

REVIEW ARTICLE

The influence of probiotics on gastrointestinal tract infections among children attending childcare: A systematic review and meta-analysis

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Email: h.ahmad@federation.edu.au**Abstract**

Current literature related to the impact of probiotics on the incidence of gastrointestinal tract infections (GITIs) has shown mixed results and no systematic review available with pooled analysis exists. Thus, the aim of this systematic review was to provide contemporary evidence regarding the overall and strain-specific influence of probiotics in preventing GITIs among infants and children attending childcare centres. The review shortlisted 18 RCTs after screening through the initial search results of 779 articles. However, only 15 trials were deemed eligible, addressing at least one outcome in the pooled analysis. It is concluded that the supplementation of probiotics (overall effect) may reduce the risk of GITI episode by 26%, with *Lactocaseibacillus paracasei*, *Limosilactobacillus reuteri* and *Lactocaseibacillus rhamnosus* GG being specifically potent probiotic strains in reducing GITI episode, duration of infection and absence from childcare respectively. There is insufficient evidence to determine the effect of *Bifidobacterium animalis* subsp. *lactis* BB-12 based on the findings of the trials included in this review.

KEYWORDS

childcare centres, children, gastrointestinal tract infections, probiotics, systematic review

INTRODUCTION

Children at childcare centres compared to children cared at home are more susceptible to frequent infections due to high exposure to pathogens (more socialization) and due to a developing immune system (Hullegie et al., 2016). Research demonstrates that children experience two to three times increased risk of moderate to severe gastrointestinal tract infection (GITI) at the time they commence attending centre-based care (Enserink et al., 2013, 2014). Young children who experience infectious diseases have the potential to undergo significant life-long physical and psychological developmental impacts (Snell-Bergeon et al., 2012). Furthermore, children are not the only stakeholder impacted by the spread of infections in

childcare centres. Parents and their employers, the health sector, and governments, may also be impacted to some extent, by childcare centre infections (Yin et al., 2013). For example, Enserink et al. (2014), found that the costs for care and treatment of a single GITI episode experienced by a child attending childcare in 2014 was an estimated US\$337.65 (US\$181.30 - US\$493.69), which was twice the cost required to manage a GITI episode in a child who did not attend childcare.

Probiotics are “live microbial feed supplements which beneficially affect the host, improving its intestinal microbial balance” (Fuller, 1989, p. 366). There are a wide range of micro-organisms used as probiotics; however, the most common include lactic acid bacteria (LAB) predominantly the genus: lactobacilli, bifidobacteria,

streptococci, *Enterococcus*, *Pediococcus* and certain yeast such as *Saccharomyces boulardii* (Galdeano et al., 2019). Nevertheless, past studies have shown that not all the micro-organisms used as probiotics may have a beneficial impact on the incidence of GITIs (Hojsak et al., 2016; Merenstein et al., 2010b, 2011; Szajewska, 2014). Therefore, conducting a meta-analysis that includes many different strains may not be a useful strategy to evaluate the individual effect of the various probiotic strains (Szajewska et al., 2014). Previous meta-analyses have been limited as they have either included both children and adults (Hao et al., 2015; Wang et al., 2016) or have focussed on respiratory tract infections in childcare centres (Laursen & Hojsak, 2018). Within this context, a systematic review and meta-analysis regarding the links between probiotics and GITIs among children attending childcare centres has not been conducted and warrants the need for the current study. The aim of this study was to systematically review contemporary evidence and analyse the overall and strain-specific impact of probiotics in preventing GITIs, while also examining the impact each strain has on reducing the duration of GITI, antibiotic use and absence from childcare centres among infants and children attendees.

METHODS

A systematic review and meta-analysis was conducted following the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions* - 2011 (Higgins & Green, 2011). The systematic review and meta-synthesis did not require ethical approval.

Trial type

Randomised Control Trials (RCT) either open or blind trials, provided participants were randomized.

Type of participants

Healthy children (from birth to eight years) attending childcare centres.

Types of interventions

Any probiotic intervention, either a single strain or a combination, compared with placebo, other intervention, or no intervention in the control arm, administered at any dosage, duration and regimen.

Types of outcomes

Prevention and/or reduction in the incidence and severity of GITI, and days missed from childcare due to infection and antibiotic use.

EXCLUSION CRITERIA FOR THE TRIALS

- Probiotics combined with functional ingredients (e.g. vitamins, prebiotics etc.).
- Trials published in a language other than English.
- Trials conducted with children over eight years of age and adults.
- Trials where children had congenital immune deficiency or chronic illnesses.

SEARCH STRATEGY AND RETRIEVAL OF ELIGIBLE TRIALS

Electronic databases included MEDLINE/PubMed, CINAHL complete, Cochrane library, SCOPUS (Elsevier), WEB of science and Trip Databases were searched. Relevant RCTs that evaluated the impact of probiotic on the incidence and severity of GITI among children attending childcare centres were retrieved using extensive range of search terms (Appendix A). Databases were searched from Jan 1995 to Jan 2021. Furthermore, manual screening of reference lists from previously published RCTs and reviews was undertaken to identify additional trials.

TRIAL SELECTION, DATA EXTRACTION AND QUALITY ASSESSMENT

Two of the authors (HHA and DT) individually screened all trials by title and abstract that were retrieved using search terms and additional search strategy. Full texts were then retrieved of all relevant trials. The inclusion and exclusion criteria were applied on all full text retrieved trials. In case of disagreement between the two authors (HHA and DT), the third author (BP) assisted to reach consensus.

Similarly, two authors (HHA and DT) individually extracted all relevant data from the included trials on Microsoft Excel. The third author (BP) double checked all entries to resolve any discrepancies. The extracted data included author, year and country of trial, sample size (including total and sample size of each individual arm in the trial) and participant's age. Details concerning intervention and controls were also extracted along with the probiotic strain and dose, the duration of intervention and results of each trial arm.

For the evaluation of risk of bias, the Cochrane Collaboration's tool for assessing the risk of bias was incorporated (Higgins & Green, 2011). The tool included bias assessment related to randomization, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, outcome data completeness, selective reporting and other biases.

DATA ANALYSIS

The data were prepared in Microsoft Excel and imported to RevMan (5.4 version) to undertake meta-analysis. For continuous level variables, such as absence from childcare due to infection (days) and duration of GITI symptoms (days), mean and standard deviation (SD) were included to calculate mean difference with 95% confidence intervals. Dichotomous variables such as number of subjects with GITI episodes and antibiotic use, total events and population sizes were included to calculate, and report results in the form of risk ratio and 95% confidence intervals. For trials that did not provide event numbers, mean, and sample size were used to calculate the total number of events, while trials that did not provide SD, 95% CI and sample size were used to calculate SD. The data for antibiotic use and days missed from childcare due to infection for Laursen et al. (2017) and Hojsak et al. (2016) studies were extracted from a 2018 review (Laursen & Hojsak, 2018), given the same authors had published previous trials. Analysis was conducted using random-effects model and where applicable χ^2 test value, p and the I^2 statistic were reported for the test of heterogeneity. Furthermore, heterogeneity was considered high, moderate or low based on the I^2 value, High $I^2 > 50\%$, Moderate $I^2 > 25\%$ but $< 50\%$ and Low $I^2 < 25\%$ (Higgins et al., 2003).

RESULTS

As outlined in Figure 1, 18 trials were initially included in the systematic review with 15 being deemed eligible for comparison for at least one outcome in the meta-analysis. The three trials that were not included in the meta-analysis (Merenstein et al., 2010b, 2011; Smerud et al., 2008) reported outcomes in different statistical measures, which could not be compared with the other 15 trials.

CHARACTERISTICS OF INCLUDED TRIALS

Table 1 presents detailed characteristics of the included trials, however the summary of key characteristics of

the 18 RCTs (Corsello et al., 2017; Gutierrez-Castrellon et al., 2014; Hatakka et al., 2001; Hojsak et al., 2010, 2016; Kumpu et al., 2012; Lau et al., 2018; Laursen et al., 2017; Merenstein et al., 2010a, 2010b, 2011; Nocerino et al., 2017; Pedone et al., 2000; Prodeus et al., 2016; Saavedra et al., 2004; Smerud et al., 2008; Thibault et al., 2004; Weizman et al., 2005) are explained below.

As such, the combined number of children in the trials were 6653. Noteworthy variations were found between the trials with respect to the age of the children, duration of use, dose range, dose form, probiotic strain and number of experimental arms in the trial. The age of the children ranged between three months to seven-and-half years, the duration of use ranged between three to ten months. Probiotic dose ranged between 10^7 and 10^{11} colony-forming units per day (CFU day⁻¹), while the forms of probiotic used included liquid, powder, semi-solid (rice) and oil. With respect to probiotic strain, three trials (Hatakka et al., 2001; Hojsak et al., 2010; Kumpu et al., 2012) included *Lacticaseibacillus rhamnosus* GG, four trials (Hojsak et al., 2016; Merenstein et al., 2010b, 2011; Weizman et al., 2005) included *Bifidobacterium animalis* subsp. *lactis* BB-12, two trials (Corsello et al., 2017; Nocerino et al., 2017) included *Lacticaseibacillus paracasei*, one trial (Pedone et al., 2000) included *Lacticaseibacillus casei* (yogurt was present in both experimental and control group), and one trial (Gutierrez-Castrellon et al., 2014) included *Limosilactobacillus reuteri*.

Six trials included multiple strains of probiotic with two (Merenstein et al., 2010a; Prodeus et al., 2016) of them included probiotic *Lacticaseibacillus casei* plus yogurt strains—*Streptococcus thermophilus* and *Lactobacillus delbrueckii* subsp. *bulgaricus*, three included two strains, *Bifidobacterium animalis* subsp. *lactis* BB-12 and *Streptococcus thermophilus* (Saavedra et al., 2004), *Bifidobacterium breve* and *Streptococcus thermophilus* (Thibault et al., 2004), *Bifidobacterium animalis* subsp. *lactis* BB-12 and *Lacticaseibacillus rhamnosus* GG (Laursen et al., 2017), and one study (Smerud et al., 2008) included three strains—*Lacticaseibacillus rhamnosus* GG, *Bifidobacterium animalis* subsp. *lactis* BB-12 and *Lactobacillus acidophilus*. Three trials included multiple arms, where one trial changed the dose of same probiotic (Saavedra et al., 2004), one trial used two different probiotic strains (Weizman et al., 2005) and one trial used the same probiotic and dosage but was administered in a different form (milk and rice) (Nocerino et al., 2017).

QUALITY ASSESSMENT OF THE TRIALS

Table 2 provides description about seven potential risks of bias for each trial. High risk of inadequate or no

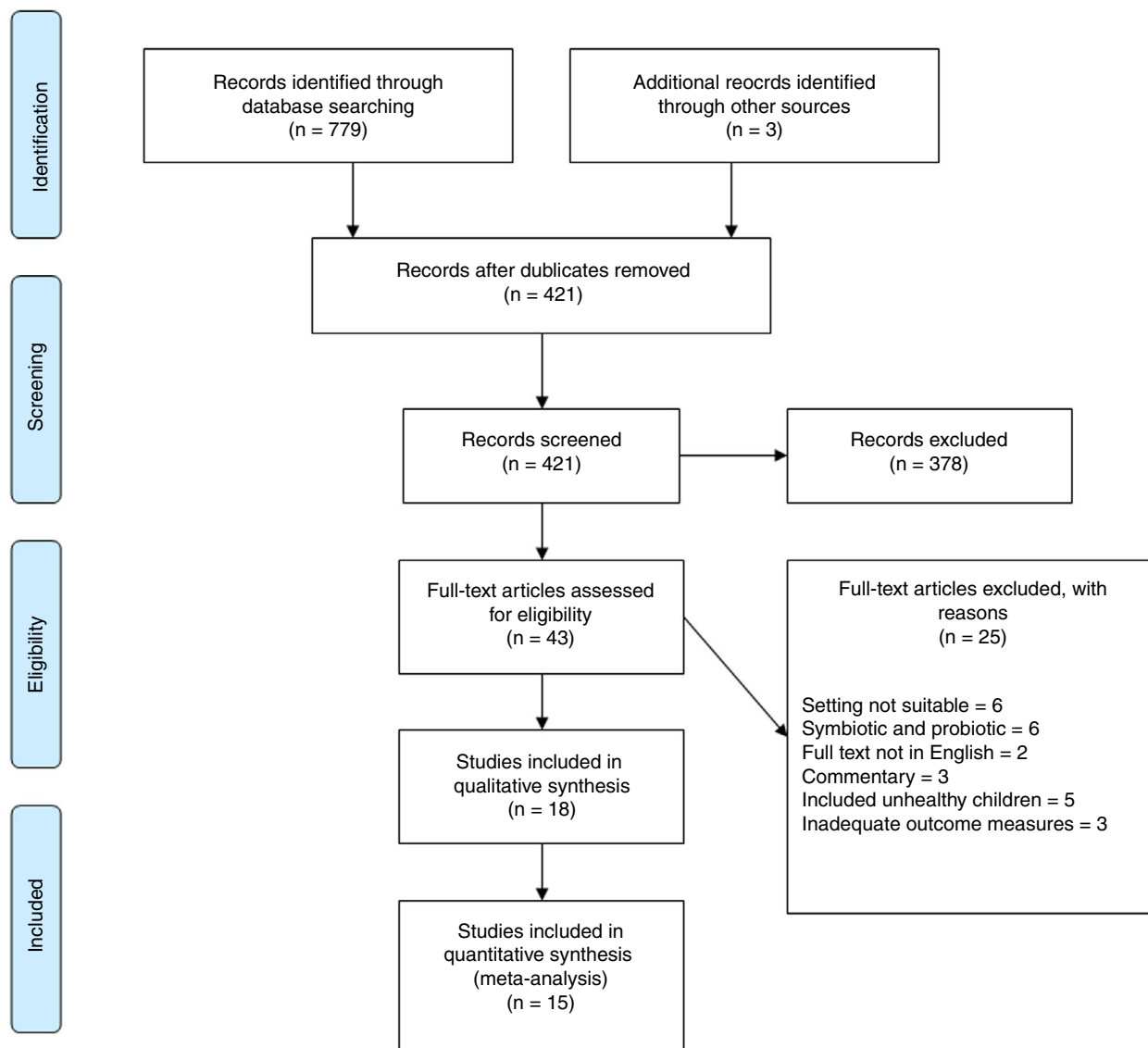


FIGURE 1 Study screening and selection

randomization was found in only one trial, high and unclear risk of inadequate or no allocation concealment, blinding of participant and personal and blinding of outcome assessment was found in six trials (Table 2). Three trials were at high risk of reporting incomplete outcome data, and nine trials were at high or unclear risk of inadequate selective reporting and nine trials were industry-funded, which may create other forms of bias (Table 2).

OVERALL PROBIOTIC EFFECT (ALL STRAINS)

Effect of probiotics on the number of children with GITI episodes

Ten trials (Figure 2) including 3669 children reported the effect of probiotics on the number of children with

GITI episodes. The supplementation of probiotic had a significant effect on the reduction of number of subjects having at least one GITI episode (relative risk: 0.74, 95% CI: 0.58 to 0.95, $p = 0.02$). However, there was a high level of statistical heterogeneity found among these trials ($\text{Chi}^2 = 56.62$, $p < 0.01$, $I^2 = 82\%$).

Duration of GITI symptom (days)

Among all included trials, only five trials provided data that were pooled to test for overall effect (Figure 3). In total, 2802 children were included in the selected five trials. The analysis showed no significant difference of GITI duration between probiotic intervention group and placebo group (MD: -0.23 , 95% CI: -0.75 to 0.29 , $p = 0.38$). Also, there was a high statistical heterogeneity found among these trials ($\text{Chi}^2 = 81.69$, $p < 0.01$, $I^2 = 94\%$).

TABLE 1 Characteristics of the include trials

Author (Year), Country - Sorted by year low to high	Participants [Sample size (A = Experimental group B = Comparative group) & participant's age]	Type and concentration of intervention A = Experimental group (dose) B = Comparative group (dose)	Intervention duration	Results A = Experimental group B = Comparative group
Pedone (2000), France	Initial = 928 Analysis on: A = 384 B = 395 Age = 6–24 months	A = Milk fermented with yogurt culture (1×10^7 - CFU ml ⁻¹) and <i>Lactocaseibacillus</i> <i>casei</i> (3.2×10^8 - CFU ml ⁻¹). B = Milk fermented with same yogurt only (1×10^7 - CFU ml ⁻¹)	12 weeks	One episode of diarrhoea A = 61 (15.9%) B = 87 (22%), $p = 0.03$ Duration of diarrhoea A = 3.95 ± 2.30 days B = 3.53 ± 2.09 days, $p = 0.24$
Hatakka (2001), Finland	Initial = 594 Analysis on: A = 252 B = 261 Age = 1 to 6 years	A = Milk with <i>Lactocaseibacillus rhamnosus</i> GG ($5 - 10 \times 10^5$ - CFU ml ⁻¹) B = Same milk without probiotic	7 months	GIT symptoms days A = 2.9 (2.6 – 3.2) B = 3.0 (2.7 – 3.4), $p = 0.57$ Absence due to illness A = 4.9 (4.4 – 5.5) B = 5.8 (5.3 – 6.4), $p = 0.03$ All Antibiotic use A = 119 (47%) B = 144 (55%)
Saavedra (2004), USA	Initial = 131 Analysis on: A = HS group (39) A = LS group (39) B = Placebo group (40) Age = 3 to 24 months	A = Formula supplemented with <i>Bifidobacterium</i> <i>animalis</i> subsp. <i>lactis</i> BB–12 and <i>Streptococcus thermophilus</i> (1×10^7 - CFU g ⁻¹) [HS - formula] A = Same formula supplemented at a concentration of 1×10^6 CFU g ⁻¹ [LS - formula] B = Similar without probiotic	Mean = 7 months	Values are frequency (95% CI) reported per 100 subject-days. Episodes of loose or watery stools A(HS) = 1.68 (1.40, 1.96) A (LS) = 1.87 (1.55, 2.19) B = 1.96 (1.64, 2.28), $p > 0.05$ Childcare absenteeism due to illness A(HS) = 1.86 (1.57, 2.15) A (LS) = 2.07 (1.74, 2.41) B = 1.89 (1.57, 2.20), $p > 0.05$ Use of antibiotics A(HS) = 3.19 (2.81, 3.56) A (LS) = 2.47 (2.11, 2.84) B = 0.78 3.60 (3.17, 4.02), $p < 0.01$ with placebo for both groups

(Continues)

TABLE 1 (Continued)

Author (Year), Country - Sorted by year low to high	Participants [Sample size (A = Experimental group B = Comparative group) & participant's age]	Type and concentration of intervention A = Experimental group (dose) B = Comparative group (dose)	Intervention duration	Results A = Experimental group B = Comparative group
Thibault (2004), Paris	Initial = 971 Analysis on: A = 464 B = 449 Age = 4–6 months	A = Formula fermented with <i>Bifidobacterium breve</i> and <i>Streptococcus thermophilus</i> B = Standard infant formula No dose	3 months	Incidence of diarrhea episodes A = 263/464 (56.7%) B = 251/449 (55.9%), $p > 0.05$ Average duration of diarrhea episodes (days) A = 5.36 ± 2.99 B = 5.25 ± 2.83 , $p > 0.05$
Weizman (2005), Israel	Initial = 201 Analysis on: A1 (BB-12) = 73 A2 (<i>L. reuteri</i>) = 68 B = 60 Age = 4 to 10 months old	A1 = Formula supplemented with <i>Bifidobacterium animalis</i> subsp. <i>lactis</i> BB-12 (1×10^7 CFU g ⁻¹) A2 = Formula supplemented with <i>Limosilactobacillus reuteri</i> (1×10^7 CFU g ⁻¹) B = Formula with no probiotic Dose consumed = 1.2×10^9 CFU day ⁻¹	12 weeks	Days with diarrhea A1 = 0.37 (0.08–0.66) A2 = 0.15 (0.12–0.18) B = 0.59 (0.34–0.84), $p < 0.01$ Episodes of diarrhea A1 = 0.13 (0.05–0.21) A2 = 0.02 (0.01–0.05) B = 0.31 (0.22–0.40), $p < 0.01$ Absences from childcare A1 = 0.41 (0.19–0.63) A2 = 0.14 (0.07–0.35) B = 0.43 (0.22–0.64), $p = 0.02$
Smerud (2008), Norway	Initial = 240 Analysis on: A = 97 B = 102 Age = 12–36 months	A = Probiotic milk drink with three strains - <i>Lactocaseibacillus rhamnosus</i> GG (10^8 CFU ml ⁻¹), <i>Lactobacillus acidophilus</i> (10^7 CFU ml ⁻¹) and <i>Bifidobacterium animalis</i> subsp. <i>lactis</i> BB-12 (10^7 CFU ml ⁻¹) B = Ordinary fermented milk drink	7 months	Gastrointestinal symptoms (days) A = 1.7 B = 3.00, $p = 0.02$ Absence due to illness (days) A = 7.5 B = 8.5, $p = 0.16$
Hojesak (2010), Croatia	Initial = 281 Analysis on: A = 139 B = 142 Age = 13 to 86 months	A = <i>Lactocaseibacillus rhamnosus</i> GG in 100 ml fermented milk (10^9 CFU day ⁻¹) B = Fermented milk with no added probiotic	3 months	Number of children with gastrointestinal infections A = 20 (14.4%) B = 32 (22.5%), $p = 0.08$ Absence from childcare (days) A = 3.1 (0–21.0) B = 5.1 (0–23), $p < 0.01$

TABLE 1 (Continued)

Author (Year), Country - Sorted by year low to high	Participants [Sample size (A = Experimental group B = Comparative group) & participant's age]	Type and concentration of intervention A = Experimental group (dose) B = Comparative group (dose)	Intervention duration	Results A = Experimental group B = Comparative group
Merenstein (2010a), USA	Initial = 638 Analysis on: A = 314 B = 324 Age = 3 to 6 years	A = <i>Lactocaseibacillus casei</i> (1×10^8 CFU g^{-1}) combined with yogurt culture - <i>Streptococcus thermophilus</i> and <i>Lactobacillus delbrueckii</i> subsp. <i>bulgaricus</i> (4×10^7 CFU g^{-1}). B = Sweetened, flavoured nonfermented acidified dairy drink	90 days	Incidence rate of GITI per 100 person day A = 1.2 (0.10) B = 1.6 (0.15), $p = 0.04$ Antibiotic use A = 58 B = 69, $p < 0.01$
Merenstein (2010b), USA	Initial = 180 Analysis on: A = 87 B = 95 Age = 1 to 3 years	A = Probiotic <i>Bifidobacterium</i> <i>animalis</i> subsp. <i>lactis</i> BB-12 (1×10^{10} CFU 100 ml^{-1}) B = Identical without probiotic	90 days	Missed Days of school due to illness per 100 person day A = 2.82 B = 2.51, $p = 0.37$ Rate of diarrhea per 100 person day A = 1.19 B = 1.06, $p = 0.73$
Merenstein (2011), USA	Initial = 172 Analysis on: A = 91 B = 81 Age = 2-4 years old	A = <i>Bifidobacterium</i> <i>animalis</i> subsp. <i>lactis</i> BB-12 (1×10^{10} CFU 100 ml^{-1}) in yogurt B = Yogurt without probiotic	90 days	Missed days of school because of illness per 100 person day A = 2.54 B = 2.42, $p = 0.87$ Rate of diarrhea per 100 person day A = 0.67 B = 0.96, $p = 0.36$
Kumpu (2012), Finland	Initial = 523 Analysis on: A = 251 B = 250 Age = 2-6 years	A = Probiotic <i>Lactocaseibacillus rhamnosus</i> GG (10^8 CFU day^{-1}) B = Similar without probiotic	28 weeks	Number of days per month with at least one gastrointestinal symptom A = 0.93 (95% CI: 0.88-0.98) B = 0.95 (95% CI: 0.90-1.00) Antibiotics use A = 35% (89/251) B = 34% (86/250), $p = 0.80$

(Continues)

TABLE 1 (Continued)

Author (Year), Country - Sorted by year low to high	Participants [Sample size (A = Experimental group B = Comparative group) & participant's age]	Type and concentration of intervention A = Experimental group (dose) B = Comparative group (dose)	Intervention duration	Results A = Experimental group B = Comparative group
Gutiérrez-Castrellon (2014), Mexico	Initial = 336 Analysis on: A = 168 B = 168 Age = 6–36 months	A = <i>Limosilactobacillus reuteri</i> (1×10^8 CFU day ⁻¹) B = Similar product without probiotic	12 weeks	Number of diarrhea episodes A = 42 B = 69, $p = 0.03$ Mean duration of diarrhea episodes A = 1.4 (1.0) B = 2.5 (0.9), $p = 0.01$ Days of school absenteeism per child A = 1.9 (0.7) B = 3.4 (1.2), $p = 0.03$ Days using antibiotics per child A = 2.7 (0.9) B = 4.1 (1.3), $p = 0.04$
Hojsak (2016), Croatia	Initial = 210 Analysis on: A = 104 B = 106 Age = 1.43–7.48 years	A = Sachet containing 1 g of powder, <i>Bifidobacterium</i> <i>animalis</i> subsp. <i>lactis</i> BB-12 (10^9 CFU day ⁻¹ + maltodextrin) B = Only maltodextrin	90 days	Number of children with gastrointestinal infections A = 14 (13.5%) B = 11 (10.4%) $p = 0.49$ Duration of gastrointestinal infections (median, range) (days) A = 3 (1–7 days) B = 2 (1–5 days) $p = 0.15$ Antibiotic use between groups (mean antibiotic prescribed per child) A = 0.4 B = 0.38 $p = 0.69$
Prodeus (2016), Moscow	Initial = 600 Analysis on: A = 300 B = 299 Age = 3 to 6 years	A = <i>Lactocaseibacillus casei</i> (10^{10} CFU 100 g^{-1}) Combined with yogurt— <i>Streptococcus thermophilus</i> and <i>Lactobacillus delbrueckii</i> subsp. <i>bulgaricus</i> (10^9 CFU 100 g^{-1}) B = Flavoured nonfermented acidified dairy drink without probiotics	3 months	GITI A = 2 B = 4 (no further analysis due to small number) Absence from childcare mean (SD) A = 1.64 (3.76) B = 1.61 (3.96), $p = 0.97$

TABLE 1 (Continued)

Author (Year), Country - Sorted by year low to high	Participants [Sample size (A = Experimental group B = Comparative group) & participant's age]	Type and concentration of intervention A = Experimental group (dose) B = Comparative group (dose)	Intervention duration	Results A = Experimental group B = Comparative group
Nocerino (2017), Italy	Initial = 432 Analysis on: A1 = 137 A2 = 118 B = 122 Age = 12–48 months	A1 = Fermented dairy milk with <i>Lactocaseibacillus paracasei</i> (5.9×10^{11} CFU) A2 = Fermented rice with same probiotic B = Maltodextrin with similar energy content	3 months	Acute gastroenteritis, n (%) [number of episodes] A1 = 18 (13.1) [21] A2 = 23 (19.5) [26] B = 38 (31.1) [47] A1 and B, $p < 0.01$ A2 and B, $p = 0.04$
Corsello (2017), Italy	Initial = 146 Analysis on: A = 66 B = 60 Age = 12 to 48 months	A = Cow's Milk Fermented with <i>Lactocaseibacillus paracasei</i> (5.9×10^9 CFU) B = Maltodextrins	3 months	Acute gastroenteritis, n (%) (number of episodes) A = 12 (18.2) (19) B = 24 (40.0) (28), $p < 0.01$ School absence mean (95%CI) A = 2 (1 to 3) days B = 8 (4 to 12) days
Laurson, 2017, Denmark	Initial = 290 Analysis on: A = 143 B = 142 Age = 8 to 14 months	A = <i>Bifidobacterium animalis</i> subsp. <i>lactis</i> BB-12 and <i>Lactocaseibacillus rhamnosus</i> GG at a concentration of 10^9 CFU each plus maltodextrin. B = Maltodextrin powder	6 months	Number of children with ≥ 1 episode of diarrhea n (%) A = 91 (64) B = 79 (56), $p = 0.15$ Duration of diarrheal episodes (median – IQR) A = 2.0 (1.0–3.0) B = 1.0 (1.0–3.0), $p = 0.43$ Days absent from child care because of illness
Lau (2018), Malaysia	Initial = 520 Analysis on: A = 109 B = 110 Age = 2–6 years	A = <i>Bifidobacterium longum</i> (5×10^9 CFU day ⁻¹) plus maltodextrin B = Only maltodextrin	10 months	Illness (total) A = 13.0 (9.0–19.0) B = 13.0 (8.0–19.9), $p = 0.31$ GIT symptoms Number of times A = 0.47 (0–4) B = 0.38 (0–6), $p = 0.99$ Days A = 0.52 (0–6) B = 0.41 (0–6), $p = 0.99$

(Continues)

TABLE 2 Quality assessment of the trials

Author -Year	A	B	C	D	E	F	G
Corsello - 2017	2	2	2	2	2	2	3 (Funded)
Gutierrez-Castrellon –2014	2	2	2	2	2	2	3 (Funded)
Hatakka - 2001	2	2	2	2	2	2	3
Hojsak - 2010	2	3	2	2	2	2	2
Hojsak - 2016	2	2	2	2	2	2	3 (Funded)
Kumpu - 2012	2	1	3	3	2	3	3 (Funded)
Laursen - 2017	2	2	2	2	2	2	3 (Funded)
Lau - 2018	2	2	2	2	1	3	3 (Funded)
Merenstein – 2010a	2	2	2	2	2	3	3 (Conflict of interest)
Merenstein – 2010b	2	2	2	2	2	3	3 (Conflict of interest)
Merenstein – 2011	2	2	2	2	2	3	3 (Conflict of interest)
Nocerino - 2017	2	2	2	2	2	2	3 (Funded)
Pedone - 2000	1	3	3	3	1	1	3
Prodeus - 2016	2	2	2	2	2	2	3
Saavedra - 2004	2	3	1	3	2	3	3
Smerud - 2008	2	3	3	3	1	3	3 (Funded)
Thibault - 2004	2	3	3	3	2	2	3
Weizman- 2005	2	3	3	3	2	3	3 (Funded)

Note: Quality criteria: A: Random sequence generation/ randomization (selection bias); B: Allocation concealment (selection bias); C: Blinding of participant and personal (performance bias); D: Blinding of outcome assessment (detection bias); E: Incomplete outcome data (attrition bias); F: Selective reporting (reporting bias); G: Other bias.

Number 1 indicates high risk, 2 indicates low risk and 3 indicates unclear risk of bias.

Absence from childcare due to infection

When examining the duration of days children absent from childcare due to infection, nine trials (Figure 4) included 2769 children. The pooled analysis demonstrated children supplemented with probiotics compared with a placebo had no significant effect on the duration of days children were absent from childcare due to an infection (MD: -0.47 , 95% CI: -0.99 to 0.06 , $p = 0.08$). Also, there was high statistical heterogeneity found between included trials ($\text{Chi}^2 = 137.38$, $p < 0.01$, $I^2 = 93\%$).

Antibiotic use

Among all included trials, only seven trials provided data that can be pooled to test for overall effect (Figure 5). In total, 2689 children were included in the selected seven trials. The pooled analysis demonstrated that probiotic treatment compared with placebo did not significantly reduce the risk of antibiotic use (relative risk: 0.92 , 95% CI: 0.81 to 1.05 , $p = 0.23$). Although, there was a low

level of statistical heterogeneity found among these trials ($\text{Chi}^2 = 8.71$, $p = 0.27$, $I^2 = 20\%$).

EFFECT OF DIFFERENT TYPES OF PROBIOTIC STRAINS ON THE OUTCOMES (STRAINS WITH TWO OR MORE RCTS)

Lactacaseibacillus rhamnosus GG

Absence from childcare due to infection

Two trials (Figure 4) including 794 children reported on the duration of days children were absent from childcare due to infection. The pooled analysis demonstrated that children supplemented with probiotics compared with placebo had significantly less days absent from childcare due to infection (MD: -1.14 , 95% CI: -2.49 to -0.34 , $p = 0.01$). However, there was a statistical high heterogeneity found between included trials ($\text{Chi}^2 = 0.41$, $p = 0.08$, $I^2 = 68\%$).

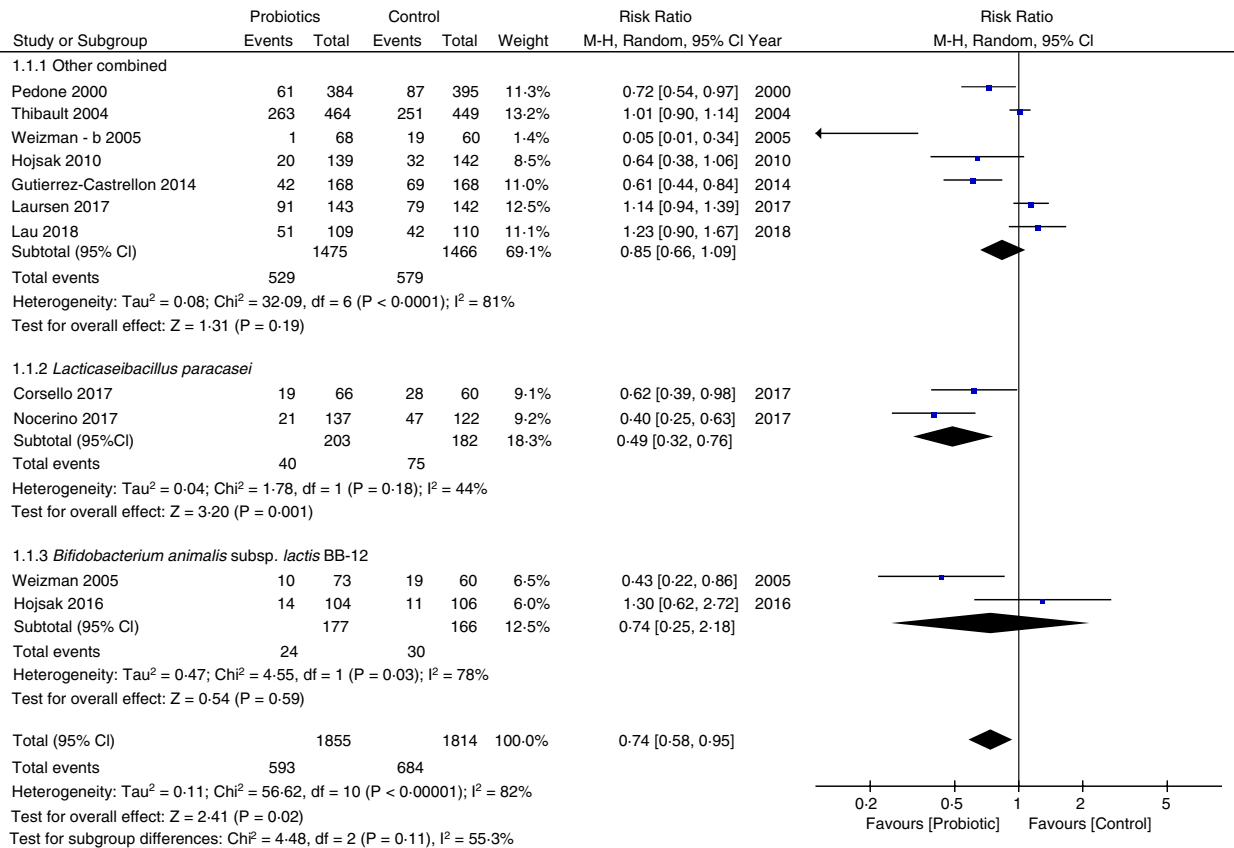


FIGURE 2 Overall and strain-specific effect of probiotics on the incidence of GITIs. Weizman et al. (2005) study included two experimental arms which are illustrated as Weizman 2005 (*Bifidobacterium animalis* subsp. *lactis* BB-12) and Weizman - b 2005 (*Limosilactobacillus reuteri*)

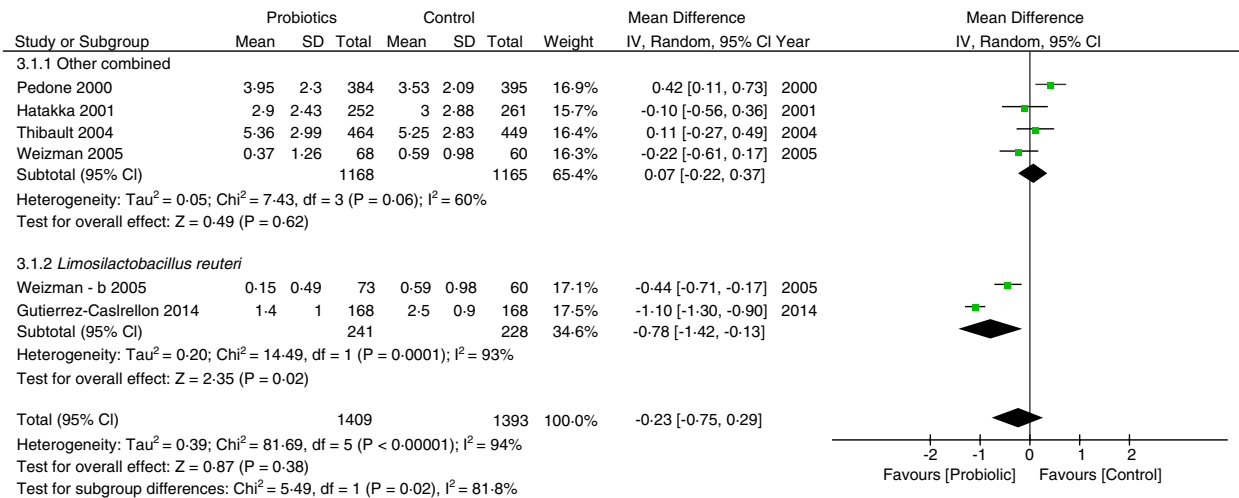


FIGURE 3 Overall and strain-specific effect of probiotics on the duration of GITI symptoms; data is presented in days. Weizman et al. (2005) study included two experimental arms which are illustrated as Weizman 2005 (*Bifidobacterium animalis* subsp. *lactis* BB-12) and Weizman - b 2005 (*Limosilactobacillus reuteri*)

Antibiotic use

Three trials including 1295 children reported antibiotic use (Figure 5). The pooled analysis demonstrated that probiotic treatment compared with placebo did

not significantly reduce the risk of antibiotic use (relative risk: 0.89, 95% CI: 0.75 to 1.06, $p = 0.18$). Although, there was a low level of statistical heterogeneity found among these trials (Chi² = 2.74, $p = 0.25$, I² = 27%).

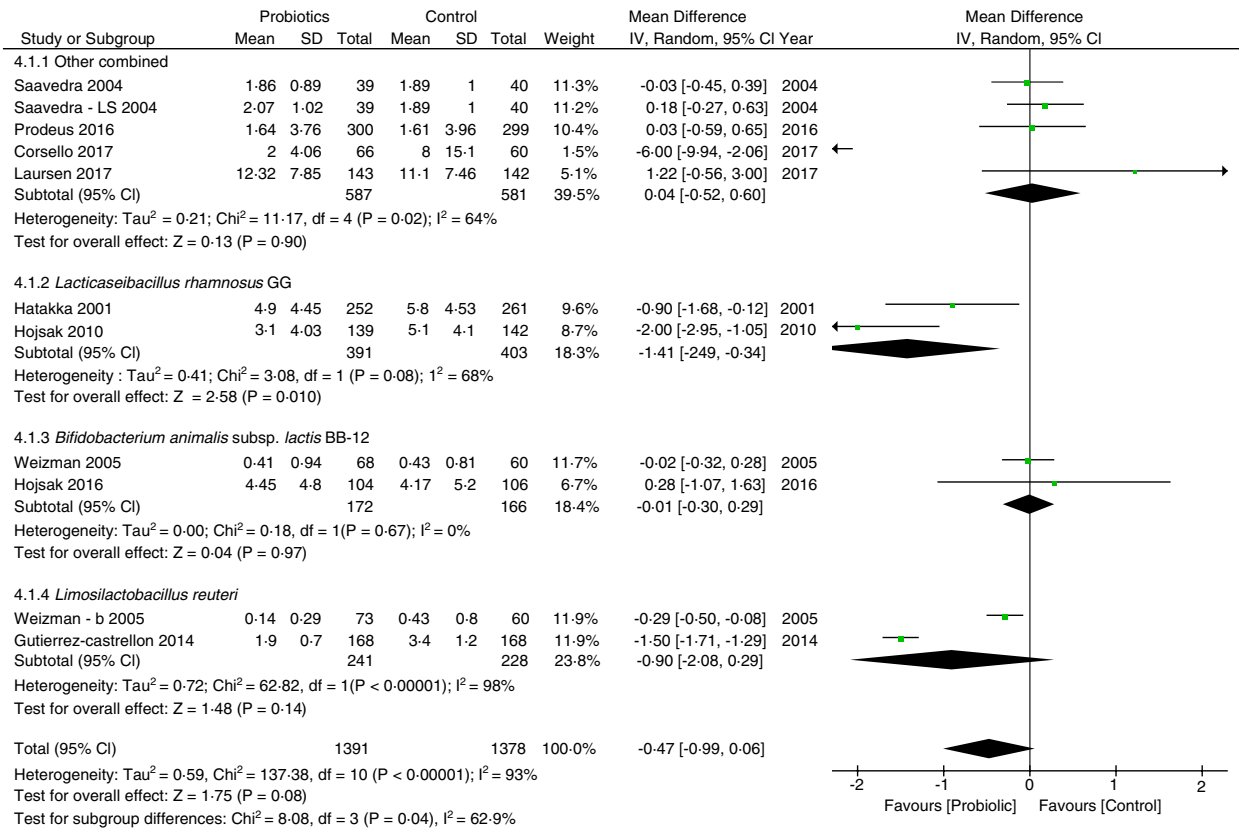


FIGURE 4 Overall and strain-specific effect of probiotics on the absence from childcare due to infection; data are presented in days. Weizman (2005) and Saavedra (2004) included two experimental arms which are illustrated as Weizman 2005 (*Bifidobacterium animalis* subsp. *lactis* BB-12) and Weizman - b 2005 (*Limosilactobacillus reuteri*), Saavedra 2004 (high-supplement formula) and Saavedra - LS 2004 (low supplement formula) respectively

Bifidobacterium animalis subsp. *lactis* BB-12

Effect of probiotics on the number of subjects with GITI episodes

Two trials (Figure 2) including 343 children reported this outcome. The supplementation of probiotic had no significant effect on the reduction of number of subjects having at least one GITI episode (relative risk: 0.74, 95% CI: 0.25 to 2.18, $p = 0.59$). However, there was a high level of statistical heterogeneity found among these trials ($\text{Chi}^2 = 4.55$, $p = 0.03$, $I^2 = 78\%$).

Absence from childcare

Two trials (Figure 4) including 338 children reported on the duration of days children absent from childcare due to infection. The pooled analysis demonstrated that children supplemented with probiotics compared with placebo had no significant effect on the duration of days children

absent from childcare due to infection (MD: -0.01 , 95% CI: -0.30 to 0.29 , $p = 0.97$).

Antibiotic use

Two trials including 343 children reported antibiotic use (Figure 5). The pooled analysis demonstrated that probiotic treatment compared with placebo did not significantly reduce the risk of antibiotic use (relative risk: 1.08, 95% CI: 0.80 to 1.46, $p = 0.62$).

Lactocaseibacillus paracasei

Effect of probiotics on the number of subjects with GITI episodes

Two trials (Figure 2) including 385 children reported this outcome. The supplementation of probiotic had a significant effect on the reduction of number of subjects having at least one GITI episode (relative risk: 0.49, 95% CI:

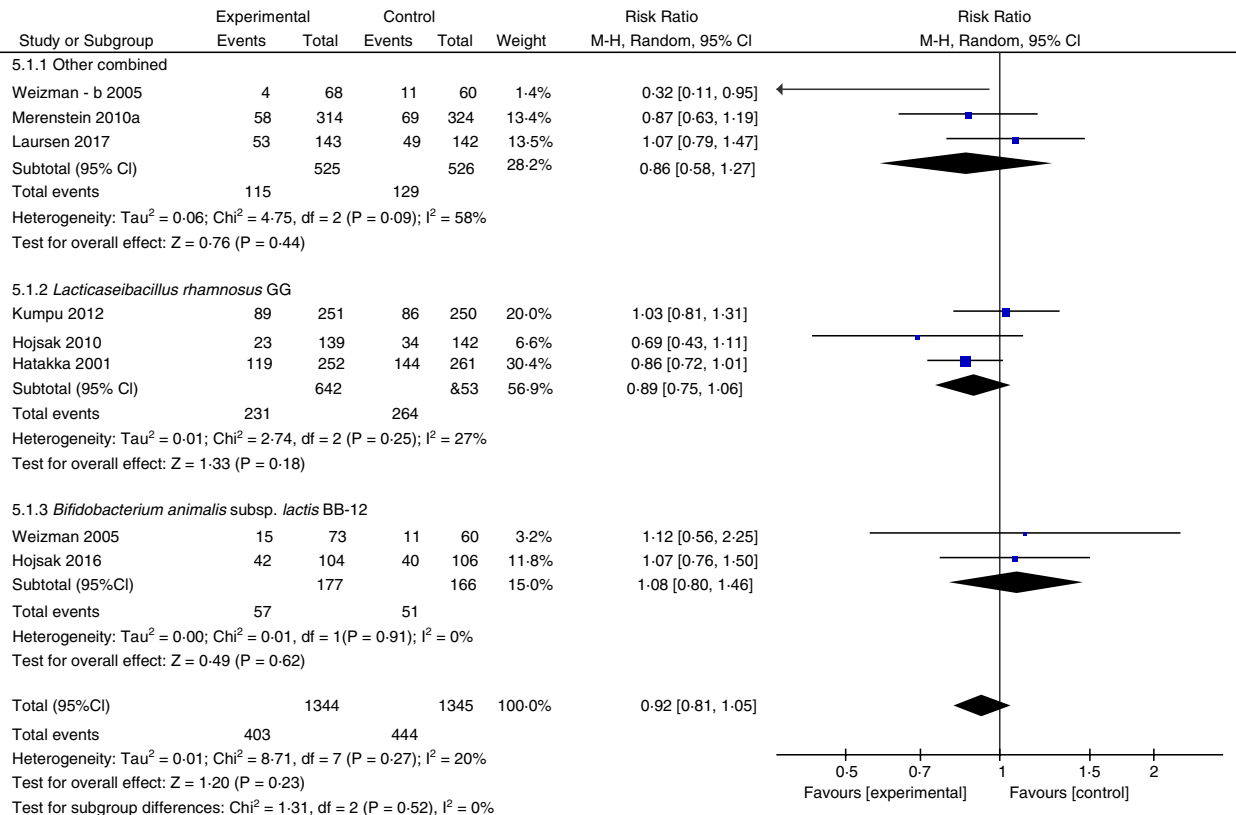


FIGURE 5 Overall and strain-specific effect of probiotics on the antibiotic use. Weizman et al. (2005) study included two experimental arms which are illustrated as Weizman 2005 (*Bifidobacterium animalis* subsp. *lactis* BB-12) and Weizman - b 2005 (*Limosilactobacillus reuteri*)

0.32 to 0.76, $p < 0.01$). However, there was a moderate level of statistical heterogeneity found among these trials ($\text{Chi}^2 = 1.78$, $p = 0.18$, $I^2 = 44\%$).

Limosilactobacillus reuteri

Duration of GITI symptom (days)

Two trials including 469 children reported this outcome (Figure 3). The analysis showed a significant difference of GITI episode duration between probiotic intervention group and placebo group (MD: -0.78 , 95% CI: -1.42 to -0.13 , $p = 0.02$). However, there was a high statistical heterogeneity found among these trials ($\text{Chi}^2 = 14.49$, $p < 0.01$, $I^2 = 93\%$).

Absence from childcare

Two trials (Figure 4) including 469 children reported on the duration of days children absent from childcare due to infection. The pooled analysis demonstrated that children supplemented with probiotics compared with placebo showed no significant difference on the duration of days

children were absent from childcare due to infection (MD: -0.90 , 95% CI: -2.08 to 0.29 , $p = 0.14$). Also, there was a statistical high heterogeneity found between the included trials ($\text{Chi}^2 = 62.82$, $p < 0.01$, $I^2 = 98\%$).

DISCUSSION

The supplementation of probiotic (overall effect) showed that the risk of GITI episode can be reduced by 26% (relative risk: 0.74, 95% CI: 0.58 to 0.95, $p = 0.02$). The study demonstrates that the risk can be even further reduced to 51% (relative risk 0.49, 95% CI 0.32–0.76, $p < 0.01$) if a specific strain of probiotic (*Lacticaseibacillus paracasei*) was used. It must be noted, not all probiotic strains were found effective in reducing the risk for GITI episodes since, the supplementation of *Bifidobacterium animalis* subsp. *lactis* BB-12 had no significant effect on reducing the number of children having at least one GITI episode. Also, the two trials (Merenstein et al., 2010b, 2011) which were not included in the pooled analysis suggests lack of efficacy of *Bifidobacterium animalis* subsp. *lactis* BB-12 in reducing incidence of diarrheal events ($p = 0.73$ & $p = 0.36$ respectively – Table 1). These results are consistent with past meta-analyses examining children with respiratory tract

infections in the home and childcare environment (Laursen & Hojsak, 2018; Wang et al., 2016). However, the information related to *Lacticaseibacillus paracasei* is novel in the childcare centre context as no previous systematic review and meta-analyses conducted on children in childcare centres were able to combine two or more trials (incorporating *Lacticaseibacillus paracasei*) to conduct pooled analysis.

With respect to the duration of symptoms, the overall results did not show any significant effect of probiotic on the reduction of GITI symptom duration when compared with placebo and these results are again consistent with the past meta-analyses conducted on respiratory tract infections (Laursen & Hojsak, 2018; Wang et al., 2016). However, the strain-specific analysis suggested otherwise which highlighted that the probiotic *Limosilactobacillus reuteri* did significantly reduce the GITI symptom duration by at-least three-quarter of a day (19 h) (MD: -0.78 , 95% CI: -1.42 to -0.13 , $p = 0.02$) when compared with placebo. The trial by Szajewska et al. (2014) and Dinleyici et al. (2015) suggested similar results and concluded that *Limosilactobacillus reuteri* may reduce the duration of infectious diarrhoea between 15 and 32 h, however, the setting (hospital) of these trials was different. Although seemingly this effect appears negligible (less than a day) but it holds noteworthy clinical significance. The combine effect on the overall population can result in the reduction of hundreds of days of GITI symptoms, which can save a substantial amount of money through reduction in direct and indirect childcare absence costs (Enserink et al., 2014; Yin et al., 2013).

Like the duration of GITI symptoms, absence from childcare due to infection was not significantly reduced in the overall probiotic group. However, the sub-group analysis by strain illustrates that the probiotic *Lacticaseibacillus rhamnosus* GG significantly reduced absence by almost a day due to infection (MD: -1.14 , 95% CI: -2.49 to -0.34 , $p = 0.01$) and again *Bifidobacterium animalis* subsp. *lactis* BB-12 had neither clinically nor statistically significant impact on absenteeism from childcare due to infection (MD: -0.01 , 95% CI: -0.30 to 0.29 , $p = 0.97$). These findings (overall and *Bifidobacterium animalis* subsp. *lactis* BB-12) are consistent with the systematic review and meta-analysis conducted in 2018 with the respiratory tract infection focus (Laursen & Hojsak, 2018).

The pooled analysis of seven trials including different strains demonstrated that probiotic treatment compared with placebo did not significantly reduce the risk of antibiotic use. Furthermore, none of the sub-group analysis by strain demonstrated any significant reduction in the risk of antibiotic use. However, the use of *Lacticaseibacillus rhamnosus* GG reduced the risk but not significantly (relative risk: 0.89, 95% CI: 0.75 to 1.06, $p = 0.18$) and the use of *Bifidobacterium animalis* subsp. *lactis* BB-12 non-significantly increased the risk of use of antibiotics

(relative risk: 1.08, 95% CI: 0.80 to 1.46, $p = 0.62$). Again, these sub-group findings are consistent with the systematic review and meta-analysis conducted in 2018 with the respiratory tract infection focus (Laursen & Hojsak, 2018).

LIMITATIONS

Despite the use of meta-analysis, a number of limitations were noted. For example, the quality, dose, dosage form, trial duration and location varied critically between the included trials. Although, this study provides additional evidence related to the role of *Lacticaseibacillus paracasei* and *Limosilactobacillus reuteri* but the results should be interpreted with caution, since the data informing the pooled analysis is only present within two trials for both strains. Furthermore, the data for some trials were not included in the meta-analysis due to statistical inconsistency in the reported outcomes measures compared to other trials given the data were not reported in same statistical measures across trials to assist with pooled analysis.

IMPLICATION FOR FUTURE RESEARCH

For future research, it is recommended to:

- Use combination of strains preferably three or more since three different probiotic strains (*Lacticaseibacillus paracasei*, *Limosilactobacillus reuteri* & *Lacticaseibacillus rhamnosus* GG) have shown beneficial effect, thus there is value in researching their combine effect.
- Compare the efficacy of *Bifidobacterium animalis* subsp. *lactis* BB-12 with other probiotic strains in the same trial given that there is insufficient evidence to determine the effect of *Bifidobacterium animalis* subsp. *lactis* BB-12.
- Incorporate powder dosage form due to various compliance related issues reported in previous trials, such as the significant variation in liquid dose (110 ml to 520 ml) reported in Hatakka et al. (2001).
- Use intervention period for six-months or more, and if possible, analyse the incidence of infections in both arms by each month over the intervention period to highlight any difference after considering the confounding factors. None of the past trials included in this review have estimated the variation in immune response over time, thus it is worth researching short and medium-term effect of probiotic supplementation.
- Use immune system biomarkers such as cytokines and chemokines to better correlate and understand clinical symptoms, lab data and influence of probiotics on the immune system of the body.

CONCLUSION

The review concludes that the supplementation of probiotics (overall effect) may reduce the risk of GITI episode by 26%. *Lacticaseibacillus paracasei*, *Limosilactobacillus reuteri* and *Lacticaseibacillus rhamnosus* GG are potent probiotic strains in reducing GITI episode, duration of infection and absenteeism from childcare respectively. There is insufficient evidence to determine the effect of *Bifidobacterium animalis* subsp. *lactis* BB-12 based on the findings of the trials included in this review.

CONFLICT OF INTEREST

Authors have no conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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APPENDIX A

The baselines search terms were adopted from Wang et al. (2016) and Laursen and Hojsak (2018) and were modified according to the requirements of the current review. An example is provided below

Database - Medline

(MH "Probiotics") OR (MH "Lactobacillus") OR (MH "Lactobacillus sakei" [current name: *Lactobacillus sakei*]) OR (MH "Lactobacillus rhamnosus" [current name: *Lactobacillus rhamnosus*]) OR (MH "Lactobacillus reuteri" [current name: *Limosilactobacillus reuteri*]) OR (MH "Lactobacillus plantarum" [current name: *Lactiplantibacillus plantarum*]) OR (MH "Lactobacillus pentosus" [current name: *Lactiplantibacillus pentosus*]) OR (MH "Lactobacillus paracasei" [current name: *Lactobacillus paracasei*]) OR (MH "Lactobacillus johnsonii") OR (MH "Lactobacillus gasseri") OR probiotic* OR LGG OR BB12 OR "BB-12" OR Lactobacill* OR Bifidobacter* OR helveticus OR saccharomyces OR reuteri OR paracasei OR lactis OR casei OR breve OR animalis OR boulandii OR bifidum OR rhamnosus OR acidophilus OR probiotic* OR "lactic acid bacteria" OR "Streptococcus thermophilus" OR "S. thermophilus" OR "fermented milk" OR Lactococc* OR "Saccharomyces" OR "Bacillus mesentericus" OR "B. mesentericus" OR "Enterococcus faecalis" OR "E. faecalis" OR "Enterococcus faecium" OR "E. faecium" OR "Bacillus clausii" – current name: *Alkalihalobacillus clausii* OR "B. clausii" OR "Clostridium butyricum" OR "C. butyricum" OR "E. coli Nissle" OR "Escherichia coli Nissle"

And

(MH "Infant") OR (MH "Child") OR (MH "Pediatrics") OR Child OR infant OR child* OR infan* OR pediatric OR paediatric

And

(MH "Child, Preschool") OR (MH "Child Care") OR (MH "Child Day Care Centers") OR preschool OR daycare OR "day care" OR childcare OR "child care" OR "daycare centre" OR "childcare centre"

And

(MH "Gastrointestinal Diseases") OR (MH "Gastrointestinal Tract") OR (MH "Gastroenteritis") OR (MH "Dysentery") OR (MH "Diarrhea") OR "gastrointestinal infections" OR GIT OR GITI OR diarrhea OR dairrhoea OR vomiting

And

PT "randomized controlled trial" OR "clinical trial" OR "control trial" OR RCT OR "clinical control trial"

Result: 175