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Original Article

Lactobacillus GG in the prevention of gastrointestinal and respiratory tract infections in children who attend day care centers: A randomized, double-blind, placebo-controlled trial☆

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SUMMARY

Background & aims: The aim of our study was to investigate the role of *Lactobacillus GG* (LGG) in the prevention of gastrointestinal and respiratory tract infections in children who attend day care centers.
Methods: We conducted a randomized, double-blind, placebo-controlled trial in 281 children who attend day care centers. They were randomly allocated to receive LGG at a dose of 10^9 colony-forming units in 100 ml of a fermented milk product (LGG group, $n = 139$) or placebo that was the same post-pasteurized fermented milk product without LGG (placebo group, $n = 142$) during the 3-month intervention period.
Results: Compared to the placebo group, children in the LGG group had a significantly reduced risk of upper respiratory tract infections (RR 0.66, 95% CI 0.52 to 0.82, NNT 5, 95% CI 4 to 10), a reduced risk of respiratory tract infections lasting longer than 3 days (RR 0.57, 95% CI 0.41 to 0.78, NNT 5, 95% CI 4 to 11), and a significantly lower number of days with respiratory symptoms ($p < 0.001$). There was no risk reduction in regard to lower respiratory tract infections (RR 0.82, 95% CI 0.24 to 2.76). Compared with the placebo group, children in the LGG group had no significant reduction in the risk of gastrointestinal infections (RR 0.63, 95% CI 0.38 to 1.06), vomiting episodes (RR 0.60, 95% CI 0.29 to 1.24), and diarrheal episodes (RR 0.63, 95% CI 0.35 to 1.11) as well as no reduction in the number of days with gastrointestinal symptoms ($p = 0.063$).
Conclusion: LGG administration can be recommended as a valid measure for decreasing the risk of upper respiratory tract infections in children attending day care centers.

1. Introduction

Children who attend day care centers are at 2–3 times greater risk for developing a respiratory tract infection and 2.2–3.5 times greater risk for developing a gastrointestinal infection than children who stay at home.[1] This increased number of acute diseases translates into a significant financial burden for both the family and society.[2] The increased costs are not only related to medical care visits and costs of medication but also to the time away from work and/or for payment for someone to look after a sick child. Illness of a child results in sick leave for a parent ranging from 5.6 to 28.8 days per year.[3] Providing a reliable strategy for the prevention of day care-acquired infections could be, therefore, of a significant importance.

Several studies have examined the role of probiotics in the prevention of respiratory tract and gastrointestinal infections in healthy individuals,[4–6] particularly those in children's day care centers.[7–9] Although randomized controlled trials have shown a modest effect, the results are not uniform. Therefore, prospective studies are required to confirm that effect.

The aim of this study was to investigate whether *Lactobacillus GG* (LGG) administration could play a beneficial role in the prevention of gastrointestinal and respiratory tract infections in children who attend day care centers.

Abbreviations: LGG, *Lactobacillus* GG; RR, relative risk; CI, 95% confidence interval; NNT, number needed to treat.

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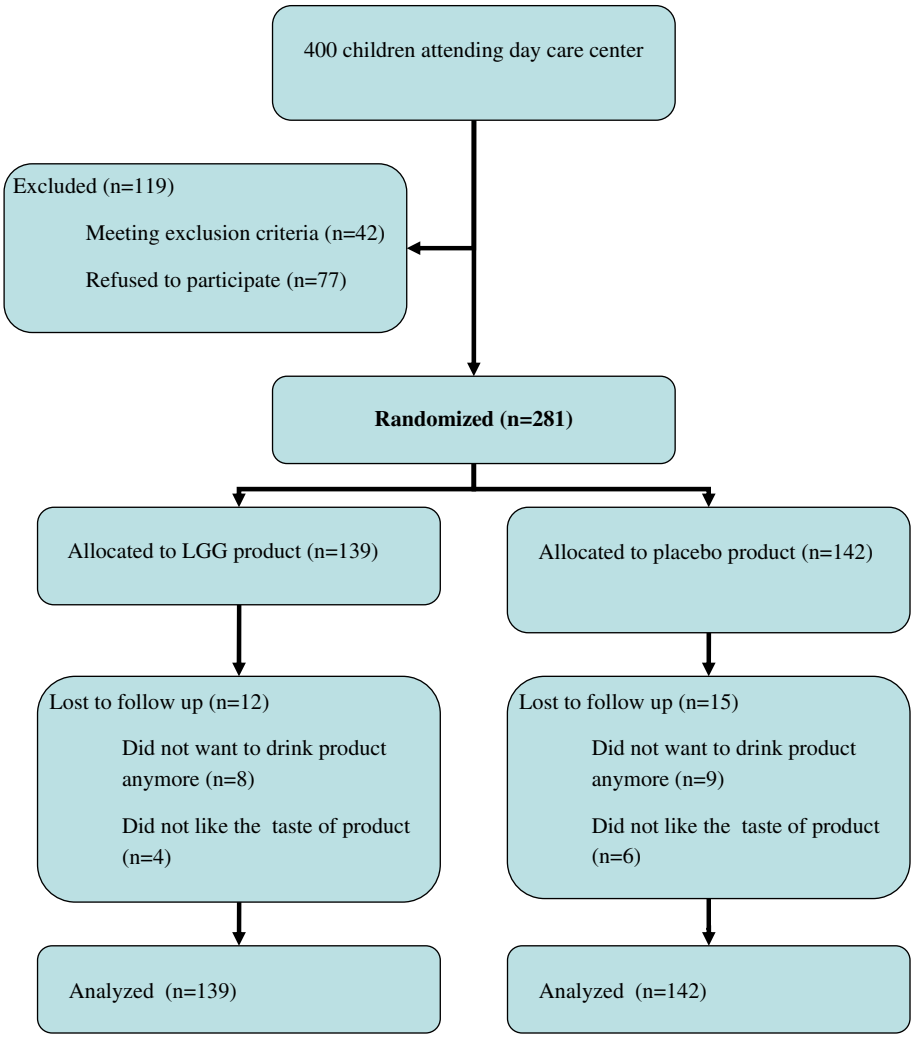

Fig. 1. Diagram of the trial according to CONSORT statement.[19]

2. Methods

All children of the same socioeconomic background who attended day care centers located in 4 separate locations in the Zagreb area, were eligible for the study. Enrolled children were those whose parents or legal guardians provided written informed consent and who did not meet any of the exclusion criteria. Excluded were children with cow's milk allergy (probiotics were given in a fermented cow's milk product); those who were receiving probiotic and/or prebiotic products prior to or at the time of enrollment; those who had a neoplasm, other chronic severe illness, or immunodeficiency; and children who disliked fermented milk products.

The study design was a prospective, randomized, double-blind, placebo-controlled trial. The tested probiotic, *Lactobacillus rhamnosus* strain *GG* (LGG strain from Valio), was administered in 100 ml of a fermented milk product at a dose of 10^9 colony-forming units (CFU). The placebo was the same post-pasteurized fermented milk product (100 ml) without LGG. Both study products were administered every day during the 3-month intervention period (from November 19, 2007 to February 20, 2008). Both products were supplied by Dukat Dairy Industry dd (leading dairy company in Croatia), who had no role in the conception, design, or conduct of the study as well as in the analysis or interpretation of the data. The LGG product and placebo were packed in identical bottles; they were of the same color, weight, smell, and taste (normal taste of fermented milk product, without added flavor). They were sent to the day care center once in two weeks. Company performed tests in every shipment with an aim to prove stability and concentration of the LGG. Both the research staff and children were unaware of the real nature of the product. The unblinding procedure was performed after the study was completed and after the statistical analyses were finalized.

The primary outcomes were as follows: (1) number of children with gastrointestinal infections, defined as diarrhea with 3 or more loose or watery stools within 24 hours with or without vomiting; (2) number of children with respiratory tract infections. Both upper and lower respiratory tract infections had to be confirmed by the physician.

Secondary outcomes were as follows: 1) number of children with vomiting episodes; 2) number of children with diarrheal episodes; 3) number of gastrointestinal infections lasting longer than 2 days; 4) number of children with upper respiratory tract infection, including rhinitis, pharyngitis, sinusitis, otitis, and the common cold; 5) number of children with lower respiratory tract infections, including pneumonia, bronchitis, and bronchiolitis; 6) number of respiratory tract infections lasting longer than 3 days; 7) total number of days with respiratory and gastrointestinal

Table 1
Baseline characteristics and differences between study groups: chi-square test.

Variable	LGG group ($N = 139$)	Placebo group ($N = 142$)	Significance level (P value)
Age[a] (months)	51.9 (13–86)	53.6 (13–83)	0.45
Female gender, No. (%)	61 (43.9%)	63 (44.4%)	0.94
Weight at the start of the study (kg)[a]	18.9 (10.3–36.0)	19.5 (10.3–34.5)	0.28
Height at the start of the study (cm)[a]	107.1 (78.0–136.0)	108.1 (79.0–133.0)	0.52
Weight difference before and after study (kg)[b]	0.5	0.5	0.66
Height difference before and after study (cm)[b]	1.5	1.5	0.89

Abbreviation: LGG, *Lactobacillus* GG.
[a] Mean; difference analyzed with Student *t* test.
[b] Median; difference analyzed with Mann–Whitney U test.

symptoms; and 8) number of days absent from day care center due to infections.

Children were assigned to one of the treatment groups (experimental or control) following a randomization procedure performed with computer-generated numbers. Under the supervision of the parents or day care educator, children received either the LGG preparation or placebo once daily during the 3-month intervention period. They were not allowed to consume any other product containing probiotics or prebiotics. To encompass a period when the majority of infections occur, we decided to start the study in November and to finish in February.

Every child had a study chart in which all data regarding product consumption, infections, or side effects were entered. Every 10 days, study investigators contacted parents to find out whether their child had developed any infections or side effects. Infections were diagnosed by local general practitioners, who were responsible for the care of each child. They were asked to record details of all infections that the child experienced during the intervention period.

The study was conducted following the principles of the Helsinki Declaration and good clinical practice guidelines. The protocol was approved by the Children's Hospital Ethical Committee and the Central Ethical Committee of the Zagreb University Medical School. Written informed consent was obtained from the parent or guardian of each child included in the study. The study was registered at the International Standard Randomized Controlled Trial Number Register (Study number: ISRCTN16959643).

We assumed that the difference between the control and experimental groups was 20%,[8] with parameters $\alpha = 0.05$, power = 0.90, and controls per case subject = 1; based on this, the minimum total sample size for use of the Fisher exact two-tailed test would be 266 (133 subjects per group) (*GPower, version 3.0.9*). On the other hand, for logistic regression of a binary dependent variable using several independent variables, at 80% power at a 0.05 two tailed significance level, to detect a change in Prob (Y = 1) from the value of 0.05 at the mean of X to 0.100 when X is increased to one standard deviation above the mean, requires a minimal sample size of 262. Two primary outcomes will be examined using logistic regression (number of gastrointestinal and respiratory infections). The model will test whether the independent variables (age and gender) predict the dependent/criterion variable (presence of respiratory and presence of gastrointestinal infections).

2.1. Statistical analysis

Descriptive statistics were used to describe the basic features according to age, gender, duration of the intervention, and disease symptoms. Normality of the data distribution was analyzed with the Smirnov–Kolmogorov test. The X^2 test was used to estimate differences in the distribution of qualitative variables. Differences in quantitative variables, according to their distribution, were analyzed with the parametric *t* test or the nonparametric Mann–Whitney test. Multiple binary logistic regression was performed to determine significant predictors of gastrointestinal and respiratory tract infections. All statistical tests were two-tailed tests and performed at the 5% level of significance. Statistical software SPSS (version 15.1; SPSS, Chicago) was used for all statistical analyses. To calculate the relative risk (RR), 95% confidence interval (CI), and number needed to treat (NNT), StatsDirect (version 2.5.6. [2006-04-15]; Iain E. Buchan) was used. The difference between the study groups was considered significant when the p value was <0.05 or when the 95% CI for RR did not exceed 1.0 (equivalent to $p < 0.05$). All analyses were performed on the intention-to-treat basis, in which all of the participants in a trial are analyzed according to the intervention to which they were assigned, whether or not they received it.

3. Results

As shown in Fig. 1, there were 281 children enrolled in the study; 139 received the LGG supplemented fermented milk product and 142 received the placebo product. There was no statistically significant difference between the groups in regard to age, gender, weight and height at the beginning of the study, or difference in weight and height prior to and after the intervention (Table 1).

Considering the primary outcomes, the risk of respiratory tract infections was significantly reduced in the LGG group compared with the placebo group (RR 0.63, 95% CI 0.51 to 0.79, NNT 5, 95% CI 3 to 8). In contrast, the risk of gastrointestinal infections did not significantly differ between the LGG and placebo groups (RR 0.63, 95% CI 0.38 to 1.06) (Table 2).

Moreover, secondary outcomes related to respiratory tract infections were also significantly different between groups. Children in the LGG group had a lower risk of episodes of respiratory tract infections lasting longer than 3 days compared to children in the placebo group (RR 0.57, 95% CI 0.41 to 0.78, NNT 5, 95% CI 4 to 11) (Table 3). According to the study results, the beneficial effect of probiotics was limited to upper respiratory tract infections (RR 0.66, 95% CI 0.52 to 0.82, NNT 5, 95% CI 4 to 10). A significant difference between the LGG group and the placebo group was not confirmed for the risk of lower respiratory tract infections (RR 0.82, 95% CI 0.24 to 2.76). A bacterial cause was determined and treated with antibiotics in 34 of 142 children in the placebo group and in 23 of 139 children in the LGG group ($p = 0.12$). They were treated with antibiotics due to: acute otitis media (8 children in LGG group vrs 13 in placebo group, $p = 0.28$); pharyngitis (10 children in LGG

Table 2
Primary outcome measures and differences between study groups: chi-square test.

Variable	LGG group ($N = 139$)	Placebo group ($N = 142$)	P value	Relative risk (95% CI)	NNT (95% CI)
Number of children with gastrointestinal infections	20 (14.4%)	32 (22.5%)	0.08	0.63 (0.38 to 1.06)	NS
Number of children with respiratory tract infections	60 (43.2%)	96 (67.6%)	<0.001	0.63 (0.51 to 0.79)	5 to benefit (3–8 to benefit)

Abbreviations: CI, confidence interval; LGG, *Lactobacillus* GG; NNT, number needed to treat; NS, not significant.

Table 3
Secondary outcome measures and differences between study groups: chi-square test.

Variable	LGG group ($N = 139$)	Placebo group ($N = 142$)	*P* value	Relative risk (95% CI)	NNT (95% CI)
Number of children with vomiting episodes	10 (7.2%)	17 (12.0%)	0.17	0.60 (0.29 to 1.24)	NS
Number of children with diarrheal episodes	16 (11.5%)	26 (18.3%)	0.11	0.63 (0.35 to 1.11)	NS
Number of gastrointestinal infections lasting longer than 2 days	14 (10.1%)	12 (8.5%)	0.64	0.98 (0.91 to 1.06)	NS
Number of children with upper respiratory tract infections	58 (41.7%)	95 (66.9%)	<0.001	0.66 (0.52 to 0.82)	5 to benefit (4–10 to benefit)
Number of children with lower respiratory tract infections	4 (2.9%)	5 (3.5%)	0.759	0.82 (0.24 to 2.76)	NS
Number of respiratory infections lasting longer than 3 days	39 (28.1%)	70 (49.3%)	<0.001	0.57 (0.41 to 0.78)	5 to benefit (4–11 to benefit)
Total duration of respiratory symptoms (days)[a]	0 (0–21)	4 (0–22)	<0.001	–	–
Total duration of gastrointestinal symptoms (days)[a]	0 (0–7)	0 (0–11)	0.06	–	–
Absence from day care center due to infections (days)[b]	3.1 (0–21.0)	5.1 (0–23)	<0.001	–	–

Abbreviations: CI, confidence interval; LGG, *Lactobacillus* GG; NNT, number needed to treat; NS, not significant.
[a] Median; difference analyzed with Mann–Whitney U test.
[b] Mean (95% CI); difference analyzed with Student *t* test.

group vrs 14 in placebo group, $p = 0.43$), purulent rinitis (4 children in LGG group vrs 6 in placebo group, $p = 0.54$) and pneumonia (one child in both groups).

There was no difference in the number of children with vomiting or diarrheal episodes between the groups (RR 0.60, 95% CI 0.29 to 1.24; RR 0.63, 95% CI 0.35 to 1.11; respectively) (Table 3). Likewise, there was no difference between groups in the risk of episodes of gastrointestinal infections lasting longer than 2 days (RR 0.98, 95% CI 0.91 to 1.06). None of the children developed a bacterial infection (all stool samples were negative). All children were treated symptomatically, and none required antibiotic treatment.

The total number of days with respiratory symptoms was significantly higher in the placebo group compared to the LGG group ($p < 0.001$). However, a significant difference between groups was not found for the total number of days with gastrointestinal symptoms ($p = 0.06$).

The rate of absence from daycare centers due to infections was lower in the LGG group compared to the placebo group ($p < 0.001$) (Table 3).

Children who received the placebo had a 2.88 times greater chance of acquiring a respiratory tract infection than children who received LGG (OR = 2.88, CI 1.70–4.88) (Table 4). Regarding gastrointestinal infections, the chance of developing an infection if not receiving LGG was not significantly higher (OR = 1.72, CI 0.92–3.20) (Table 5).

No side effects or adverse effects were noted during the study.

4. Discussion

Our study shows that consumption of probiotics on a daily basis in children who attend day care centers can significantly reduce the number of upper respiratory tract infections. The efficacy of probiotics in the prevention of infections in children who attend day care centers has been investigated in several studies, which have yielded contradictory results.[7–9] In a randomized, double-blind, placebo-controlled study ($n = 571$ children, age range: 1–6 years), administration of LGG resulted in a relative reduction of 17% in the number of children suffering from respiratory tract infections with complications.[8] On the other hand, results from a study evaluating *Bifidobacterium lactis* or *Lactobacillus reuteri* versus placebo ($n = 220$ children, age range: 4 to 10 months) did not show a beneficial probiotic effect on the rate and duration of respiratory illnesses.[7] Our study confirms the beneficial effects of LGG; LGG treatment substantially reduced the total number of respiratory tract infections. However, this finding applies only to upper respiratory tract infections, perhaps due to the small number of infections affecting the lower respiratory tract (4 in LGG group and 5 in placebo group). LGG treatment also reduced the number of respiratory tract infections that lasted longer than 3 days. Moreover, the NNT to prevent one respiratory tract infection was only 5, and the odd of acquiring a respiratory tract infection in the placebo group was 2.88 times higher than that in the LGG group. On the other hand, our study also showed that patients who were treated with LGG had a significantly lower total number of days with respiratory symptoms ($p < 0.001$), which was not shown by previous studies.[8] Although our study showed reduction of antibiotic prescription in children who were treated with LGG, difference was not significant ($p = 0.12$) which is in contrary to previous studies.[7,8]

Concerning the role of probiotics in the prevention of gastrointestinal infections, 2 studies have examined the role of LGG. One randomized, double-blind, placebo-controlled study ($n = 571$ children, age range: 1–6 years) revealed no difference between the LGG and placebo groups in the number of days with gastrointestinal symptoms or in the proportion of children without diarrhea.[8] Another randomized placebo-controlled trial, performed in 204 undernourished children 6 to 24 months of age, demonstrated a significant reduction in the number of diarrheal episodes in the probiotic group.[4] Studies using other probiotic strains have also produced contradictory results.[7,9] Our study showed no significant effect of LGG treatment not only on the number of gastrointestinal infections, but also on the number of diarrheal and vomiting episodes. Furthermore, LGG treatment did not reduce the total number of days with gastrointestinal symptoms.

Regard to day care center absenteeism due to infections, our study confirmed previous results[8] that use of probiotics significantly reduces absence from day care centers due to illness ($p < 0.001$).

As for the mechanisms responsible for the beneficial role of probiotics, studies have documented direct antimicrobial effects, improvement in mucosal barrier function, and immunomodulating activity due to the effects of probiotics on both innate and adaptive

Table 4
Predictors of respiratory tract infections: multiple binary logistic regression.

Predictor	OR (95% CI)	*P* value
Placebo group	2.88 (1.70–4.88)	<0.001
Female gender	0.65 (0.39–1.10)	0.12
Younger age	1.02 (1.01–1.21)	0.001

Table 5
Predictors of gastrointestinal infections: multiple binary logistic regression.

Predictor	OR (95% CI)	*P* value
Placebo group	1.72 (0.92–3.20)	0.09
Female gender	0.73 (0.39–1.36)	0.33
Younger age	1.04 (0.98–1.08)	0.61

immunity.[10] *In vivo* and *in vitro* studies have shown that activation of macrophages,[11] improvement in natural killer cell activity,[12] increased numbers of IgA-, IgM-, and IgG-secreting cells in the circulation, and increased fecal IgA concentrations[13–15] provide beneficial effects on the balance of pro- and anti-inflammatory cytokines (i.e., decreases in fecal alpha 1-antitrypsin, urinary eosinophil protein X, and tumor necrosis factor-α activity and increases in TGF-β activity).[14,16–18]

We are aware of several limitations to our study. First, most of the infections diagnosed during the study period in both groups of children were of unproven etiology and the diagnosis and treatment was based on clinical judgment. However, treatment of all infections led to a good clinical response. Second, the rate of severe infections was very low and, therefore, no clear effect of LGG could be proven. Third, study lasted for 3 months, during winter period, and because of that the season with highest risk of gastrointestinal infections was missed. However, the duration of the study was limited to 3 months because it was hard to expect children to drink 100 ml of fermented milk daily longer than 3 months and the number of children who attend day care centers during summer in Croatia is significantly reduced. Forth, respiratory infections can be mixed with allergic reactions (asthma) and thus relying on a number of physicians without strict criteria for diagnosis and the nature of the illness may cause bias and finally, there was no mechanism to ascertain no other probiotic intake. However, all parents who decided to participate in the study agreed not to give other probiotic preparations. Knowing all mentioned above we can suggest that well-performed cost-benefit studies are required before introducing LGG as a preventive strategy.

In conclusion, considering the significant decrease in the number of upper respiratory tract infections in children treated with LGG and knowing that the NNT was only 5, we can recommend treatment with LGG as a valid measure for the prevention of upper respiratory tract infections in children who attend day care centers.

Contributors

Author's contributions: Study concept and design: Hojsak and Kolaček. Acquisition of data: Hojsak, Snovak, Abdović, Mišak, Kolaček. Analysis and interpretation of data: Hojsak, Szajewska, Milošević, Kolaček. Drafting of the manuscript: Hojsak, Kolaček, Szajewska. Critical revision of the manuscript for important intellectual content: Hojsak, Szajewska, Kolaček. Administrative, technical, and material support: Hojsak, Snovak, Abdović, Mišak.

Conflict of Interest

Before, during, or after the study, none of the authors received any funds for their work, which was exclusively voluntary. All authors have stated that they have no conflict of interest.

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All authors have participated in the study and preparation of the manuscript and have seen and approved the final version.

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