence of AAD** Defined by study authors **Incidence of CDAD** Defined by study authors Follow-up: Not reported for pediatric subsample

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Li, 2014[14] China	3 single or multi-centre RCTs published between 2005 and 2013 Databases were searched up to July 2013	N = 508 *H. pylori*-positive, symptomatic children who received antibiotics for 7 to 14 days as part of triple therapy for *H. pylori* eradication Eligible and actual ages of participants not reported other than as "children"	Intervention Probiotics Duration of probiotic regimen ranged from 7 days to 3 months Comparator Placebo or no additional treatment comparator	**Diarrhea** Incidence (events/total)Definition not reported **Constipation** incidence (events/total) Definition not reported **Nausea/Vomiting** (events/total) Definition not reported Follow-up: Ranged from 4 weeks to 3 months following initiation of antibiotics

AAD = Antibiotic associated diarrhea; AE = adverse events; CDAD; *Clostridium difficile*-associated diarrhea; CFU = colony forming units; *H*. = *Helicobacter*; HpSA = *H. pylori* stool antigen; L. = Lactobacillus; mg = milligram; PIs = Principal Investigators; PPI = proton pump inhibitor; RCT = randomized controlled trial; RUT = Rapid urease test; UBT = urea breath test

Table 3: Characteristics of Included Guidelines

Group and/or First Author, Year, Country	Objective	Guideline Development Group, Intended Users	Methodology
CPS (Marchand), 2019[18] **Canada**	To provide recommendations to guide physicians in the judicious use of probiotics for children	CPS Nutrition and Gastroenterology Committee Intended users: physicians	Committee indicated intent to develop the Position Statement; CPS Board approval received Conducted a literature review of relevant RCTs and meta-analyses Recommendations written and reviewed by expert committee and approved by the Board of Directors Reviewed by the Committee three years after publication, and annually thereafter for committee to reaffirm, revise, or retire position statement
ESPGHAN (Szajewska), 2016[3] **Poland**	To provide recommendations for the use of probiotics for the prevention of AAD	ESPGHAN WG; group composition details were not presented. Intended users: health care professionals and patients	Conducted a SR of SRs and RCTs published subsequent to the most recent SR Systematic literature search was conducted through multiple databases. Searches were conducted up to November 2015 Methodological quality of RCTs was assessed using Cochrane Collaboration's tool for assessing RoB. The GRADE system was used to assess the quality of the evidence and the strength of the recommendations. Recommendations were formulated based on consensus of the WG. Recommendations were only formulated if at least 2 RCTs were available for a given probiotic. If only 1 RCT, whether or not there was a clinical benefit, no recommendation was formulated. Draft circulated among WG for review, comment, discussion of feedback, and incorporation of changes.

Group and/or First Author, Year, Country	Objective	Guideline Development Group, Intended Users	Methodology
			Recommendations formulated and graded by WG, who voted anonymously on each recommendation using an online survey. Disagreements were discussed and resolved until consensus Final document submitted to ESPGHAN Council for acceptance

AAD = antibiotic associated diarrhea; CPS = Canadian Paediatric Society; ESPGHAN = European Society for Pediatric Gastroenterology, Hepatology and Nutrition; GRADE = Grading Recommendations Assessment, Development and Evaluations; RoB = Risk of Bias; WG = Working Group

Table 4: Grade of Recommendations and Level of Evidence for Guidelines

Grade of Recommendations	Strength of Evidence
ESPGHAN / Szajewska, 2016[3]	
Strength of recommendation 1. Strong = the evidence showed that the benefit of the intervention clearly outweighs the undesirable effects "WG recommends" 2. Conditional = 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) "WG suggests"	Quality of evidence: High= very confident the true effect lies close to that of the estimate of the effect. Moderate = moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low = Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low = Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

WG = Working Group

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[5]

Strengths	Limitations
Fang, 2019[7]	
• Research questions and inclusion criteria included the components of PICO • Review authors used a comprehensive literature search strategy • Study selection was performed in duplicate • Data extraction was performed in duplicate • RoB was assessed using a satisfactory technique • Appropriate methods for statistical combination of results were used • Review authors assessed the potential impact of RoB in individual studies on the results of the meta-analyses • Review authors accounted for RoB in individual studies when interpreting/discussing the results of the review • Heterogeneity was appropriately handled in the review • Review authors carried out an adequate investigation of publication bias • Authors reported no conflict of interest	• No explicit statement that the review methods were established prior to the conduct of the review • Explanation for only including RCTs was not provided • A list of excluded studies and reasons for exclusion were not provided • Generally, included studies were described in adequate detail, but details regarding comparators and study settings were missing • Authors did not report on the sources of funding for included studies
Goldenberg, 2017[8]	
• Research questions and inclusion criteria included the components of PICO • The review contained an explicit statement that the methods were registered a priori. Post hoc analyses were justified • Review authors used a comprehensive literature search strategy, which was provided. The searches were conducted in <24 months of completion of the review • Study selection was performed in duplicate • Data extraction was performed in duplicate • A list of excluded studies and reasons for exclusions were provided • Included studies were described in adequate detail • Review authors used a satisfactory technique for assessing RoB in individual studies • Review authors reported on the sources of funding for studies included in the review • Appropriate methods for statistical combination of results were used • Review authors assessed the potential impact of RoB in individual studies on the results of the meta-analyses • Review authors accounted for RoB in individual studies when interpreting/discussing the results of the review • Heterogeneity was appropriately handled in the review • Review authors carried out an adequate investigation of publication bias • Potential sources of conflict were identified	• Explanation for only including RCTs was not provided

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[5]

Strengths	Limitations
Xu, 2017[9]	
• Research questions and inclusion criteria included the components of PICO • Review authors used a comprehensive literature search strategy • Study selection was performed in duplicate • Data extraction was performed in duplicate • Reasons for exclusions provided in PRISMA flow diagram • Included studies described in adequate detail where possible • RoB was assessed using a satisfactory technique • Appropriate methods for statistical combination of results were used • Review authors accounted for RoB in individual studies when interpreting/discussing the results of the review • Heterogeneity was appropriately discussed in the review • Review authors carried out an adequate investigation of publication bias • Authors reported no conflict of interest	• No explicit statement that the review methods were established prior to the conduct of the review • Explanation for only including RCTs was not provided • List of excluded studies not provided • Authors did not report on the sources of funding for included studies • Review authors did not assess the potential impact of RoB in individual studies on the results of the meta-analyses •
Lau, 2016[10]	
• The research questions and inclusion criteria for the review include the components of PICO • The review authors used a comprehensive literature search strategy • Review authors provided a list of reasons for exclusions in the form of a PRISMA flow diagram • Included studies were described in adequate detail • Review authors used appropriate methods for statistical combination of results • Review authors provided a satisfactory explanation for, and discussion of, heterogeneity observed in the results of the review • Review authors carried out an adequate investigation of publication bias and discussion of its likely impact on the results of the review • Review authors provided a statement of no conflict of interest	• Methods were included in the report of the review, however the report did not contain an explicit statement that the review methods were established prior to the conduct of the review • Review authors did not explain their selection of the study designs for inclusion in the review • It is unclear if study selection was performed in duplicate • It is unclear if study extraction was performed in duplicate • Review authors did not provide a list of excluded studies • Review authors did not assess the RoB in included individual studies • Review authors did not report on the sources of funding for the studies included in the review
Goldenberg, 2015[4]	
• Research questions and inclusion criteria included the components of PICO • The review contained an explicit statement that the methods were registered a priori. Post hoc analyses were justified • Review authors used a comprehensive literature search strategy, which was provided. The searches were conducted in <24 months of completion of the review • Study selection was performed in duplicate • Data extraction was performed in duplicate	• Explanation for only including RCTs was not provided

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[5]

Strengths	Limitations
• A list of excluded studies and reasons for exclusions were provided • Included studies were described in extensive detail • Review authors used a satisfactory technique for assessing RoB in individual studies • Review authors reported on the sources of funding for studies included in the review • Appropriate methods for statistical combination of results were used • Review authors assessed the potential impact of RoB in individual studies on the results of the meta-analyses • Review authors accounted for RoB in individual studies when interpreting/discussing the results of the review • Heterogeneity was appropriately handled in the review • Review authors carried out an adequate investigation of publication bias • Potential sources of conflict were identified	
McFarland, 2015[11]	
• Research questions and inclusion criteria included the components of PICO • Authors reported an a priori planned search strategy, inclusion/exclusion and analysis plan • Authors used a comprehensive search strategy, searched multiple databases, trials registries, and grey literature were searched. Key words searched were provided; searches were conducted within 24 months of completion of the review • Data extraction was performed in duplicate • A list of excluded studies was provided and exclusions were justified • Included studies were described in adequate detail • Review authors used a satisfactory technique for assessing the RoB in individual studies included in the review • Review authors reported on sources of funding for included studies • Review authors justified combining data in a meta-analysis and used an appropriate weighted technique to combine study results and adjust for heterogeneity • Review authors provide a satisfactory explanation for, and discussion of, heterogeneity in the results • Review authors investigated publication bias	• The study protocol was not registered a priori • Review authors did not explain their selection of the study designs for inclusion in the review • A search strategy was developed but not provided; references of included studies were not searched • It is unclear if study selection was performed in duplicate • Results of the review were not discussed in terms of RoB. • There was no explicit statement regarding conflict of interest or funding received for conducting the review
Szajewska, 2015[12]	
• Research questions and inclusion criteria included the components of PICO • An explicit statement that the review methods were established prior to the conduct of the review was made	• Review authors did not explain their selection of the study designs for inclusion in the review • It is unclear if study selection was performed in duplicate • A list of excluded studies was not provided

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[5]

Strengths	Limitations
• A comprehensive literature search strategy was used and key words were provided • Data were extracted by one reviewer and "assessed" by a second reviewer. Disagreements were resolved by discussion • Reasons for exclusions were reported • Review authors used a satisfactory technique for assessing the RoB in individual studies included in the review • Review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis • Review authors account for RoB in individual studies when interpreting/ discussing the results of the review • Review authors investigated publication bias • Review authors provided a declaration of personal interests	• Studies were not described in adequate detail • Review authors did not report on sources of funding for included studies • Deviations from the planned analyses were reported but not justified.
Szajewska, 2015[13]	
• Research questions and inclusion criteria included the components of PICO • An explicit statement that the review methods were established prior to the conduct of the review was provided • A comprehensive literature search strategy was used and key words were provided • Data were extracted by one reviewer and "assessed" by a second reviewer. Disagreements were resolved by discussion • Reasons for exclusions were reported • Review authors used a satisfactory technique for assessing the RoB in individual studies included in the review • Review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis • Review authors account for RoB in individual studies when interpreting/ discussing the results of the review • Review authors investigated publication bias • Review authors provided a declaration of personal interests	• Review authors did not explain their selection of the study designs for inclusion in the review • It is unclear if study selection was performed in duplicate • A list of excluded studies was not provided • Studies were not described in adequate detail • Review authors did not report on sources of funding for included studies
Li, 2014[14]	
• Research questions and inclusion criteria included the components of PICO • Study authors used a comprehensive literature search strategy • Data extraction was performed in duplicate • Reasons for exclusions were reported via PRISMA flow diagram • Included studies were described in adequate detail • Appropriate methods for statistical combination of results were used • Authors provided a satisfactory explanation for, and	• The report did not contain an explicit statement that the review methods were established prior to the conduct of the review • Authors did not explain their selection of study designs for inclusion in the review • It is unclear if study selection was performed in duplicate • A list of excluded studies was not provided • Sources of funding were not identified for included studies • Risk of bias in included studies was not assessed.

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[5]

Strengths	Limitations
discussion of, the heterogeneity observed in the results of the review • Review authors carried out an adequate investigation of publication bias and determined it was not likely to impact on the results of the review • Review authors provided a statement of no conflict of interest	

RCT = randomized controlled trial; ROB = Risk of Bias; PICO = Population, Intervention, Comparator, Outcome;

Table 6: Strengths and Limitations of Guideline using AGREE II[6]

Strengths	Limitations
CPS (Marchand), 2019[18]	
• Target users were clearly identified • Methods for formulating the recommendations are described in adequate detail • Health benefits, side effects, and risks were considered in formulating the recommendations • The document was externally reviewed as it was published in a journal • A procedure for updating the guideline is in place • Key recommendations are easily identifiable • The recommendations are as specific as the evidence allows. Uncertainty is stated in the guideline • Conflicts of interest were declared	• Evidence and recommendations were not critically appraised • Patient perspectives do not appear to have been considered • Systematic search methods were not described in adequate detail • The strengths and limitations of the body of evidence are not described • Facilitators and barriers to application were not described and support tools were not provided • Resource implications were not considered • Auditing and monitoring criteria were not presented
ESPGHAN (Szajewska), 2016[3]	
• The scope and purpose were clearly stated. • A systematic review was conducted using the databases DARE, CENTRAL, MEDLINE, MEDLINE and EMBASE. • Target users were clearly defined • Evidence was provided • The document was externally reviewed as it was published in a journal • Recommendations were graded using the GRADE system. • Conflicts of interest were declared. Some of the authors worked on advisory boards, consulted or received support from industry.	• Patient preferences do not appear to have been considered • Resource implications do not appear to have been considered • Unclear if a policy was in place for updating the guideline; although this is an update to a previous publication it is likely there is a policy.

CENTRAL = Cochrane Central Register of Controlled Trials; CPS = Canadian Paediatric Society; DARE = Database of Abstracts of Reviews of Effects; GRADE = Grading of Recommendations Assessment, Development, and Evaluation

Appendix 4: Main Study Findings and Authors' Conclusions

Table 7: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Fang, 2019[7]	
Diarrhea Incidence; 3 RCTs, n = 348 Probiotic, 2.2% vs comparator, 9.5% RR = 0.30, 95% CI: 0.10 to 0.85 Test for overall effect: z = 2.26; *P* = 0.02	"In conclusion, the current moderate-quality evidence suggested that Lactobacillus, as an adjunct to triple therapy, can increase H. pylori eradication rates as well as reduce the incidence of therapy-related diarrhea in children." (*p14*)[7]
Goldenberg, 2017[8]	
AAD Incidence (6 RCTs, n = 1141) Risk with probiotics, 103/1,000 vs risk with comparator, 271/1,000; 95% CI, 79 to 133 RR = 0.38, 95% CI: 0.29 to 0.49 **CDAD** Incidence (6 RCTs, n = 1141) Events with probiotic, 14/566 vs comparator, 43/575 RR = 0.35, 95%CI, 0.19 to 0.63 Test for overall effect: z = 3.52; *P* = 0.00044 **C. difficile infection** Incidence (2 RCTs, n = 253) Events with probiotic, 34/127 vs comparator, 41/126 RR = 0.82, 95% CI: 0.56 to 1.21 Test for overall effect: z = 1.00; *P* = 0.32 **AE** Incidence (4 RCTs, n = 888) Events with probiotic, 0/439 vs comparator, 0/449 RR = 0.0, 95% CI: 0.0 to 0.0 Test for overall effect: z = 2.30; *P* = 0.021	Not specific to findings in pediatric populations
Xu, 2017[9]	
AAD Reduction AAD (prevention and treatment), 30 RCTs Events not reported Pooled OR = 0.33, 95% CI: 0.29 to 0.39; *P* < 0.01 *favours probiotic vs comparator* Subgroup analyses: Prevention of AAD, 21 RCTs Events not reported Pooled OR = 0.34, 95% CI: 0.28 to 0.41; *P* < 0.01 *favours probiotic vs comparator*	"In conclusion, we found evidence that Bifidobacterium preparations might improve efficacy for pediatric AAD. However, confirmation of these conclusions in rigorously controlled, randomized trails is required before more firm conclusions about this therapy can be draw." (*p112*)[9]

Table 7: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Treatment of AAD, 9 RCTs Events not reported Pooled OR = 0.32, 95% CI: 0.23–0.43; P < 0.01 *favours probiotic vs comparator*	
Lau, 2016[10]	
CDAD Incidence 65.9% reduction in CDAD with probiotics Events not reported RR = 0.341, 95% CI: 0.153 to 0.759; *P* = 0.008	"…this study found that probiotic supplementation is a valuable adjunct in the routine care of patients receiving antibiotic therapy." (*p35*)[10] "…the significant reduction in the incidence of CDAD achieved with probiotic supplementation and the apparent lack of significant negative side effects…" (*p35*)[10]
Goldenberg, 2015[4]	
Incidence of Diarrhea Pooled – all types of probiotics (N = 3898; 22 RCTs) Risk with probiotics, 88/1000 vs comparator, 191/1000 RR = 0.46, 95% CI: 0.35 to 0.61 Sub-analysis - species with >1 included study *Lactobacillus rhamnosus (4 RCTs)* RR = 0.35, 95% CI: 0.22 to 0.56 *Saccharomyces boulardii (4 RCTs)* RR = 0.40, 95% CI: 0.17 to 0.96 **AE** (N = 2455; 16 RCTs) Risk with probiotics, 33/1000 vs comparator, 35/1000 RR = 0.00, 95% CI: -0.01 to 0.01	"Moderate quality evidence suggests a protective effect of probiotics in preventing AAD. Our pooled estimate suggests a precise (RR 0.46; 95% CI 0.35 to 0.61) probiotic effect with a NNT of 10. Among the various probiotics evaluated, evidence suggests that Lactobacillus rhamnosus or Saccharomyces boulardii at 5 to 40 billion colony forming units/day may be appropriate given the modest NNT and the likelihood that adverse events are very rare. It is premature to draw conclusions about the efficacy and safety of other probiotic agents for pediatric AAD."(*p20-21*)[4]
McFarland, 2015[11]	
AAD Overall incidence across 23 probiotic treatments (22 studies) Pooled RR = 0.43, 95% CI: 0.33 to 0.56, *P* < 0.001 Incidence for individual strains lyophilized *S. boulardii* (4 studies) Pooled RR = 0.43, 95% CI: 0.21 to 0.86, *P* = 0.02 *L. rhamnosus* GG (4 studies) Pooled RR = 0.44, 95% CI: 0.21 to 0.95, *P* = 0.04 Results driven by 1 large study. When deleted, pooled RR becomes non-significant P = 0.22. Authors suggested study flaws, rather than strain explain divergent outcomes.	"The results of this review indicate that only lyophilized *S. boulardii* has sufficient evidence to support its use to prevent pediatric AAD." (p*193*)[11]
Szajewska, 2015[12]	
AAD Overall incidence (5 studies)	"In summary, current evidence justifies the use of LGG for preventing AAD, although a number of questions

Table 7: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Probiotic, 21/219 events vs comparator, 52/226 events RR = 0.48, 95% CI: 0.26 to 0.89; Test for overall effect, *z* = 2.33; *P* = 0.02 <u>Incidence in children taking antibiotics for common infections (4 studies)</u> Probiotic, 19/185 **events** vs comparator, 46/196 **events** RR = 0.52, 95% CI: 0.25 to 1.05; Test for overall effect, *Z* = 1.81; *P* = 0.07 <u>Incidence in children taking antibiotics for *H. pylori* eradication (1 study)</u> Probiotic, 2/34 events vs comparator, 6/30 events RR = 0.29, 95% CI: 0.06 to 1.35 Test for overall effect: *Z* = 1.57; *P* = 0.12	remain unanswered and the QoE calls for caution." (*p1156*)[12]
Szajewska, 2015[13]	
AAD <u>Overall incidence (6 studies)</u> <u>Events not reported</u> RR = 0.43, 95% CI: 0.30 to 0.60 <u>Incidence in children taking antibiotics for common infections (4 studies)</u> Probiotic, 35/612 events vs comparator, 98/596 events RR = 0.36, 95% CI: 0.21 to 0.61 Overall effect: *Z* = 3.78, *P* = 0.0002 <u>Incidence in children taking antibiotics for *H. pylori* eradication therapy (2 studies)</u> Probiotic, 39/225 events vs comparator, 73/220 events RR = 0.53, 95% CI, 0.38 to 0.74 Overall effect: Z = 3.67, *P* = 0.0002 **CDAD** <u>Incidence (2 studies)</u> Probiotic, 4/286 events vs comparator, 18/293 events RR = 0.25, 95% CI, 0.08 to 0.73 Overall effect: *Z* = 2.54, *P* = 0.01	"As numerous different probiotic products are available, it is important to know the efficacy of a specific product, not of probiotics in general. The current meta-analysis helps to resolve such uncertainty. In cases in which an antibiotic is recommended, moderate quality evidence showed that the use of S. boulardii reduced the risk of AAD. The findings apply to both children and adults." (*p799*)[13] "Although available data are encouraging, it seems that the prudent use of antibiotics remains the best method of preventing AAD." (*p799*)[13]
Li, 2014[14]	
Diarrhea incidence <u>(3 studies)</u> Probiotics, 4/111 events vs comparator, 22/106 events OR = 0.16, 95% CI, 0.06 to 0.45 **Constipation incidence** <u>(2 studies)</u>	"In summary, the current limited evidence suggests that probiotics supplementation in triple therapy for H. pylori infection may have beneficial effects on eradication and therapy related side-effects, particularly diarrhea, in children." (*p160*)[14]

Table 7: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Probiotics, 4/78 events vs comparator 4/73 events OR = 0.94, 95% CI, 0.23 to 3.90 **Nausea/vomiting incidence** (3 studies) Probiotics, 9/111 events vs comparator 18/106 events OR = 0.39, 95% CI, 0.09 to 1.77	

AAD = Antibiotic-associated diarrhea; AE = adverse events; CI = confidence interval; CDAD = Clostridium difficile associated diarrhea; H. = Heliobacter; LGG = Lactobacillus rhamnosus GG; NNT = Number needed to treat; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; S = Saccharoymyces

Table 8: Summary of Recommendations in Included Guidelines

Evidence	Recommendations
CPS (Marchand), 2019[18]	
Based on literature review of RCTs and meta-analyses	"Keeping in mind that the effect of probiotics is both strain- and disease-specific, physicians should consider recommending probiotics to: • Prevent antibiotic-associated diarrhea."[18] "Physicians should be aware of the small risks of invasive infections with using some strains of probiotics in immunocompromised patients, and more rarely in the healthy child."[18] "Physicians should advocate for further research to define which strains and dose of probiotics should be used in specific conditions"[18]
ESPGHAN(Szajewska), 2016[3]	
Based on several systematic reviews and RCTs of evidence identified since the most recent systematic review	*L rhamnosus GG (LGG)* • "If the use of probiotics for preventing AAD in children is considered, the WG recommends using *L rhamnosus GG.*" (*p497*)[3] • Quality of evidence = moderate • Strength of recommendation = strong *Saccharomyces boulardii* • "If the use of probiotics for preventing AAD in children is considered, the WG recommends using S boulardii for preventing AAD in children." (*p503*)[3] • Quality of Evidence: Moderate • Strength of recommendation = strong • "If the use of probiotics for preventing C difficile associated diarrhea in children is considered the WG suggests using S. boulardii" (*p503*)[3] • Quality of evidence = low • Strength of recommendation = conditional

Table 8: Summary of Recommendations in Included Guidelines

Evidence	Recommendations
	Probiotics with insufficient evidence to make recommendations: *Single probiotics:* • Bacillus clausii *Mixture of probiotics:* • Bacillus lactis/Streptococcus thermophiles • L acidophilus/L bulgaricus • L acidophilus/Bifidobacterium infantis • L acidophilus/Bifidobacterium breve • L rhamnosus GG/ Bb-12/L acidophilus La-5 • B longum PL03/L rhamnosus KL53A/L plantarum PL02 • L rhamnosus E/N, Oxy, Pen • L acidophilus/ L rhamnosus/L bulgaricus/ L casei/ Str thermophiles/ B infantis/ B breve • Kefir • Yogurt

AAD = antibiotic associated diarrhea; WG = Working Group; RCT = randomized controlled trial

Appendix 5: Overlap between Included Systematic Reviews

Primary Study Citation	Fang 2019[7]	Goldenberg 2017[8]	Xu 2017[9]	Lau 2016[10]	Goldenberg 2015[4]	McFarland 2015[11]	Szajewska 2015[12]	Szajewska 2015[13]	Li 2014[14]
Shahraki 2017	X								
Zhu 2017	X								
Bin 2015								X	
Fox 2015					X				
Georgieva 2015		X							
Zhao 2014								X	
Ahmad 2013						X			X
Casem 2013								X	
Feng 2013			X						
Hong 2013			X						
Kodadad 2013					X				
Shan 2013		X		X	X	X		X	
Tang 2013			X						
Tong 2013			X						
Li 2012			X						
Tolone 2012									X
Wang 2012			X						
Wang & Fang 2012			X						
Xi 2012			X						
Zeng 2012					X	X			
Zhu 2012			X						
Huang 2011			X						
Meng 2011			X						
Shao 2011			X						
Xu 2011			X						
Yao 2011			X						
Saneeyan 2011					X	X			
Ge 2010			X						
Goo 2010			X						

Primary Study Citation	Fang 2019[7]	Goldenberg 2017[8]	Xu 2017[9]	Lau 2016[10]	Goldenberg 2015[4]	McFarland 2015[11]	Szajewska 2015[12]	Szajewska 2015[13]	Li 2014[14]
King 2010							X		
He 2009			X						
Ke 2009			X						
Ma 2009			X						
Merenstein 2009					X	X			
Pancheva 2009		X							
Szajewska, 2009	X				X	X	X		X
Destura 2008						X			
Diao 2008			X						
Gan 2008			X						
Liu 2008			X						
Szymansky 2008					X	X			
Ruszczynski 2008		X		X	X	X			
Conway 2007					X	X			
Liu 2007			X						
Yan 2007			X						
Zhou 2007			X						
Lou 2006			X						
Plewinska 2006	X								
Zhao 2006			X						
Correa 2005					X	X			
Kotowska 2005		X		X	X	X		X	
Sykora 2005	X				X				
Pancheva 2004						X			
Erdve 2004					X	X		X	
Xie 2004									
LaRosa 2003					X	X			

Primary Study Citation	Fang 2019[7]	Goldenberg 2017[8]	Xu 2017[9]	Lau 2016[10]	Goldenberg 2015[4]	McFarland 2015[11]	Szajewska 2015[12]	Szajewska 2015[13]	Li 2014[14]
Seki 2003						X			
Jirapinyo 2002					X	X			
Arvola 1999		X		X	X	X	X		
Vanderhoof 1999					X	X	X		
Vaisanen 1998						X	X		
Benhamou 1999					X	X		X	
Contardi 1991					X				
Tankanow 1990					X	X			
Destura unpublished					X				
Georgieva unpublished					X				