

Does probiotic milk prevent infections in children attending daycare centres?

Trial: Hatakka K, Savilahti E, Pönkä A, et al. Effect of long term consumption of probiotic milk on infections in children attending day care centres: double blind, randomised trial. *BMJ* 2001; 322: 1327-1329.

Question

In children attending daycare centres (population), does long term consumption of probiotic milk (intervention) prevent infections (outcome)?

Trial details

Objective: To examine whether long term consumption of a probiotic milk could reduce gastrointestinal and respiratory infections in children in daycare centres.

Design: Randomised, double-blind, placebo-controlled study over 7 months.

Setting: 18 daycare centres in Helsinki, Finland.

Participants: 571 healthy children aged 1–6 years; 282 in the intervention group (mean age, 4.6 years; SD, 1.5 years) and 289 in the control group (mean age, 4.4 years; SD, 1.5 years).

Intervention: Milk with or without *Lactobacillus* GG. Average daily consumption of milk in both groups was 260mL.

Main outcome measures: Number of days with respiratory and gastrointestinal symptoms, absences from daycare because of illness, respiratory tract infections diagnosed by a doctor, and courses of antibiotics.

Results: Children in the *Lactobacillus* group had fewer days of absence from daycare because of illness (4.9 days [95% CI, 4.4–5.5] versus 5.8 days [95% CI, 5.3–6.4]; absolute difference, 16% [$P=0.03$]). Corresponding age-adjusted findings were 5.1 days (95% CI, 4.6–5.6) for the *Lactobacillus* group versus 5.7 days (95% CI, 5.2–6.3) for the control group; age-adjusted difference, 11% ($P=0.09$). There was also a relative reduction of 17% in the number of children having respiratory infections with complications and lower respiratory tract infections (unadjusted absolute reduction, 8.6%; 95% CI, –17.2% to –0.1%; $P=0.05$; age-adjusted odds ratio, 0.75; 95% CI, 0.52–1.09; $P=0.13$) and a 19% relative reduction in courses of antibiotic for respiratory infection in the *Lactobacillus* group (unadjusted absolute reduction, –9.6%; 95% CI, –18.2 to –1.0; $P=0.03$; adjusted odds ratio, 0.72; 95% CI, 0.50–1.03; $P=0.08$).

Conclusions: *Lactobacillus* GG may reduce respiratory infections and their severity among children in daycare. The effects of the probiotic *Lactobacillus* GG were modest but consistently in the same direction.

beneficial effect on the host immune response by altering intestinal microbial balance.

Trial methods

This was a randomised, double-blind, placebo-controlled trial carried out in 18 daycare centres in children aged 1–6 years over 7 months, which included winter. Daycare staff, parents, children and investigators were blinded or unaware of treatment allocation. Randomisation was effectively concealed, as children were allocated to intervention or control groups by a computer-generated block-randomisation procedure, with stratification on the basis of age and daycare centre. The randomisation procedure was successful in equalising baseline characteristics between placebo and active groups, apart from the control group having slightly younger children and more children with more than five recent infections. There was excellent follow-up, with nearly 90% of children completing the study, although reasons for withdrawal were not stated. Groups were analysed on an intention-to-treat basis. A random selection of 100 faecal samples was assessed to confirm compliance. Outcome measures included days of respiratory or gastrointestinal symptoms, days of absence from daycare because of illness, and number of upper respiratory tract infections complicated by lower respiratory tract infections.

In summary, this trial was well designed and conducted. The average compliance in both groups was 60%. Unfortunately, there was a difference in age distribution between the two groups after randomisation.

The investigators decided before the study that a minimum clinically relevant beneficial effect would be a 20% difference between the groups. Thus, based on previously reported episodes of illness in children attending daycare, they used a power calculation to estimate that, to detect a 20% difference with a power (or sensitivity) of 90% with 95% confidence, they needed to enrol 250 children per group. They were able to achieve this goal.

New information

The authors claim that milk containing *Lactobacillus* GG slightly reduced the incidence of respiratory infections and antibiotic treatment in children. The effect of probiotics was modest when adjustments were made for age.

Of the measured variables — days of any illness, days of respiratory or gastrointestinal symptoms, and absence because of illness — only for absence because of illness was there a difference between the intervention and control groups that approached statistical significance, although there was a trend towards less illness for the other variables in the *Lactobacillus* group.

It is useful to look at the tables of results in the article in question. Table 2 presents the raw data, and it is clear from scanning both the unadjusted and age-adjusted results that the effect is modest at best. The unadjusted days of absence because of illness was 4.9 days in the probiotic group and 5.8 days in the control group (ie, an improvement of 0.9 days); when adjusted for

Commentary

Rationale for the trial

Children attending daycare centres are more likely to suffer gastrointestinal and respiratory infections than children cared for at home or in small family groups.¹ There are public health and economic consequences, including direct medical costs and the indirect cost of parents taking time off work to care for sick children.² Studies support the use of probiotics to reduce the incidence of antibiotic-associated diarrhoea^{3,4} and to hasten recovery from rotavirus diarrhoea.⁵ Probiotic bacteria may have a

age, the difference between the probiotic group and the control group was 0.6 days. This raises the question of whether a reduction of 0.6 days in duration of absence because of illness is actually clinically useful. When the episodes of illness were diagnosed by a doctor (Table 3 of the article), the overall episodes of illness and courses of antibiotics prescribed for infections were significantly reduced for the probiotic group.

Of all antibiotic courses prescribed, there were 119 in the probiotic group versus 144 in the control group, with an absolute percentage reduction of 8.0% (95%CI, -16.6 to 1.0). The *P* value was 0.07, thus approaching, but not reaching, statistical significance. However, the age-adjusted results (reported as odds ratios) are less impressive and the statistical significance of these findings is further reduced, with a 95% confidence interval crossing unity, and a *P* value of 0.17 — not significant. The results are thus entirely consistent with a chance difference.



Implications for clinical practice

This is the first large, high quality study to examine this interesting research question.⁶ There were no reported harmful effects of the *Lactobacillus* GG; costs were not fully explored in the report.

The author of the accompanying editorial stated that probiotics “show promise but bigger studies are needed”.⁷ This is not entirely correct, as the study was adequately powered to detect a 20% difference and it failed to report a convincing clinical effect. However, it is likely that further clinical research will be undertaken in this and related areas, such as the use of probiotics to hasten recovery from acute gastroenteritis in children and the prevention of antibiotic-associated diarrhoea.

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Competing Interests

None identified.

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