Review Article

Efficacy of probiotic use in acute rotavirus diarrhea in children: A systematic review and meta-analysis

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Abstract

Background: Probiotic therapies with different strains demonstrated some beneficial effects, although some studies did not show any significant effects. This study assessed systematically the current knowledge on the effect of probiotic bacteria on duration of acute rotavirus diarrhea in children compared with control.

Methods: The PubMed, Cochrane Controlled Trial Register (CCTR) and Ovid (Wolters Kluwer Health) were searched between 1980 to June 15, 2013. Randomized controlled trials including the administration of probiotics for treatment of rotavirus diarrhea in infants and children were reviewed.

Results: A total number of 1244 articles were found through the aforementioned search. 203 articles were selected after the first screening of title and abstract. The intervention group included subjects who received probiotic strains and dosage in any conditions. Placebo or any similar vehicle without probiotic was used in the controlled trials. Finally, 14 articles were selected. The outcomes from each study were considered in the duration of diarrhea. Statistical analyses were performed with Stata software. The pooled estimate of efficacy of probiotics in prevention or treatment of disease yielded in all studies a mean difference of 0.41 (CI 95%: -0.56 to –0.25; p<0.001). The pooled estimate of efficacy of l*actobacillus rhamnosus* GG and other probiotics significantly reduced the duration of diarrhea. Among trials, the overall reduction of LGG was 0.47 (CI 95%: -0.80 to -0.14; P= 0.020).

Conclusion: In conclusion, probiotics exert positive effect in reducing the duration of acute rotavirus diarrhea compared with control.

Keywords: Probiotics, Rotavirus, Acute Diarrhea, Children

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Diarrhea is one of the major causes of morbidity and mortality in both developed and developing countries (1, 2). Rotavirus has been recognized as the most common cause of severe diarrhea in children and infants all over the world since the 1970s (3, 4). Annually, 600,000 child deaths from rotavirus occurred in children under 5 years globally (5, 6). Nearly 85% of rotavirus-associated-diarrhea are observed in the poorest regions of Africa and Asia (7-12). The treatment of rotavirus diarrhea has remained approximately unchanged over the past 35 years (4). Oral rehydration, breast feeding, and early refeeding are still the most important approaches in the control of rotavirus diarrhea in infants and children (3). Several vaccines are currently being used against rotavirus infection; although challenges to vaccination still remains to be resolved (13, 14). Adjuvant therapy has been examined for oral rehydration solution (ORS) with probiotics since 1998 (1, 15).

Recently, probiotic therapy has been investigated in several studies in which the therapeutic effect on rotavirus-associated diarrhea in children was distinguished (16-18), so they have been included in the recent guidelines for the management of acute diarrhea in children of the European Society for Pediatric Infectious Diseases (ESPID) (19-22). Probiotics are defined as live microorganisms which when administered in adequate numbers confer a health benefit on the host (23-26). A previous study concluded that pooled estimates found that probiotics offer a safe and effective method to prevent and treat acute pediatric diarrhea (27). The mechanisms responsible for the beneficial role of probiotics, are studies that have documented direct antimicrobial effects, improve mucosal barrier function, and immunomodulating activities due to the effects of probiotics on both innate and adaptive immunity (28, 29). *Lactobacillus*, b*ifidobacterium* and s*accharomyces* are the most commonly used probiotic strains in the treatment of diarrhea, but other microorganisms, including e*nterococcus*, s*treptococcus*, *Escherichia coli* species have also been used (21, 30).

After oral administration, probiotic bacteria remain transiently in the human intestine. The efficiency of probiotic, bacteria in the treatment of infectious diarrhea in adults and infants was shown in several studies (31-33). In some studies, the efficiency of probiotics in reducing the course of acute diarrhea in young children was attributed to the consumption of fermented milk (24, 34-36). In some research studies, lactobacillus GG was effective in the treatment of rotavirus diarrhea (26, 31, 35, 37-40). Whereas, lactobacillus acidophilus and bifidobacteria did not manage rotavirus diarrhea in some studies (1). Probiotic therapies with different strains of bacteria indicated some beneficial effects, although some studies did not show any significant effects (20). In this regard, the aim of this study was to review systematically the current knowledge on the effect of probiotic bacteria on duration of acute rotavirus diarrhea in children compared with control.

Methods

The papers in PubMed, Cochrane Controlled Trial Register (CCTR) and Ovid (Wolters Kluwer Health) which were published between 1980 to June 15, 2013 were searched. Furthermore, the references of other clinical trial and review articles have been searched. The search terms included “probiotic”, “treatment”, “rotavirus” and “diarrhea”. A total number of 1244 articles were generated through the aforementioned search. 203 articles were selected after the first screening of title and abstract. The graphical demonstration of the process of opting eligible trails is presented in figure1.

Randomized controlled trials (RTCs) that administer probiotics for treatment of rotavirus diarrhea in infants and children were included in this review. The intervention group was subjected to receive probiotic strains and dosage in any conditions. Placebo or any similar vehicle without probiotic was used in the controlled trials. Moreover, abstract studies and non-randomized controlled trial (non-RCT) articles as well as studies published in languages other than English were excluded from the review. In addition, the present review did not deal with the studies carried out through methodology of prevention or incidence of rotavirus diarrhea, non-rotavirus diarrhea, and antibiotic-associated diarrhea, animal model studies. Consequently, 14 articles were selected regarding these exclusion criteria.

For their reviews, the outcomes were abstracted data from each study using outcomes that included duration of diarrhea. The length of time diarrhea lasts often depends on what caused it. We surveyed the duration agent in these trials, since the results of frequency are insufficient.

The full articles extracted from the selected studies including the inclusion criteria were reviewed by two persons (M.S.R) and (E.A), and the reviewers assessed the data extraction independently and entered the data into a computer program. All studies were examined according to the list: author, year of publication, study design, age of patients, type of intervention (strain, dose, duration and vehicle), control group, concomitant treatment, diarrhea duration and the outcomes described above them that showed in tables 1.

To measure the duration of diarrhea, each study was analyzed separately. Trials were divided into three main subdivisions. Measurements of diarrhea duration were converted to days, maintaining the number of significant digits in the original units of time. We could not calculate frequency, since the frequency symptom was not reported in major trials. We calculated an absolute difference between probiotics and control groups for each of the outcomes in each study. In the meta-analysis, outcomes across the included studies were examined for evidence of publication bias using funnel plots.

Table1. Initial features of trials

Study	Location	Age range (Months)	Probiotic treatment				Control group	Concomitant treatment	Diarrhea duration
			Strain	Dose (CFU)	Duration(day)	Vehicle			
Abbaskhaniyan et al. 2012 [1]	Iran	6-72	L. acidophilus &Bifidobacteria	10^7	3 times per day	yogurt	Placebo (non-probiotic yogurt)	ORS	< 3 d
Dutta et al. 2011 [20]	India	6-24	Lactobacillus Sporogenes (Bacillus coagulans)	6×10^7	Twice a day for 5 days	Tablet dispersed in water	Placebo	ORT	< 3 d
Dalgic et al. 2011 [3]	Turkey	1-28	Saccharomyces boulardii	250 mg	Once a day for 5 days.		Oral and / or parenteral solutions.	ORS	< 96 h
Grandy et al. 2010 [9]	Bolivia	1-23	Group A. Saccharomyces boulardii, Group B. A compound Containing L. acidophilus & L. rhamnosus& B. longum& S. boulardii		Twice a day for 5 days	Dissolved in water	Placebo	ORT	
Ritchie et al. 2010 [46]	Australian	4-24	Lactobacillus casei strain GG	5×10^9	3 times for 3 days	Capsule contained 5 ml of sterile Nacl 0.9 %	Placebo	ORS or intravenous solution with Ringer's lactate	< 7 days
Narayanappa D, 2008 [47]	India	3-36	Probiotic (Bifilac)	1 sachet	3 times for 14 days	Sachets	placebo	Standard therapy (ORS)	≤ 3 d
Szymanski et al. 2006 [48]	Poland	2 – 72 (Rotavirus infection : 45%)	Lactobacillus rhamnosus GG	1.2×10^{10}	Twice daily for 5 days	Freezed dried	Placebo		1 - 5 d
Sarker et al. 2005 [49]	Bangladesh	4-24	L. paracasei	5×10^{10}	Twice daily for 5 days	ORS	Placebo (Whey-protein / skim-milk powder blend)	ORS	< 48 h
Rosenfeldt et al. 2002 [50]	Denmark	6-36	L. rhamnosus 19070-2 &L.reuteri DSM 12246	4×10^{10}	Twice daily for 5 days	Consisted of lyophilized	Placebo		≤ 7 d
Guandalini et al. 2000 [51]		1-36	Lactobacillus GG	At least 1010 CFU/250ml		ORS	ORS + Placebo	ORS	
Simakachorn et al. 2000 [52]	Thailand	3-24	*L. acidophilus* LB	5×10^9	Twice daily for 5 days	Sachet	Placebo	ORT for the first 4 hours. Second, undiluted formula or breast milk fed with ORS.	< 5 days
Shornikova et al. 1997 [53]	Russia	1-36	LGG	5×10^9	Twice daily for 5 days	Bag of dried power in 5 ml of water & mixed with ORS or another drink or food	Placebo (the cellulose powder)	ORT	< 5 days
Shornikova et al. 1997 [44]		6-36	*L. reuteri*	Small dosage (10^7CFU) Large dosage (10^{10}CFU)	Once a day up to 5 days		Placebo		
Kaila et al. 1992 [39]	Finland	7-37	*L. casei* strain GG	$10^{10\text{-}11}$	125 gr twice daily	Fermented milk product	Placebo (fermented-then-pasteurized yogurt, with $<10^3$cfu lactic acid bacteria)	ORT twice	<7days

[a] CFU, colony-forming units

A priori Subgroup analysis was planned to distinguish the modification of reductions in diarrhea by LGG type in LGG probiotics group and non-LGG probiotics groups. The Stata 9 software (Stata Corp, College Station, Tex) was used for statistical analysis to perform the meta-analysis of the RCTs with random effect. Continuous outcomes (duration of diarrhea) are presented as standardized mean difference (SMD) between the probiotic treatment and controls with 95% confidence intervals. Heterogeniuity of data was tested by I^2 index and sources of heterogeneity were identified through accomplishing subgroup analysis.

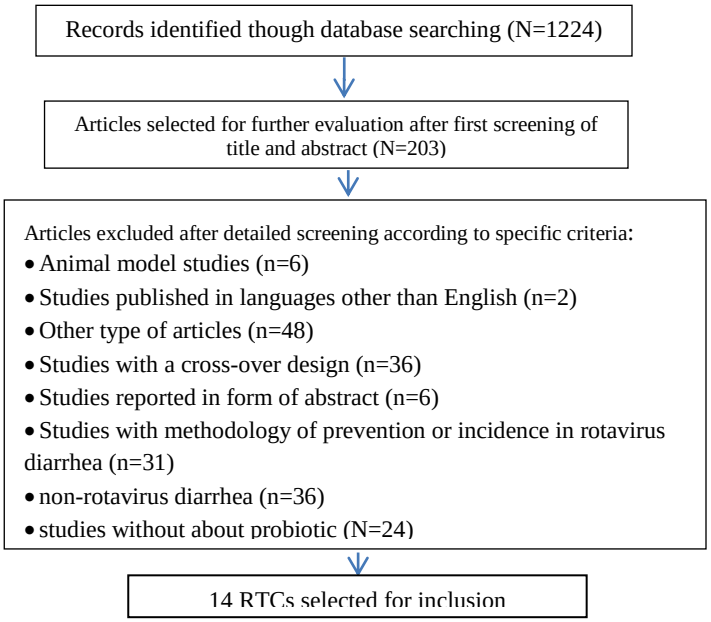

Figure 1. Flow design of the identification eligibility trial for inclusion

Results

The literature review resulted to 1224 documents, of which 14 were assessed for eligibility and were included in the meta-analysis. Finally, a total of 1149 patients were included in these studies. We categorized these trials as kind of probiotics to three subgroup analysis, l*actobacillus rhamnosus* GG and non-LGG, and all trials were categorized as the other group (n=14). Major strain of probiotic used was *L. rhamnosus* GG. The age range of patients were 1-72 months. In the major trials, they administered the probiotics available either as capsules, tablets, powders, or granules. In two trials they used them by premixing with a selection of food vehicle such as fermented milk or yogurt.

The pooled estimate of efficacy of probiotics in the prevention of disease yielded in all studies a mean difference of 0.41 (95% CI -0.56 to –0.25; p<0.001) and a heterogeneity (I2) of 39.9% (figure 2). The pooled estimate of efficacy of LGG probiotics and others had significant reduction in duration of diarrhea and non-LGG probiotics show low I2 score (figures 3 and 4). Among trials with the data on the effects of LGG, two results had positive point estimates and six results attained statistical significance with an overall reduction of 0.47 (95% CI -0.80 to -0.14; P=0.020) and a heterogeneity (I2) of 57.8%. The funnel plot for publication bias had an asymmetrical distribution (figure 5). Among trials, administering probiotics available as capsules, tablets, granules and powders with a selection of food vehicle had no significant difference in the protective point estimates. And the protective effect by mode of delivery was not influenced by the patient's age.

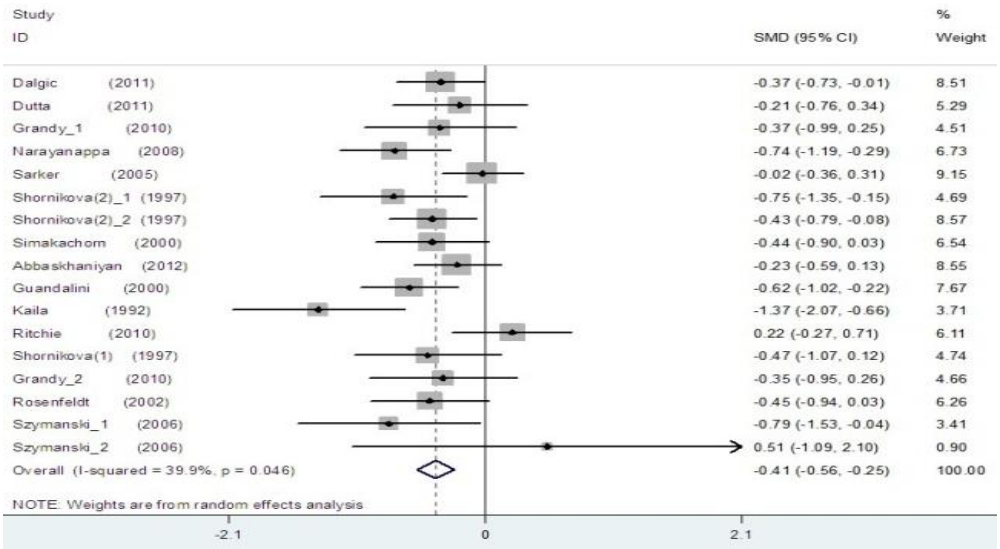

Figure 2. The effect size for the overall effects of probiotics in the duration of diarrhea

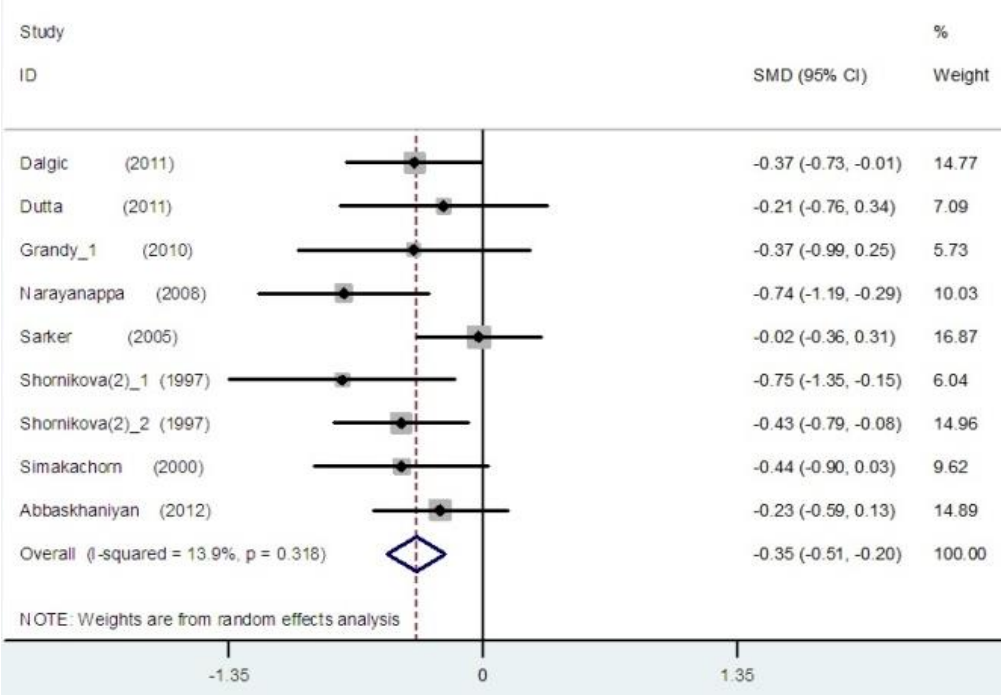

Figure 3. The effect size for effects of non-LGG probiotics in the duration of diarrhea

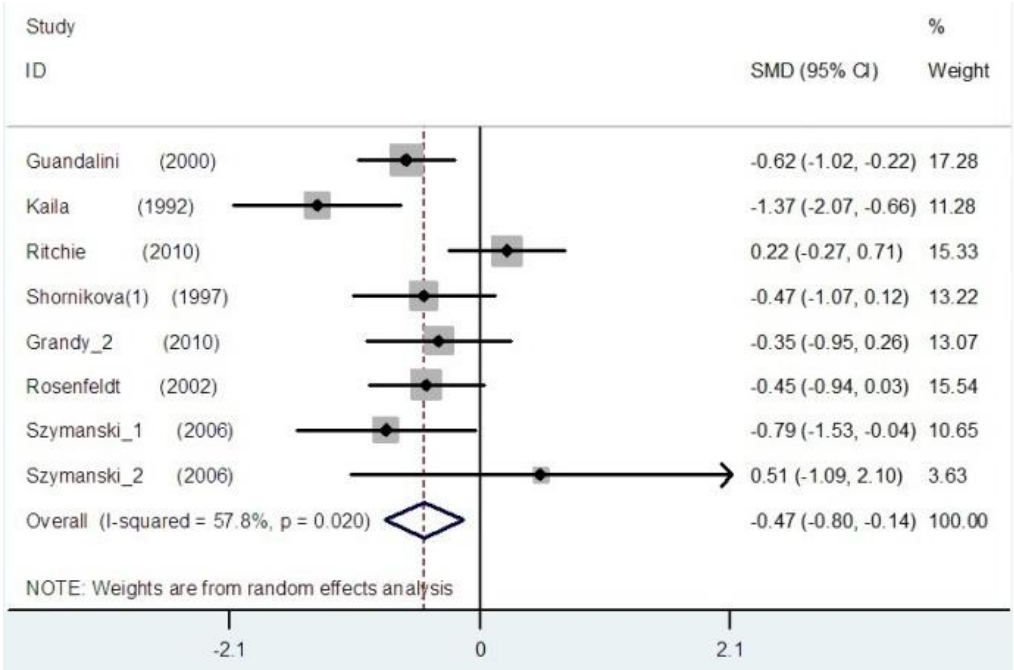

Figure 4. The effect size for effects of non-LGG probiotics in the duration of diarrhea

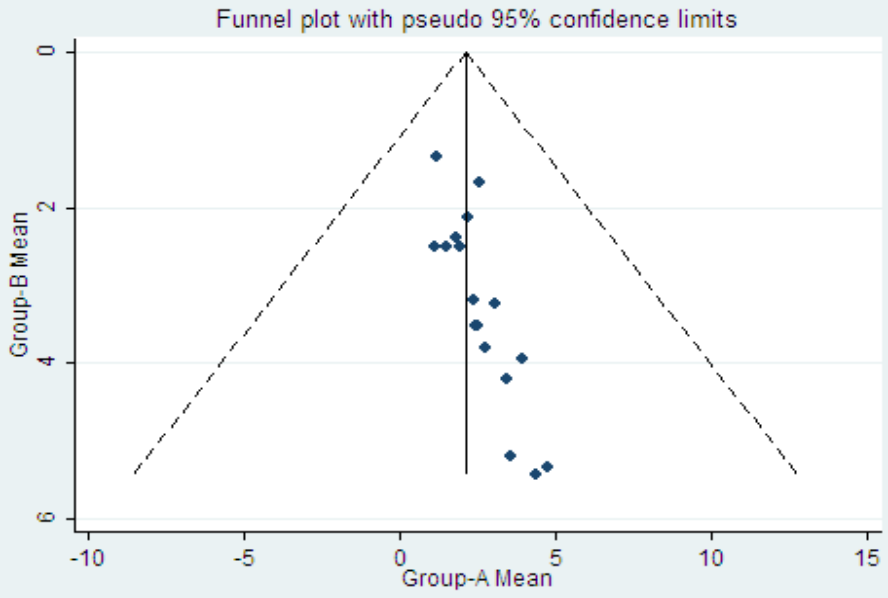

Figure 5. Funnel plot for enrolled studies

Discussion

In this meta-analysis, the efficacy of probiotics in the treatment of acute rotavirus diarrhea in children was investigated by reviewing several studies, which yielded contradictory results. The results of the present study showed that probiotics had a positive effect in reducing the duration of acute rotavirus diarrhea in children in comparison with control. Previously published meta-analyses used from studies that focused on researches related to high-income countries in the hospital, were restricted to infants and children (26, 41). The results of one-meta-analysis which compared lactobacillus rhamnosus 66 with placebo, demonstrated reduction of healthcare-associated diarrhea (42). We selected 14 trials according to inclusion criteria and surveyed the duration agent in these trials. The major trials had protective point estimates; most of them attained statistical significance. Three trials had statistically non-significance and non-protective point estimates. Significant differences in effectiveness have been observed in different species. This can be seen in several illustrations of these RCTs that Rosenfeldt et al. showed that *lactobacillus rhamnosus* and *lactobacillus reuteri* improved acute diarrhea in hospitalized children and reduced the duration of rotavirus expulsion (42). In line with the recent finding, Szajewska et al. noted that the use of probiotics can reduce the period of diarrhea, especially rotavirus diarrhea between 20 to 24 hours (25). In one such study reported that the b*ifidobacterium lactis* had a complementary role in the treatment of rotavirus gastroenteritis and other probiotics may also have a positive effect in rotavirus diarrhea compared with placebo (43). Moreover, the efficacy of *lactobacillus reuteri* in hospitalized children with rotavirus diarrhea was demonstrated in one study. These bacteria shortened the duration of diarrhea with a dose-dependent effect (44). Lactobacillus GG (3×10^9 cfu/g twice daily for a maximum of 6 d) reduced the first half period of diarrhea in outpatient children and significantly reduced rotavirus shedding (45). Another study indicated that there is a dose-response relevance involved. Although these differences were statistically significant, but further studies are still recommended.

In conclusion, the value of meta-analysis is that it provides an instrument to incorporate trials with the above differences and reach to a pooled estimate of the efficacy of different probiotics. The extracted data from the RCTs demonstrated adequate evidence for the positive significant effect of probiotics in the reduction of duration of acute rotavirus diarrhea. To prove this evidence requires such research with identical dosage and methodology to be performed before further conclusions can be drawn.

Conflict of interest: Author no conflict of interest.

References

1. Abbaskhanian A, Rezai MS, Karami H, Hasanpour A. The effect of fermented yogurt on rotavirus diarrhea in children. Health Med 2012; 6: 1600-4.
2. Bern C, Martines J, De Zoysa I, Glass RI. The magnitude of the global problem of diarrhoeal disease: a ten-year update. B World Health Organ 1992; 70: 705-14.
3. Dalgic N, Sancar M, Bayraktar B, Pullu M, Hasim O. Probiotic, zinc and lactose free formula in children with rotavirus diarrhea: Are they effective? Pediatr Int 2011; 53: 677-82.
4. Teran CG, Teran-Escalera CN, Villarroel P. Nitazoxanide vs. probiotics for the treatment of acute rotavirus diarrhea in children: a randomized, single-blind, controlled trial in Bolivian children. Int J Infect Dis 2009; 13: 518-523.
5. Parashar UD, Gibson CJ, Bresee JS, Glass RI. Rotavirus and severe childhood diarrhea. Emerg Infect Dis 2006; 12: 304-6.
6. Mackintosh KA, Knowles ZR, Ridgers ND, et al. Using formative research to develop change: a curriculum-based physical activity promoting intervention. BMC Public Health 2007; 11: 831.
7. Dubey AP, Rajeshwari K, Chakravarty A, Famularo G. Use of VSL [sharp] 3 in the treatment of rotavirus diarrhea in children: preliminary results. J Clin Gastroenterol 2008; 42: S126-9.
8. Fischer TK, Viboud C, Parashar U, et al. Hospitalizations and deaths from diarrhea and rotavirus among children <5 years of age in the United States, 1993-2003. J Infect Dis 2007; 195: 1117-25.
9. Grandy G, Medina M, Soria R, Teran CG, Araya M. Probiotics in the treatment of acute rotavirus diarrhoea. A randomized, double-blind, controlled trial using two different probiotic preparations in Bolivian children. BMC Infect Dis 2010; 10: 253-9.
10. Kawai K, O'Brien MA, Goveia MG, Mast TC, El Khoury AC. Burden of rotavirus gastroenteritis and distribution of rotavirus strains in Asia: a systematic review. Vaccine 2012; 30: 1244-54.
11. Chen SC, Tan LB, Huang LM, et al. Rotavirus infection and the current status of rotavirus vaccines. J Formos Med Assoc 2012; 111: 183-93.
12. Tate JE, Burton AH, Boschi-Pinto C, et al. 2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis. Lancet Infect Dis 2011; 12: 136-41.
13. Colbere-Garapin F, Martin-Latil S, Blondel B, et al. Prevention and treatment of enteric viral infections: possible benefits of probiotic bacteria. Microbes Infect 2007; 9: 1623-31.
14. Lopez S, Arias CF. Multistep entry of rotavirus into cells: a Versaillesque dance. Trends Microbiol 2004; 12: 271-8.
15. Costa-Ribeiro H, Ribeiro TCM, Mattos AP, et al. Limitations of probiotic therapy in acute, severe dehydrating diarrhea. J Pediatr Gastr Nutr 2003; 36: 112-15.
16. Sullivan A, Nord CE. The place of probiotics in human intestinal infections. Int J Antimicrob Agents 2002; 20: 313-9.
17. Van Niel CW, Feudtner C, Garrison MM, Christakis DA. Lactobacillus therapy for acute infectious diarrhea in children: a meta-analysis. Pediatrics 2002; 109: 678-84.
18. Guarino A, Canani RB, Spagnuolo MI, Albano F, Di Benedetto L. Oral bacterial therapy reduces the duration of symptoms and of viral excretion in children with mild diarrhea. J Pediatr Gastr Nutr 1997; 25: 516-9.
19. Passariello A, Terrin G, Cecere G, et al. Randomised clinical trial: efficacy of a new synbiotic formulation containing Lactobacillus paracasei B21060 plus arabinogalactan and xilooligosaccharides in children with acute diarrhoea. Aliment Pharm Therap 2012; 35: 782-8.
20. Dutta P, Mitra U, Dutta S, et al. Randomized controlled clinical trial of Lactobacillus sporogenes (Bacillus coagulans), used as probiotic in clinical practice, on acute watery diarrhoea in children. Trop Med Int Health 2011; 16: 555-61.
21. Isolauri E. Probiotics for infectious diarrhoea. Gut 2003; 52: 436-37.
22. Fuller R. Probiotics in man and animals. J Appl Bacteriol 1989; 66: 365-78.
23. Ahmadi E, Mortazaviyan AM, Fazeli MR, Ezzatpanah H, Mohammadi R. The effects of inoculant variables on the physicochemical and organoleptic properties of Doogh. Int J Dairy Technol 2012; 65: 274-81.
24. Kopp-Hoolihan L. Prophylactic and therapeutic uses of probiotics: a review. J Am Diet Assoc 2001; 101: 229-38; quiz 239-41.
25. Szajewska H, Mrukowicz JZ. Probiotics in the treatment and prevention of acute infectious diarrhea in infants and children: a systematic review of published randomized,

double-blind, placebo-controlled trials. J Pediatr Gastr Nutr 2001; 33: S17-25.

26. McFarland LV. Meta-analysis of probiotics for the prevention of antibiotic associated diarrhea and the treatment of Clostridium difficile disease. Am J Gastroenterol 2006; 101: 812-22.
27. Hojsak I, Abdovic S, Szajewska H, et al. Lactobacillus GG in the prevention of nosocomial gastrointestinal and respiratory tract infections. Pediatrics 2010; 125: e1171-7.
28. Hojsak I, Snovak N, Abdovic S, et al. Lactobacillus GG in the prevention of gastrointestinal and respiratory tract infections in children who attend day care centers: a randomized, double-blind, placebo-controlled trial. Clin Nutr 2010; 29: 312-16.
29. Yan F, Polk DB. Probiotics as functional food in the treatment of diarrhea. Curr Opin Clin Nutr 2006; 9: 717-21.
30. Szajewska H, Kotowska M, Mrukowicz JZ, Armańska M, Mikołajczyk W. Efficacy of Lactobacillus GG in prevention of nosocomial diarrhea in infants. J Pediatr 2001; 138: 361-5.
31. Pereg D, Kimhi O, Tirosh A, et al. The effect of fermented yogurt on the prevention of diarrhea in a healthy adult population. Am J Infect control 2005; 33: 122-5.
32. Salvatore S, Hauser B, Devreker T, et al. Probiotics and zinc in acute infectious gastroenteritis in children: are they effective? Nutrition 2007; 23: 498-506.
33. Guerin-Danan C, Meslin JC, Chambard A, et al. Food supplementation with milk fermented by Lactobacillus casei DN-114 001 protects suckling rats from rotavirus-associated diarrhea. J Nutr 2001; 131: 111-7.
34. Isolauri E, Juntunen M, Rautanen T, Sillanaukee P, Koivula T. A human Lactobacillus strain (Lactobacillus casei sp strain GG) promotes recovery from acute diarrhea in children. Pediatrics 1991; 88: 90-7.
35. Salminen S, Ouwehand AC, Isolauri E. Clinical Applications of Probiotic Bacteria. Int Dairy J 1998; 8: 563-72.
36. Fuller R, Gibson GR. Probiotics and prebiotics: microflora management for improved gut health. Clin Microbiol Infec 1998; 4: 477-80.
37. Canani RB, Cirillo P, Terrin G, et al. Probiotics for treatment of acute diarrhoea in children: randomised clinical trial of five different preparations. BMJ 2007; 335: 340.
38. Raza S, Graham S, Allen S, et al. Lactobacillus GG promotes recovery from acute nonbloody diarrhea in Pakistan. Pediatr Infect Dis J 1995; 14: 107-11.
39. Kaila M, Isolauri E, Saxelin M, Arvilommi H, Vesikari T. Viable versus inactivated lactobacillus strain GG in acute rotavirus diarrhoea. Arch Dis Child 1995; 72:51–53.
40. Szajewska H, Mrukowicz JZ. Use of probiotics in children with acute diarrhea. Pediatric Drugs 2005; 7: 111-22.
41. Szajewska H, Wanke M, Patro B. Meta-analysis: the effects of Lactobacillus rhamnosus GG supplementation for the prevention of healthcare associated diarrhoea in children. Aliment Pharm Ther 2011; 34: 1079-87.
42. Rosenfeldt V, Benfeldt E, Nielsen SD, et al. Effect of probiotic Lactobacillus strains in children with atopic dermatitis. J Allergy Clin Immunol 2003; 111: 389-95.
43. Erdogan O, Tanyeri B, Torun E, et al. The comparition of the efficacy of two different probiotics in rotavirus gastroenteritis in children. J Trop Med 2012; 2012: 787240.
44. Shornikova AV, Casas IA, Mykkanen H, et al. Bacteriotherapy with Lactobacillus reuteri in rotavirus gastroenteritis. Pediatr Infect Dis J 1997; 16: 1103-7.
45. Guarino A, Canani RB, Spagnuolo MI, et al. Oral bacterial therapy reduces the duration of symptoms and of viral excretion in children with mild diarrhea. J Pediatr Gastr Nutr 1997; 25: 516-19.
46. Ritchie BK, Brewster DR, Tran CD, et al. Efficacy of Lactobacillus GG in aboriginal children with acute diarrhoeal disease: a randomised clinical trial. J Pediatr Gastroenterol Nutr 2010; 50: 619-24.
47. Narayanappa D. Randomized double blinded controlled trial to evaluate the efficacy and safety of Bifilac in patients with acute viral diarrhea. Indian J Pediatr 2008; 75: 709-13.
48. Szymanski H, Pejcz J, Jawien M, et al. Treatment of acute infectious diarrhoea in infants and children with a mixture of three Lactobacillus rhamnosus strains–a randomized, double blind, placebo controlled trial. Aliment Pharm Therap 2006; 23: 247-53.
49. Sarker SA, Sultana S, Fuchs GJ, et al. Lactobacillus paracasei strain ST11 has no effect on rotavirus but

ameliorates the outcome of nonrotavirus diarrhea in children from Bangladesh. Pediatrics 2005; 116: e221-8.

50. Rosenfeldt V, Michaelsen KF, Jakobsen M, et al. Effect of probiotic Lactobacillus strains on acute diarrhea in a cohort of nonhospitalized children attending day-care centers. Ped Infect Dis J 2002; 21: 417-9.
51. Guandalini S, Pensabene L, Zikri MA, et al. Lactobacillus GG administered in oral rehydration solution to children with acute diarrhea: a multicenter European trial. J Pediatr Gastroenterol Nutr 2000; 30: 54-60.
52. Simakachorn N, Pichaipat V, Rithipornpaisarn P, et al. Clinical evaluation of the addition of lyophilized, heat-killed Lactobacillus acidophilus LB to oral rehydration therapy in the treatment of acute diarrhea in children. J Pediatr Gastroenterol Nutr 2000; 30: 68-72.
53. Shornikova AV, Isolauri E, Burkanova L, Lukovnikova S, Vesikari T. A trial in the Karelian Republic of oral rehydration and Lactobacillus GG for treatment of acute diarrhoea. Acta Paediatr 1997; 86: 460-5.