

Funding: Policy research programme, Department of Health.

Competing interests: None declared.

Ethical approval: Not required.

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Accepted: 5 June 2007

Probiotics for treatment of acute diarrhoea in children: randomised clinical trial of five different preparations

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BMJ 2007;335:340-2

doi:10.1136/bmj.39272.581736.55

ABSTRACT

Objective To compare the efficacy of five probiotic preparations recommended to parents in the treatment of acute diarrhoea in children.

Design Randomised controlled clinical trial in collaboration with family paediatricians over 12 months. **Setting** Primary care.

Participants Children aged 3-36 months visiting a family paediatrician for acute diarrhoea.

Intervention Children's parents were randomly assigned to receive written instructions to purchase a specific probiotic product: oral rehydration solution (control group); *Lactobacillus rhamnosus* strain GG; *Saccharomyces boulardii*; *Bacillus clausii*; mix of *L delbrueckii* var *bulgaricus*, *Streptococcus thermophilus*, *L acidophilus*, and *Bifidobacterium bifidum*; or *Enterococcus faecium* SF68.

Main outcome measures Primary outcomes were duration of diarrhoea and daily number and consistency of stools. Secondary outcomes were duration of vomiting and fever and rate of admission to hospital. Safety and tolerance were also recorded.

Results 571 children were allocated to intervention. Median duration of diarrhoea was significantly shorter ($P<0.001$) in children who received *L rhamnosus* strain GG (78.5 hours) and the mix of four bacterial strains (70.0 hours) than in children who received oral rehydration solution alone (115.0 hours). One day after the first probiotic administration, the daily number of stools was significantly lower ($P<0.001$) in children who received *L rhamnosus* strain GG and in those who received the probiotic mix than in the other groups. The remaining preparations did not affect primary outcomes. Secondary outcomes were similar in all groups.

Conclusions Not all commercially available probiotic preparations are effective in children with acute

diarrhoea. Paediatricians should choose bacterial preparations based on effectiveness data.

Trial registration number Current Controlled Trials ISRCTN56067537.

INTRODUCTION

Several probiotic micro-organisms are effective in reducing the severity and duration of acute diarrhoea in children: *Lactobacillus rhamnosus* (formerly "*Lactobacillus casei* strain GG" or "*Lactobacillus GG*"), *L plantarum*, several strains of bifidobacteria, *Enterococcus faecium* SF68, the yeast *Saccharomyces boulardii*, and preparations containing a mix of strains. Several trials with probiotic preparations have been conducted in different settings and with different end points. Meta-analyses of probiotic efficacy are also available,¹⁻⁴ though few meet the criteria of properly controlled trials.⁴

In a study of Italian children with diarrhoea, probiotics were the most commonly prescribed treatment.⁵ With the increasing availability and widespread use of probiotics, it is important to identify the most effective preparations. We evaluated the efficacy of five probiotic preparations for the treatment of acute diarrhoea in children.

METHODS

The study was a prospective single blind randomised controlled trial in which parents of children with acute diarrhoea received written instructions to purchase a specific brand of probiotic. Diarrhoea was defined as three or more outputs of loose or liquid stools a day. Eligible children were those aged 3-36 months who were seen in family paediatricians' offices from October 1999 to September 2000 because of diarrhoea. We included in the study all

This article is an abridged version of a paper that was posted on bmj.com on 10 August 2007. Cite this version as: *BMJ* 10 August 2007, doi: 10.1136/bmj.39272.581736.55 (abridged text, in print: *BMJ* 2007;335:340-2).

Table 1 | Micro-organism load (according to product label when the study was performed), administration, and main characteristics of preparations analysed

Groups	Micro-organisms	Strains	Dose (twice daily)	Brand*	Price (€)
2	<i>Lactobacillus casei</i>	Rhamnosus GG	6×10 ⁹ CFU/dose	Dicoflor 60	10.50
3	<i>Saccharomyces boulardii</i>	<i>S boulardii</i> It	5×10 ⁹ live micro-organisms/dose	Codext†	8.50
4	<i>Bacillus clausii</i>	O/C84, N/R84, T84, SIN84	10 ⁹ CFU/dose	Enterogermina†	6.50
5	<i>L delbrueckii</i> var <i>bulgaricus</i> , <i>L acidophilus</i> , <i>Streptococcus</i> <i>thermophilus</i> , <i>B bifidum</i>	LMG-P17550, LMG-P 17549, LMG-P 17503, LMG-P 17500	10 ⁹ CFU, 10 ⁹ CFU, 10 ⁹ CFU, 5×10 ⁸ CFU/dose	Lactogermina†	10.50
6	<i>Enterococcus faecium</i>	SF 68	7.5×10 ⁷ CFU/dose	Bioflorin†	10.50

CFU=colony forming units.

*All sold in coloured cardboard boxes.

†Composition, brand name, and costs of these probiotic preparations have changed since study ended.

children with diarrhoea lasting less than 48 hours. Exclusion criteria were malnutrition, severe dehydration, coexisting acute systemic illnesses, immunodeficiency, underlying severe chronic diseases, cystic fibrosis, food allergy or other chronic gastrointestinal diseases, use of probiotics in the previous three weeks, use of antibiotics or any antidiarrhoeal medication in the previous three weeks and during the study, and poor compliance (defined by administration of less than four doses of the study medication).

All children were given oral rehydration solution for three to six hours and then fed with full strength formula containing lactose or cows' milk, depending on age. Microbiological investigation was performed only if required for specific clinical reasons. Children were also randomised to oral rehydration alone; *Lactobacillus* GG; *S boulardii*; *Bacillus clausii*; mix of *L delbrueckii* var *bulgaricus*, *Streptococcus thermophilus*, *L acidophilus*, and *Bifidobacterium bifidum*, or *E faecium* strain SF68 (table 1).

Patients were randomly allocated to each group and the parent of each child received written instructions to purchase the assigned probiotic product. Probiotic preparations were prescribed for five days and administered orally in 20 ml water according to the manufacturers' instructions. All the probiotic products used in this study were available only in pharmacies and had a similar brand image and price. The group of children who received only oral rehydration served as controls.

The primary outcome measures were the total duration of diarrhoea and the number of stools a day and their consistency. Secondary outcome measures were the incidence and median duration of vomiting, fever, and the number of hospital admissions in each group.

On enrolment parents received a coded reporting form on which to record clinical data. They were instructed to record daily the number of faecal outputs and their consistency, the type and doses of probiotic preparation taken by the child, the presence of vomiting and fever, any necessity for hospital admission, and all adverse events. Investigators collecting the reporting forms were blinded to the assigned treatment.

Estimate of sample size

Based on the results of a preliminary open trial⁶ we calculated we needed 45 participants in each group. To investigate secondary outcomes, we doubled the number of patients and allowed for a 10% drop out.

RESULTS

A total of 600 children with acute diarrhoea were eligible for inclusion: 29 were excluded and 571 were randomised to receive intervention and contributed data to the intention to treat analysis (see bmj.com).

The baseline features of the patients enrolled in the six groups were similar. The total duration of diarrhoea was significantly lower in children receiving *Lactobacillus* GG (group 2) and in those receiving the bacterial mix (group 5) than in patients receiving oral rehydration alone (group 1) (table 2). Daily stool output was significantly lower ($P<0.001$) in groups 2 and 5, starting the day after

Table 2 | Primary outcome index: duration of diarrhoea (hours) in study groups

Group	Treatment	Median (IQR) duration (hours)	Estimated difference (95% CI)*	P value†
1	Oral rehydration solution alone	115.5 (95.2-127)	—	—
2	<i>Lactobacillus casei</i> subsp <i>rhamnosus</i> GG	78.5 (56.5-104.5)	-32 (-41 to -23)	<0.001
3	<i>Saccharomyces boulardii</i>	105.0 (90-104.5)	-5 (-13 to 5)	0.38
4	<i>Bacillus clausii</i>	118.0 (95.2-128.7)	1 (-7 to 8)	0.76
5	<i>L delbrueckii</i> var <i>bulgaricus</i> , <i>L acidophilus</i> , <i>Streptococcus thermophilus</i> , <i>B bifidum</i>	70.0 (49-101)	-37 (-47 to -25)	<0.001
6	<i>Enterococcus faecium</i> SF 68	115.0 (89-144)	2 (-5 to 11)	0.61

IQR=interquartile range.

*Compared with oral rehydration solution alone.

†Mann-Whitney U test. P value for comparison with oral rehydration solution alone.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Several probiotic products are marketed in many European countries for the treatment of acute diarrhoea in children

WHAT THIS STUDY ADDS

The efficacy of probiotic preparations for the treatment of children with acute diarrhoea is related to the strain of bacteria

the first probiotic administration. Median stool outputs per day did not differ between groups 2 and 5. Stool consistency, as judged by the scoring system, differed significantly ($P < 0.001$) with preparations 2 and 5 versus the other groups. The median daily scores did not differ between groups 2 and 5 (see bmj.com).

None of the secondary outcome measures we evaluated was significantly modified in children receiving probiotic preparations or in the control group.

DISCUSSION

In an evaluation of five probiotic preparations in children with diarrhoea we found substantial differences in efficacy. Two preparations reduced the duration and severity of diarrhoea, whereas the three others had no significant effect. A recent Cochrane meta-analysis found mild therapeutic benefit from probiotics that was generally reproducible regardless of organism.⁴ In the only comparative trial reported previously, three preparations were tested in 46 children.⁷

Probiotics have progressively gained in credibility for the treatment of diarrhoeal diseases. In most countries, however, micro-organisms purported to have probiotic properties are considered to be food additives rather than drugs. Consequently, only safety features and not proof of efficacy are required for marketing.

Lactobacillus GG was associated with a shorter duration of diarrhoea. Proof of efficacy of this strain has been obtained in children in hospitals and outpatients in both industrialised and developing countries, and the results we obtained closely resembled those obtained in a similar setting with the same strain.⁶ The other effective preparation was a mix of four strains. A formula with *St thermophilus* and *B bifidum*, two of these four strains, protected against diarrhoea in chronically sick children aged below 24 months.⁸ The three other preparations we evaluated had no or little clinical effect. This was unexpected in the case of *S boulardii* because a previous controlled trial showed it to be beneficial, although this was in children with more severe diarrhoea than in our trial.⁹ A previous trial with *Streptococcus faecium* strain SF68 resulted in clinical improvement in children with diarrhoea associated with respiratory infection and treated with parenteral antibiotics,¹⁰ though it had no effect in adults with diarrhoea.¹¹ None of the preparations had a significant effect on secondary outcomes.

Possible confounding

We cannot exclude the possibility that expectations of parents confounded our results. However the brands investigated were among the most widely used, were not advertised, and were available only in pharmacies at the time of the study. The lack of preconceptions about the efficacy of treatment seems supported by our finding that only one of the two most widely used probiotic brands in Italy was effective (group 2) whereas the other was not (group 4). A high or low cost might have affected expectations either positively or negatively, but parents were probably unaware of the comparative costs of the products investigated.

In conclusion, the efficacy of probiotic preparations for the treatment of childhood acute diarrhoea is related to the individual strains of bacteria. We believe that probiotic preparations should be classified as drugs, and physicians should select preparations for which evidence of efficacy, in a given clinical condition, is supported by solid data.

We are grateful to Jean Ann Gilder for editing the text. The research was not sponsored by any pharmaceutical or food company, including yoghurt companies.

Contributors: See bmj.com.

Competing interests: None declared.

Funding: None.

Ethical approval: Ethics committee of University of Naples Federico II.

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Accepted: 18 June 2007