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Review Article

The use of Probiotics to Prevent Diarrhoea in Young Children Attending Child Care Centres: a Review

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ABSTRACT

The incidence of diarrhoeal disease in children has been reduced due to 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 centres. 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 oligo- or polysaccharides, that stimulate growth of beneficial bacteria in the gastrointestinal tract (GIT) and are commonly used in combination with probiotics.

The initial searches identified 5860 papers 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 endpoints, were not standardised. 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 diarrhoea or both. However the studies support a reduction of around 20% in diarrhoeal 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 diarrhoeal disease in children attending child care centres (risk ratio 0.72-0.82). Further research is needed to better define the most effective probiotic organisms and the optimal dosage.

INTRODUCTION

Diarrhoeal 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 diarrhoea and in the management of necrotising enterocolitis, travellers' diarrhoea and diarrhoea in infants(1). In this paper we will review the use of probiotics in the prevention of diarrhoeal disease in children and in particular those who spend at least part of the day in a child care centre.

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 child care practices and the exposure of children to additional risks of infection at earlier ages. While 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 child care, 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 child care day centres.

Any place that children congregate together has increased rates of infectious disease (3). Children are susceptible hosts and often have less than ideal personal hygiene habits. Staff are required to provide frequent personal care with the opportunity of spreading infection to all the group. It is hardly surprising that child care facilities are classified as a hazardous workplace for staff due to an increased prevalence of infectious disease and musculo-skeletal problems from lifting (4). Child care centres have shown increased rates of diarrhoea, respiratory tract infections, hepatitis A, H. influenzae, and many other childhood illnesses (3, 5-7).

To meet the need for continuing care a network of child care centres has been established in Australia and other western countries and the system is now spreading to all countries throughout our region. These centres 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 child care centres, causes considerable inconvenience for working parents. There is also a substantial economic impact through the direct health care costs, as well as parents having to take time off work to look after their sick child (8).

Diarrhoeal disease is a particular risk in these centres 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 centres in Australia (and most other countries) are conservative and any child diagnosed with diarrhoea, is excluded from child care centres. The working definition

of diarrhoea used by child care centres and parents is based on consistency of stools and the number of stools per day, but particularly the latter.

Interventions for the prevention of diarrhoea 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 is an important preventive measure in child care centres (19-22).

Probiotics have been consumed by humans since time immemorial, in the form of fermented milks, yoghurts 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, formalised 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 yoghurts 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 micro organisms 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 Sanders 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 (24).

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 non-digestible carbohydrates (oligo- or polysaccharides), protein, peptides or some types of lipid. Wang and Gibson demonstrated that, in the presence of fructo-oligosaccharides, bifidobacteria grew better than bacteroides, clostridia or coliforms. (28). Prebiotics are generally considered to be safe, as they are naturally present in several kinds of food, but over-consumption in humans can lead to flatulence, bloating and diarrhoea. A product used by humans that contains a mixture of probiotics and prebiotics, it is often referred to as a ‘synbiotic’. Breastmilk 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 colonised from external sources, particularly the maternal genitourinary tract and gradually stabilizes over the next 18 months (26, 30). Colonisation 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. caesarean section), gestational age (prematurity), length of hospitalisation, 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 five 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 non-commensal 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 world wide obesity epidemic. It has been postulated that changes in energy availability may be a function of each persons' microbiome and this could be a factor in the aetiology of obesity (33-34).

The specific aim of this paper is to review the use of probiotics and prebiotics, usually in combination, in the prevention of community acquired diarrhoeal disease in children and in particular those who spend at least part of the day in a child care centre.

METHODOLOGY

The databases that were searched to compile this review were PubMed, Science Direct, 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 papers were retrieved and evaluated where the article included children aged <4 years and the paper reported a prevention study in community dwelling children attending child day care centres. Exclusions included trials reporting the treatment of diarrhoea, or the prevention of side effects while children were under treatment, such as the prevention of diarrhoea in children being treated with antibiotics. Papers 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 papers were also followed up in Science Citations (Web of Knowledge) to find further relevant studies and reviews.

RESULTS

The initial searches revealed a large number of publications related to probiotics; approximately 5860 papers were found in PubMed, but only 154 included “trial”. The vast majority of papers were uncontrolled trials, case studies, discussions and non systematic 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 diarrhoea, but none are on the prevention of diarrhoea 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 the prevention irritable bowel syndrome (Osborn, Huertas-Ceballos). There were 95 papers that were found using the search words trial, diarrhoea and child. But after reading the full texts, only seven papers were found that could be included in this review.

In addition to the Cochrane reviews, further systematic literature reviews related to probiotics and diarrhoea were located in other refereed journals. A systematic review by Szajewska included trials on prevention, but in this review only three studies were considered with sample sizes of 10, 15 and 204 (35). The latter study was in Peru among undernourished indigent children (36).

Lewis and Freedman reviewed the use of probiotics in the prevention of diarrhoea and concluded: “There is a plethora of data on probiotics from in vitro and animal experiments; with the exception of diarrhoea due to rotavirus infection in children, there is little evidence from randomised studies that probiotics have a significant beneficial action in preventing diarrhoea of any cause” (37). Their review included mostly studies on the use of probiotics for the treatment of diarrhoea and only one study of prevention in children. In the most comprehensive meta-analysis of probiotic use in the prevention of diarrhoea, of 690 studies identified by Sazawal, only 28 met the criteria for inclusion in the review (38). But they included only one trial of community acquired diarrhoea 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 diarrhoea, there is a lack of data from community-based trials”, a conclusion well warranted since only one trial was reviewed.

Minocha reviewed the use of probiotics in children in day care centres using data from two trials and “suggested that probiotics may promote good health in day care centres (39). A review of the use of prebiotics, including inulin, oligofructose, and galactooligosaccharides found no evidence to “recommend prebiotics for the prevention of diarrhea” (40). While some evidence has been found for the use of probiotics to prevent traveller’s diarrhoea, a major systematic review found no studies had been undertaken in children (41).

Details of the seven randomised 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 endpoints, including the definitions of diarrhoea were not standardised, but the majority of trials used an intention to

treat analysis. The lack of standardisation 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 diarrhoea or both. No quantitative estimate of effect can be given because of the variety of endpoints used. However the studies support an effect of the magnitude found in the Cupday Study, a reduction of around 20% in diarrhoeal episodes or days of illness (43)

DISCUSSION

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

In the studies that reached the criteria for inclusion in the review there were several different probiotic organisms used and a variety of endpoints 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 colonise 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 pre-school aged children, a few conclusions can be drawn. The first conclusion is that in all of the papers concerned about the risk of infection in children attending child care. 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 as safe and few side effects were reported. The second conclusion is that overall probiotics are effective in reducing the rate of diarrhoea in children attending child care centres, 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.

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 diarrhoeal disease in children attending child care centres. Further research is needed to better define the most effective probiotic organisms and the optimal dosage.

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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 necrotising 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 diarrhoea. <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 diarrhoea 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 show statistically significant results favouring probiotics over active/non active controls (RR 0.49; 95% CI 0.32 to 0.74). However, intention to treat analysis showed non-significant results overall (RR 0.90; 95% CI 0.50 to 1.63).

TABLE 2. Summary of randomized double-blind placebo-controlled prevention trials of probiotics for diarrhoea prevention in children

Trial	Location	Inclusion criteria	Exclusion criteria	Age (months)
Pedone (1999)	France	Child Day care facilities N=287	Long term medication, breastfed, allergy, malabsorption	12–24
Pedone (2000)	France	Child Day care facilities. Multicentre N=928 Healthy children attending day care 5 days per week	Long term medication, breastfed, allergy, malabsorption	6-24
Hakatta (2001)	Finland	Children aged attending municipal day care centres in Helsinki N=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 N=131 Healthy children,	Breastfed GIT disease or allergy.	3-24
Thibault 2004	France	Healthy infants attending Child care centres or >2 siblings at home. N=968	Breastfed. On special diets Had chronic diarrhoea	4-6

Wiezman (2005)	Israel	Infants attending child care centres N=201 Healthy term infants.	Chronic illness medication	4-10
Giovanni (2007)	Italy	Preschool children with allergic asthma/rhinitis N=187	Chronic illness medication	24-60
Binns (2007)	Australia	Healthy children attending day care centres in Perth	Allergy to milk products, chronic diarrhoea	12-36

Probiotic strain	Dose	Intervention	Outcomes	Type of diarrhea	Results
<i>Lactobacillus casei</i>	10 ⁸ cfu/ml 125 or 250g according to age	For the duration of hospital stay with formula	Episodes of disease; duration of diarrhea	Nosocomial	Reduced duration of diarrhoeal episodes
<i>L bulgaris & S thermophilus or Lactobacillus casei</i>	10 ⁷ cfu/g or 3.2X10 ⁸ cfu/g	Comparison of two types of yoghurt/fermented milks	Duration of diarrhoea	Community acquired	Reduced number of episodes in group 2. (RR = 0.72) Duration NS
<i>Lactobacillus rhamnosus GG</i>	5-10x10 ⁵ 200 mls milk per day	RCT for 7 months over winter	Incidence of diarrhea; and other GIT and Respiratory symptoms	Community acquired	Decreased days absent, respiratory and GI symptoms and reduced

			Number of days with symptoms		antibiotics.
<i>Lactobacillus bifidus BB12</i>	10 ⁷ cfu/g	18 months	Health and GIT symptoms	Community acquired	Antibiotic use decreased Diarrhoea NS
<i>Lactobacillus bifidus BBC50</i>	Fermented formula, no live bacteria	RCT for 5 months	Health and GIT symptoms	Community acquired	No difference incidence, duration of diarrhea episodes, and hospital admissions
<i>Lactobacillus bifidus BB12</i> or <i>lactobacillus reuteri</i>	10 ⁷ cfu/g	RCT 21 months Control plus 2 trial groups	Illness episodes including diarrhoea	Community acquired	Episodes of diarrhea reduced by >50%
<i>Lactobacillus casei</i>	10 ⁸ cfu/ml 100mls/day	RCT for 12 months	Duration of episodes of diarrhea;	Community acquired	Duration of episodes of diarrhoea was shortened by 0.8days
<i>Bifidobacterium lactis</i> (BL: CNCM I-3446) and a prebiotic blend	2.10%/100 g dry weight	RCT for 7 months over winter	Number of episodes of diarrhea	Community acquired	Number of episodes of diarrhoea reduced RR 0.82 (0.73-0.94)