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Probiotics for preventing healthcare-associated diarrhea in children: A meta-analysis of randomized controlled trials

Probiotyki w zapobieganiu biegunce szpitalnej: metaanaliza badań z randomizacją

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ABSTRACT

Aim: To systematically update evidence on the efficacy of using probiotics for the prevention of healthcare-associated diarrhea in children. **Methods:** MEDLINE, EMBASE, The Cochrane Library, Health Source: Nursing/Academic Edition, two clinical trials and reference lists were searched in June 2013, for randomized controlled trials (RCTs) performed in children aged 1 month to 18 years that compared the effects of the administration of probiotics with placebo or no intervention. The primary outcome measure was the incidence of healthcare-associated diarrhea. **Results:** Six RCTs involving 1343 children met the inclusion criteria. Administration of *Lactobacillus rhamnosus* GG (LGG) compared with placebo reduced the risk of healthcare-associated diarrhea (2 RCTs, $n = 823$, RR 0.37; 95% CI 0.23–0.59), reduced the risk of rotavirus gastroenteritis (3 RCTs, $n = 1043$, RR 0.49, 95% CI 0.28–0.86), but did not reduce the risk of asymptomatic rotavirus infection (2 RCTs, $n = 301$, RR 1.39, 95% CI 0.74–2.62). Administration of *Bifidobacterium bifidum* & *Streptococcus thermophilus* compared with placebo reduced the risk of healthcare-associated diarrhea (1 RCT, $n = 55$, RR 0.22, 95% CI 0.05–0.96), rotavirus gastroenteritis (1 RCT, $n = 55$, RR 0.27, 95% CI 0.08–0.87), and rotavirus asymptomatic infection (1 RCT, $n = 55$, RR 0.27, 95% CI 0.08–0.87). Administration of two other probiotics (*i.e.*, *Lactobacillus reuteri* DSM 17938 and *Lactobacillus delbrueckii* H2B20) was ineffective. **Conclusion:** In hospitalized children, the administration of LGG, compared with placebo, reduced the incidence of healthcare-associated diarrhea, including rotavirus diarrhea. Evidence on the effects of other probiotics, whether positive or negative, is limited.

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Background

Healthcare-associated infections (HCAI) are defined as those occurring 48 h or more after admission to a hospital. They are a major problem for a patient's safety and are linked to a prolonged hospital stay, long-term disability, increased resistance of microorganisms to antimicrobials, massive additional financial burden, and excess deaths [1]. The risk of acquiring HCAI is international and varies between 5% and 15% [1]. In children, gastrointestinal infections, particularly of rotavirus origin, remain a leading cause of HCAI [1]. A recent meta-analysis showed that the risk of developing rotavirus healthcare-associated diarrhea was 2.9 per 100 hospitalizations, and the risk was higher during epidemic months (8.1:100 hospitalizations) [1].

Prevention of HCAI is a priority for settings and institutions committed to making healthcare safer. However, it is a challenge. Next to the isolation of sick patients, one of the cheapest interventions, although not fully satisfying, is improved hand hygiene according to the World Health Organizations' guidelines [2]. There are data suggesting a positive impact of mass vaccination against rotavirus on a reduction in nosocomial rotavirus gastroenteritis among pediatric patients [3]. Unfortunately, the high cost of these vaccines is an obstacle to their widespread use in many countries, thus maintaining interest in simple, effective, low-cost strategies for preventing HCAI.

Probiotics are live microorganisms thought to improve the microbial balance of the host, counteract disturbances in intestinal flora, and reduce the risk of colonization by pathogenic bacteria [4]. In children, there are convincing data to support the use of probiotics with documented efficacy for the treatment of acute gastroenteritis and the prevention of antibiotic-associated diarrhea [5, 6]. Previously, we documented that in hospitalized children, the administration of *Lactobacillus rhamnosus* GG (LGG), compared with placebo, reduced the overall incidence of healthcare-associated diarrhea, including rotavirus gastroenteritis [7].

The objective of this systematic review and meta-analysis, which adds to our previous report [8], was to systematically review data on the efficacy of use of various probiotics, alone or in combination, for the prevention of healthcare-associated diarrhea in children. Only data related to a specific probiotic strain or their combinations are reported. This is because it is known that not all probiotics are equal, and pooling data on different probiotics have been repeatedly questioned [8, 9].

Methods

The methods for this systematic review and meta-analysis were described in detail in our earlier review [8]. In brief, the guidelines from the Cochrane Collaboration for undertaking and reporting the results of a systematic review and meta-analysis and the PRISMA statement [10] were followed. Randomized controlled trials (RCTs) reporting incidence outcomes for healthcare-associated diarrhea were considered for inclusion. Participants had to be children aged 1 month to 18 years who were admitted to the hospital for any reason other than gastrointestinal infections. The interventions of interest compared use of probiotics (any strain or dose) *versus* placebo or no treatment for the prevention of healthcare-associated diarrhea. The primary outcome measure was the incidence of healthcare-associated diarrhea as defined by the investigators. The secondary outcome measures were the incidence of rotavirus gastroenteritis, the incidence of asymptomatic rotavirus infection, the duration of diarrhea, and the duration of hospitalization.

We searched MEDLINE, EMBASE, The Cochrane Library, including the Cochrane Central Register of Controlled Trials, Health Source: Nursing/Academic edition, and reference lists, with no language restrictions, through June 2013. The search strategy included the use of a validated filter for identifying RCTs, which was combined with a topic-specific strategy using the following PubMed MeSH terms: 1. (prevention OR prevent OR prevent* OR preventive therapy OR prophylaxis); 2. (diarrhea OR diarrhoe* OR diarhe* OR dysenter* OR gastro enteritis OR diarrhea OR diarrh* OR gastritis OR gastrit* OR gastroenteritis OR gastroenterocolitis OR vomit* OR intestinal infection* OR gastrointestinal infection* OR rotavirus); 3. (lactobacillus OR lactobacill* OR l acidophilus OR l casei OR l delbrueckii OR l helveticus OR l johnsonii OR l paracasei OR l plantarum OR l reuteri OR l rhamnosus OR l salivarius); 4. (Sacharomyces OR saccharomyce* OR s bulardii OR streptococcus OR streptococc* AND thermophilus OR enterococcus OR enterococc* AND faecium); 5. (Bifidobacterium OR bifidobacter* OR b animalis OR b bifidum OR b breve OR b infantis OR b lactis OR b longum); 6. 3 OR 4 OR 5; 7. 6 AND 1 AND 2. In addition, we searched two trial registries (ClinicalTrials.gov, www.clinicaltrials.gov, and EU Clinical Trials Register, www.clinicaltrialsregister.eu).

Using a standardized data extraction form, one author (MW) extracted the following data items: author, year of publication, language, study setting, methodological design, exclusion criteria for participants, patient characteristics (age, diagnosis), number of patients allocated to each group, types of interventions, and outcome measures. The data were entered into a computer program. The Cochrane Review Manager (RevMan) (version 5.2.6 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2013) was used for statistical analysis and to perform a meta-analysis of the RCTs.

The risk of bias was assessed as described in the Cochrane Handbook for Systematic Reviews of Interventions, and it included the assessment of the adequacy of sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, and the extent of loss to follow-up (*i.e.*, incomplete outcome data). In all cases, an answer of 'yes' indicates a low risk of bias, and an answer of 'no' indicates a high risk of bias [11].

Heterogeneity was quantified by χ^2 and I^2. The quantity, I^2, describes the percentage of total variation across studies that is due to heterogeneity rather than to chance. Negative values of I^2 are made equal to zero so that I^2 lies between 0% and 100%. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. The

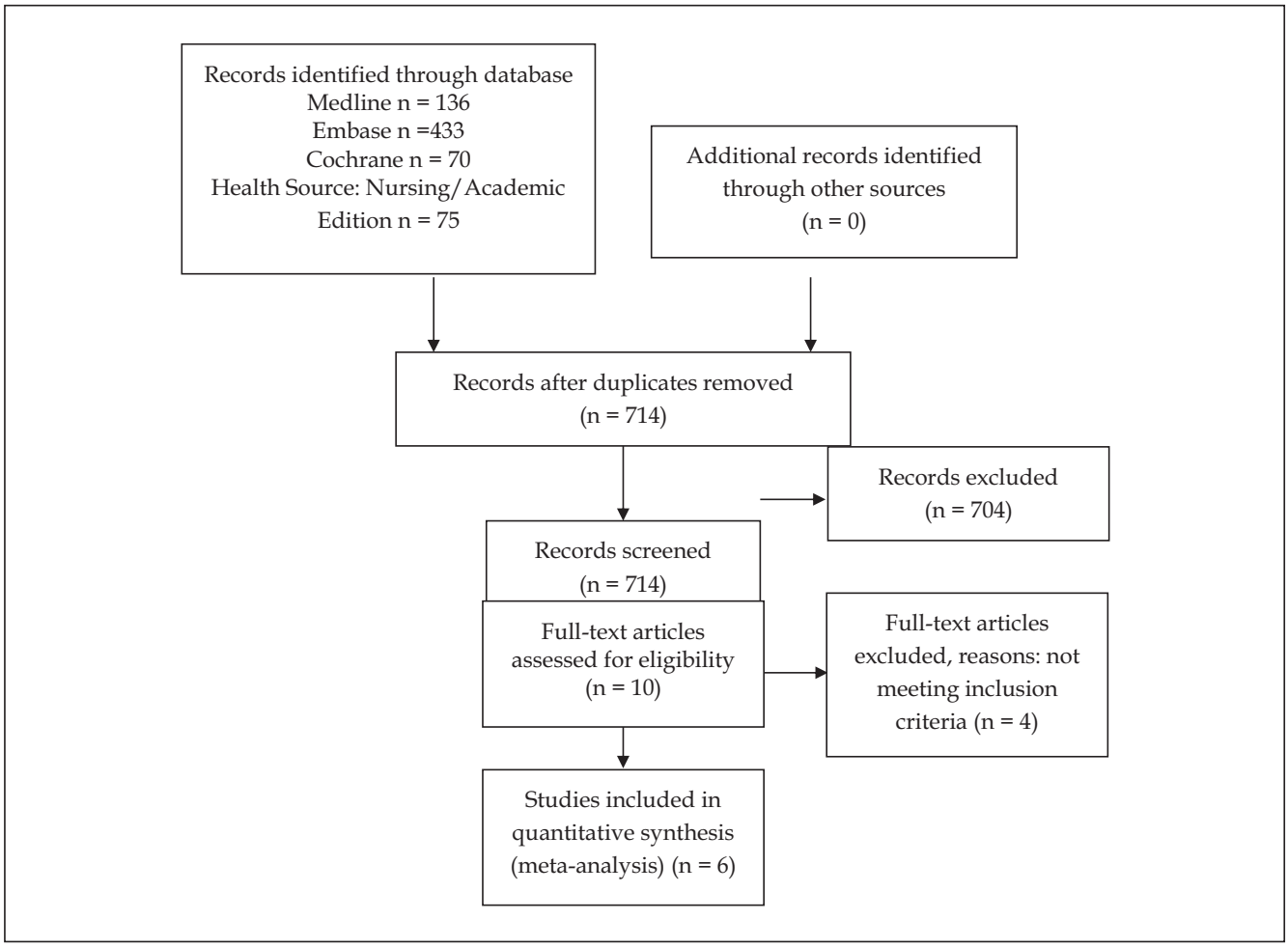

Fig. 1 – Identification process for eligible trials
Ryc. 1 – Proces identyfikacji badań

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% CI). The data were analyzed using RevMan.

Results

Description of studies

Fig. 1 shows the flow of studies through the selection process. A total of 714 records were identified from the primary electronic databases. Ten potentially relevant studies were identified for full-text review. Six RCTs met the inclusion criteria [12–17]. The characteristics of the included trials are presented in Table I. Excluded studies are described in Table II. The included RCTs randomized a total of 1343 patients (690 in the experimental group and 653 in the control group). Five included studies were double blind, placebo-controlled trials [13–16, 18]. All trials had some methodological limitations such as unclear allocation concealment [13–15, 17] and/or no intention-to-treat analysis [14, 18].

Population

Patients were hospitalized in pediatric departments for acute or chronic diseases. In the study by Saavedra et al. [18], children were admitted to a chronic medical care hospital. The most common reason for hospitalization was upper respiratory tract infection. One exception was the study by Hojsak et al. [13], in which children with respiratory tract infections were excluded, as this was one of the outcomes. Patients' ages ranged from 1 month to 18 years. Five RCTs [14–18] included only infants and young children under the age of 48 months. In contrast, in the study by Hojsak et al. [13], the mean age of the participants was 9.9 years, and children below the age of 12 months were excluded. Exclusion criteria for participants were mostly similar and included breastfeeding [15, 16,

Table I – Methodological quality summary and characteristics of included studies
Tabela I – Wiarygodność metodologiczna i charakterystyka włączonych badań

Author (country)	Methodological quality summary[a]				Characteristics of included trials				
	Adequate sequence generation	Allocation concealment	Blinding	Population	Exp/Cont (Follow-up)	Probiotic dose	Control	Duration of intervention (follow-up period)	Primary outcome (definition)
Hojsak et al. (Croatia) [13]	Yes (computer-generated numbers)	Unclear	Yes (DB)	>12 mo with acute and/or chronic diseases (mean age: 10 ± 5 y)	376/366 (100%)	LGG 10^9 CFU daily in 100 ml of fermented milk product	Placebo (post-pasteurized fermented milk product without LGG)	During hospital stay (7 days after discharge)	Gastrointestinal tract infections (diarrhea with ≥3 loose or watery stools within 24 h with or without vomiting). AAD was not considered.
Mastretta et al. (Italy) [14]	No (odd and even random sampling numbers)	Unclear	Yes (DB)	1–18 mo with acute and/or chronic diseases (mean age: 10 mo)	134/135 (follow up 114/106, *i.e.*, 82%)	LGG 2 capsules of 10^{10} CFU on admission, and 1 capsule daily during hospitalization	Placebo (oligosaccharides)	During hospital stay (3 days after discharge)	Rotavirus infections (diarrhea defined as ≥3 loose stools at least 24 h after admission with Rotavirus antigen detected in stool sample)
Szajewska et al. (Poland) [15]	Unclear (as reported in the paper); computer –generated numbers as clarified by the authors	Unclear	Yes (DB)	1–36 mo with acute and/or chronic diseases (mean age: 11 mo)	45/36 (100%)	LGG 6×10^9 CFU in 1 sachet twice daily	Placebo (maltodextrin)	During hospital stay (3 days after discharge)	Diarrhea (≥3 loose or watery stools in a 24-h period). AAD was not excluded
Wanke et al. (Poland) [16]	Yes (computer-generated numbers)	Yes (independent person prepared the randomization schedule and oversaw the packaging and labeling of the study products)	Yes (DB)	1 to 48 mo with acute and/or chronic diseases (mean age: 11.5 mo)	54/52 (100%)	*L. reuteri* DSM 17938 10^8 CFU in 5 drops daily	Placebo	During hospital stay (3 days after discharge)	Diarrhea (≥3 loose or watery stools in a 24-h period). AAD was not excluded
Penna et al. (Spain) [17]	Yes (computer-generated numbers)	Unclear	Unclear	1–36 mo with acute and/or chronic diseases	72/67 (100%)	*L. delbrueckii* 2.6×10^8 in fermented milk product	Placebo	During hospital stay	Diarrhea (≥3 loose or watery stools in a 24-h period)
Saavedra et al. (North America) [18]	Yes (block randomization)	Yes	Yes (DB)	5–24 mo with chronic diseases (mean age 11 mo)	29/26 (100%)	Milk formula enriched with *B. bifidum* 1.9×10^8 CFU and *S. thermophilus* 0.14×10^8	Placebo (formula without probiotic)	During hospital stay	Diarrhea (≥5 loose or watery stools in a 24-h period)

[a] In all cases, an answer of 'yes' indicates a low risk of bias, and an answer of 'no' indicates a high risk of bias. AAD: antibiotic-associated diarrhea; CFU, colony-forming units; DB, double-blinding.

Table II – Characteristics of excluded studies
Tabela II – Charakterystyka wykluczonych badań

Study (author)	Reason for exclusion
Dani et al. [20]	Different population (intensive care unit patients)
Honeycutt et al. [21]	Different population (intensive care unit patients)
Mihatsch et al. [22]	Different population (preterm infants)
Rojas et al. [23]	Different population (preterm infants)

18], probiotic use within 7 days before admission [13, 15, 16], acute gastroenteritis [13–18], gastroenteritis in the first 24 h after admission [15, 17], and chronic gastrointestinal diseases [13, 15, 16].

Interventions

Only a limited number of probiotic microorganisms were tested. Three RCTs tested LGG [13–15] at a daily dose ranging from 1×10^9 CFU [13] to 1×10^{10} CFU [14] to 6×10^9 CFU [15]. Other probiotics were tested in single trials only, and they included *Lactobacillus reuteri* DSM 17938 [16] at a dose of 10^8 CFU, *Lactobacillus delbrueckii* [17] at a dose of 2.6×10^8 CFU, and *Bifidobacterium bifidum* (1.9×10^8 CFU) & *Streptococcus thermophilus* (0.14×10^8 CFU) [18]. The probiotics were delivered in the form of fermented milk [13, 17], capsules [14], sachets [15], drops [16], or milk formula supplemented with probiotics [18]. In all of the studies, probiotic administration lasted for the duration of the hospital stay.

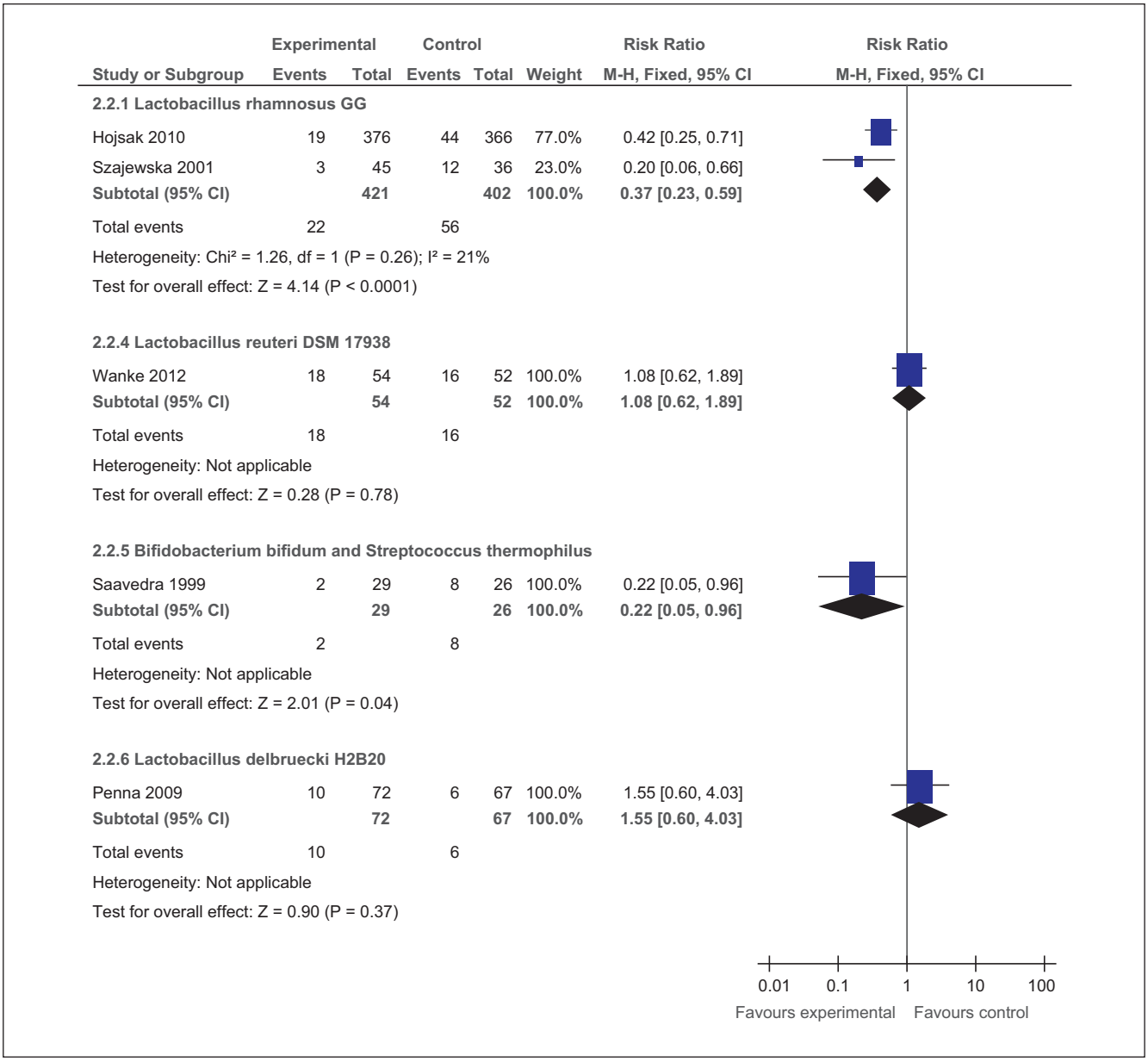

Fig. 2 – Probiotics for the prevention of healthcare-associated diarrhea
Ryc. 2 – Probiotyki w zapobieganiu biegunce szpitalnej

Outcome measures

In five of the included RCTs [13, 15–18], the primary outcome measure was the incidence of diarrhea. In one RCT [14], the primary outcome measure was rotavirus gastroenteritis. Stool samples for rotavirus testing were collected at admission [14, 16] when diarrhea occurred during hospitalization [13–16, 18], once a week [15, 18], at discharge [14] or at 72 h after discharge if there was no diarrhea during the hospital stay [14]. In one study [17] no rotavirus testing was performed.

Effects of interventions

Diarrhea (Fig. 2)
The pooled results of 2 RCTs [13, 15] showed that administration of LGG compared with placebo reduced the risk of healthcare-associated diarrhea ($n = 823$, RR 0.37, 95% CI 0.23–0.59). One small RCT [18] showed that administration of *B. bifidum* & *Str. thermophilus* compared with placebo reduced the risk of healthcare-associated diarrhea ($n = 55$, RR 0.22, 95% CI 0.05 to 0.96). Administration of two other probiotics (*i.e.*, *L. reuteri* DSM 17938 and *L. delbrueckii* H2B20) did not reduce the risk of diarrhea.

Rotavirus gastroenteritis (Fig. 3)
The pooled results of 3 RCTs [13–15] showed that administration of LGG compared with placebo significantly reduced the risk of rotavirus gastroenteritis (3 RCTs, $n = 1043$, RR 0.49, 95% CI % CI 0.28–0.86). One small RCT [18] showed that administration of *B. bifidum* & *Str. thermophilus* compared with placebo reduced the risk of rotavirus gastroenteritis ($n = 55$, RR 0.27, 95% CI 0.08–0.87).

Asymptomatic rotavirus infection (Fig. 4)
The pooled results of 2 RCTs showed that administration of LGG compared with placebo did not reduce the risk of asymptomatic rotavirus infection (2 RCTs, $n = 301$, RR 1.39, 95% CI 0.74–2.62) [14, 15]. In contrast, administration of *B. bifidum* & *Str. thermophilus* compared with placebo reduced the risk of rotavirus asymptomatic infection (1 RCT, $n = 55$, RR 0.27, 95% CI 0.08–0.87) [18].

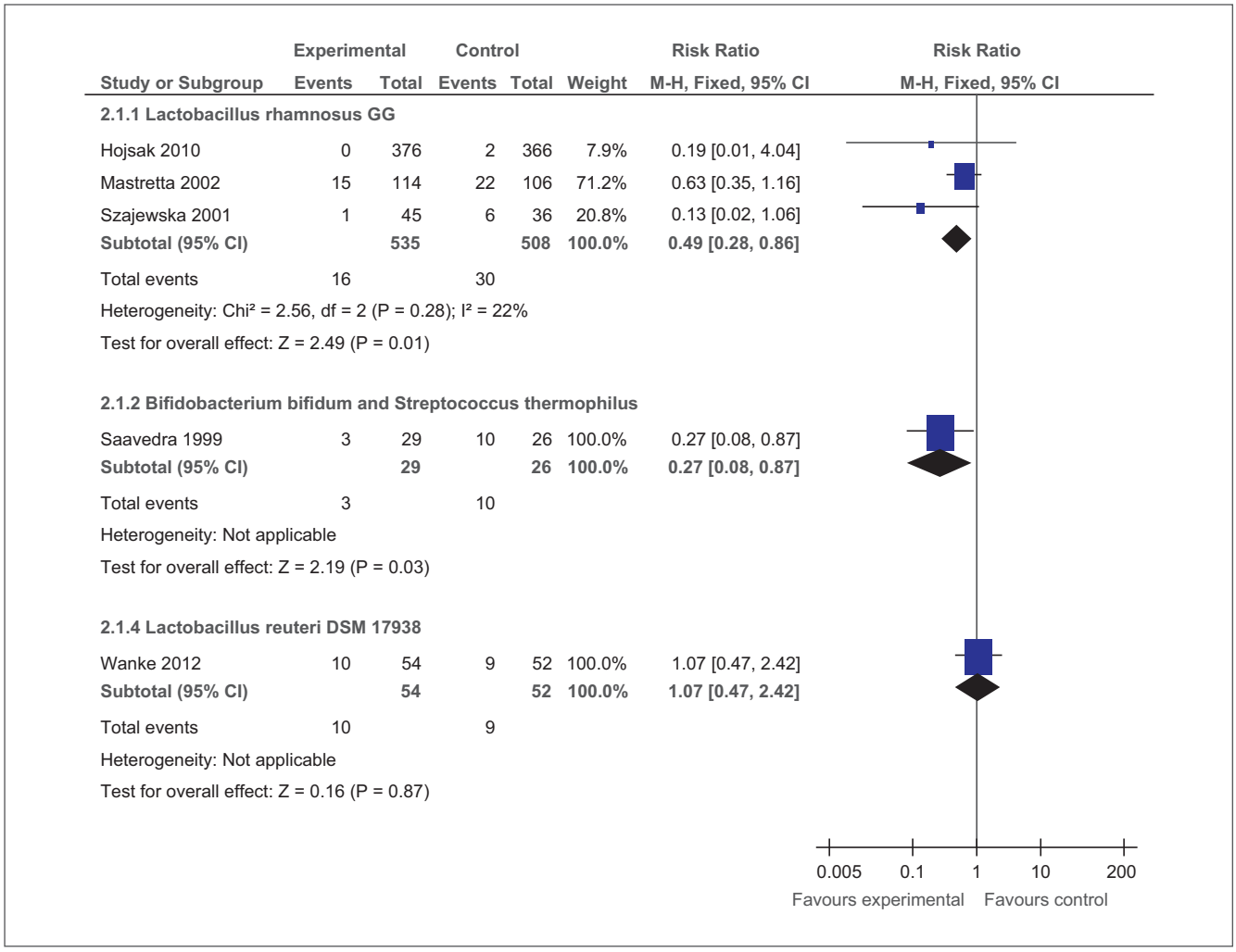

Fig. 3 – Probiotics for the prevention of rotavirus gastroenteritis
Ryc. 3 – Probiotyki w zapobieganiu biegunce rotawirusowej

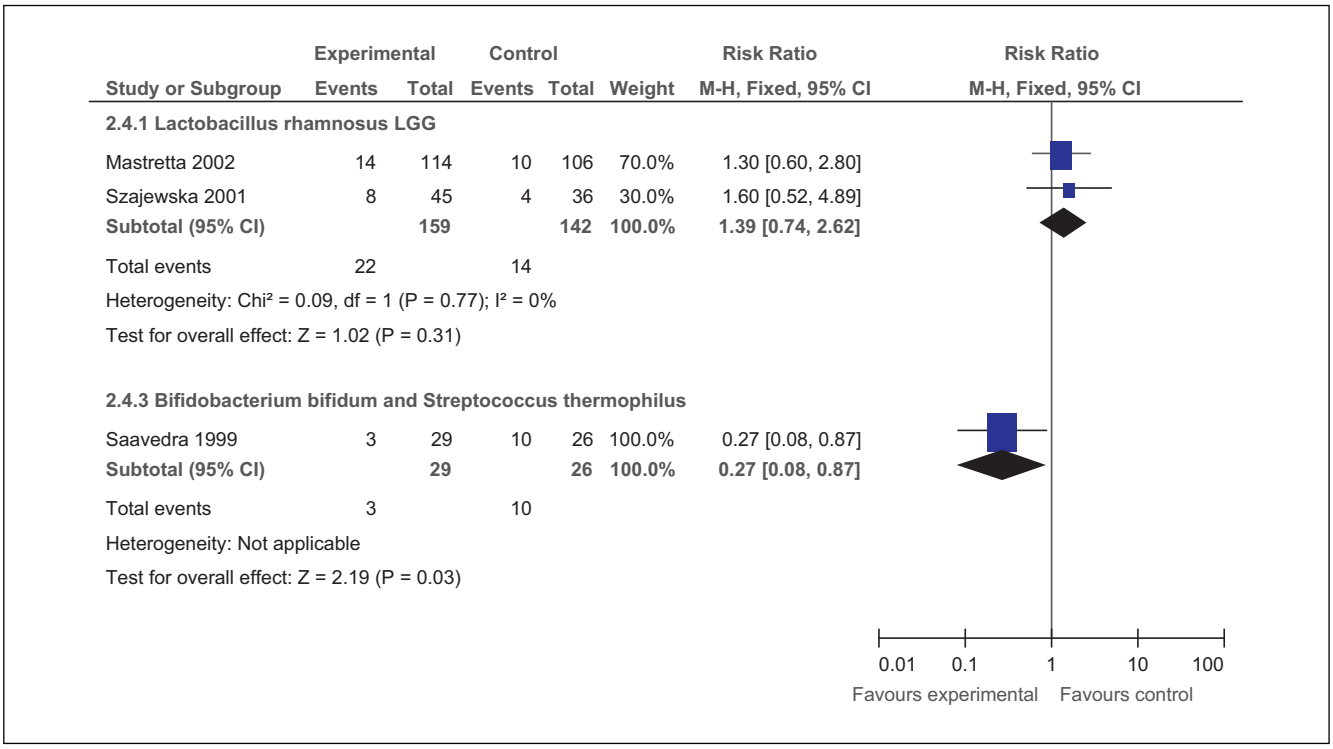

Fig. 4 – Probiotics for the prevention of asymptomatic rotavirus infection
Ryc. 4 – Probiotyki w zapobieganiu bezobjawowej infekcji rotawirusowej

Duration of hospitalization
Five trials reported data about the duration of hospitalization [13–16, 18]. However, we were not able to perform a meta-analysis because of the different presentations of the results (mean with standard deviation, mean with no standard deviation or median). However, none of the studies reported a significant difference between the probiotic groups and the placebo groups for the duration of hospital stay and duration of diarrhea.

Harms
The probiotics were well tolerated, and no harm was reported in the included trials.

Discussion

Summary of evidence

This systematic review and meta-analysis demonstrated that only a limited number of probiotics for preventing healthcare-associated diarrhea have been evaluated. Only some of them may reduce the risk of diarrhea and rotavirus gastroenteritis in hospitalized children. As reported earlier by us, the strongest evidence is with regard to LGG. In hospitalized children, the use of LGG reduced the overall incidence of healthcare-associated diarrhea, including rotavirus gastroenteritis. Evidence limited to one RCT suggests the efficacy of *B. bifidum* & *Str. thermophilus*. Other studied probiotics, *i.e.*, *L. reuteri* DSM 17938 and *L. delbrueckii* H2B20, were ineffective. However, again, the evidence is limited to single trials only.

Strengths and limitations

This systematic review adds to previously published data, as it allowed identification of all probiotics whose efficacy for preventing nosocomial infections has been assessed. Thus, in addition to LGG, the efficacy of which was reported by us previously [8], we included data on other microorganisms. This is valuable as, worldwide, the availability of probiotic products differs. Thus, our systematic review may have practical implications. It allows one to answer the question of which of the locally available probiotics, if any, are effective. In contrast to the authors of many other meta-analyses, we abstained from pooling data on different probiotics. This is because it has been repeatedly questioned, also by our group, whether it is appropriate to pool data on different probiotic microorganisms [18]. We strongly support the view that pooling data from different genera, species, and strains may result in misleading conclusions.

Efforts were made to identify all published evidence. For example, we searched several databases with no language restrictions. However, the possibility of missing data cannot be excluded. Publication bias remains a possible source of important bias.

Agreements and disagreements with other studies or reviews

To our knowledge, except for our review on the efficacy of LGG [8] there are no other systematic reviews that have focused exclusively on the effectiveness of probiotics for the prevention of healthcare-associated diarrhea in hospitalized children.

Conclusions

In the absence of other effective measures, evidence supporting the use of LGG to reduce the risk of healthcare-associated diarrhea is encouraging. With regard to the other probiotics studied, data, whether positive or negative, are too limited to draw reliable conclusions. In the future, after a more universal introduction of rotavirus vaccination, the burden of nosocomial diarrhea and responsible pathogens may change as recently documented. In some countries, such as the US, norovirus has emerged as the leading cause of medically attended gastroenteritis [19]. If so, the efficacy of probiotics for preventing nosocomial diarrhea needs to be reassessed. Further studies are also recommended to address the cost-effectiveness of using LGG, or other probiotics with documented efficacy, for the prevention of healthcare-associated diarrhea. Although none of the included studies reported adverse events, standardized and clear adverse event reporting is essential for future trials.

Authors' contributions/Wkład autorów

HS initially conceptualized this study. MW was responsible for data collection, data analysis, data interpretation, and preparation of the first draft of the manuscript. All authors contributed to (and agreed upon) the final version.

Conflict of interest/Konflikt interesu

HS has participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for Arla, Biogaia, Biocodex, Danone, Dicofarm, Hipp, Nestle, Nestle Nutrition Institute, Nutricia, Mead Johnson, Merck, and Sequoia. MW declared no conflict of interest with regard to this manuscript.

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Ethics/Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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