Probiotics and Child Care Absence Due to Infections: A Randomized Controlled Trial

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OBJECTIVES: The risk of infections is higher in children attending child care compared with children cared for at home. This study examined the effect of a combination of probiotics on absence from child care because of respiratory and gastrointestinal infections in healthy infants aged 8 to 14 months at the time of enrollment in child care.

METHODS: The ProbiComp study was a randomized, double-blind, placebo-controlled study. A total of 290 infants were randomly allocated to receive a placebo or a combination of Bifidobacterium animalis subsp lactis and Lactobacillus rhamnosus in a dose of 10^9 colony-forming units of each daily for a 6-month intervention period. Absence from child care, occurrence of infant symptoms of illness, and doctor visits were registered by the parents using daily and weekly Web-based questionnaires.

RESULTS: Median absence from child care was 11 days (interquartile range: 6–16). Intention-to-treat analysis showed no difference between the probiotics and placebo groups (P = .19). Additionally, there was no difference in any of the secondary outcomes between groups; the number of children with doctor-diagnosed upper or lower respiratory tract infections, the number of doctor visits, antibiotic treatments, occurrence and duration of diarrhea, and days with common cold symptoms, fever, vomiting, or caregivers’ absence from work.

CONCLUSIONS: A daily administration of a combination of B animalis subsp lactis and L rhamnosus for 6 months did not reduce the number of days absent from child care in healthy infants at the time of enrollment in child care.
The risk of respiratory and gastrointestinal infections is 2 to 3 times greater in children attending child care compared with children cared for at home, especially in young children aged 0 to 2 years, and it is most pronounced within the first months after enrollment in child care. The increased exposure to infections in child care has been associated with factors such as crowding and sharing of toys, leading to increased risk of disease transmission between infants. Moreover, many children stop being breastfed when they start in child care, which is also likely to increase the risk of infections because breastfeeding has been shown to protect against infections. In Denmark, 90% of all 1-to-2-year-old children are attending child care, and on average each child is absent from child care because of illness 12 days each year. Infection during childhood is a distress to families but also a financial burden to society, both in terms of lost working days of parents and medical costs. Therefore, strategies for prevention are of great importance.

The effect of probiotics in the prevention of infections in preschool-aged children has been investigated in several randomized controlled trials. Recent reviews and meta-analyses have suggested an effect of probiotics in the treatment and prevention of upper respiratory infections and gastrointestinal infections in children but also indicated that the effect of probiotics is strain dependent. Bifidobacterium animalis subsp. lactis (BB-12) and Lactobacillus rhamnosus (LGG) are 2 probiotic strains that have been widely examined, and researchers in studies of healthy preschool-aged children have reported a reduction in the incidence or duration of respiratory infections, and gastrointestinal infections, and a reduction in days absent from school or child care. Proposed beneficial effects of probiotics include interactions with both the innate and adaptive immune systems, which may increase resistance against pathogens. Many probiotic studies have been performed in preschool-aged children, but to our knowledge, no previous study has investigated the effect of probiotics on infections during the time of enrollment in child care. The primary objective of the ProbiComp study was to examine the effect of a daily administration of a combination of the strains BB-12 and LGG for 6 months on absence from child care because of respiratory and gastrointestinal infections in Danish infants when starting child care.

METHODS
Study Design and Subjects
The ProbiComp study was a double-blind, placebo-controlled parallel study in which Danish infants aged 8 to 14 months were randomly assigned to either probiotics or a placebo for a 6-month period. Infants were recruited during 2 autumn seasons, from mid-August to mid-December in 2014 and 2015. Written information about the study was sent to parents of 11,516 infants living in the capital region of Denmark by using extractions from the National Danish Civil Registry, resulting in parents and legal guardians of 290 infants (2.5%) giving written, informed consent to participate. Infants were eligible for inclusion if they were single born and expected to start in child care at age 8 to 14 months between September and February. Exclusion criteria were birth weight <2500 g, gestational age <36 weeks, severe chronic illnesses, regular medication, antibiotic treatment within 4 weeks before baseline examination, or non-Danish-speaking parents. Intake of supplements or fermented milk products with probiotics was not allowed for 2 weeks up to baseline and during the whole intervention period, and intake of other yogurt products was limited to 1 to 2 meals per week. The onset of intervention was up to 12 weeks before expected start in child care. The study protocol was approved by the Committees on Biomedical Research Ethics for the Capital Region of Denmark (H-4-2014-032), and the study was registered at clinicaltrials.gov (identifier NCT02180581).

Study Product and Randomization
The study product was provided for free by Chr Hansen A/S (Hørsholm, Denmark) and consisted of 1.0 g of maltodextrin powder, with or without a combination of the 2 probiotics BB-12 and LGG at a dose of 109 colony-forming units (CFUs) each (BB-12 and LGG are registered trademarks of Chr Hansen A/S). Active sachets were analyzed for long-term storage stability at 25 °C/60% relative humidity, and the products were within the specification after 24 months. The powder was provided in identical sachets, and the placebo and active powder did not differ in smell, taste, or color. Neither study personnel nor parents were aware of the nature of the product, and unblinding took place only after completion of data collection and main statistical analyses. The infants were assigned to receive either probiotics or a placebo by using block randomization (randomization.com) with a block size of 8. The sachets were provided to the families for the entire 6-month intervention period at baseline and were packed in boxes labeled with unique participant identification numbers to ensure allocation concealment. A randomization list and boxes with sachets were prepared by a university employee with no involvement in the study. Parents were instructed to dissolve 1 sachet in a small amount of infant food or drink daily and not to add the product to hot food or drinks. They
were asked to register daily whether the infants had ingested the product. Registration sheets and unused sachets were returned by the parents at the end of the intervention to evaluate compliance.

Data Collection

Clinical examinations at the start and end of intervention were performed at the University of Copenhagen’s Department of Nutrition, Exercise and Sports in Denmark. Naked body weight was measured to the nearest 5.0 g by using a digital scale (TANITA BD-815 MA; Frederiksberg Vaegtfabrik, Frederiksberg, Denmark). Length was measured to the nearest 0.1 cm by using a portable measuring board (QuickMedical Medical Equipment and Supplies, Issaquah, WA). The mean of 3 measurements was used. At baseline, the parents were interviewed about household characteristics and infant history of illness since birth. At both visits, questions about breastfeeding and the use of infant formula were asked.

During the intervention period, occurrence of infant symptoms of illness, absence from child care, and so on were registered by the parents in weekly and daily Web-based questionnaires. On a weekly basis, doctor visits, doctor-diagnosed respiratory infections, antibiotic treatments, absence from child care, and caregivers’ absence from work because of infant illness were registered. Reasons for absence from child care were categorized independently by 2 study personnel. Parents evaluated daily if an infant was ill or not. If the infant was ill, symptoms of the common cold (runny or stuffy nose and/or cough), fever, vomiting, and diarrhea were registered. All Web-based questionnaires could be answered retrospectively for ≤7 days. To minimize the occurrence of missing data, the parents received reminders via short message service and were contacted by e-mail or telephone if questionnaires were not answered.

Primary and Secondary Endpoints

The primary endpoint was the number of days absent from child care because of respiratory or gastrointestinal infections, which are defined as symptoms related to the respiratory or gastrointestinal tracts. Secondary endpoints were the number of days absent from child care because of other illnesses (not infections), the number of infants with doctor-diagnosed upper respiratory tract infections (URTIs) (eg, sinusitis, sore throat, otitis media, and pseudo croup) and lower respiratory tract infections (LRTIs) (eg, pneumonia and bronchitis), the number of URTIs per infant, the number of infants with at least 1 episode of diarrhea (defined as ≥3 loose or watery stools in 24 hours, and a minimum of 48 hours separating episodes), the number of diarrheal episodes per infant, the duration of diarrheal episodes, the number of days with vomiting, the number of days with fever (>38°C), the number of days with symptoms of the common cold (defined as a minimum of 2 consecutive days with symptoms of either runny or stuffy nose and/or cough), the number of doctor visits because of infections or other illnesses, the number of antibiotic treatments, and the number of days caregivers were absent from work because of infant illnesses.

Adverse Events

Each month, the parents reported in Web-based questionnaires if their infants had experienced any symptoms, illnesses, or unexpected events not described in the daily and weekly questionnaires during the last month. The clinically responsible physician evaluated all reported symptoms.

Sample Size Calculation

Sample size was calculated on the basis of Hojsak et al.11 who showed a 39% reduction in the number of days absent from child care because of infections for a 3-month intervention period. The average number of days absent from child care because of infections was 5.1 days in the placebo group. A conservative estimate of an SD of 5.0 was also derived from the same article. In the current study, a 6-month intervention period would amount to children attending child care for an average of 4.5 months (because of enrollment before admission to child care). A 25% reduction leads to effect size of 1.925 (obtained as 0.25 × 5.1 × 4.5/3). The resulting sample size calculation, assuming α = .05 and power = 0.85, showed that 244 children (122 in each of the 2 groups) had to be recruited. To allow for a 20% dropout, 153 children had to be recruited per group.

Statistical Analyses

Baseline characteristics are shown as mean (SD) or median (interquartile range [IQR]) for continuous variables and n (%) for categorical variables. Compliance was compared between groups by using a 2-sample t test. For the primary outcome, the effect of probiotics was evaluated by using a Poisson regression model with robust SEs (to adjust for any misspecification of the model). To take into account the difference in time from baseline to start in child care among infants, the number of intervention days after start in child care was included as an offset. Secondary outcomes, measured as days or episodes, were analyzed by using similar Poisson regression models but with total number of intervention days as an offset. The effect of probiotics on the number of children with at least 1 episode of a URTI, LRTI, or diarrhea was evaluated by using logistic regression. Adjustment for age, sex, intervention year, and enrollment.
period within each year (August to September, October, November to December) was included. These were selected before data analysis, and because of the randomized design, adjustments were limited to variables related to the study design and/or based on biological grounds. Analysis of the duration of diarrheal episodes included only infants with reported episodes (>0) and was analyzed by using mixed-effects Poisson regression, with infant as a random effect and otherwise the same adjustment as for the analysis of diarrheal episodes per child including all children. Additionally, all analyses were repeated and included adjustment for occurrence of URTIs since birth. As shown in Table 1, the randomization produced similar distributions in the 2 groups in regard to sociodemographic factors, anthropometrics, and breastfeeding. A small difference was seen in health status since birth, with more infants having at least 1 episode of a doctor-diagnosed URTI since birth in the probiotic group compared with the placebo group (12.7% and 5.0%, respectively). The median intervention period was 183 days (IQR: 182–189), and 35% of the infants were included in the months of August to September, 33% in October, and 32% in November to December. The infants started child care at an average age of 10.6 months (SD: 1.1) and after a median of 12 days (IQR: 5–21) after onset of the intervention. Median compliance was 97.0% (IQR: 94.0–99.0) and did not differ between the 2 groups (P = .92). Furthermore, parents in both groups completed 99.0% (IQR: 96.2–100) of daily questionnaires and 98.2% (IQR: 92.3–100) and 100% (IQR: 92.7–100) of weekly questionnaires in the probiotic and placebo groups, respectively. For daily and weekly questionnaires, 3.3% and 5.5% of records in the probiotic group and 3.0% and 4.8% of the records in the placebo group were missing.

RESULTS

As shown in Fig 1, 290 infants were randomly assigned in the study (145 and 146 allocated to the probiotic and the placebo group, respectively. Three infants were excluded before the baseline examination because of antibiotic treatments, and 2 families withdrew their consent, resulting in a total of 285 infants for the ITT analyses. Twenty-five infants (8.8%) withdrew during the study (14 in the probiotic group) after a median of 12 weeks of intervention (range: 1–29). In both groups, dropouts were primarily because of parents finding study activities too time consuming (n = 14) or because the parents wanted to give the infants probiotics (n = 7).
had a mean age of 10.0 months (SD: 0.7), weight of 9.4 kg (SD: 1.0), and length of 73.9 cm (SD: 2.8).

**Primary and Secondary Endpoints**

There was no difference in absence from child care between the probiotics and placebo groups (probiotics compared with placebo: 1.14 days (95% confidence interval [CI] –0.55 to 2.82). Likewise, no effect of probiotics was found for any of the secondary endpoints (Table 2). Per-protocol analyses showed similar results to ITT (Supplemental Table 3) except that infants in the probiotic group had significantly more days with fever than infants in the placebo group (mean difference 1.84, 95% CI: 0.06 to 3.63, P = .04). However, additional adjustment for occurrence of at least 1 episode of a URTI since birth rendered this effect nonsignificant (1.39, 95% CI: –0.41 to 3.18, P = .13). All other conclusions remained unchanged (data not shown).

**Adverse Events**

There were no reported adverse events related to the study product.

**DISCUSSION**

In this study, a daily administration of the 2 probiotic strains BB-12 and LGG, in a dose of 10^9 CFU per day of each for 6 months, did not reduce days absent from child care because of respiratory or gastrointestinal infections in Danish infants aged 8 to 14 months at the time of enrollment in child care.

Our results support findings from a Norwegian study in 1- to 3-year-old children in which no effect of a combination of the strains LGG and BB-12 (1.5 × 10^10 CFU per day of each) was found on respiratory infections or absence from child care during their first winter in child care.18 However, the number of days with gastrointestinal symptoms was significantly reduced in the probiotic group compared with the placebo group.18 Similarly, a 12-week intervention with formula supplemented with BB-12 (1.2 × 10^9 CFU per day) resulted in fewer and shorter episodes of diarrhea in 4- to 10-month-old Israeli infants in child care, but there was no effect on respiratory infections.17 A recent study by Hojsak et al12 in healthy 1- to 6-year-old Croatian children showed no preventive effect on respiratory or gastrointestinal infections or a reduced absence from child care in a 3-month intervention with BB-12 administered in a dose of 10^9 CFU per day. Previously, the same authors investigated the probiotic LGG in a similar setting and found a significantly reduced risk of URTIs and 39% fewer days absent from child care because of illness (3.1 and 5.1 days in the probiotic and placebo groups, respectively).11 A reduced risk of respiratory infections and a reduction in the number of days absent from child care was also reported in 2 independent Finnish studies of children of the same age as those studied by Hojsak et al11,12 in a subgroup analysis13 and an analysis not adjusted for age.15 In
TABLE 2 Absence From Child Care and Respiratory and Gastrointestinal Infections in the 2 Groups During the 6-Month Intervention Period

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>Placebo, n = 142</th>
<th>LGG and BB-12, n = 143</th>
<th>Placebo Mean Difference (95% CI)</th>
<th>LGG and BB-12 Versus Placebo Odds Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days absent from child care because of infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days absent from child care (total)</td>
<td>11.0 (6.1–17.0)</td>
<td>11.0 (5.0–15.4)</td>
<td>1.14 (–0.55 to 2.82)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Days absent from child care because of respiratory infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days with symptoms of common cold</td>
<td>25 (13.0–43.8)</td>
<td>24 (14.0–41.0)</td>
<td>1.94 (–4.70 to 8.59)</td>
<td>–</td>
<td>.59</td>
</tr>
<tr>
<td>Number of children with ≥1 episode of an URTI</td>
<td>54 (38)</td>
<td>47 (33)</td>
<td>—</td>
<td>1.22 (0.74 to 2.00)</td>
<td>.43</td>
</tr>
<tr>
<td>Number of LRTI episodes per child</td>
<td>0 (0–1)</td>
<td>0 (0–1)</td>
<td>0.15 (–0.07 to 0.37)</td>
<td>—</td>
<td>.17</td>
</tr>
<tr>
<td>Number of children with ≥1 episode of an LRTI</td>
<td>25 (18)</td>
<td>31 (22)</td>
<td>—</td>
<td>0.74 (0.41 to 1.34)</td>
<td>.33</td>
</tr>
<tr>
<td>Gastrointestinal infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days with fever</td>
<td>11.0 (7.0–18.0)</td>
<td>10.0 (5.3–14.0)</td>
<td>1.48 (–0.16 to 3.12)</td>
<td>—</td>
<td>.08</td>
</tr>
<tr>
<td>Number of antibiotic treatments</td>
<td>0 (0–1)</td>
<td>0 (0–1)</td>
<td>0.03 (–0.18 to 0.23)</td>
<td>—</td>
<td>.70</td>
</tr>
<tr>
<td>Doctor visits</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illness (total)</td>
<td>2 (1–4)</td>
<td>2 (1–4)</td>
<td>0.22 (–0.06 to 0.51)</td>
<td>—</td>
<td>.12</td>
</tr>
<tr>
<td>Infections</td>
<td>2 (1–4)</td>
<td>2 (0–3)</td>
<td>0.25 (–0.23 to 0.75)</td>
<td>—</td>
<td>.30</td>
</tr>
<tr>
<td>Other illness</td>
<td>0 (0–1)</td>
<td>0 (0–1)</td>
<td>–0.03 (–0.23 to 0.17)</td>
<td>—</td>
<td>.78</td>
</tr>
<tr>
<td>Caregiver absence from workplace because of child illness (d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illness (total)</td>
<td>7.0 (4.0–13.0)</td>
<td>7.0 (3.0–11.9)</td>
<td>1.02 (–0.48 to 2.52)</td>
<td>—</td>
<td>.18</td>
</tr>
<tr>
<td>Infections</td>
<td>6.0 (3.0–8.0)</td>
<td>5.0 (2.0–9.4)</td>
<td>0.61 (–0.84 to 1.85)</td>
<td>—</td>
<td>.34</td>
</tr>
<tr>
<td>Other illnesses</td>
<td>0.0 (0.0–2.0)</td>
<td>1.0 (0.0–2.0)</td>
<td>0.41 (–0.29 to 1.11)</td>
<td>—</td>
<td>.25</td>
</tr>
<tr>
<td>Days absent from child care because of illness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illness (total)</td>
<td>13.0 (9.0–19.0)</td>
<td>13.0 (8.0–19.9)</td>
<td>0.94 (–0.89 to 2.77)</td>
<td>—</td>
<td>.31</td>
</tr>
<tr>
<td>Other illnesses (not infections)</td>
<td>1.0 (0.0–3.9)</td>
<td>1.0 (0.0–5.0)</td>
<td>–0.19 (–0.90 to 0.51)</td>
<td>—</td>
<td>.59</td>
</tr>
</tbody>
</table>

---. no data.

a Values are median (IQR) or n (%).
b All randomly assigned children with data on outcome (of 290 randomly assigned children, no data are available for 5 children who dropped out before intervention started, and data are additionally missing for 2 children for the primary outcome because of dropout before starting day care). N = 285–285.
c Estimates are presented as the number of days or episodes (back-transformed to original scale) and analyzed by using Poisson regression with robust SEs and the duration of intervention as an offset (duration of intervention after starting day care for primary outcome) unless otherwise stated. Sex, age, intervention year, and enrollment period within each year are included as covariates.
d Binary outcomes are analyzed by using logistic regression. Sex, age, intervention year, duration of intervention, and enrollment period within each year are included as covariates.
e Doctor-diagnosed URTIs (eg, sinusitis, sore throat, otitis media, and pseudo croup) and LRTIs (eg, pneumonia and bronchitis).
f Only infants with ≥1 episode of diarrhea were included in analysis. An estimate is given as the number of episodes and analyzed by using mixed Poisson regression with child as a random effect. Sex, age, intervention year, and enrollment period within each year are included as fixed effects.

Both of these studies, the probiotic LGG was administered daily for 7 months but in a lower dose (1–2 x 10⁸ CFU per day) than in our study. A preventive effect on infections has also been suggested in child care studies in which researchers examined other probiotic strains than those in the current study. For example, a 6-month intervention with Lactobacillus ruterri DSM 17938 resulted in a significant reduction in both frequency and duration of diarrhea and respiratory tract infections in 6- to 36-month-old children,²¹ and Lactobacillus acidophilus NCFM alone or in combination with B animalis subsp lactis Bi-07 reduced influenza-like symptoms such as fever and rhinorrhea in children aged 3 to
5 years. The explanation as to why results between studies are inconclusive could be related to several factors, such as the duration of studies, the probiotic dose, the ages of participants, and strain-specific effects. Recent meta-analyses showed that the LGG probiotic was most effective in the treatment of acute gastroenteritis in doses of $10^{10}$ CFU per day or more.28 Although the dose dependency seems less clear in the prevention of respiratory and gastrointestinal infections, the dose of $2 \times 10^9$ CFU per day used in the current study may be too low to show a potential beneficial effect.

The infants in our study were on average 10 months old at baseline, and 47.4% were still breastfeeding. The average age of termination of breastfeeding for these infants was 12.1 months (SD: 1.6). In contrast, Smerud et al18 and Weizman et al17 only included infants who were not breastfed at baseline. The age of the children in other studies in child care centers were older than 1 year.11–13,15 Breast milk is an important factor in the developing immune system and in the protection against infections during infancy, and it contains numerous components that are thought to modulate immunologic responses, such as cytokines, oligosaccharides, leukocytes, and immunoglobulin A.36 Also, 68.1% of the infants received infant formula from baseline to an average age of 12.8 months (SD: 1.4), with 33.5% of the formulas supplemented with probiotics and 57.2% supplemented with prebiotics. Parents were instructed not to provide the infants with other supplements or yogurt products with added probiotics, but because products with probiotics are widely available in Denmark, it cannot be ruled out that the infants consumed other products supplemented with probiotics. Products with prebiotics were not prohibited during the study, and prebiotics have been shown to promote growth, especially of bifidobacterium in the gut.37 A potential immunoprotective effect of breastfeeding and/or probiotics and prebiotics may thus have reduced the power of the current study. Another important consideration is that the infants were of generally good health, and the families were recruited after replying to an invitation. This resulted in a self-selected population of primarily well-educated, high-income families with a special interest in the study. Considering the aforementioned factors, the results from this study cannot be readily extrapolated to children in other age groups or in different settings.

A strength of this study is the low drop-out rate of 8.7%, which was considerably lower than expected. Self-reported compliance was high, and comprehensive daily and weekly records of infant illness were collected with limited missing data (~6%), showing no indication of a differential bias between groups. Besides missing data, a limitation of the current study is that data on infant illness were collected by using parental questionnaires. Although parents were instructed only to report URTIs and LRTIs if diagnosed by a doctor, etiology of illness and the rate of bacterial and viral infections could not be confirmed. However, the ProbiComp study was performed in a real-life setting, and the use of parent-reported information may thus reflect the effectiveness of the intervention, which is highly relevant in a public health perspective.

CONCLUSIONS

A daily administration of a combination of the probiotics BB-12 and LGG for 6 months did not reduce the number of days absent from child care in Danish infants aged 8 to 14 months at the time of enrollment in child care. This study does not support the use of probiotics in the prevention of respiratory and gastrointestinal infections in infants.

ACKNOWLEDGMENTS

We thank participating infants, their families, as well as the study team for their contribution to the study.

ABBREVIATIONS

BB-12: Bifidobacterium animalis subsp lactis
CI: confidence interval
CFU: colony-forming unit
IQR: interquartile range
ITT: intention to treat
LGG: Lactobacillus rhamnosus
LRTI: lower respiratory tract infection
URTI: upper respiratory tract infection
REFERENCES


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