Probiotics for the Prevention of Nosocomial Diarrhea in Children

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ABSTRACT

This document provides recommendations developed by the ESPGHAN Working Group on Probiotics and Prebiotics on the role of probiotics in the prevention of nosocomial diarrhea in children based on a systematic review of previously completed systematic reviews and of subsequently published randomized controlled trials. The quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation guidelines. Recommendations were given only if at least 2 randomized controlled trials examined the same probiotic strain. Based on currently available evidence the Working Group recommends using *Lactobacillus rhamnosus* GG if the use of probiotics for preventing nosocomial diarrhea in children is considered.

Key Words: guideline, healthcare-associated, hospital-acquired, microbiota, randomized controlled trial, systematic review

(*JPGN* 2018;66: 3–9)

What Is Known

- Nosocomial infections have several negative impacts on patients and on the healthcare system.
- The incidence of nosocomial diarrhea in children in developed countries is still high, regardless of preventive measures.

What Is New

- Overall 8 randomized controlled trials investigated the role of probiotics in the prevention of nosocomial diarrhea.
- Currently available evidence showed that administration of Lactobacillus rhamnosus GG reduces the risk of nosocomial diarrhea.

Received January 25, 2017; accepted April 30, 2017.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (*www.jpgn.org*).

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DOI: 10.1097/MPG.0000000000001637

Nosocomial, hospital-acquired, or healthcare-associated infections, by definition develop during a hospital stay, meaning that they are not present or incubating on hospital admission; usually infections that occur >48 hours after the admission are considered nosocomial (1). Nosocomial infections have several negative impacts on patients and on the healthcare system; they prolong the hospital stay, worsen the treatment outcome, increase resistance of microorganisms to antimicrobials, and therefore, significantly increase the cost of health care (2). The incidence of nosocomial infections in children in developed countries is still high, ranging from 5.1% to 11.6% depending on time of the year and type of a hospital ward (3). In children, gastrointestinal infections account for the majority of hospital-acquired infections (4–6), and rotavirus is still a major pathogen. There are data implying that vaccination against rotavirus decreases the nosocomial diarrhea; however, vaccination is not universally implemented (7). Although standard preventive measures, mainly hand hygiene, isolation of sick children, and reduction in the number of hospitalized patients can decrease infection spreading, they cannot provide total prevention (8,9). The administration of probiotics, defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host, on the prevention of nosocomial diarrhea (10) was reported as a measure for the prevention of nosocomial diarrhea (11,12).

The aim of this document by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Working Group (WG) on Probiotics and Prebiotics was to perform a systematic review of the literature and, based on relevant evidence, to give recommendations on the use of probiotics in the prevention of nosocomial diarrhea. Furthermore, this review aims to provide clinically relevant data about specific probiotic strains and doses used in the prevention of nosocomial diarrhea.

METHODS

The same methodology for developing guidelines previously used by the WG (13,14) was applied to the current position paper. The article provides a review of previously completed systematic reviews and of randomized controlled trials (RCTs) published after these reviews. The current meta-analysis includes all published RCTs; this means RCTs included in previous systematic reviews and RCTs published subsequently. For systematic reviews/meta-analyses, the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), and MEDLINE 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 January 2017.

The primary outcome measure was nosocomial diarrhea as defined by the investigators and regardless of the cause. The secondary outcome was nosocomial gastroenteritis caused by rotavirus. Included participants were infants and children up to 18 years of age. Neonates and premature babies were excluded from the analysis. As in previous guidelines, the focus was on 6 taxonomic probiotic groups *(Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus*, and/or *Bacillus).*

To assess the methodological quality of the included RCTs, the Cochrane Collaboration's tool for assessing risk of bias was used. The 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 (15).

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 (CIs). All analyses were based on the random effects model.

Each section of the report represents a summary of the evidence followed by the key recommendations. Recommendations are graded by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (16) developed by the Grading of Recommendations Assessment, Development and Evaluations Working Group. In order to follow the suggested presentation of recommendations by GRADE, we used the wording "the WG *recommends*" for strong recommendations, and "the WG *suggests*" for conditional (weak) recommendations.

As in our previous documents (13,14), the WG adopted the position of the US Food and Drug Administration Guidance for Industry (17) 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 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.

Because of known differences in the effects of different probiotic strains, the WG gave recommendations only for specific probiotic strains or combination of strains. Pooled data of all probiotic trials were presented only for the sake of completeness, but no recommendation on the use of probiotics in general was given.

A draft of the article was sent to the WG members for review and further comments. Comments were discussed by email or in person, and changes were incorporated as necessary. Recommendations were formulated and graded and disagreement was resolved by thorough discussion, until full consensus was reached.

RESULTS

Table 1 presents the characteristics of the included RCTs. Majority of RCTs defined nosocomial diarrhea as passage of 3 or more loose or watery stools (2,18–23). Only Saavedra et al (24) defined it as the passage of 5 or more liquid stools a day. Majority of studies did not report on antibiotic treatment during diarrheal episodes (19–23).

For the assessment of methodological quality and potential risk of bias, see Figure 1.

Probiotics Overall

There were 2 systematic reviews and meta-analyses evaluating the role of probiotics in the prevention of nosocomial diarrhea (11,12).

A 2011 meta-analysis (search date: June 2011), included only RCTs which investigated the effects of *Lactobacillus rhamnosus* GG (LGG). Three RCTs involving 1092 children were identified. Overall, this meta-analysis showed that the administration of LGG for the duration of hospital stay lowered the rate of diarrhea (2 RCTs, RR 0.37, 95% CI 0.23–0.59), and symptomatic rotavirus gastroenteritis (3 RCTs, RR 0.49, 95% CI 0.28–0.86) (11).

A more recent meta-analysis (12) (search date: June 2013) included all probiotic strains. Six RCTs involving 1343 participant met the inclusion criteria. The following strains were evaluated in included trials: LGG (3 RCTs), *L reuteri* DSM 17,938 (1 RCT), *L delbrueckii* H2B20 (1 RCT), and the combination of *Bifidobacterium bifidum* and *Streptococcus thermophilus* (1 RCT).

TABLE 1. Characteristics of the included trials

Reference	Country	Participants (age)	Probiotic dose, CFU/per day	Duration of intervention	Follow-up	Type of hospital	Manufacturer	Sponsor
Lactobacillus rhamnosus GG								
Hojsak (2010) (2)	Croatia	Children >12 mo to 18 y	LGG 10^9 CFU/day	During hospital stay (median 5 days)	Yes,7 days after discharge	Acute and chronic	Dukat (Croatia), strain from Valio (Finland)	–
Mastretta (2002) (23)	Italy	infants (1–18 mo)	LGG 2×10^{10} CFU first day and 10^{10} CFU/day afterwards	During hospital stay (mean 5.2 days)	Yes, 72 h after discharge	Acute and chronic	Dicofarm SpA (Rome, Italy)	–
Szajewska (2001) (19)	Poland	Infants and children (1–36 mo)	LGG 6×10^9 CFU twice daily	During hospital stay (median 9 days)	Yes, 3 days after discharge	Acute and chronic	Dicofarm SpA (Rome, Italy)	Partially by Medical University of Warsaw
Lactobacillus reuteri DSM 17938								
Urbanska (2016) (20)	Poland	Infants and children (1–48 mo)	*L reuteri* DSM 17938 $\times 10^9$ CFU/day	During hospital stay (mean 5.6 days)	Yes, 3 days after discharge	Acute and chronic	BioGaia AB (Lund, Sweden)	Fully by Medical University of Warsaw
Wanke (2012) (21)	Poland	Infants and children (1–48 mo)	*L reuteri* DSM 17938 $\times 10^8$ CFU/day	During hospital stay (median7.5 days)	Yes, 3 days after discharge	Acute and chronic	BioGaia AB (Lund, Sweden)	Partially by Medical University of Warsaw which received donation from BioGaia AB, Sweden
Bifidobacterium animalis subsp *lactis* (BB-12)								
Hojsak (2015) (18)	Croatia	Children >12 mo to 18 y	*B animalis* subsp *lactis* 10^9 CFU/day	During hospital stay (median 5 days)	Yes,7 days after discharge	Acute and chronic	Chr Hansen A/S (Horsholm, Denmark)	Sponsored by Chr Hansen A/S (Horsholm, Denmark)
Lactobacillus delbrueckii H2B20								
Penna (2009) (22)	Brazil	Infants (1–36 mo)	*L delbrueckii* H2B20 2.6×10^8 CFU/g of supplemented powdered milk	During hospital stay (mean 4.5 days)	No	Acute and chronic	Universidade Federal de Viçosa, Minas Gerais	Not mentioned
Bifidobacterium bifidum and *Streptococcus thermophilus*								
Saavedra (1994) (24)	USA	infants (5–24 mo)	*B bifidum* 1.9×10^8 CFU and *S thermophilus* 0.14×10^8 CFU	During hospital stay (mean 81 days)	No	Long-term care, children with chronic illnesses	Carnation Nutritional Products (Glendale, CA)	National Institutes of Health and Carnation Nutritional Products

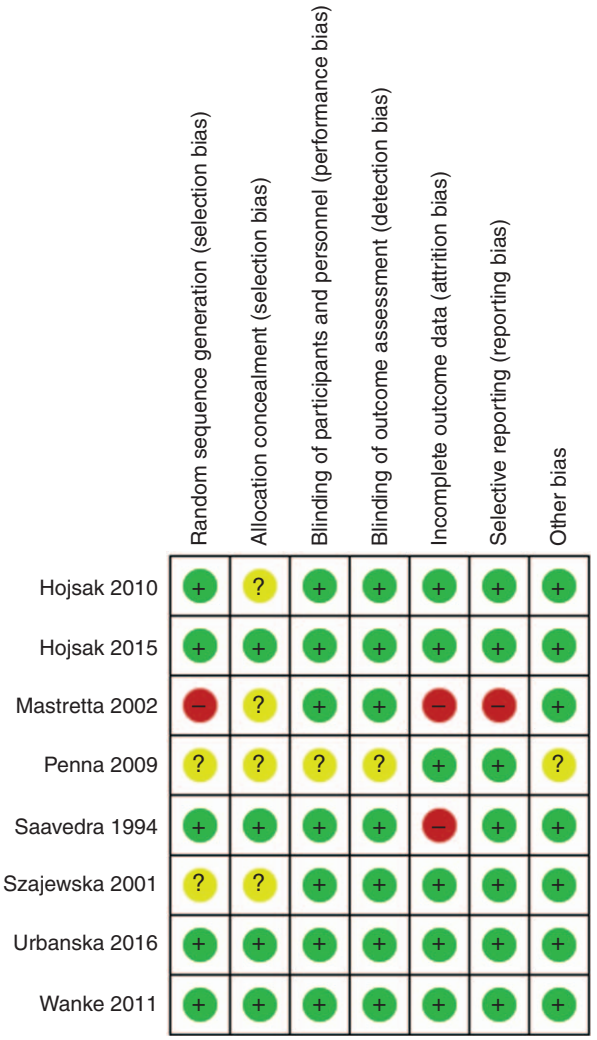

FIGURE 1. Methodological quality summary.

The current review included 8 RCTs (6 RCTs already included in the previous systematic reviews and 2 subsequently published RCTs) involving 2254 children (2,18–24). One RCT published in 2016 (25) was excluded from the analysis because the experimental group received not only a probiotic (LGG) but also vitamins B and C, and zinc; therefore, positive effect of the supplementation cannot be attributed solely to LGG.

Overall, treatment with probiotics (as a group) compared with placebo or no treatment had no effect on the risk of nosocomial diarrhea (2,18–22,24) (7 RCTs, n = 2034, RR 0.72, 95% CI 0.40–1.28, random effect model). Heterogeneity was found ($Chi^2 = 19.44$, $P = 0.003$, $I^2 = 69\%$; Fig. 2).

Probiotics reduced the risk of nosocomial rotavirus diarrhea; however, the difference between groups was of a borderline significance (2,18–21,23,24) (7 RCTs, n = 2115, RR 0.65, 95% CI 0.42–1.01). No heterogeneity was found ($Chi^2 = 5.89$, $P = 0.44$, $I^2 = 0\%$; Fig. 3).

There was no significant difference in asymptomatic shedding of rotavirus (19,23,24) (3 RCTs, n = 356, RR 0.87, 95% CI 0.32–2.37). Heterogeneity was found ($Chi^2 = 5.92$, $P = 0.05$, $I^2 = 66\%$; Fig. 4).

Probiotic Strains With Recommendation

Lactobacillus rhamnosus GG

Recommendation: If probiotics for preventing nosocomial diarrhea in children are considered, the WG recommends using *L rhamnosus* GG (at least 10^9 CFU/day, for the duration of hospital stay).
Quality of evidence: Moderate
Strength of recommendation: Strong

No new studies were identified after the 2011 systematic review and meta-analysis (11), which included 3 RCTs (2,19,23). The LGG dose used in the included studies varied from 10^9 CFU/day (2) through 2×10^{10} CFU/day (23) to 12×10^9 CFU/day (19).

RCTs varied in the methodological quality; none of the included studies had a low risk of bias. Limitations included unclear random sequence generation, unclear allocation concealment, incomplete outcome data, and selective reporting. Intention-to-treat analysis was performed in 2 trials. Using the GRADE, the overall quality of evidence was rated as moderate (Supplemental Digital Content 1, Table, *http://links.lww.com/MPG/B4*).

LGG administration reduced the risk of nosocomial diarrhea from 13.9% to 5.2% (2 RCTs, n = 823, RR 0.35, 95% CI 0.19–0.65; number needed to treat, number needed to treat (NNT), 12, 95% CI 8–21). No significant heterogeneity was found ($Chi^2 = 1.26$, $P = 0.26$, $I^2 = 21\%$; Fig. 2).

Three trials (2,19,23) (n = 1043) evaluated the effect of LGG on the risk of rotavirus-induced nosocomial diarrhea. Compared with the placebo group, in the LGG group the risk of rotavirus nosocomial diarrhea was reduced; however, the difference between groups was not significant (RR 0.43, 95% CI 0.17–1.13). No significant heterogeneity was found ($Chi^2 = 2.56$, $P = 0.28$, $I^2 = 22\%$; Fig. 3).

Two studies evaluated the risk of asymptomatic rotavirus shedding (19,23). There was no difference between groups (RR 1.39, 95% CI 0.74–2.62; Fig. 4).

Lactobacillus reuteri DSM 17938

Recommendation: Because of the lack of efficacy, *L reuteri* DSM 17938 should not be considered for the prevention of nosocomial diarrhea in children.
Quality of evidence: High
Strength of recommendation: Strong

The effect of *L reuteri* DSM 17938 was evaluated in 2 RCTs (n = 290) (20,21), which showed no effect toward overall nosocomial diarrhea (RR 1.11, 95% CI 0.68–1.81; Fig. 2) and symptomatic rotavirus infection (RR 1.14, 95% CI 0.52–2.52; Fig. 3). Both studies had a low risk of bias. Using the GRADE, the overall quality of evidence was rated as high (Supplemental Digital Content 1, Table, *http://links.lww.com/MPG/B4*). Studies used different doses of the same probiotic strain (10^8 CFU/day (21) and 10^9 CFU/day (20)).

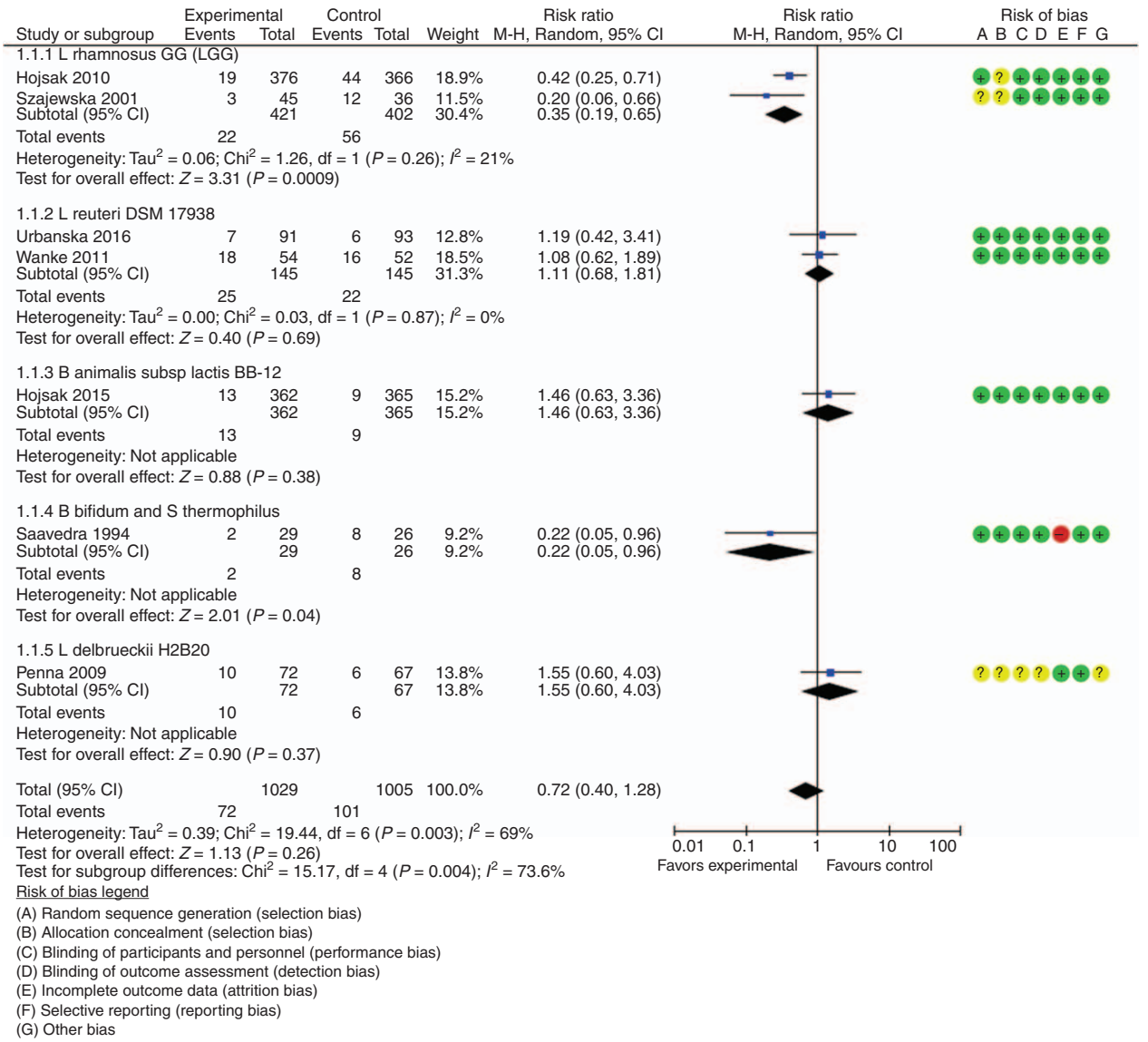

FIGURE 2. Effect of individual probiotic strains and probiotics as a group for preventing nosocomial diarrhea.

Probiotics With Insufficient Evidence to Make a Recommendation

Bifidobacterium animalis subsp *lactis (BB-12)*

One large (n = 727) (18), double-blind, placebo-controlled RCT demonstrated that administration of *B animalis* subsp *lacti*s (BB-12) was not effective in preventing nosocomial diarrhea occurring more than 48 hours after admission in hospitalized children older than 1 year (RR 1.46, 95% CI 0.63–3.36; Fig. 2) or rotavirus diarrhea (RR 0.5, 95% CI 0.05–5.54; Fig. 3). The incidence of nosocomial gastrointestinal infections was, however, low in both groups that may have negatively influenced the outcome. Because there was only 1 RCT with *B animalis* subsp *lactis* (BB-12), the WG cannot make a recommendation for this strain.

Based in the negative results of this large, high-quality RCT, it is highly unlikely that the same study will be repeated.

Lactobacillus delbrueckii H2B20

One RCT (n = 139) (22) investigating *L delbrueckii* H2B20 found no difference in the risk for nosocomial diarrhea between groups (RR 1.55, 95% CI 0.60–4.03; Fig. 2). The risk for rotavirus infection was not assessed.

Bifidobacterium bifidum and *Streptococcus thermophilus*

One RCT (n = 55) (24) showed that the combination of *B bifidum* and Str *thermophilus* reduced the risk of nosocomial diarrhea (RR 0.22, 95% CI 0.05–0.96; NNT 6, 95% CI 3.0–248.8; Fig. 2). There was no effect of this combination of probiotics on rotavirus diarrhea (RR 0.36, 95% CI 0.08–1.69; Fig. 3); however, the rotavirus shedding was reduced (RR 0.27, 95% CI 0.08–0.87; Fig. 4).

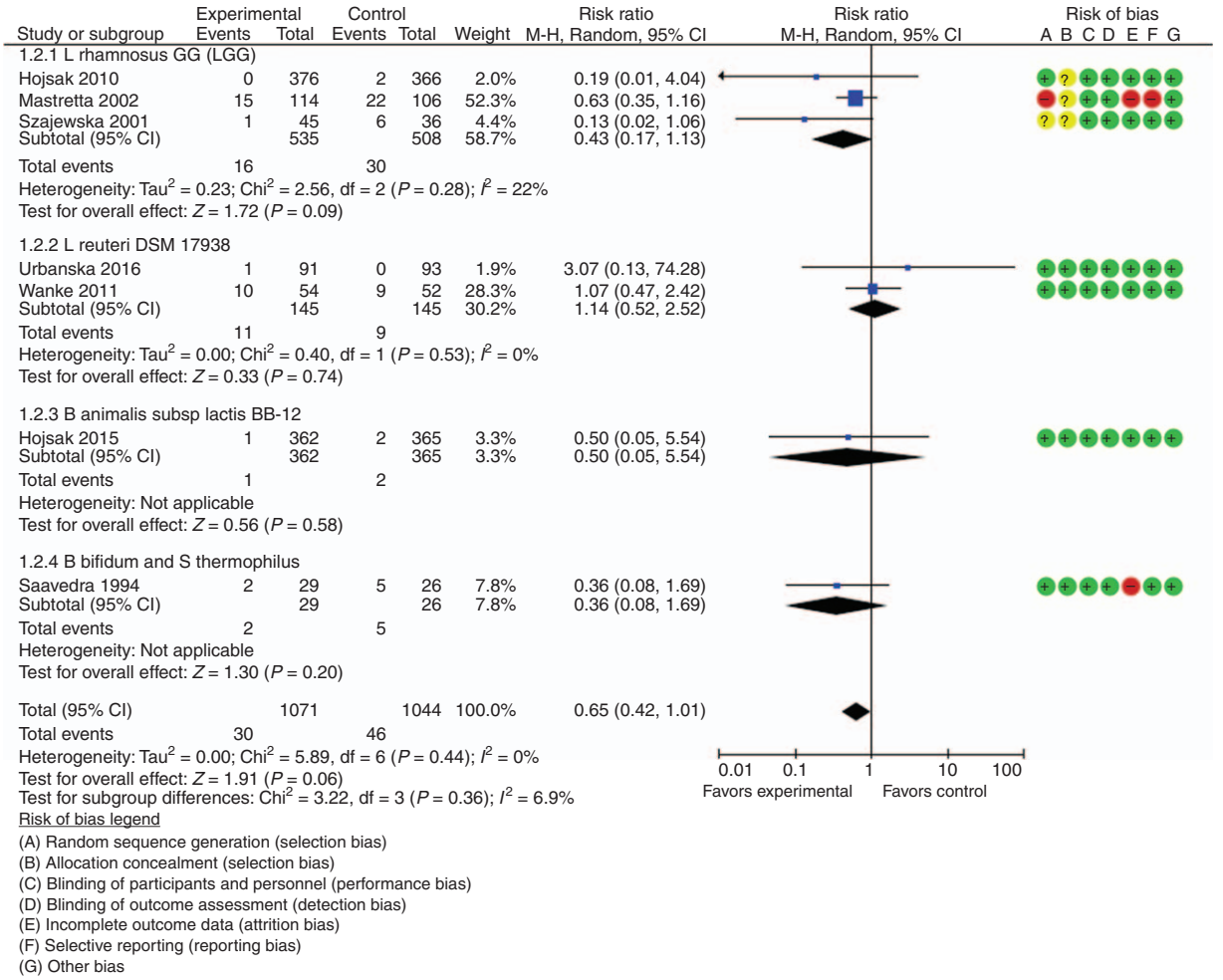

FIGURE 3. Effect of individual probiotic strains and probiotics as a group for preventing nosocomial rotavirus diarrhea.

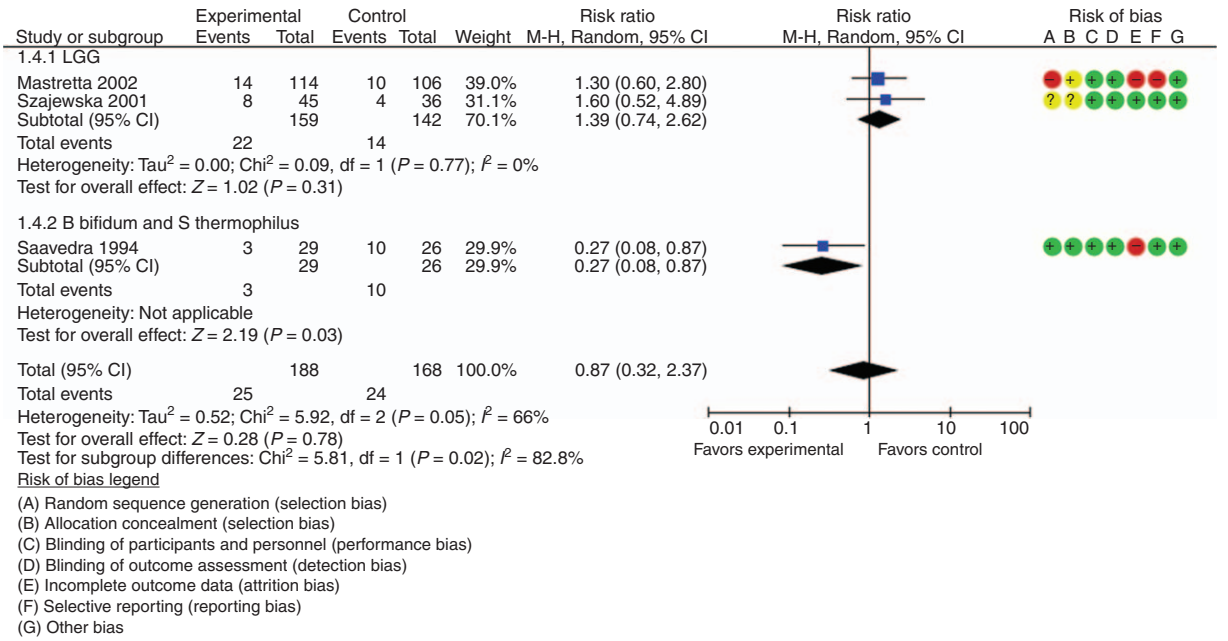

FIGURE 4. Effect of individual probiotic strains and probiotics as a group for preventing asymptomatic rotavirus shedding.

Adverse Effects

Altogether, 6 studies (2,18–21,24) mentioned adverse effects. Of these studies, 5 (2,18,19,21,24) found no adverse effects and 1 study (20) reported no significant difference in the incidence of adverse effects (ie, abdominal pain, flatulence) between groups.

SUMMARY

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. If the use of probiotics for preventing nosocomial diarrhea in children is considered, the WG recommends using *L rhamnosus* GG.

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