



REVIEW ARTICLE

The use of Probiotics to Prevent Diarrhea in Young Children Attending Child Care Centers: A Review

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The incidence of diarrheal disease in children has been reduced because of public health measures, improved hygiene, and a better understanding of nutrition. However, it remains a particular problem where young children come into close contact with other children, such as in child day care centers. Probiotics are defined as products that contain an adequate dose of live microbial agents that have been shown in target-host studies to confer a health benefit. They have been used for the treatment and prevention of many diseases, but particularly of gastrointestinal diseases. Prebiotics are inactive food components, commonly oligosaccharides or polysaccharides, that stimulate growth of beneficial bacteria in the gastrointestinal tract and are commonly used in combination with probiotics.

The initial searches identified 5860 articles from the PubMed database, but only 154 included the keyword "trial." Probiotics share the problem of limited systematic research with other traditional medications and foods, and only seven studies were included in the final analysis. A variety of probiotic organisms and prebiotics were used in the studies, and the end points were not standardized. However, examination of the six studies that used live cultures showed that five studies resulted in a decrease in either the number of episodes or the duration of diarrhea or both. However, the studies support a reduction of around 20% in diarrheal episodes or days of illness. Findings of this review have important implications for working parents. The regular use of a probiotic or probiotic/prebiotic combination will reduce the incidence and duration of diarrheal disease in children attending childcare centers (risk ratio, 0.72–0.82). Further research is needed to better define the most effective probiotic organisms and the optimal dosage.

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1. Introduction

Diarrheal disease remains an important cause of morbidity and mortality throughout our region, and despite advances in nutrition and hygiene, the incidence remains high. Probiotics have been used for the treatment and prevention of many diseases, but particularly of gastrointestinal diseases. Benefits have been found for the use of probiotics in the prevention of antibiotic-induced diarrhea and in the management of necrotizing enterocolitis, travelers' diarrhea, and diarrhea in infants.¹ In this article, we will review the use of probiotics in the prevention of diarrheal disease in children and in particular those who spend at least part of the day in a childcare center.

In many traditional societies, all adults in the family are required to work to provide for food and additional income. In these

extended families, children are cared for by grandparents or other children old enough to provide some care, but not yet old enough to work in the fields. In the 21st century, family structures and work patterns have changed in both developed and developing countries. This has resulted in changes in childcare practices and the exposure of children to additional risks of infection at earlier ages. Although substantial progress has been made in improving child health, there are still many children who die from preventable causes. Each year, an estimated 9 million children die before their 5th birthday, and diarrheal disease remains one of the top two causes of morbidity and mortality in children in the Asia Pacific region and worldwide.² Many of these children will have been cared for in the least part of their lives by other members of the family or in formal childcare, as modern lifestyles have often led to both parents being absent from the home during the day for employment, particularly in the rapidly growing cities. Children are then cared for in other homes, day care homes, or formal or informal childcare day centers.

Any place that children congregate together has increased rates of infectious disease.³ Children are susceptible hosts and often have

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less-than-ideal personal hygiene habits. Staff are required to provide frequent personal care with the opportunity of spreading infection to all the groups. It is hardly surprising that childcare facilities are classified as a hazardous workplace for staff because of an increased prevalence of infectious disease and musculoskeletal problems from lifting.⁴ Childcare centers have shown increased rates of diarrhea, respiratory tract infections, hepatitis A, *Haemophilus influenzae*, and many other childhood illnesses.^{3,5-7}

To meet the need for continuing care, a network of childcare centers has been established in Australia and other western countries, and the system is now spreading to all countries throughout our region. These centers provide an invaluable service to parents who work and who do not have access to carers in the extended families of previous generations. But the increased risk of childhood diseases has its consequences for the family, as infection may spread to other children and family members once the child returned home. The exclusion of unwell children from attending childcare centers causes considerable inconvenience for working parents. There is also a substantial economic impact through the direct health care costs and parents having to take time off work to look after their sick child.⁸

Diarrheal disease is a particular risk in these centers and has been the subject of many studies.⁹⁻¹⁵ In Australia, higher levels of infection led to the publication of national guidelines, which have resulted in a considerable improvement in hygiene standards.¹⁶ The guidelines for centers in Australia (and most other countries) are conservative, and any child diagnosed with diarrhea is excluded from childcare centers. The working definition of diarrhea used by childcare centers and parents is based on consistency of stools and the number of stools per day, but particularly the latter.

Interventions for the prevention of diarrhea include the promotion of breastfeeding, improved nutrition and the availability of clean water supplies.^{17,18} Frequent and careful washing of hands by staff and attention to hygiene are important preventive measures in childcare centers.¹⁹⁻²²

Probiotics have been consumed by humans since time immemorial, in the form of fermented milks, yogurts, and other fermented foods. They have commonly been used to treat a variety of gastrointestinal complaints. The type of fermented product used depends on the availability in the particular culture. For example in Korea, where dairy products were less readily available, the health benefits of kimchi (fermented vegetable products with lactobacilli) have been widely proclaimed.

The Russian microbiologist, Ilya Metchnikov, who received the 1908 Nobel prize in medicine for his discovery of the process of phagocytosis, formalized the concept of "probiotics," a Greek word meaning "for life," more than a century ago. He introduced the term "probiotic" to describe live microbial supplements designed to improve "health." While working at the Pasteur Institute in Paris, he promoted the use of fermented milk (lactobacilli) to promote health.²³ Metchnikov provided the first scientific explanation of the beneficial effects of yogurt when he suggested that lactic acid produced by lactobacilli could inhibit the growth of "unhealthy" bacterial species. There are several more recent definitions of probiotics in common use including "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" or "live viable microorganisms that, when taken by mouth, exert beneficial effects upon the host."²³ However, Sanders²⁴ recommends that the term "probiotic" be restricted in use to products that meet specific scientific criteria, namely products that contain an adequate dose of live microbial agents that have been shown in target-host studies to confer a health benefit.

Probiotics may be used alone or combined with prebiotics.²⁵ Prebiotics are inactive food components that stimulate growth of

beneficial bacteria in the gastrointestinal tract (GIT) and potentially have benefits on human health.²⁶ Prebiotics are defined as "non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth, and/or activity, of one or a limited number of beneficial bacteria in the colon and thus improve host health."²⁷ Prebiotics may be nondigestible carbohydrates (oligosaccharides or polysaccharides), protein, peptides, or some types of lipid. Wang and Gibson²⁸ demonstrated that, in the presence of fructo-oligosaccharides, bifidobacteria grew better than bacteroides, clostridia, or coliforms. Prebiotics are generally considered to be safe as they are naturally present in several kinds of food, but overconsumption in humans can lead to flatulence, bloating, and diarrhea. A product used by humans that contains a mixture of probiotics and prebiotics is often referred to as a "synbiotic." Breast milk contains natural prebiotics, human milk oligosaccharides, which explains the bifidobacteria-dominated microflora seen in breastfed infants.

A mature adult human has approximately 10 times more bacteria than human cells, and the composition and quantification has been the subject to research since bacteria were first systematically described.²⁹ At birth, the GIT is sterile, but it soon colonized from external sources, particularly the maternal genitourinary tract and gradually stabilizes over the next 18 months.^{26,30} Colonization depends on environmental factors, such as the method of infant feeding and the level of hygiene, and becomes more like an adult flora as the child begins to consume solid foods. Other factors that influence the colonization pattern include the mode of delivery (vaginal delivery vs. cesarean section), gestational age (prematurity), length of hospitalization, antibiotic use after birth, and exposure to older siblings and other children. The normal gut flora in the adult contains about 500 species existing in a symbiotic relationship with the host.²⁶ Recognizing the importance of our microbiological load to human health, the National Institutes of Health is now midway through the 5-year Human Microbiome Project as part of its Roadmap for Medical Research. The advent of modern analytical systems has enabled this project to proceed and has revealed significant variation in the microbiological flora of the gastrointestinal luminal contents and the mucosal community composition.³¹ The ultimate aim of this research is to modify the human microbiome through specifically targeted antibiotics with probiotics and prebiotics to promote optimal health.³²

The microflora of the GIT has several important nutritional functions, including protection of the GIT against epithelial injury, protection against infection from noncommensal microbes, stimulation of immune functions, regulation of host fat storage, and stimulation of intestinal angiogenesis.³¹ The role of intestinal flora in the degradation of indigestible dietary carbohydrates has become of interest with the current worldwide obesity epidemic. It has been postulated that changes in energy availability may be a function of each person's microbiome, and this could be a factor in the etiology of obesity.^{33,34}

The specific aim of this article is to review the use of probiotics and prebiotics, usually in combination, in the prevention of community-acquired diarrheal disease in children, and in particular those who spend at least part of the day in a childcare center.

2. Methodology

The databases that were searched to compile this review were PubMed, ScienceDirect, CINAHL, the Cochrane Library, and Web of Knowledge. In addition, reference lists of the articles obtained during the search were reviewed. The search was restricted to English language publications and used the following search terms: diarrhoea (diarrhea) children (child), prevention, and probiotics. Full articles were retrieved and evaluated where the article

included children aged less than 4 years, and the paper reported a prevention study in community-dwelling children attending child day care centers. Exclusions included trials reporting the treatment of diarrhea or the prevention of side effects while children were under treatment, such as the prevention of diarrhea in children being treated with antibiotics. Articles from developing countries were excluded as many of these used samples that included children with malnutrition or who were likely to be exposed to high levels of infection. The selected articles were also followed up in Science Citations (Web of Knowledge) to find further relevant studies and reviews.

3. Results

The initial searches revealed a large number of publications related to probiotics; approximately 5860 articles were found in PubMed, but only 154 included "trial." The vast majority of articles were uncontrolled trials, case studies, discussions, and nonsystematic reviews. Probiotics share the problem of limited systematic research with other traditional medications and foods. The limited opportunities for commercial patents and the difficulty of research, including the need for daily doses of probiotics, have resulted in fewer trials than would be expected. However, included in the array of literature on probiotics in general are 18 Cochrane reviews and 4 Cochrane protocols. The Cochrane reviews included the use of probiotics in the prevention and treatment of antibiotic-induced diarrhea, but none are on the prevention of diarrhea in children living in the community. See Table 1 for details of the Cochrane reviews that have found positive benefits for the use of probiotics. Two areas where Cochrane reviews have shown no benefit in the use of probiotics in children have been in the prevention of allergies and prevention of irritable bowel syndrome.^{44,45} There were 95 articles that were found using the search words trial, diarrhoea, and child. But after reading the full texts, only seven articles were found that could be included in this review.

In addition to the Cochrane reviews, further systematic literature reviews related to probiotics and diarrhea were located in other refereed (peer-reviewed) journals. A systematic review by Szajewska et al³⁵ included trials on prevention, but in this review, only three studies were considered with sample sizes of 10, 15, and 204. The latter study was in Peru among undernourished indigent children.³⁶

Lewis and Freedman³⁷ reviewed the use of probiotics in the prevention of diarrhea and concluded: "There is a plethora of data on probiotics from in vitro and animal experiments; with the exception of diarrhea due to rotavirus infection in children, there is little evidence from randomized studies that probiotics have

a significant beneficial action in preventing diarrhea of any cause." Their review included mostly studies on the use of probiotics for the treatment of diarrhea and only one study of prevention in children. In the most comprehensive meta-analysis of probiotic use in the prevention of diarrhea, of 690 studies identified by Sazawal et al,³⁸ only 28 met the criteria for inclusion in the review. But they included only one trial of community-acquired diarrhea in children, the trial from Peru referred to above.³⁶ However, they concluded that "although there is some suggestion that probiotics may be efficacious in preventing acute diarrhea, there is a lack of data from community-based trials," a conclusion well warranted since only one trial was reviewed.

Minocha³⁹ reviewed the use of probiotics in children in day care centers using data from two trials and suggested that probiotics may promote good health in day care centers. A review of the use of prebiotics, including inulin, oligofructose, and galactooligosaccharides found no evidence to "recommend prebiotics for the prevention of diarrhea."⁴⁰ Although some evidence has been found for the use of probiotics to prevent traveler's diarrhea, a major systematic review found that no studies had been undertaken in children.⁴¹

Details of the seven randomized clinical trials that met the criteria for inclusion in this study are shown in Table 2. In one case, the study reported a trial of fermented milk, where the probiotic had been inactivated by processing, and the study showed no effect.⁴² A variety of probiotic organisms and prebiotics were used in the studies. The end points, including the definitions of diarrhea were not standardized, but most trials used an intention-to-treat analysis. The lack of standardization makes meta-analysis difficult. However, an examination of the six studies that used live cultures shows that five resulted in a decrease in either the number of episodes or the duration of diarrhea or both. No quantitative estimate of effect can be given because of the variety of end points used. However, the studies support an effect of the magnitude found in the CUPDAY Study, a reduction of around 20% in diarrheal episodes or days of illness.⁴³

4. Discussion

Children are usually excluded from childcare centers when they develop any illness, even a relatively minor one. Diarrheal disease almost always results in automatic exclusion until the illness episode has passed. Improved hygiene in childcare centers has been shown to reduce the rates of diarrheal disease.¹² This is a problem of concern to parents with young children, and the use of probiotics provides a possible solution.

Table 1 Cochrane reviews of the use of probiotics in children

Cochrane review	Conclusion
AlFaleh KM, Bassler D. Probiotics for prevention of necrotizing enterocolitis in preterm infants. <i>Cochrane Database of Systematic Reviews</i> 2008, Issue 1. Art. No.: CD005496. DOI: 10.1002/14651858.CD005496.pub2.	Enteral supplementation of probiotics reduced the risk of severe necrotizing enterocolitis and mortality in preterm infants. This analysis supports a change in practice in premature infants >1000 g at birth.
Allen SJ, Okoko B, Martinez EG, Gregorio GV, Dans LF. Probiotics for treating infectious diarrhea. <i>Cochrane Database of Systematic Reviews</i> 2003, Issue 4. Art. No.: CD003048. DOI: 10.1002/14651858.CD003048.pub2.	Probiotics appear to be a useful adjunct to rehydration therapy in treating acute infectious diarrhea in adults and children.
Johnston BC, Supina AL, Ospina M, Vohra S. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. <i>Cochrane Database of Systematic Reviews</i> 2007, Issue 2. Art. No.: CD004827. DOI: 10.1002/14651858.CD004827.pub2.	The per-protocol analysis for 9/10 trials reporting on the incidence of diarrhea shows statistically significant results favoring probiotics over active/nonactive controls (RR: 0.49; 95% CI: 0.32–0.74). However, intention-to-treat analysis showed nonsignificant results overall (RR: 0.90; 95% CI: 0.50–1.63).

RR = relative risk; CI = confidence interval.

Table 2 Summary of randomized, double-blind, placebo-controlled prevention trials of probiotics for diarrhea prevention in children

Trial	Location	Inclusion criteria	Exclusion criteria	Age (mo)	
Pedone (1999)	France	Child day care facilities; <i>N</i> = 287	Long-term medication, breastfed, allergy, malabsorption	12–24	
Pedone (2000)	France	Child day care facilities; multicenter, <i>N</i> = 928 healthy children attending day care 5 days/wk	Long-term medication, breastfed, allergy, malabsorption	6–24	
Hakatta (2001)	Finland	Children aged attending municipal day care centers in Helsinki; <i>N</i> = 571	History allergy to cow's milk, lactose intolerance, severe food allergy, and severe chronic disease	12–72	
Saavedra (2004)	USA	Healthy children attending day care in Baltimore; <i>N</i> = 131 healthy children	Breastfed GIT disease or allergy	3–24	
Thibault (2004)	France	Healthy infants attending childcare centers or >2 siblings at home; <i>N</i> = 968	Breastfed; on special diets; had chronic diarrhea	4–6	
Wiezman (2005)	Israel	Infants attending childcare centers; <i>N</i> = 201 healthy term infants	Chronic illness medication	4–10	
Giovanni (2007)	Italy	Preschool children with allergic asthma/rhinitis; <i>N</i> = 187	Chronic illness medication	24–60	
Binns (2007)	Australia	Healthy children attending day care centers in Perth	Allergy to milk products, chronic diarrhea	12–36	
Probiotic strain	Dose	Intervention	Outcomes	Type of diarrhea	Results
<i>Lactobacillus casei</i>	10 ⁸ cfu/mL, 125 or 250 g according to age	For the duration of hospital stay with formula	Episodes of disease; duration of diarrhea	Nosocomial	Reduced duration of diarrheal episodes
<i>L. bulgaris</i> & <i>S. thermophilus</i> or <i>Lactobacillus casei</i>	10 ⁷ cfu/g, or 3.2 × 10 ⁸ cfu/g	Comparison of two types of yogurt/fermented milks	Duration of diarrhea	Community acquired	Reduced number of episodes in Group 2. (RR = 0.72), duration: NS
<i>Lactobacillus rhamnosus</i> GG	5–10 × 10 ⁵ , 200 mL milk per day	RCT for 7 mo over winter	Incidence of diarrhea; and other GIT and respiratory symptoms Number of days with symptoms	Community acquired	Decreased days absent, respiratory and GI symptoms and reduced antibiotics
<i>Lactobacillus bifidus</i> BB12	10 ⁷ cfu/g	18 mo	Health and GIT symptoms	Community acquired	Antibiotic use decreased, diarrhea NS
<i>Lactobacillus bifidus</i> BBC50	Fermented formula, no live bacteria	RCT for 5 mo	Health and GIT symptoms	Community acquired	No difference incidence, duration of diarrhea episodes, and hospital admissions
<i>Lactobacillus bifidus</i> BB12 or <i>Lactobacillus reuteri</i>	10 ⁷ cfu/g	RCT 21 mo, control plus 2 trial groups	Illness episodes including diarrhea	Community acquired	Episodes of diarrhea reduced by >50%
<i>Lactobacillus casei</i>	10 ⁸ cfu/mL, 100 mL/d	RCT for 12 mo	Duration of episodes of diarrhea	Community acquired	Duration of episodes of diarrhea was shortened by 0.8 days
<i>Bifidobacterium lactis</i> (BL: CNCM I-3446) and a prebiotic blend	2.109/100 g, dry weight	RCT for 7 mo over winter	Number of episodes of diarrhea	Community acquired	Number of episodes of diarrhea reduced RR 0.82 (0.73–0.94)

GIT = gastrointestinal tract; RR = relative risk; NS = not significant; RCT = randomized controlled trial.

In the studies that reached the criteria for inclusion in the review, there were several different probiotic organisms used, and a variety of end points measured. The most common probiotics were from the lactobacilli group of lactase-producing bacteria (e.g., *Lactobacillus acidophilus*) and bifidobacteria. There were also differences in the use of prebiotics, in type and quantity, as part of the preventive regime. To be effective, probiotics must be administered on a regular basis, probably at least daily and must be acid stable, have an ability to colonize the intestine, and bring health benefits to the host, and all of the preparations used met these criteria. The requirement for daily administration places a burden on parents and carers and explains the dropout rates in some of the studies.

From the heterogeneous studies available, which together include approximately 540,000 child-days of preschool-aged children, a few conclusions can be drawn. The first conclusion is that in

all the articles, there was a concern about the risk of infection in children attending childcare. In the modern era, illness of children has a significant impact on the family dynamics and is of economic importance, as parents have to take time off work to care for their ill child. The studies regarded the probiotic combinations used to be safe, and few side effects were reported. The second conclusion is that overall probiotics are effective in reducing the rate of diarrhea in children attending childcare centers, probably at least a 20% reduction in episodes and days of significant illnesses. No statement can be made from the available evidence as to which combination of probiotics and prebiotics is the most effective. Similarly, no statement can be made on the most effective daily dose to be used. More research is required to define the most effective probiotics and whether (and which) prebiotics should be included and the optimal dosage schedule for prevention.

5. Conclusions

Findings of this study have important implications for working parents. Evidence from the trials reviewed in this study show that the regular use of a probiotic or probiotic/prebiotic combination will reduce the incidence and duration of diarrheal disease in children attending childcare centers. Further research is needed to better define the most effective probiotic organisms and optimal dosage.

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