

# Probiotics in Acute, Antibiotic-associated and Nosocomial Diarrhea: Evidence in Pediatrics

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## Abstract

**Introduction:** Probiotics are live microorganisms which, when administered in adequate amounts, provide beneficial action in humans. There are numerous studies about their use to treat diarrhea in pediatrics, so it is necessary to evaluate the evidence. **Methods:** We reviewed metaanalyses and systematic reviews in the last ten years about the use of probiotics to treat acute diarrhea, diarrhea associated with antibiotics and *Clostridium difficile* and nosocomial diarrhea. **Results:** Metaanalyses show that treatment of acute diarrhea with probiotics decreases duration by one day (95% CI: 15.9 to 33.6 hours) and reduces a risk of prolongation in the following four to seven days. They provide strong recommendations with moderate evidence for *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii*. For diarrhea associated with antibiotics and *Clostridium difficile*, meta-analyses show risk reduction of between 50% and 60%, with strong recommendations for *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii* with an NNT of 10 (95% CI: 7 to 12). For nosocomial diarrhea, moderate evidence was found for the use of *Lactobacillus rhamnosus* GG, mainly in reducing the risk of symptomatic gastroenteritis due to rotavirus. Currently, sufficient evidence does not exist to give recommendation for strains *S. thermophiles* and *B. bifidum*. **Conclusion:** For reducing the duration and reducing the risk of prolongation of acute diarrhea, evidence exists only for *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii*. In addition, they reduce the risk of diarrhea associated with antibiotics by 50% to 60%. There is moderate evidence that *Lactobacillus rhamnosus* GG reduces the risk of nosocomial diarrhea.

## Keywords

Probiotics, pediatrics, diarrhea, antibiotics, hospital infections.

## INTRODUCTION

In 2014, the International Scientific Association for Probiotics and Prebiotics (ISAPP) ratified and established the definition previously proposed by the World Health Organization (WHO) of probiotics as "...live microorganisms which when administered in adequate amounts confer a health benefit on the host." (1)

Probiotics' multiple physiological actions in the human body include restoration of the gut microbiota by occupying physiological niches to prevent the colonization of opportu-

nistic pathogens, (2) improvement of the bioavailability of vitamins such as vitamin K, B12 and pyridoxine, and synthesis of other micronutrients such as linoleic acid. (3) They aid intestinal transit to facilitate absorption and reduce gas production and have an immunomodulatory effect through action on the lymphoid tissue associated with mucous membranes and play a role in production of immunoglobulin A (IgA) and local activation of macrophages. (2)

The market for, and investments in, probiotics have been growing rapidly in recent years throughout the world. In 2015, the probiotic market was valued at US\$ 33.19 billion,

and it is projected that by 2020 investment will reach US\$ 46.55 billion with an annual growth rate of 7%. (4)

Not all probiotic products are the same, and their use must depend on quality, safety, tolerability, price and efficacy. Moreover, their use must take into account the economic limitations of Colombia's health care system. (5) Currently, these microorganisms have been introduced into the market as nutritional supplements which have lower standards for approval than do registered medicines so they have lesser guarantees of quality, efficacy and safety. (6) This has led to the sale and promotion of multiple products containing probiotics many of which do not have acceptable evidence for use.

There are few studies that talk about the quality of probiotics. One study has evaluated sixteen products containing bifidobacteria to determine the true presence of the bacteria registered in the package using molecular techniques. The study found that only one product contained the bifidobacteria described on the label. (7) Other studies have found that the number of colonies reported cannot be isolated after cultivation. (8)

In recent years, there have been numerous studies about the use of probiotics to treat diarrhea in children, so it is necessary to evaluate the available evidence to help clinical practice achieve efficacy and quality.

## METHODS

A review of evidence in the current literature about probiotic treatment of diarrhea in pediatrics was conducted using the following MeSH terms: probiotics, diarrhea or gastroenteritis, antibiotic-associated diarrhea and healthcare-associated diarrhea. A search for metaanalyses, systematic reviews and the most important clinical practice guidelines for children under 18 between 2007 and 2017 was also performed. Guidelines found include those of the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN), Latin American Society of Gastroenterology, Hepatology and Pediatric Nutrition (LASPGHAN) and North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN). Studies were classified into three categories: acute diarrhea, diarrhea associated with antibiotics and *Clostridium difficile*, and nosocomial diarrhea.

## ACUTE DIARRHEA

The basis of treatment of acute diarrhea is early rehydration and early return to feeding plus zinc supplementation (due to the high prevalence of zinc deficiency in our country) as recommended by the Colombian guidelines. (9)

In 2010, a Cochrane review analyzed 63 randomized or quasi-randomized studies that compared probiotics and placebos and which included 8,014 patients. Of these, 56 studies included 6,489 children. The results show that probiotics reduced the mean duration of diarrhea by 24.7 hours (95% confidence interval [CI]: 15.9 to 33.6 hours), and decreased the risk of diarrhea lasting for more than 4 days to 59%, (relative risk [RR]: 0.41, 95% CI: 0.32 to 0.53). (10) The organisms most frequently studied were *Lactobacillus rhamnosus* GG (13 studies), *Saccharomyces boulardii* (10 studies) and enterococcus LAB (lactic acid bacteria) (5 studies). No significant differences were found in the outcomes mentioned or in the doses used. (10)

In 2013, a systematic review Applegate et al. evaluated the effect of probiotics in children under five years of age who had acute diarrhea. Infants and children taking antibiotics were excluded. We found eight studies that showed probiotics reduced the duration of diarrhea by 14% (95% CI: 3.8% to 24.2%) and reduced the frequency of diarrhea on the second day by 13.1% (CI 95%: 0.8% to 25.3%). (11) No significant difference was found in hospital stays (RR: 0.81, 95% CI: 0.42 to 1.57). Analyses of probiotic strains found that *L. rhamnosus* GG was the most consistent and reduced the duration of diarrhea by 16.0% (95% CI: -53.9 to 22.0%) with evidence of moderate quality. (11)

Since the effect of probiotics depends on the species and strain used, probiotics have been studied individually. In 2007, a metaanalysis that evaluated *S. boulardii* treatment of acute diarrhea in children from two months to 12 years of age was published. It covered five studies with 619 participants. The results showed a reduction in the duration of diarrhea by 1.1 days (95% CI: -1.3 to -0.8 days), a reduction in the risk of diarrhea persisting to days three, six and seven of 29% (RR 0.71, 95% CI: 0.56 to 0.90), 51% (RR 0.49, 95% CI: 0.24 to 0.99) and 75% (RR: 0.25; 95% CI: 0.08 to 0.83), respectively. (12) One study reported a decrease in hospital stays of one day (95% CI: 1.4 to 0.62). (13)

In 2013, a metaanalysis that evaluated *L. rhamnosus* GG treatment of acute gastroenteritis in children was published. It included 2,963 total participants, and eleven of the studies it covered, including 2,444 children, showed a reduction in the duration of diarrhea of 1.05 days (CI 95%: -1.7 to -0.4). A daily dose of  $10^{10}$  colony forming units (CFU) of *L. rhamnosus* GG or more was more effective and decreased duration of diarrhea by 1.11 days (95% CI: -1.91 to -0.31), slightly more than did a daily dose of less than  $10^{10}$  CFU which reduced duration by only of 0.9 days (95% CI: -2.5 to 0.69) (14). In addition, the risk of developing diarrhea for more than seven days was reduced by 73% (RR: 0.27, 95% CI: 0.09 to 0.78). Three of the studies including 201 patients also found that the use of *L. rham-*

nosus GG effectively treated diarrhea caused by rotavirus. Duration of diarrhea fell by 2.05 days (95% CI: -2.39 to -1,71) with respect to one with invasive origin which did not show statistically significant improvement: 0.05 days (95% CI: 0.64 to 0.74). (14)

ESPGHAN established in 2014 that the use of probiotics should be considered for management of infectious diarrhea on the basis of findings in multiple metaanalyses. It established a strong recommendation for the use of *L. rhamnosus* GG and *S. boulardii*, but the GRADE quality of evidence level was low due to limitations in the consistency of the evidence and to high level of heterogeneity of the metaanalyses. (15) *Lactobacillus reuteri* has a weak recommendation for usage and a very low level of evidence. (15) The recommended doses are shown in Table 1.

**Table 1.** Probiotics and recommended doses

Probiotic	Dosage
<i>L. rhamnosus</i> GG	1-2 * 10 <sup>10</sup> CFU/day for 5-7 days
<i>S. Boulardii</i>	250-750 mg/day for 5-7 days
<i>L. reuteri</i> DSM 17938	1-4* 10 <sup>8</sup> CFU/day for 5-7 days
<i>Lactobacillus acidophilus</i> LB	5 doses of 10 <sup>10</sup> CFU for more than 48 hours Maximum 9 doses of 10 <sup>10</sup> CFU for 4.5 days

\* Probiotics and doses recommended by ESPGHAN. (15)

In 2015, a Latin American consensus of pediatric gastroenterology reviewed the evidence of about 74 articles with recommendations for the use of probiotics in children. It established a 1A recommendation for the use of *L. reuteri* and a 1B recommendation for the use of *L. rhamnosus* GG and *S. boulardii* for treatment of infectious diarrhea. It did not specify recommended dosages. (16)

For its part, the American Academy of Pediatrics also supports the use of probiotics to treat acute infectious diarrhea in healthy children, specifically *L. rhamnosus* GG to reduce the duration of diarrhea. (17)

A worldwide review of clinical practice guidelines for the management of acute gastroenteritis in children has reported that nine of fifteen guidelines support the use of probiotics and that ten of fifteen support the use of zinc sulfate. (18) Table 2 summarizes the findings of metaanalyses and systematic reviews regarding the use of probiotics to treat acute diarrhea.

## DIARRHEA ASSOCIATED WITH ANTIBIOTICS AND *C. DIFFICILE*

Diarrhea is one of the most common complications associated with the use of antibiotics in children. Antibiotics alter the biological balance of intestinal microbiota and can lead to the growth of pathogenic bacteria such as *C. difficile* bacilli. (19) It is estimated that its incidence is 11%.

**Table 2.** Metaanalyses and systematic reviews on the use of probiotics to treat acute diarrhea

Reference	Year	Type of study	Strains	Results
Allen et al. (10)	2010	Systematic review	<i>L. rhamnosus</i> GG, <i>S. boulardii</i> , <i>Enterococcus</i> LAB	Reduction of diarrhea duration by 24.7 hours (95% CI: 15.9 to 33.6 hours) Diarrhea for more than 4 days: RR: 0.41 (95% CI: 0.32 to 0.53)
Applegate (11)	2013	Systematic review	<i>L. bulgaricus</i> , <i>Streptococcus thermophilus</i> , <i>L. rhamnosus</i> GG, <i>S. boulardii</i> , <i>L. acidophilus</i> y <i>Bifidobacterium bifidum</i> , <i>Bacillus clausii</i> , <i>Enterococcus faecium</i> , <i>L. acidophilus</i> , <i>Lactobacillus casei</i> , <i>Lactobacillus plantarum</i> , <i>Bifidobacterium infantis</i>	Duration of diarrhea reduced by 14.0% (95% CI: -24.2 to -3.8%) Frequency of diarrhea on day 2 reduced by 13.1% (95% CI: -25.3 to -0.8%)
Szajewska et al. (12)	2007	Metaanalysis	<i>S. boulardii</i>	Reduction of duration of diarrhea by 1.1 days (95% CI: -1.3 to -0.8 days) Persistence of diarrhea on Day 3 RR: 0.71 (95% CI: 0.56 to 0.909), On day 6 RR: 0.49 (95% CI: 0.24 to 0.99), On day 7 RR 0.25; 95% CI: 0.08-0.83
Szajewska et al. (14)	2013	Metaanalysis	<i>L. rhamnosus</i> GG	Reduction of duration of diarrhea by 1.05 days (95% CI: -1.7 to -0.4) Persistence of diarrhea at 7 days RR: 0.27 (95% CI: 0.09 to 0.78)

Children under two are the most commonly affected group with an incidence of up to 18%.  $\beta$ -lactam antibiotics are the most commonly associated antibiotics. (20)

In 2012, Videlock and colleagues published a metaanalysis about the use of probiotics to treat diarrhea associated with antibiotics. It covered 10 pediatric studies and a population of 1,246 children. The results showed a 52% reduction of the risk of developing diarrhea associated with antibiotics when probiotics were used (RR: 0.48, 95% CI: 0.35 to 0.65) independent of the probiotic strain used and the type of antibiotic used. (21) Analysis of probiotic strains analysis included studies of adults. *L. rhamnosus* GG showed a risk reduction of 60% (RR: 0.40, 95% CI: 0.2 to 0.81) while *S. boulardii* reduced risk by 56% (RR: 0.46, 95% CI: 0.3 to 0.7). There was less heterogeneity with respect to *L. rhamnosus* GG. (21)

In 2015, Goldenberg and colleagues published a Cochrane collaboration metaanalysis which was reviewed in 2016 in the Journal of the American Medical Association (JAMA). It analyzed 23 pediatric studies with a population of 3,938 participants for whom probiotics were used alone or in combination. The results found that the incidence of diarrhea associated with antibiotics in the group taking probiotics was 8% (163/1,992) while it was 19% (364/1,906) in the control group which did not receive probiotics. Overall risk reduction was 54% (RR: 0.46, 95% CI: 0.35 to 0.61) with a number needed to treat (NNT) of 10 patients to prevent an event (95% CI : 7 to 12). (22, 23) GRADE analysis of evidence showed a moderate evidence quality, and no serious adverse events occurred. The probiotics with the best evidence were *L. rhamnosus* GG (four studies, n = 711) and *S. boulardii* (four studies, n = 1611) at doses of 5 to 40 CFU/day. (22, 24)

In 2015, a metaanalysis of five studies with 455 patients investigated the effectiveness of *L. rhamnosus* GG for prevention of diarrhea associated with antibiotics in adults and children. It found a reduction of risk by 52% but only in the pediatric population (RR: 0.48, 95% CI : 0.26 to 0.89). The GRADE quality of evidence was moderate, with an NNT to prevent an event of 8 patients (NNT: 8, 95% CI: 6 to 40). (25)

A metaanalysis that evaluated studies of *S. boulardii* in six pediatric populations covering a total of 1,653 patients found that the risk of diarrhea associated with antibiotics in children receiving placebos was 20.9% while it was only 8.8% in children who received the probiotic: the reduction of risk was 57% (RR: 0.43, 95% CI: 0.3 to 0.6). (25) That metaanalysis also showed that in two studies with 579 patients, *S. boulardii* reduced the incidence of diarrhea associated with *C. difficile* by 75%, (RR: 0.25, 95% CI: 0.08 to 0.73). (23)

A 2013 systematic review by the Cochrane Collaboration of *C. difficile* infections found that administration of probiotics to pediatric patients reduced the risk of *C. difficile* infections by 60% (RR: 0.40, 95% CI: 0.17 to 0.96). The

review covered three studies which included a total of 300 treated patients and 305 controls. The *L. rhamnosus* GG and *S. boulardii* strains were used in these studies. (26).

A 2016 metaanalysis that included four pediatric studies covering 938 patients found a statistically significant 66% reduction in the risk of *C. difficile* infection (RR: 0.341, 95% CI 0.153 to 0.759, p = 0.008). (27) Strains of *L. rhamnosus* GG and *S. boulardii* showed the best risk reductions of 6.7% and 58.5% respectively. The study of *S. boulardii* also included information about adult patients. (27)

Based on these studies, ESPGHAN reviewed the data from more than 21 randomized clinical trials in 2016. The studies covered the 3255 patients included in these metaanalyses and found that the use of probiotics reduced the risk of diarrhea associated with antibiotics by 52% (RR: 0.48, 95% CI: 0.37 to 0.61) with an incidence of 21.2% compared to an incidence of 9.1% in patients who did not receive probiotics. (28)

ESPGHAN reaffirmed that the probiotics with the best evidence are *L. rhamnosus* GG and *S. boulardii*, but concluded that dosage has not been clearly established. Nevertheless, it suggested that the greatest effect in children has been achieved with high doses of *L. rhamnosus* GG (1-2 x 10<sup>10</sup> CFU). It strongly recommended its use for the prevention of diarrhea associated with antibiotics and graded the quality of the evidence as moderate. (28) It also concluded that there is no established dosage for *S. boulardii* but said that it should not be less than 250 mg nor more than 500 mg in children. Its recommendation was strong, and the quality of evidence was moderate. (28) In addition, on the basis of two studies with 579 patients which showed a 75% reduction in risk of *C. difficile* infections using *S. boulardii*, it recommended this probiotic but with low quality of evidence (RR: 0.25, 95% CI: 0.08 to 0.73). (29, 30) Finally, it mentioned that *B. clausii* has no effect on the risk of diarrhea associated with antibiotics, nor does it have an effect when used in combinations of probiotics. (28) It recommended that the probiotic be administered simultaneously with the antibiotic and continued for the duration of antibiotic treatment.

For its part, the Latin American Consensus issued recommendation 1B for *L. rhamnosus* GG and *S. boulardii* for use in diarrhea associated with antibiotics. (16) Tables 3 and 4 summarize the findings of metaanalyses and systematic reviews of the use of probiotics to treat diarrhea associated with antibiotics and *C. difficile*.

## NOSOCOMIAL DIARRHEA

Nosocomial infections occur after the first 48 hours of hospital stay. In children, the most common infection associated with health care is rotavirus gastroenteritis. (31) A metaanalysis from 2012 showed that the incidence of

rotavirus-associated diarrhea is 2.9 per 100 hospitalizations and that its epidemiological peak can reach as high as 8 per 100 hospitalizations. (32) In this field, the use of probiotics seems to be effective in prevention.

A metaanalysis of three studies that evaluated the effect of *L. rhamnosus* GG on diarrhea associated with health care was published in 2011. It found that taking this probiotic reduced the risk of diarrhea by 63% (RR: 0.37, 95% CI: 0.23 to 0.59) and symptomatic gastroenteritis due to rotavirus by 51% (RR 0.49, 95% CI: 0.28 to 0.86). However, no differences were found in the length of hospital stays. (33)

A 2014 metaanalysis that collected data from six randomized clinical trials, including the three previously mentioned studies of the use of *L. rhamnosus* GG, covered 1,343 patients and confirmed the previously described reduction of the risk of diarrhea by 63 % (RR: 0.37, 95% CI: 0.23 to 0.59). In addition, one of the studies included showed that the combination of *B. bifidum* and *S. thermophilus* reduced the risk of diarrhea associated with health care by 78% (n = 55; RR: 0.27; 95%: 0.08 to 0.87) as well as reducing

the risk of symptomatic gastroenteritis due to rotavirus (n = 55, RR: 0.27, 95% CI: 0.08 to 0.87). (34) In contrast, two other studies found that *L. reuteri* DSM 17938 and *Lactobacillus delbrueckii* H2B20 were not effective for reducing the incidence of nosocomial diarrhea. (34)

A new study published in 2016 evaluated *L. reuteri* DSM 17938 in a population of 148 children. It found no difference in the risk of diarrhea associated with health care (RR: 1.19, 95% CI: 0.43 to 3.27). (35)

Based on these studies, the Latin American Consensus issued a 1B recommendation for treatment with *S. thermophilus*, *B. bifidum* and *L. rhamnosus* GG for prevention of nosocomial diarrhea. (16) However, in June 2017, ESPGHAN's working group on probiotics for treatment of nosocomial diarrhea published its recommendations, also based in part on a review of the two previously mentioned metaanalyses, and issued a strong recommendation of the use of *L. rhamnosus* GG with moderate evidence in favor (36). Due to the high quality evidence showing due to lack of efficacy of *L. reuteri* DSM 17938 for preventing nosocomial diarr-

**Table 3.** Metaanalyses and systematic reviews regarding use of probiotics to treat diarrhea associated with antibiotics

Reference	Year	Type of study	Strains	Results
Vidlock et al. (21)	2012	Metaanalysis	<i>L. rhamnosus</i> GG <i>S. boulardii</i> <i>L. acidophilus</i> . <i>B. infantis</i> <i>Bifidobacterium longum</i> . <i>L. plantarum</i> <i>B. longum</i> . <i>L. rhamnosus</i> y <i>L. plantarum</i>	Risk of diarrhea: RR: 0.48; 95% CI: 0.35 to 0.65
Goldenberg et al. (22)	2015-2016	Systematic review	<i>L. acidophilus</i> y <i>L. casei</i> <i>S. boulardii</i>	Risk of diarrhea: RR: 0.46; 95% CI: 0.35 to 0.61; NNT: 10;
B. Johnston et al. (23)			<i>L. casei</i> <i>imunitas</i> . <i>Lactobacillus bulgaricus</i> y <i>S. thermophilus</i> <i>C. butyricum</i> <i>L. plantarum</i> <i>Bifidobacterium</i> y <i>L. acidophilus</i> <i>L. acidophilus</i> . <i>L. bulgaricus</i> . <i>B. bifidum</i> y <i>S. thermophilus</i> <i>L. acidophilus</i> <i>Lactobacillus paracasei</i> spp. <i>L. rhamnosus</i> GG. <i>L. acidophilus</i> y <i>Bifidobacterium</i>	95% CI: 7 to 12
Szajewska et al. (24)	2015	Systematic review y metaanalysis	<i>L. rhamnosus</i> GG	Risk of diarrhea: RR: 0.48; 95% CI: 0.26 to 0.89; NNT: 8; 95% CI: 6 to 40
Szajewska (25)	2015	Systematic review y metaanalysis	<i>S. boulardii</i>	Risk of diarrhea: RR: 0.43; 95% CI: 0.3 to 0.6

**Table 4.** Metaanalyses and systematic reviews on the use of probiotics to treat diarrhea associated with *C. difficile*

Reference	Year	Type of study	Strains	Results
Goldenberg et al. (26)	2013	Systematic review	<i>L. rhamnosus</i> GG <i>S. boulardii</i>	Risk of diarrhea: RR: 0.40; 95% CI: 0.17 to 0.96
Lau et al. (27)	2016	Systematic review	<i>Lactobacillus</i> GG <i>S. boulardii</i>	Risk of diarrhea: RR: 0.341; 95% CI: 0.153 to 0.759; p: 0.008

hea, ESPGHAN recommends against its use. ESPGHAN did not issue recommendations for or against *S. thermophilus*, *B. bifidum*, *L. delbrueckii* H2B20 and *Bifidobacterium animalis* subsp. *lactis* (BB-12®) because there was insufficient evidence since only studies with two or more randomized clinical trials of probiotics were analyzed. (36)

Table 5 summarizes the findings of metaanalyses and systematic reviews about the use of probiotics to treat nosocomial diarrhea.

## SAFETY

Currently, there are no systematic reviews that analyze adverse effects and safety of probiotic administration, but evidence to date has demonstrated no serious adverse effects. (37) Nevertheless, cases of fungemia and bacteremia secondary to the administration of probiotics have been described in patients with risk factors such as immunosuppression, hospitalization in an intensive care unit (ICU) with a central catheter, and severe or cardiac structural disease. In these cases, the use of probiotics is not recommended. (38, 39)

## CONCLUSION

Evidence shows that administration of probiotic strains *L. rhamnosus* GG and *S. boulardii* reduce duration of acute

diarrhea by one day and also reduce the risk of prolongation of diarrhea to four and seven days. Administration of these probiotics is strongly recommended, but the quality of evidence remains low due to the heterogeneity of the studies. There is evidence that *L. rhamnosus* GG and *S. boulardii* reduce risk of diarrhea associated with antibiotics and *c. difficile* by 50% to 60% with an NNT of 10, moderate quality evidence, and a strong recommendation for use. Finally, there is evidence in favor of *L. rhamnosus* GG for reducing the risk of nosocomial diarrhea, especially symptomatic gastroenteritis due to rotavirus. There is insufficient evidence about *S. thermophilus* and *B. bifidum*. The use of *Lactobacillus* GG and *S. boulardii* should be considered in combination with standard treatment for management of diarrhea in children, remembering that its use should be individualized in each patient, weighing its costs and benefits.

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## Conflicts of interest

The authors have no conflicts of interest related to this article.

**Table 5.** Metaanalyses and systematic reviews on the use of probiotics to treat nosocomial diarrhea or diarrhea associated with health care

Reference	Year	Type of study	Strains	Results
Szajewska et al. (33)	2011	Metaanalysis	<i>L. rhamnosus</i> GG	Diarrhea risk: RR: 0.37; 95% CI: 0.23 to 0.59 Rotavirus diarrhea risk: RR: 0.49; 95% CI: 0.28 to 0.86
Wanke et al. (34)	2014	Metaanalysis	<i>L. rhamnosus</i> GG <i>B. bifidum</i> y <i>S. thermophilus</i>	Risk of diarrhea <i>L. rhamnosus</i> GG: RR: 0.37; 95% CI: 0.23 to 0.59 Risk of diarrhea <i>B. bifidum</i> and <i>S. thermophilus</i> : RR: 0.27; 95% CI: 0.08 to 0.87

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