Probiotics for the Prevention of Antibiotic-Associated Diarrhea in Children

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ABSTRACT

This article provides recommendations, developed by the Working Group (WG) on Probiotics of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition, for the use of probiotics for the prevention of antibiotic-associated diarrhea (AAD) in children based on a systematic review of previously completed systematic reviews and of randomized controlled trials published subsequently to these reviews. The use of probiotics for the treatment of AAD is not covered. The recommendations were formulated only if at least 2 randomized controlled trials that used a given probiotic (with strain specification) were available. The quality of evidence (QoE) was assessed using the Grading of Recommendations Assessment, Development, and Evaluation guidelines. 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 diarrhea, the WG recommends using *Lactobacillus rhamnosus* GG (moderate QoE, strong recommendation) or *Saccharomyces boulardii* (moderate QoE, strong recommendation). If the use of probiotics for preventing *Clostridium difficile*-associated diarrhea is considered, the WG suggests using *S boulardii* (low QoE, conditional recommendation). Other strains or combinations of strains have been tested, but sufficient evidence is still lacking.

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Antibiotic-associated diarrhea (AAD) is a common and challenging complication observed in the ambulatory and hospital settings alike that occurs in up to a third of all patients treated with antibiotics (1). It is defined as diarrhea that occurs in relation to antibiotic treatment with the exclusion of other etiologies. This relation does not necessarily translate into an immediate adverse reaction to antibiotics, because AAD may occur after a few weeks and even up to a few months after the administration of the antibiotics (2). Thus, in the latter situation, caution is needed to differentiate AAD from an episode of infectious gastroenteritis. The risk of AAD is higher when there is a use of aminopenicillins without/with clavulanate, cephalosporins, clindamycin, and, in general, any antibiotic that is active against anaerobes (3). Almost any oral and intravenous antibiotic treatment can, however, cause AAD (3). Clinically, AAD may present as mild diarrhea, but it can present as well as fulminant pseudomembranous colitis. Usually, no pathogen is identified. In the most severe forms and in an increasing number of patients with chronic conditions such as those with inflammatory bowel diseases, cystic fibrosis, and cancer, however, the causative agent is often identified as *Clostridium difficile* (4).

The use of probiotics, defined as ''live microorganisms that, when administered in adequate amounts, confer a health benefit on the host,'' (5) and/or fermented products such as yogurt has been reported as a measure to prevent the occurrence of AAD. The rationale for the use of these products relies on the hypothesis that AAD is caused by dysbiosis that is triggered by antibiotic use and that the probiotic intervention favorably modulates the intestinal microbiota (1).

The aim of this position paper by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Working Group (WG) on Probiotics and Prebiotics is to provide recommendations for the use of probiotics for preventing AAD in children.

METHODS

The same methodology that had been used previously by the WG for developing guidelines on the use of probiotics for the management of acute gastroenteritis (6) was applied for developing the present position paper. In brief, the document provides a review of previously completed systematic reviews and of randomized controlled trials (RCTs) published subsequently to these reviews. For systematic reviews/meta-analyses, the *Cochrane Database of Systematic Reviews* and the *Database of Abstracts of Reviews of Effects* (DARE) were searched. For subsequently published trials (starting from the date of the most recent search in the included reviews), CENTRAL (Cochrane Central Register of Controlled Trials), MEDLINE, and EMBASE were searched up to July 2015 and again in November 2015.

The focus was on 6 taxonomic groups *(Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus,* and/or *Bacillus).* The list of individual probiotics to be considered was established based on the results of the Cochrane review evaluating probiotics for preventing AAD in children (7) and the list of commonly used probiotics developed by the World Gastroenterology Organization (8).

The WG is aware that taxonomically equivalent probiotic microorganisms may be supplied by different manufacturers. At least 1 study indicated that the manufacturing process may influence properties of probiotic bacteria (9). At present, whether or not these manufacturing differences translate into differences in vivo, as well as clinical outcomes, however, remains unclear. Consequently, the taxonomically equivalent probiotics are presented jointly, regardless of the manufacturer. The WG also realizes that the same brand may have a different composition in different locations; nevertheless, this position paper deals with strain(s) rather than brands or commercial names. Finally, depending on the country, the same probiotic microorganism(s) may be available as food supplements, available as registered pharmaceutical products, and/or incorporated into foods (10). In this document, the effectiveness of probiotics was analyzed regardless of the registration status. Health care professionals and consumers should, however, be aware of possible variations in the manufacturing and safety profiles of the products, which may be different when the strain is registered as a drug and also with regard to the claims allowed.

The primary outcome measures were diarrhea/AAD and *C difficile*-associated diarrhea (all as defined by the investigators).

To assess the methodological quality of the included RCTs (included in the previously published meta-analyses and subsequently published RCTs not included in the systematic reviews), the Cochrane Collaboration's tool for assessing risk of bias was used. This tool includes the following criteria: adequacy of sequence generation, allocation concealment, and blinding of participants, personnel and outcome assessors; incomplete outcome data; and selective reporting (11).

For reporting the effect, the results for individual studies and pooled statistics are reported as the risk ratio (RR) between the experimental and control groups with 95% confidence intervals (95% CIs). In other circumstances, we report the findings as reported by the authors of the included studies.

When synthesizing the evidence, each section presents a summary of the evidence followed by the key recommendations. The GRADE system, developed by the Grading of Recommendations Assessment, Development and Evaluations Working Group (12), was used to grade the strength of evidence and grades of recommendations used in these guidelines. In brief, the GRADE system offers 4 categories of the quality of the evidence (ie, high, moderate, low, and very low) and 2 categories of the strength of recommendation (ie, strong or conditional [weak]) (Table 1). The GRADE system suggests presenting recommendations in the active voice (13). Thus, we used the wording ''the WG *recommends*'' for strong recommendations, and ''the WG *suggests*'' for conditional [weak] recommendations.

As in our previous document (6), the WG adopted the position of the US Food and Drug Administration Guidance for Industry (14) that at least 2 adequate and well-controlled studies, each convincing on its own, are needed to establish the effectiveness of an intervention. Consequently, the recommendations were formulated only if at least 2 RCTs that used a given probiotic were available. If there was only 1 RCT, regardless of whether or not it showed a benefit, no recommendation was formulated. Moreover, if the strain specification was not given and/or the probiotic product was not otherwise identifiable, no recommendation was made.

For the sake of completeness, we report the pooled data (meta-analysis) of all probiotic trials. No recommendation on the use of probiotics in general was, however, made, because pooling data on different probiotics has been repeatedly questioned (15). Instead, because various probiotic strains differ in their effects, preference was given to reporting evidence and recommendations related to a specific probiotic strain or their combinations separately.

TABLE 1. The grades of the quality of evidence and strength of recommendation set by the GRADE Working Group

Quality of evidence	High quality	We are very confident that the true effect lies close to that of the estimate of the effect.
	Moderate quality	We are 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 quality	Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
	Very low quality	Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.
Strength of recommendation	Strong	When the evidence showed that the benefit of the intervention clearly outweighs the undesirable effects.
	Conditional (weak)	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).

GRADE = Grading of Recommendations Assessment, Development and Evaluations.

A draft of the position paper was sent to the WG members for review and further comments. All of the critical feedback was discussed through e-mail or during personal contacts, and changes were incorporated as necessary. Recommendations were formulated and graded. The WG members voted anonymously on each recommendation using an online electronic survey tool (SurveyMonkey Inc, Palo Alto, CA, *www.surveymonkey.com*). Any disagreement following voting was resolved by discussion, and for all recommendations, a full consensus was reached. A finalized document was submitted to the ESPGHAN Council for final acceptance before publication.

The WG recommendations may need to be modified by different countries considering differences in health care systems, local values and preferences, including availability, quality, and costs of probiotics, and should help local policy makers to decide whether to use routinely probiotics with documented efficacy for preventing AAD in children receiving antibiotics based on local cost-effectiveness analysis. This is particularly important in low- and middle-income countries.

Clearly, an individual patient's risk of developing AAD or *C difficile*-associated diarrhea depends on a number of factors such as class of antibiotic(s), duration of antibiotic treatment, age, need for hospitalization, comorbidities, and previous episodes of AAD or *C difficile*-associated diarrhea (1–3). These risk factors should be considered when making decisions on the use of probiotics in children for preventing AAD or *C difficile*-associated diarrhea. The WG acknowledges that the judicious use of antibiotics remains the best method of preventing AAD.

The conclusions of this document may require revision in the future as new information becomes available. It is the intention of the WG to revise the recommendations not later than 5 years from now and produce an updated document.

PROBIOTICS OVERALL

A number of systematic reviews and meta-analyses have shown that probiotics as a group are effective in preventing AAD (7,16,17).

A 2012 meta-analysis by Hempel et al (16) collected data from 82 RCTs that evaluated the efficacy of probiotics for preventing AAD in subjects of all ages. Probiotics, as a group, reduced the risk of AAD (63 RCTs, n = 11,811 participants, RR 0.58, 95% CI 0.50–0.68). Sixteen RCTs were carried out in infants and young children and reported a reduced risk of AAD with probiotic administration (RR 0.55, 95% CI 0.38–0.80). In the majority of trials, *Lactobacillus*-based interventions, alone or in combination with other genera, were used. Strains were poorly documented. The quality of evidence was low. Of 63 included trials, 59 lacked adequate information to assess the overall risk of bias. There was no placebo group in some trials. Included trials used different definitions of diarrhea/AAD, and in some, no definition of these outcomes was provided. Moreover, significant heterogeneity between trials for both primary and secondary outcomes was detected. The authors concluded that the evidence is insufficient to determine whether this association varies systematically by population, antibiotic characteristic, or probiotic preparation.

A 2013 systematic review with a meta-analysis assessed the efficacy and safety of probiotics for preventing *C difficile*-associated diarrhea or *C difficile* infection in adults and children (17). A complete case analysis (ie, participants who completed the study) showed that compared with placebo or no treatment, administration of probiotics reduced the risk of *C difficile*-associated diarrhea by 64% (23 RCTs, n = 4213, RR 0.36, 95% CI 0.26–0.51) in adults and children. In children, probiotic administration reduced the risk of *C difficile*-associated diarrhea from 5.9% to 2.3% (3 RCTs, n = 605, RR 0.40, 95% CI 0.17–0.96) (17).

For this report, 21 RCTs involving 3255 children were included (18–38). Among them, 11 RCTs were included in 2 strain-specific systematic reviews initiated as part of the development of these guidelines (39,40). One unpublished study (29) was identified in the systematic review by Johnston et al (7). For characteristics of the included RCTs, see Table 2, and for a methodological quality summary, see Figure 1. The pooled results of 21 RCTs showed that compared with placebo or no intervention, probiotics as a class reduced the risk of AAD by 52% (21.2% vs 9.1%, respectively; RR 0.48, 95% CI 0.37–0.61) (Fig. 2). Only 2 probiotics were evaluated in >1 RCT. These were *Lactobacillus rhamnosus* GG (LGG) and *Saccharomyces boulardii*. Compared with placebo, the administration of probiotics also reduced the risk of *C difficile*-associated diarrhea (4 RCTs, n = 938, RR 0.34, 95% CI 0.15–0.76) (Fig. 3).

PROBIOTICS WITH RECOMMENDATIONS

L rhamnosus GG (LGG)

RECOMMENDATION. If the use of probiotics for preventing AAD in children is considered, the WG recommends using *L rhamnosus* GG.
QUALITY OF EVIDENCE: Moderate.
STRENGTH OF RECOMMENDATION: Strong

TABLE 2. Characteristics of the included trials

Reference	Participants (age)	Probiotic dose (CFU/day)	Duration of intervention	Follow-up	Antibiotic/s (administration)	Definition of diarrhea or AAD	Manufacturer	Sponsor
Lactobacillus rhamnosus GG								
Arvola et al (19)	N = 119, inpatients, (2 wk–13 y)	2×10^{10}	For the duration of antibiotic therapy	3 mo	Penicillin, Amoxicillin, Cephalosporins, Erythromycin, Trimetoprim-sulfa	≥3 watery stools/day for minimum of 2 consecutive days	Not reported	Finnish Foundation for Gastroentero-logical Research
King et al (20)	N = 15, inpatients (21 days–11 y)	30×10^{9}	For the duration of antibiotic therapy	Not mentioned	Various	≥3 loose stools in 24 h	Not reported	Not reported
Szajewska et al (22)	N = 66, inpatients, (mean age 12 y; age range not reported)	1×10^{9}	For the duration of antibiotic therapy (7 days)	6 wk	Amoxicillin, Clarithromycin (oral)	≥3 loose or watery stools per day for at least 48 h	Dicofarm, Rome, Italy	Medical University of Warsaw
Vaisanen et al (21)	N = 59, outpatients (5 mo–11 y)	4×10^{8}	For the duration of antibiotic therapy (7 days)	Not mentioned	Amoxicillin (oral)	Defined by parents	Not reported	Not reported
Vanderhoof et al (18)	N = 188, outpatients (6 mo–10 y)	$1–2 \times 10^{10}$	For the duration of antibiotic therapy (10 days)	10 days	Amoxicillin, amoxicillin/ clavulanate, cefprozil, clarithromycin, other (oral).	≥2 liquid stools/day	CAG Functional Food	Grant from CAG Nutrition, a division of ConAgra
Saccharomyces boulardii								
Bin et al (27)	N = 205, exact data not given (22 mo–16 y)	250 mg $(0.5 \times 10^{10})^{*}$	For the duration of antibiotic treatment (14 days)	No data	Amoxicillin, clarithromycin, metronidazole	Diarrhea: increase in the frequency of bowel movements (>3/day) or a decrease in stool consistency (Bristol stool scale 5 or 6)	No information given	Biocodex, Paris, France, Chinese brand name: YiHuo. *S boulardii* CNCM I-745
Casem et al (24)	N = 140, hospitalized and outpatients (6 mo–18 y)	500 mg $(1 \times 10^{10})^{*}$	For the duration of antibiotic treatment (SB group 7.29 ± 0.92 days; control group 7.59 ± 1.17 days)	No data	Various (oral or intravenous)	Diarrhea: ≥3 loose or watery stools per day for a minimum of 48 h during and/or up to 2 wk after the end of antibiotic treatment	Not reported	Not reported
Erdeve et al (25)	N = 466, exact data not given (1–15 y)	250 mg $(0.5 \times 10^{10})^{*}$	Exact data not given	No data	Sulbactam-ampicillin, azithromycin (not mentioned)	Exact definition not given	Not reported	Not reported

Reference	Participants (age)	Probiotic dose (CFU/day)	Duration of intervention	Follow-up	Antibiotic/s (administration)	Definition of diarrhea or AAD	Manufacturer	Sponsor
Kotowska et al (23)	N = 269, inpatients and outpatients (6 mo–14 y)	500 mg (1×10^{10})*	For the duration of antibiotic treatment (SB group 7.8 ± 1 days; control group 8.1 ± 1 days)	2 wk	Various (oral or intravenous)	Diarrhea: ≥3 loose or watery stools per day for a minimum of 48 h during and/or up to 2 wk after the end of antibiotic treatment. AAD: As above, caused by *C difficile* or for otherwise unexplained diarrhea	No information given (Enterol Biocodex—information from the authors)	No information given (Medical University of Warsaw—information from the authors)
Shan et al (26)	N = 333, inpatients (6 mo–14 y)	500 mg (1×10^{10})*	For the duration of antibiotic treatment (exact data not given)	2 wk	Various (intravenous)	Diarrhea: ≥3 loose or watery stools per day or during ≥48 h, occurring during and/or up to 2 wk after the end of antibiotic treatment	One of the investigators serves as a consultant in Biocodex	Bioflor, China
Zhao et al (28)	N = 240 (7–9 y ± 2 y)	500 mg (1×10^{10})*	For the duration of antibiotic treatment (14 days)	8 wk	Amoxicillin, clarithromycin	No definition given	Not reported	Not reported
Bacillus clausii								
Destura et al (29)	N = 323, inpatients and outpatients (mean age 4 y)	4×10^9	Until end of antibiotic therapy (7–21 days)	Until end of antibiotic therapy (7–21 days)	Penicillins, cephalosporin, coamoxyclav/ampicillin-sulbactam, and others	Change in bowel habits with the passage of 3 or more liquid stools per day for at least 2 consecutive days 48 h after initiation of antibiotic therapy	Study funded by industry	Study funded by industry
Bifidobacterium lactis and Str thermophilus								
Correa et al (30)	N = 157, inpatients (6–36 mo)	*B lactis* 10^7 CFU/g and *Str thermophilus* 10^6 CFU/g	15 days	30 days	Various	Change in bowel habits with the passage of 3 or more liquid stools per day for at least 2 consecutive days	Nestle	Nestle

Reference	Participants (age)	Probiotic dose (CFU/day)	Duration of intervention	Follow-up	Antibiotic/s (administration)	Definition of diarrhea or AAD	Manufacturer	Sponsor
Bifidobacterium longum PL03/Lactobacillus rhamnosus KL53A/Lactobacillus plantarum PL02								
Szymanski et al (34)	N = 78, inpatients and outpatients (5 mo–16 y)	2×10^8	For the duration of antibiotic treatment	During and/or up to 2 weeks after the end of the antibiotic therapy	Amoxicillin with or without clavulanate, cephalosporins, penicillin, macrolides, aminoglycosides	≥3 loose or watery stools per day for a minimum of 48 h, occurring during and/or up to 2 weeks after the end of the antibiotic therapy	IBSS Biomed	IBSS Biomed SA, Cracow, Poland (study products)
Lactobacillus acidophilus and *Lactobacillus bulgaricus*								
Tankanow et al (31)	N = 38, outpatients (5 mo–6 y)	20.4×10^8	10 days (minimum 5 days)	10 days (minimum 5 days)	Amoxicillin	>1 abnormal loose bowel movement per day	Hynson, Westcott, and Dunning Products	Supported in full by Hynson, Westcott & Dunning Products
Lactobacillus acidophilus and *Bifidobacterium infantis*								
Jirapinyo et al (32)	N = 18, inpatients (1–36 mo)	3 capsules daily	7 days	Not stated	Broad-spectrum antibiotics (mainly cefotaxime)	Not stated	Not reported	Not reported
Lactobacillus acidophilus and *Bifidobacterium breve*								
Contardi et al (37)	N = 40, outpatients (1 mo–3 y)	3×10^9	For 10 days	Not stated	Amoxicillin	Not reported	Not reported	Not reported
Lactobacillus rhamnosus E/N, Oxy, Pen								
Ruszczyński et al (35)	N = 240, inpatients and outpatients (3 mo–14 y)	4×10^{10}	For the duration of the antibiotic treatment	During and/or up to 2 weeks after the end of the antibiotic therapy.	Penicillins; broad-spectrum penicillins, cephalosporins, macrolides, clindamycin	≥3 loose stools per day for a minimum of 48 h, occurring during and/or up to 2 wk after the end of the antibiotic therapy	Biomed Lublin (Lakcid Forte)	Funded in part by Biomed, Lublin, Poland, and the Medical University of Warsaw
Lactobacillus rhamnosus GG, *Bifidobacterium lactis* Bb-12, and *Lactobacillus acidophilus* La-5								
Fox et al (33)	N = 70, outpatients (1 y–12 y)	LGG (5.2×10^9), Bb-12 (5.9×10^9) and La-5 (8.3×10^9)	Same duration as their antibiotic treatment	Duration of treatment plus 1week	β-lactams, macrolides, tetracyclines	Diarrhea, classified at different levels of severity: for example, less severe (stool frequency ≥2/day for 2 or more days with stool consistency ≥5 on the BSS); more severe (stool frequency ≥3/day for 2 or more days with stool consistency ≥6 on the BSS)	Parmalat (Brisbane, Queensland, Australia)	Parmalat (Brisbane, Queensland, Australia)

Reference	Participants (age)	Probiotic dose (CFU/day)	Duration of intervention	Follow-up	Antibiotic/s (administration)	Definition of diarrhea or AAD	Manufacturer	Sponsor
Lactobacillus acidophilus and *Lactobacillus rhamnosus* and *Lactobacillus bulgaricus and Lactobacillus casei* and *Str thermophilus* and *Bifidobacterium infantis* and *Bifidobacterium breve*								
Khodadad et al (38)	N = 66, inpatients (3–14 y)	1×10^9 CFU/day	For the duration of *Helicobacter pylori* eradication therapy (4 wk?; not clearly stated)	Not stated	Amoxicillin, furazolidone	Not stated	Protexin Co, UK	Not reported
Kefir								
Merenstein et al (36)	N = 125, outpatients (1–5 y)	At least half of a 150 mL drink containing 7 to 10^9 CFU bacteria and yeast	For the duration of antibiotic treatment (10 days)	14 days	Antibiotics for upper respiratory tract infections (not specified otherwise)	Not reported	Probugs (Lifeway Foods, Inc, Chicago, IL)	Lifeway Foods, Inc

AAD = antibiotic-associated diarrhea; BSS = Bristol Stool Scale; CFU = colony-forming units; SB = *S boulardii*.
* As calculated by the authors.

FIGURE 1. Methodological quality summary.

A 2015 systematic review with a meta-analysis (40) identified 5 relevant RCTs (445 participants) (18–22). The methodological quality of the trials varied (Fig. 1). Only 1 trial was at a low risk of bias. In the remaining trials, the limitations included unclear random sequence generation, unclear or no allocation concealment, and unclear or no blinding of participants and personnel. Intention-to-treat analysis was performed in only 1 trial. Using the GRADE,

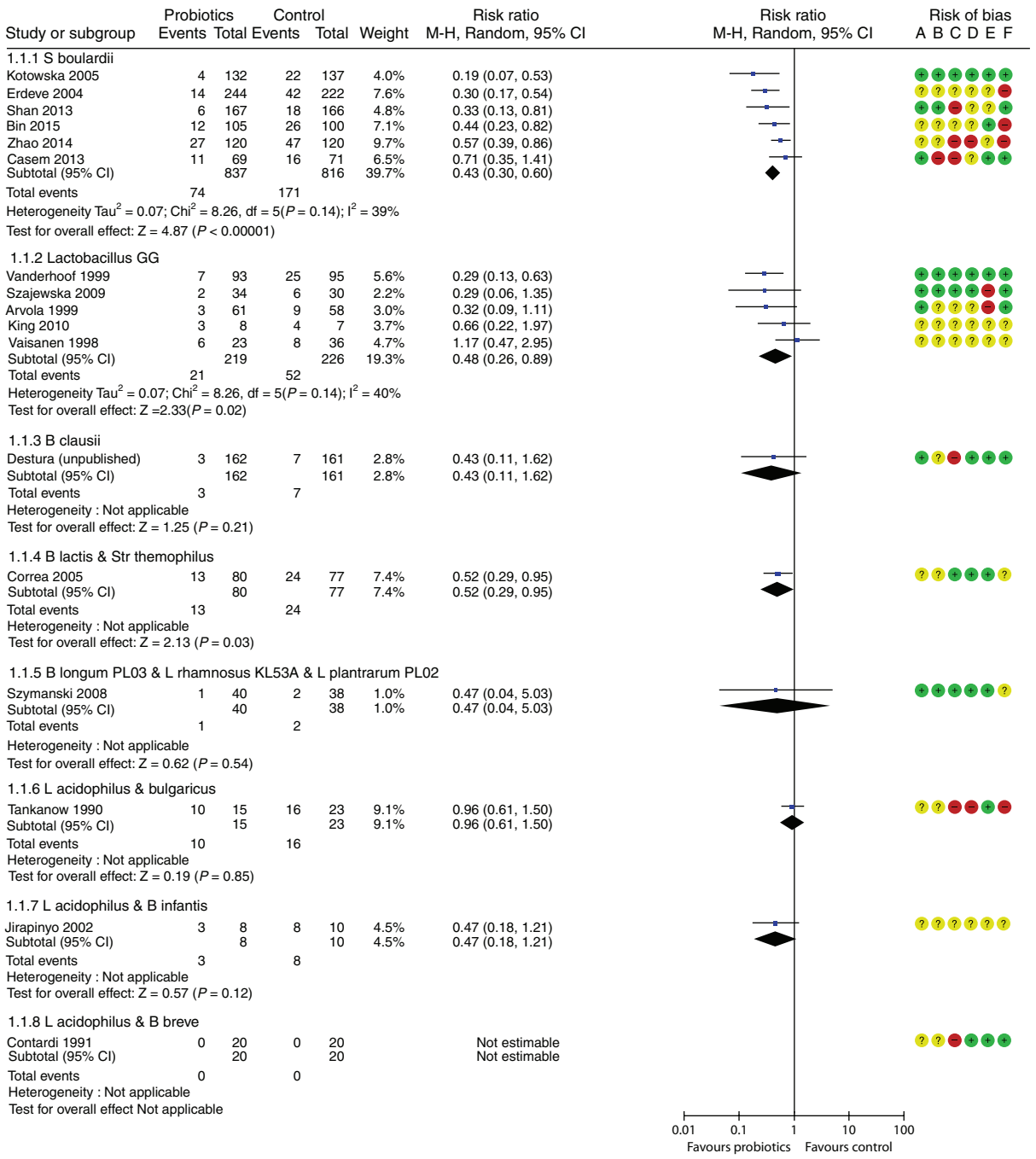

FIGURE 2. Effect of individual probiotic strains and probiotics as a group for preventing antibiotic-associated diarrhea.

(*Continued on next page*)

the overall quality of evidence was rated as moderate (Table S1, *http://links.lww.com/MPG/A587*).

Compared with placebo or no treatment, LGG administration in children reduced the risk of AAD, regardless of the reason for which probiotics were used (ie, as part of *Helicobacter pylori* eradication or for other reasons), from 23% to 9.6% (5 RCTs, n = 445, RR 0.48, 95% CI 0.26–0.89; number needed to treat, NNT, 8, 95% CI 6–40) (Fig. 2). No significant heterogeneity was found ($\chi^2 = 6.61$, $P = 0.16$, $I^2 = 40\%$). Only 1 trial (19) evaluated the effect of LGG on the risk of *C difficile*-associated diarrhea in children and found no effect (RR 0.95, 95% CI 0.06–14.85) (Fig. 3).

The optimal daily dose of LGG for preventing AAD remains unclear (40). In children, the best effect (reduction in the risk of AAD by 71%) was achieved with the highest dose ($1–2 \times 10^{10}$ CFU) (18). A similar effect size was, however, not achieved in another trial using the same dose (19), perhaps because of a lower baseline risk of AAD. In adults, there was no clear link between the effect size and the LGG dose.

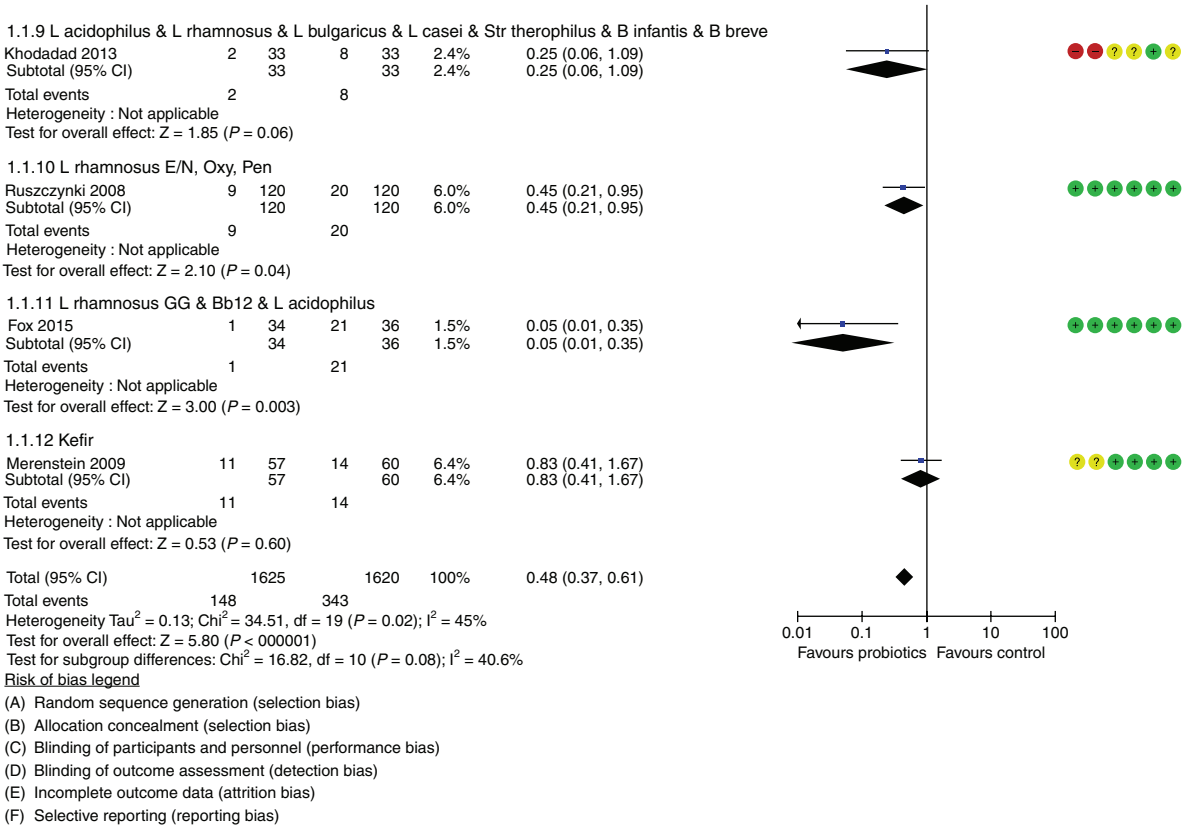

FIGURE 2. (*Continued*)

Saccharomyces boulardii

RECOMMENDATION. If the use of probiotics for preventing AAD in children is considered, the WG recommends using *S boulardii* for preventing AAD in children.
QUALITY OF EVIDENCE: Moderate.
STRENGTH OF RECOMMENDATION: Strong.
RECOMMENDATION. If the use of probiotics for preventing *C difficile*-associated diarrhea in children is considered, the WG suggests using *S boulardii*.
QUALITY OF EVIDENCE: Low.
STRENGTH OF RECOMMENDATION: Conditional.

A 2015 systematic review with a meta-analysis (39) identified 6 relevant RCTs (1653 participants) (23–28). The methodological quality of the trials varied. Only 1 trial was at a low risk of bias. In the remaining trials, the limitations included unclear random sequence generation, unclear or no allocation concealment, and unclear or no blinding of participants and personnel. Intention-to-treat analysis was performed in only 2 trials. Using the GRADE, the overall quality of evidence for AAD and *C difficile*-associated diarrhea was rated as moderate and low, respectively (Tables S2 and S3, *http://links.lww.com/MPG/A587*).

Compared with placebo or no treatment, *S boulardii* administration in children reduced the risk of diarrhea, regardless of the reason for which probiotics were used (ie, as part of *H pylori* eradication or for other reasons), from 20.9% to 8.8% (6 RCTs, n = 1653, RR 0.43, 95% CI 0.30–0.60, NNT 9, 95% CI 7–12). No significant heterogeneity was found ($\chi^2 = 8.26$, $P = 0.14$, $I^2 = 39\%$) (Fig. 2).

The administration of *S boulardii* also reduced the risk of *C difficile*-associated diarrhea in children (2 RCTs, n = 579, RR 0.25, 95% CI 0.08–0.73) (Fig. 3).

The optimal dose of *S boulardii* has not been established. A 2015 meta-analysis showed that various doses of *S boulardii* were used with no clear dose-dependent effect (39). Until more data on the optimal dose of *S boulardii* become available, a daily dose of not <250 mg but not >500 mg in children and not >1000 mg in adults could be used to match the doses used in RCTs.

PROBIOTICS WITH INSUFFICIENT EVIDENCE TO MAKE A RECOMMENDATION

Single Probiotics

Bacillus clausii

A 2011 Cochrane review (7) identified 1 unpublished RCT (29). Compared with no intervention, administration of *Bacillus clausii* (strain specification not given) had no effect on the risk of AAD (n = 323, RR 0.43, 95% CI 0.11–1.62).

Mixtures of Probiotics

Bacillus lactis/Streptococcus thermophilus

One RCT (n = 157) conducted in inpatients who were children (aged 6–36 months) showed that compared with the control formula, the administration of infant formula supplemented with *B lactis* Bb-12 and *Streptococcus thermophilus* significantly reduced

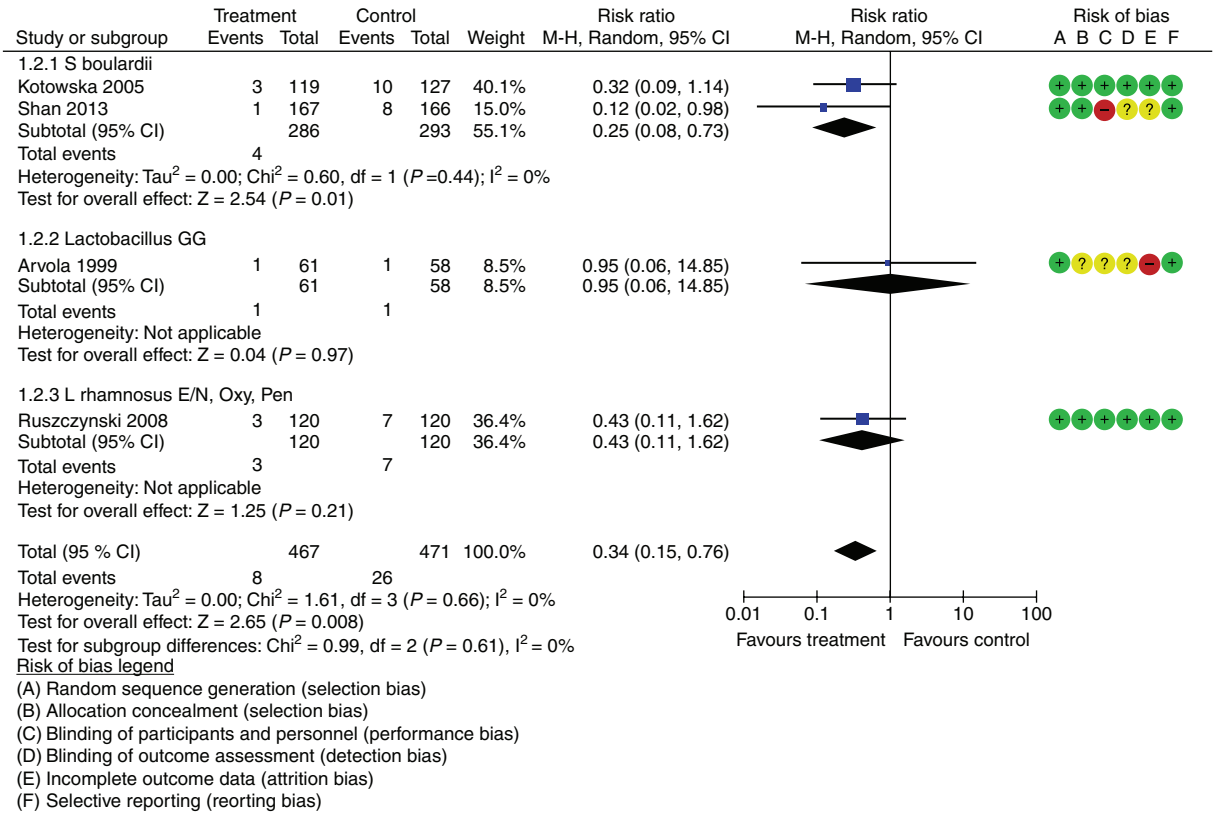

FIGURE 3. Effect of individual probiotic strains and probiotics as a group for preventing *Clostridium difficile*-associated diarrhea.

the risk of AAD (31.2% vs 16.3%, respectively; RR 0.52, 95% CI 0.29–0.95, NNT 7, 95% CI 4–62) (30).

L acidophilus/L bulgaricus

One small RCT (n = 38) showed that compared with placebo (lactose), administration of *L acidophilus/L bulgaricus* (strain specification not given) had no effect on the risk of AAD (RR 0.96, 95% CI 0.61–1.5) (31).

L acidophilus/Bifidobacterium infantis

One small RCT (n = 18) showed that compared with placebo (sugar), administration of *L acidophilus/B infantis* (strain specification not given) had no effect on the risk of AAD (8/10 vs 3/8, respectively; RR 0.47, 95% 0.18–1.21) (32).

L acidophilus/Bifidobacterium breve

One small RCT (n = 40) showed no cases of AAD in either the *L acidophilus/B infantis* (strain specification not given) group or the placebo (sugar) group (0/20 vs 0/20, respectively). Thus, the efficacy of this probiotic combination could not be evaluated (37).

L rhamnosus GG/Bb-12/L acidophilus La-5

In a multisite, double-blind, placebo-controlled RCT, children (n = 70), age 1 to 12 years, who were prescribed antibiotics were randomized to receive 200 g/day of either a yogurt containing *L rhamnosus* GG, Bb-12 and *L acidophilus* La-5 or a pasteurized placebo yogurt (containing *Streptococcus thermophilus* plus *L bulgaricus*) for the same duration as their antibiotic treatment. Compared with the placebo group, children in the probiotic group experienced a significant reduction in the risk of diarrhea (RR 0.05, 95% CI 0.01–0.35) (33).

B longum PL03/L rhamnosus KL53A/L plantarum PL02

One RCT (n = 78) showed that compared with placebo, the administration of *B longum, L rhamnosus,* and *L plantarum* had no effect on the risk of AAD (RR 0.47, 95% CI 0.04–5.03) (34).

L rhamnosus E/N, Oxy, Pen

One RCT involving 240 children showed that compared with placebo, the administration of *L rhamnosus* (strains E/N, Oxy and Pen) reduced the risk of any diarrhea (RR 0.45, 95% CI 0.21–0.95), but it did not have an effect on the risk of *C difficile*-associated diarrhea (RR 0.43, 95% CI 0.11–1.62) (35).

L acidophilus/L rhamnosus/L bulgaricus/L casei/Str thermophilus/B infantis/B breve

One RCT involving 66 children showed that compared with placebo, the administration of *L acidophilus*/*L rhamnosus*/*L bulgaricus*/*L casei*/*Str thermophilus*/*B infantis*/*B breve* (strain specification not given) reduced the risk of diarrhea (RR 0.25, 95% CI 0.06–1.09) (38).

Kefir

One RCT evaluated the effect of kefir (ie, a fermented milk containing *Lactococcus lactis*, *Lactococcus plantarum*, *Lactococcus rhamnosus*, *Lactococcus casei*, *Lactococcus lactis* subspecies *diacetylactis*, *Leuconostoc cremoris*, *B longum*, *B breve*, *Lactobacillus acidophilus*, and 1 yeast, *Saccharomyces florentinus*) on the risk of AAD. There was no significant difference between the kefir group and the group receiving heat-treated kefir (RR 0.83, 95% CI 0.41–1.67) (36).

Yogurt

Yogurt is a form of fermented milk that contains symbiotic cultures of *Streptococcus thermophilus* and *L delbrueckii* subsp. *bulgaricus.* A 2015 systematic review with a meta-analysis identified 2 relevant RCTs, both low in methodological quality. Compared with no intervention, yogurt consumption had no effect on the risk of AAD (2 RCTs, n = 314, RR 0.45; 95% CI 0.11–1.75) (41).

SAFETY

The WG abstained from evaluating the safety of probiotics, as this was thoroughly reviewed in 2011 by the US Agency for Healthcare Research and Quality (for review, (42)). Although probiotics are safe for use in otherwise healthy populations, caution should be taken in specific patient groups. Risk factors for adverse events include immunosuppression, prematurity, critical illness, presence of structural heart disease, presence of a central venous catheter, and the potential for translocation of probiotics across the bowel wall. There is a lack of data that specifically address the safety of probiotics for preventing AAD in these vulnerable populations. The risk of side effects is, however, greater in people who have severe underlying health conditions.

SUMMARY

- The WG questions pooling different probiotic strains together in a meta-analysis. Probiotic effects against AAD are strain specific; thus, the efficacy and safety of each should be established and recommendations for using these strains should be made accordingly.
- The safety and clinical effects of 1 probiotic microorganism should not be extrapolated to other probiotic microorganisms.
- A lack of evidence regarding the efficacy of a certain probiotic(s) does not mean that future studies will not establish efficacy in preventing AAD.
- There is a lack of data that specifically address the safety of probiotics for preventing AAD in children who have severe underlying health conditions.
- The WG recommends choosing a probiotic, the efficacy of which has been confirmed in well-conducted RCTs, from a manufacturer who has a regulated quality control of factors including the composition and content of the probiotic agent.
- Risk factors for the occurrence of AAD or *C difficile*-associated diarrhea such as class of antibiotic(s), duration of antibiotic treatment, age, need for hospitalization, comorbidities, and previous episodes of AAD or *C difficile*-associated diarrhea should be considered when making decisions on the use of probiotics in children for preventing AAD.
- If the use of probiotics for preventing AAD is considered, the WG recommends using *L rhamnosus* GG or *S boulardii* (moderate quality of evidence; strong recommendation).
- If the use of probiotics for preventing *C difficile*-associated diarrhea is considered, the WG suggests using *S boulardii* (low quality of evidence; conditional recommendation).

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