J Pediatr Rev. 2014;2(2):12-20

JPR

Journal of Pediatrics Review

Mazandaran University of Medical Sciences

The prophylactic effect of Lactobacillus rhamnosus GG on incidence of acute rotavirus diarrhea in children: a systematic review; randomized double-blind placebo-controlled trials

Elaheh Ahmadi[1]

Mohammad Sadegh Rezai[1*]

[1]Antimicrobial Resistant Nosocomial Infection Research Center, Mazandaran University of Medical Science, Sari, Iran

ARTICLE INFO

Article type:
Review Article

Article history:
Received: 24 Jun 2014
Revised: 20 Jul 2014
Accepted: 3 Aug 2014

Keywords:
Lactobacillus rhamnosus GG, Prevention, Rotavirus, Diarrhea

http://jpr.mazums.ac.ir

ABSTRACT

Rotavirus is one of the most common etiologic agent of severe acute diarrhea in infants and children which results in high mortality and morbidity globally. Prophylactic strategies are required to prevent acute rotavirus diarrhea. Recently, the beneficial effect of probiotic therapy in control of rotavirus diarrhea was noted in many investigations. This systematic review investigated the prophylactic effect of Lactobacillus rhamnosus GG on the incidence of acute rotavirus diarrhea in infants and children.

Databases including PubMed, Cochrane Controlled Trial Register (CCTR), Google Scholar, Science direct and Ovid (Wolters Kluwer health) were searched for articles and reviews from 1980–2013. Reviewers selected randomized clinical trials that met the study inclusion criteria. The outcome measures included incidence of rotavirus diarrhea, duration of diarrhea, and hospital stay.

The search results included three trials with 1043 eligible patients. The results indicated that the use of Lactobacillus rhamnosus GG compared with placebo significantly affected the incidence of rotavirus diarrhea without influencing the duration of hospital stay.

Some studies signified the role of Lactobacillus rhamnosus GG in preventing acute rotavirus diarrhea; however we did not find sufficient trials with certain method to evaluate this influence.

Introduction

Rotavirus infection is one of the most common etiologic agents associated with severe diarrhea in infants less than 5 years globally.[1-4] Every year, there are 114 million episodes of gastroenteritis, 24 million outpatient visits, and 2.4 million

***Corresponding Author:** Mohammad Sadegh Rezai MD, Associate professor of pediatric infectious diseases*
Mailing Address: Department of Pediatric Infectious Disease, Antimicrobial Resistant Nosocomial Infection Research Centre, Bou Ali Sina Hospital, Pasdaran Boulevard, Sari, Iran.
Tel:+981133342331
Fax:+981133342331
Email: drmsrezaeii@yahoo.com

hospitalizations worldwide.[5] Rotavirus causes 600,000 deaths each year and is responsible for 5% of all deaths in children under 5 years of age.[5-9] Although the rate of rotavirus illnesses is similar in both developed and developing countries, almost all mortality occur in developing countries.[5,10] Approximately 85% of rotavirus-associated deaths were observed in underprivileged regions of Africa and Asia.[11-16]

Prevention of acute rotavirus diarrhea is not easy but extremely essential,[17] and affordable strategies are highly beneficial in high-risk groups.[18] Hand washing is an important method in prevention since rotavirus can survive on human hands for at least four hours.[19] Therefore, personal hygiene and sanitation of food are effective ways to reduce the spread of germs, however, they are not enough to stop rotavirus infection.[20,21] Although vaccines are the most common intervention for control of rotavirus disease,[5] a cost-effective vaccine to prevent diarrhea at the population level in worldwide is not yet available.[17,22] In addition, probiotics are used for prevention and therapy of childhood diarrhea, however, there is no standard therapy for the problem.[21] The efficacy of LGG for prevention of rotavirus diarrhea is a great practical value until more cost-effective and convenient preventive methods is available.[17]

The benefits of probiotics in mild to moderate acute diarrhea in children are related to type of strain and dose of probiotics (greater for doses > 10^{10}-10^{11} colony-forming units).[23] There are lots of methods for probiotic therapy. The use of yogurt (as probiotic) in the treatment of diarrhea has been known for a long time. [1,24,25] There are conflicting data concerning the effect of all probiotics as a protective factor against rotavirus infection (probiotic as prevent and trial). Significant differences have also been noted in efficacy and mode of action of different strains.[17]

Some evidences suggested that the effect of specific probiotic strains can be statistically significant in the prevention of primary rotaviral acute watery diarrhea.[17,22] *Lactobacillus Casei* subspecies rhamnosus GG, Lactobacillus reuteri, Bifidobacterium genus and Saccharomyces boulardii seem to be capable factors for improving acute diarrhea. [10,24,26,27] Some studies found Bifidobacterium bifidum and *Streptococcus thermophilus* useful in prevention of rotavirus nosocomial diarrhea. [23,28,30] Lactobacillus Casei subspecies rhamnosus (L.GG) has been shown to reduce the duration of common viral diarrhea illness in a large multicenter study in Europe.[31] In addition, several pediatric clinical trials indicated the efficacy of L. GG in the treatment of rotavirus gastroenteritis.[17] But, the efficacy of L.GG in diarrhea prophylaxis has not been adequately addressed yet.[18] The objective of this study was to determine the efficacy of Lactobacillus casei ssp. rhamnosus (LGG) as a prophylaxis against rotavirus diarrhea in children.

Materials and Methods

Data Sources

According to our search protocol we attempted to include all recent published papers representing randomized controlled trials (RCT). The databases including PubMed, Cochrane Controlled Trial Register (CCTR), Google Scholar, Science direct and Ovid (Wolters Kluwer health) were searched from 1980-2013. Moreover, the references of other clinical trials and review articles have been considered. The search terms included “Probiotics”, “Lactobacillus” “Lactobacillus GG”, “Prevention”, “Prophylaxis”, “Incidence” “Rotavirus”, “Watery” and

Table1. Details of included studies

No	Study	Location	Sample size (treatment group; placebo group)	Age range (Months)	Probiotic treatment				Control group
					strain	Dose (CFU)	Duration (day)	Vehicle	
33	Hojsak et al, 2010	Poland	742 (376;366)	>12	L. GG	1×10^{9}	Daily	100 mL of a fermented milk product	100 mL of a fermented milk product without LGG
29	Mastretta et al, 2002	Italy	220 (114;106)	1-18	L. GG	1×10^{10}	On admission two capsules odd and one capsule for the duration of hospitalization	water	Placebo (inert oligosaccharides with indistinguishable organoleptic properties)
35	Szajewska et al, 2001	Poland	81(45;36)	1-36	L. GG	6×10^{9}	twice daily for the entire duration of their hospital stay	One sachet dissolved in water	Placebo maltodexterin

Table2. Incidence rate of nosocomial Rotavirus infections

No.	Study	Number of subjects			Incidence of Rotavirus diarrhea		Duration of diarrhea		Duration of hospital stay	
		Total	Probiotic	Control	Probiotic	Control	Probiotic	Control	Probiotic	Control
33	Hojsak et al, 2010	742	376	366	4.69	5.86	2.08	2.11	-	-
29	Mastretta et al, 2002	220	114	106	29 (25.4%) 95% CI (0.55-1.29)	32 (30.2%) 95% CI (0.55-1.29)	-	-	12 (10.5%) 95%CI (0.43-1.48)	14 (13.2%) 95%CI (0.43-1.48)
35	Szajewska et al, 2001	81	45	36	1 (2.2%) 95% CI (0.02-0.79) RR: 0.13	6 (16.7%) 95% CI (0.02-0.79) RR: 0.13	6.3±1.3	6.5±2.6	-	-

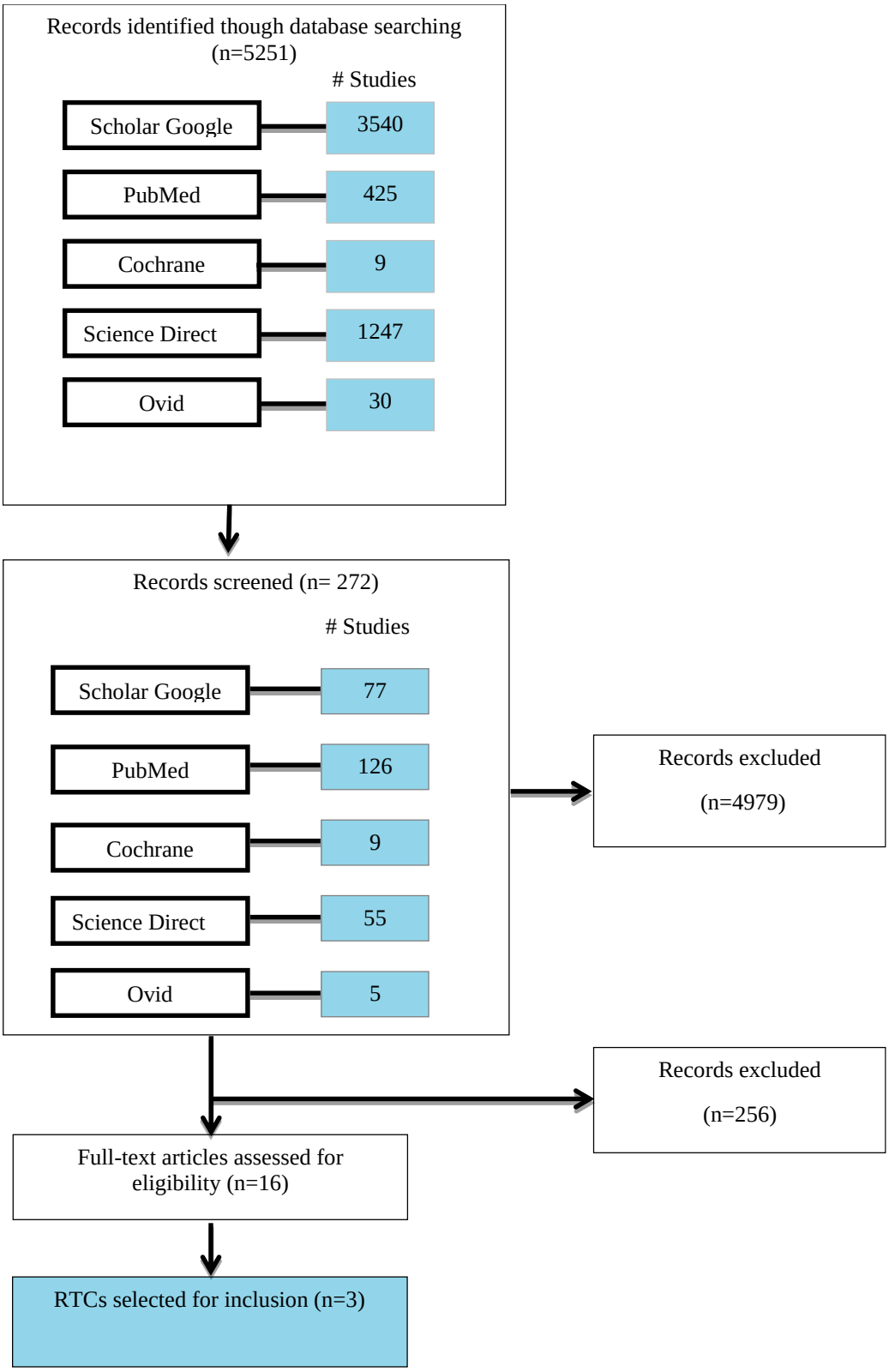

Figure1. Identification process for eligible trials

"Diarrhea". The search resulted in finding 5251 articles among which 272 were selected after first screening of titles and abstracts. The search strategy and the selected articles are detailed in Figure 1.

Study Selection criteria

Randomized controlled trials (RTCs) in which the *Lactobacillus Casei* ssp *rhamnosus* (L.GG) were administered for incidence of rotavirus diarrhea in infants and children were included in this review. In these RCTs, the dosages of Lactobacillus GG were more than 10^9 log cfu.mL^{-1} and the method of interventions were different. Placebo or any similar agent without probiotic was used in the controlled trials. Abstracts and non RCT articles as well as studies published in languages other than English were excluded from the review. Furthermore, the present review did not include studies carried out through methodology of treatment of rotavirus diarrhea, non-rotavirus diarrhea, antibiotic-associated diarrhea, and animal model studies. Reviewing the titles and/ or abstracts identified seven potentially relevant studies for full-text review. One RCT by Chouraqui et al. studied the efficacy of several probiotics as well as *Lactobacillus rhamnosus, Bifidobacterium longum*, and *Lactobacillus paracasei* with some prebiotics for prevention of diarrhea in several methods. Since the methodology of this article did not merely include the effect of LGG it was excluded from this review.[32] Also, we could not find the full text of two articles. The characteristics of four articles are illustrated in Table 1.

Data Extraction and Outcome Measures

The full text articles extracted from the selected studies that met the inclusion criteria were reviewed by the two authors. The reviewers evaluated the data extraction, independently, and entered the data into a computer program. All studies were examined according to the following list: author, year of publication, location, sample size, age range, type of probiotic therapy (strain, dose, duration and vehicle), and control group indicated in table 1. The outcome measures extracted from each study included 4 components (incidence of rotavirus diarrhea, duration of diarrhea, and hospital stay). The details are shown in Table 2. The duration of diarrhea and length of hospital stay.

Results

Search results

The flow of studies through the selection process is demonstrated in Figure 1. Authors assessed these studies independently and finally identified three RCTs that met the inclusion criteria. The RCTs included a total of 1043 patients. All of the trials were double blind, randomized placebo-controlled and were published in English. In two studies, the most common reason for hospitalization was a respiratory tract infection. Two RCTs only included infants and young children (age below 18, and 36 months); and one RCT included young infants older than the age of 12 months. Doses used in the therapeutic trials were also diverse. The dosages of LGG used in three studies were from 1×10^9 CFU [33] to 6×10^9 CFU twice daily [23] to 1×10^{10} CFU[29]. The LGG administrated with fermented milk or in capsules or sachets form. In all studies, the probiotic therapy group was compared with a placebo control group. RCTs outcome measured the incidence and spread rate of rotavirus diarrhea including primary outcome and duration of diarrhea and duration of hospital stay.

Over effect of intervention

Incidence and Prevalence of Rotavirus Diarrhea

In two RCTs, the results indicated that use of LGG significantly influenced the incidence of rotavirus diarrhea yielding contradictory results. According to Szajewska, use of LGG as compared with placebo was associated with significant reduced risk of rotavirus gastroenteritis 1(2.2%) in LGG group vs. 6 (16.7%) in control group (RR: 0.13; 95% CI: 0.02-0.79); however, the prevalence of rotavirus infection in the trial was similar in LGG and placebo group; 9(20%) in LGG group against 10 (27.8%) in placebo group. (RR: 0.72; 95% CI (0.33-1.56).[34] By the same token, in a study by Hojsak, the LGG group compared with the placebo group had a reduced risk of episodes of diarrhea that was 7 (1.9) in LGG group vs. 28 (7.7) in placebo group (RR 0.24, 95% CI: 0.10-0.50).[33] In contrast, Mastretta at al. showed that the incidence of nosocomial rotavirus infection was 27.7%. (95% CI 21.8-33.6) (61of 220 patients) and the incidence of nosocomial symptomatic rotavirus infection was 16.8% (37of 220 patients) (95% CI 11.9-21.7) but the difference was not significant (p=0.098). [29]

Duration of Rotavirus Diarrhea

The effects of LGG on duration of rotavirus diarrhea were evaluated in two trials. One RCT represented the positive effect of these bacteria in decreasing the duration of Rotavirus diarrhea. There was a reduced duration of gastrointestinal infection that lasted >2 days, 19 (5.1%) in LGG group against 45 (12.3%) in placebo group (RR 0.40, 95% CI: 0.25 -0.70)[33]. Dissimilarly, Szajewska reported that there was no difference in the duration of diarrhea between the LGG group and the placebo group (6.3±1.3 days vs. 6.5±2.6 days).[35]

Duration of Hospital Stay

None of these investigations showed significant differences between the LGG groups and the placebo groups in length of hospital stay. In the Hojsak et al. studies, the median duration of hospital intervention was 5 (3-7) in LGG group vs. 4 (4-6) in placebo group which was not significantly different.[33] Similar to recent findings, Mastretta studied the effect of L. rhamnosus GG between 26 patients which were divided in two groups (12 patients in treatment group and 14 in placebo group) and they found no reduction in length of hospitalization in treatment group compared to placebo group.[29]

Discussion

In this article, we reviewed the efficacy and outcomes of *L. casei* ssp *rhamnosus* GG in prevention of rotavirus diarrhea in pediatric patients. We were not able to accomplish a meta-analysis regarding the effect of L. GG on the incidence, duration of rotavirus diarrhea and hospitalization of the patients This was due to lack of RCTs with certain method of intervention against prevention of rotavirus diarrhea. In two studies, prophylactic administration of *Lactobacillus* GG reduced the risk of rotavirus diarrhea particularly in infants and a protective effect was mainly observed in Lactobacillus group.[29,33,34] In one RCT,*L. casei* GG was not found efficient (25% versus 30% of placebo) in protecting against rotavirus diarrhea.[29] In two trials, the effect of lactobacillus therapy on duration of diarrhea was investigated[33,34] and duration of hospital stay was also mentioned in one.[29] However, none demonstrated the positive effect of *Lactobacillus rhamnosus* GG on duration of hospital stay. Contradictory results from these trials may be caused by differences in intervention and study populations. Several trials with different methodologies were

excluded according to our protocol.[21] For example, in one RCT, a combination of L.GG with specific bovine colostrum-derived immunoglobulins was found as an effective prophylactic measure for rotavirus diarrhea in the infant mouse model.[10] Araki et al. suggested that oral administration of *Bifidobacterium breve* YIT 4064 significantly decreased rotavirus shedding in stool samples and prevented rotavirus infection.[36,37] In addition, although *Bifidobacterium bifidum* and *Streptococcus thermophilus* were shown to prevent rotavirus infection in the study by saavedra et al, the prevalence of rotavirus infection in LGG and placebo-treated infants was similar in our study. Chandra et al. found that prophylactic feeding of *L. sporogenes* had a preventive effect on the incidence and duration of acute rotavirus diarrhea.[38] Similarly, preventive administration of Lactobacillus GG reduced the symptoms of diarrhea, but no obvious prevention of rotaviral infection was noted in other studies.[2,34] Another source of heterogeneity for probiotic trials is the dose of probiotics itself. Doses used in the therapeutic trials were also diverse.[29,39,40] Thus, comparative studies are needed to determine the efficacy of various dosage regimens. The optimal schedule (high dose once daily vs lower doses more frequently) and the duration of treatment with LGG required achieving the preventive effective dose. It has been speculated that a beneficial prophylactic effect can only be expected in regular consumption of the probiotic agent. Accordingly, several mechanisms have been proposed to explain the efficacy of probiotics in prevention of diarrhea disease. The possible mechanisms include the synthesis of antimicrobial substances, competition for nutrients required for growth of pathogens, competitive inhibition of pathogens, modification of toxins or toxin receptors, and stimulation of immune response to pathogens.

Conclusion

Review of medical literatures showed the efficacy of prophylactic administration of LGG in prevention of rotavirus diarrhea in infants. The results showed that *Lactobacillus* therapy has no effect on hospital stay. According to this review, due to the heterogeneity in the results of various studies on the preventive effect of *Lactobacillus* GG in acute rotavirus diarrhea, further trials in this field seems necessary.

Conflict of Interest

None declared.

Funding/Support

None declared.

References

1. Abbaskhanian A, Rezai MS, Karami H, Hasnpour A. The effect of fermented yogurt on rotavirus diarrhea in children. Health Med 2012; 6(5): 1600-1604.
2. Nomoto K. Prevention of infections by probiotics. J Biosci Bioeng 2005; 100(6): 583-592.
3. Van Niel CW, Feudtner C, Garrison MM, Christakis DA. Lactobacillus therapy for acute infectious diarrhea in children: a meta-analysis. Pediatrics 2002; 109(4): 678-684.
4. Claeson M, Merson MH. Global progress in the control of diarrheal diseases. Pediatr Infect Dis J 1990; 9(5): 345-355.
5. Chandran A, Fitzwater S, Zhen A, Santosham M. Prevention of rotavirus gastroenteritis in infants and children: rotavirus vaccine safety, efficacy, and potential impact of vaccines. Biologics: targets & therapy 2010; 4: 213-229.

6. Parashar UD, Gibson CJ, Bresee JS, Glass RI. Rotavirus and severe childhood diarrhea. Emerg Infect Dis 2006; 12(12): 304-306.
7. Colbere-Garapin F, Martin-Latil S, Blondel B, Mousson L, Pelletier I, Autret A, et al. Prevention and treatment of enteric viral infections: possible benefits of probiotic bacteria. Microbes Infect 2007; 9(14-15): 1623-1631.
8. Goldin BR, Gorbach SL, Saxelin M, Barakat S, Gualtieri L, Salminen S. Survival of Lactobacillus species (strain GG) in human gastrointestinal tract. Dig Dis Sci 1992; 37(1): 121-128.
9. Mackintosh KA, Knowles ZR, Ridgers ND, Fairclough SJ. Using formative research to develop change: a curriculum-based physical activity promoting intervention. BMC Public Health 2007; 11: 831.
10. Pant N, Marcotte H, Brussow H, Svensson L, Hammarstrom L. Effective prophylaxis against rotavirus diarrhea using a combination of Lactobacillus rhamnosus GG and antibodies. BMC Microbiol 2007; 7: 86.
11. 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(Suppl 3 Pt 1): S126-129.
12. Fischer TK, Viboud C, Parashar U, Malek M, Steiner C, Glass R, 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(8): 1117-1125.
13. 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.
14. Kawai K, OBrien 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(7): 1244-1254.
15. Chen SC, Tan LB, Huang LM, Chen KT. Rotavirus infection and the current status of rotavirus vaccines. J Formos Med Assoc 2012; 111(4): 183-193.
16. Tate JE, Burton AH, Boschi-Pinto C, Steele AD, Duque J, Parashar UD, 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 2012; 12(2): 136-141.
17. Szajewska H, Kotowska M, Mrukowicz JZ, Armanska M, Mikolajczyk W. Efficacy of Lactobacillus GG in prevention of nosocomial diarrhea in infants. J Pediatr 2001; 138(3): 361-365.
18. Oberhelman RA, Gilman RH, Sheen P, Taylor DN, Black RE, Cabrera L, et al. A placebo-controlled trial of Lactobacillus GG to prevent diarrhea in undernourished Peruvian children. J Pediatr 1999; 134(1): 15-20.
19. Mrukowicz J, Szajewska H, Vesikari T. Options for the prevention of rotavirus disease other than vaccination. J Pediatr Gastr Nutr 2008; 46(Suppl 2): S32-S37.
20. Pacini DL, Brady MT, Budde CT, Connell MJ, V Hamparian V, Hughes JH. Nosocomial rotaviral diarrhea: pattern of spread on wards in a children's hospital. J Med Virol 1987; 23(4): 359-366.
21. Erdogan O, Tanyeri B, Torun E, Gonullu E, Arslan H, Erenberk U, et al. The comparition of the efficacy of two different probiotics in rotavirus gastroenteritis in children. J Trop Med 2012; 2012: 787240.
22. Sazawal S, Hiremath G, Dhingra U, Malik P, Deb S, Black RE. Efficacy of probiotics in prevention of acute diarrhoea: a meta-analysis of masked, randomised, placebo-controlled trials. Lancet Infect Dis 2006; 6: 374-382.
23. Guarino A, Albano F, Ashkenazi S, Gendrel D, Hoekstra JH, Shamir R, et al. European Society for Paediatric Gastroenterology, Hepatology, and Nutrition/European Society for Paediatric Infectious Diseases evidence-based guidelines for the management of acute

gastroenteritis in children in Europe: executive summary. J Pediatr Gastr Nutr 2008; 46(5): 619-621.

24. Billoo A, Memon M, Khaskheli S, Murtaza G, Iqbal K, Saeed Shekhani M, et al. Role of a probiotic (Saccharomyces boulardii) in management and prevention of diarrhoea. World J Gastroenterol 2006; 12(48): 4557.
25. 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(2): 274–281.
26. Allen S, Okoko B, Martinez E, Gregorio G, Dans L. Probiotics for treating infectious diarrhoea. Cochrane Database Syst Rev. 2004; (2): CD003048.
27. Vanderhoof JA, Young RJ. Current and potential uses of probiotics. Ann Allerg Asthma Im 2004; 93 (5 Suppl 3): S33-7.
28. Saavedra JM, Bauman N, Perman J, Yolken R, Oung I. Feeding of Bifidobacterium bifidum and Streptococcus thermophilus to infants in hospital for prevention of diarrhoea and shedding of rotavirus. The Lancet 1994; 344 (8929): 1046-1049.
29. Mastretta E, Longo P, Laccisaglia A, Balbo L, Russo R, Mazzaccara A, et al. Effect of Lactobacillus GG and breast-feeding in the prevention of rotavirus nosocomial infection. J Pediatr Gastr Nutr 2002; 35(4): 527-531.
30. Salminen S, Ouwehand A, Isolauri E. Clinical applications of probiotic bacteria. Int Dairy J 1998; 8(5-6): 563-572.
31. Costa-Ribeiro H, Ribeiro TCM, Mattos AP, Valois SS, Neri DA, Almeida P, et al. Limitations of probiotic therapy in acute, severe dehydrating diarrhea. J Pediatr Gastroenterol Nutr. 2003; 36(1):112-5.
32. Chouraqui JP, Grathwohl D, Labaune JM, Hascoet JM, de Montgolfier I, Leclaire M, et al. Assessment of the safety, tolerance, and protective effect against diarrhea of infant formulas containing mixtures of probiotics or probiotics and prebiotics in a randomized controlled trial. Am J Clin Nutr 2008; 87(5): 1365-1373.
33. Hojsak I, Abdovic S, Szajewska H, Milosevic M, Krznaric Z, Kolacek S. Lactobacillus GG in the prevention of nosocomial gastrointestinal and respiratory tract infections. Pediatrics 2010; 125(5): e1171-e1177.
34. Szajewska H, Kotowska M, Mrukowicz JZ, Armanska M, Mikolajczyk W. Efficacy of Lactobacillus GG in prevention of nosocomial diarrhea in infants. J Pediatr 2001; 138(3): 361-365.
35. 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(Suppl 2): S17-25.
36. Araki K, Shinozaki T, Irie Y, Miyazawa Y. Trial of oral administration of Bifidobacterium breve for the prevention of rotavirus infections. The Journal of the Japanese Association for Infectious Diseases 1999; 73(4): 305.
37. Chen C-C, Walker WA. Probiotics and prebiotics: role in clinical disease states. Adv Pediatr 2005; 52: 77-113.
38. Chandra R. Effect of Lactobacillus on the incidence and severity of acute rotavirus diarrhoea in infants. A prospective placebo-controlled double-blind study. Nutrition research 2002; 22(1): 65-69.
39. Saxelin M, Elo S, Salminen S, Vapaatalo H. Dose response colonisation of faeces after oral administration of Lactobacillus casei strain GG. Microb Ecol Health D 1991; 4(4): 209-214.
40. Chauviere G, Coconnier M-H, Kerneis S, Fourniat J, Servin AL. Adhesion of human Lactobacillus acidophilus strain LB to human enterocyte-like Caco-2 cells. J Gen Microbial 1992; 138(Pt 8): 1689-1696.