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Probiotic Effects on Cold and Influenza-Like Symptom Incidence and Duration in Children



WHAT'S KNOWN ON THIS SUBJECT: Selected strains of probiotics have been tested for human health benefits in a variety of disease conditions, but much less is known regarding prophylactic benefits in healthy populations.



WHAT THIS STUDY ADDS: This study adds information supporting the use of the probiotics tested for prophylaxis against cold and influenza-like symptoms and compares the efficacy of 1-strain and 2-strain preparations.

abstract

OBJECTIVE: Probiotic consumption effects on cold and influenza-like symptom incidence and duration were evaluated in healthy children during the winter season.

METHODS: In this double-blind, placebo-controlled study, 326 eligible children (3–5 years of age) were assigned randomly to receive placebo ($N = 104$), *Lactobacillus acidophilus* NCFM ($N = 110$), or *L acidophilus* NCFM in combination with *Bifidobacterium animalis* subsp *lactis* Bi-07 ($N = 112$). Children were treated twice daily for 6 months.

RESULTS: Relative to the placebo group, single and combination probiotics reduced fever incidence by 53.0% ($P = .0085$) and 72.7% ($P = .0009$), coughing incidence by 41.4% ($P = .027$) and 62.1% ($P = .005$), and rhinorrhea incidence by 28.2% ($P = .68$) and 58.8% ($P = .03$), respectively. Fever, coughing, and rhinorrhea duration was decreased significantly, relative to placebo, by 32% (single strain; $P = .0023$) and 48% (strain combination; $P < .001$). Antibiotic use incidence was reduced, relative to placebo, by 68.4% (single strain; $P = .0002$) and 84.2% (strain combination; $P < .0001$). Subjects receiving probiotic products had significant reductions in days absent from group child care, by 31.8% (single strain; $P = .002$) and 27.7% (strain combination; $P < .001$), compared with subjects receiving placebo treatment.

CONCLUSION: Daily dietary probiotic supplementation for 6 months was a safe effective way to reduce fever, rhinorrhea, and cough incidence and duration and antibiotic prescription incidence, as well as the number of missed school days attributable to illness, for children 3 to 5 years of age. *Pediatrics* 2009;124:e172–e179

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KEY WORDS

Lactobacillus acidophilus NCFM, *Bifidobacterium animalis* subsp *lactis* Bi-07, antibiotic usage, upper respiratory infections, colds, influenza, probiotics

ABBREVIATIONS

CFU—colony-forming unit

OR—odds ratio

This trial has been registered at www.clinicaltrials.gov (identifier NCT00599430).

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FINANCIAL DISCLOSURE: This clinical study was sponsored by Danisco USA. Drs Leyer and Ouwehand are employees of Danisco. They were involved in the study design, review of the findings after data analysis, and writing of the manuscript, but they had no access to the data before the analyses performed by the clinical research organization. Dr Reifer was contracted to serve as the coordinating liaison of the clinical research organization for this study. Dr Mubasher was contracted to perform statistical analyses for this study. Mr Li was contracted to coordinate the study at the clinical site.

Probiotics are live microorganisms that, when administered in adequate amounts, confer health benefits to the host.¹ Globally, researchers have studied many possible benefits of probiotic consumption, and these benefits have extended beyond the epithelial sites colonized.² Many of the reported health benefits are related to mitigating disease or treating disease symptoms, such as shortening the duration of rotavirus diarrhea,³ reducing irritable bowel syndrome symptoms,⁴⁻⁶ and treating atopic disease.⁷

As the multiple benefits of probiotics are being realized, an important application is in the area of preventing, rather than treating, disease. Toward this end, a limited number of studies evaluating the efficacy of various probiotics in health maintenance have been performed. There might be a small number of studies in part because these studies must be prospective, must involve relatively large numbers of individuals, and must have extended clinical trial durations. Two prospective probiotic studies using healthy subjects in group child care centers evaluated the contributions of specific probiotic strains in health maintenance.^{8,9} Results ranged from modest and not statistically significant effects on respiratory symptoms in children 1 to 6 years of age⁸ to strain-specific, significant reductions in fever, group child care absences, and antibiotic prescriptions but no differences in respiratory symptoms in an infant population.⁹

Probiotic studies often are conducted with a single strain; however, combinations of probiotic strains may be additive or synergistic.¹⁰ We could not find evidence of a published human trial, in the English-language literature, addressing whether a combination of probiotics would perform differently from a single strain contained in the combination. The aim of

the present prospective, double-blind, placebo-controlled study was to investigate whether the daily consumption of *Lactobacillus acidophilus* NCFM or a combination of *L acidophilus* NCFM and *Bifidobacterium animalis* subsp *lactis* Bi-07 would affect the incidence and duration of fever, rhinorrhea, and cough and the incidence of antibiotic prescriptions among otherwise healthy children.

METHODS

Study Design

The study was conducted according to the good clinical practice guidelines for a prospective, randomized, double-blind, placebo-controlled study, with 3 parallel arms. Subjects were assigned randomly to arms through a permuted block-randomization procedure, with a specific block size, by the clinical coordinator at the study site. The study protocol was approved by the ethics committee of Tongji University (Shanghai, China). Parents or guardians of all participants provided written informed consent before inclusion. The study location was a group child care center in Jinhua City, Zhejiang Province, People's Republic of China. The original study design calculated statistical power on the basis of ≥ 250 children being retained in the study.

Subjects

The study participants were healthy children between 3 and 5 years of age, without known preexisting diseases, anatomic alterations, clinical symptoms of any contraindications to dairy products (lactose intolerance or cow's milk allergy), indicators of inflammatory disease, intestinal disease, Crohn disease, colitis, celiac disease, chronic cough resulting from recurring respiratory distress-related diseases, Hirschsprung disease, cystic fibrosis, or any symptoms of constipation or

gastrointestinal functional distress (chronic diarrhea). Children were excluded if they were currently taking probiotic supplements in any form, including food, and they were prohibited from taking any food or supplement products containing probiotics. At the time of recruitment, parents and children also were instructed not to practice any traditional Chinese medicine for the duration of the study. To the best of our knowledge, the eligible children in the study did not receive any influenza vaccinations.

Test Products

The test products were consumed twice per day, 7 days/week, over a 6-month period from November 2005 to May 2006. Probiotic or placebo ingredients were provided as dry powders packaged into foil sachets. Administration of the test product occurred and was monitored by the designated group child care center representative on weekdays and occurred under the supervision of a parent, guardian, or designated family member on weekends. At the time of consumption, the contents of the sachet (1 g) were added to 120 mL of standard 1% fat milk, as provided by the group child care center, and the mixture was stirred and consumed within 15 minutes. The placebo product was composed entirely of sucrose and was sensorially indistinguishable from the active products, which had sucrose as the diluent. The probiotic product consisted either of *L acidophilus* NCFM (ATCC 700396) at a concentration of 5.0×10^9 colony-forming units (CFUs) per g, for a daily dose of 1.0×10^{10} CFUs, or a combination of 2 strains, each constituting 50% of the total count, that is, *L acidophilus* NCFM and *B animalis* subsp *lactis* Bi-07 (ATCC PTA-4802), for a daily dose of 1.0×10^{10} CFUs. The dose was chosen to represent a combination of likelihood of clinical success and commer-

cial practicality/affordability. All products were stored refrigerated at the study site until the time of use. Products were evaluated for probiotic counts over the shelf-life through pour-plating onto MRS agar with 0.05% cysteine and anaerobic incubation for 48 to 72 hours. No significant reduction in viable counts was observed over the shelf-life. In this article, the group that received only *L acidophilus* NCFM is referred to as the *L acidophilus* group, and the group that received the combination of *L acidophilus* NCFM and *B animalis* subsp *lactis* Bi-07 is referred to as the *L acidophilus/B lactis* group. The combination probiotic product from this study has been branded under the name "HOWARU Protect."

Sample Size and Power Considerations

A total sample size of 326 children was calculated for detection of a minimal difference of 20% to 40% in the incidence of influenza-like symptoms (fever, rhinorrhea, and coughing) between the placebo group and either probiotic group. By using simulations based on logistic functions, the calculations also considered a difference of 15% to 20% between the 2 treatment groups (2 strains versus 1 strain). The significance level used was set at .05. The attrition rate was assumed to be a maximum of 20% loss to follow-up monitoring, and this loss was assumed to be random, relative to group assignment.

Data Analyses

During the study, authorized representatives of the group child care center (during the week) or the parents/guardians of the subjects (on weekends) recorded episodes and duration of illness by using a standardized questionnaire. For home monitoring, parents were supplied with diaries and instructions according to the study protocol, and they reported any

study symptoms to study personnel when the children were back in school. The frequency and duration of fever, cough, and rhinorrhea were monitored. In addition, the incidence and duration of physicians' visits, vomiting, and diarrhea and the incidence of antibiotic prescriptions were monitored. An episode was defined as a continuous display of symptoms, measured in days (24 hours from the start of a school day); symptoms displayed by a child for part of a day were considered to be experienced for the whole day. Questionnaires were reviewed for accuracy by medical personnel.

As a secondary outcome, absenteeism data were collected by using official school attendance records. Actual dates of absence were matched with any influenza-like symptoms, other illnesses, or personal or unknown reasons.

Statistical Analyses

Summary statistics with mean, median, and SD were generated for continuous variables (eg, duration of symptoms and age), to summarize the location and dispersion of the data. Categorical variables (including incidence of symptoms) were summarized by using frequencies and proportions. Data were analyzed on an intent-to-treat basis. Analysis of variance techniques were used to test the similarity of mean values for duration of symptoms and age and weight distributions among the 3 study groups. Gender distributions among the 3 study groups were analyzed by using χ^2 tests. Further multivariate regression analyses and generalized linear modeling were pursued by using duration of symptoms as an outcome to test differences among study groups, with adjustment for the age and weight of the children. Odds ratios (ORs) for experiencing fever, rhinorrhea, or cough in the probiotic groups, relative to the placebo

group, were calculated. ORs were incorporated into the logit concept (logarithmic of the odds) to invoke logistic regression analyses to adjust for age and weight differences among the study groups.

Summary absenteeism statistics stratified according to study group were analyzed initially by using analysis of variance techniques. Comparisons of 1-strain and 2-strain groups with the placebo group were conducted by using Dunnett's tests for multiple comparisons. Additional analyses using logistic regression also were performed, with adjustment for age and total days absent. Estimates of the incidence of symptoms were modeled by using Poisson regression.

RESULTS

Evaluation of Baseline Characteristics

Table 1 presents the distributions of age, weight, and gender among the 3 study groups. The groups were balanced with respect to gender. However, the *L acidophilus* group tended to weigh more than the placebo and *L acidophilus/B lactis* groups, with mean weights being 18.0, 17.1, and 16.9 kg, respectively ($P = .06$). Furthermore, children assigned to the placebo group were on average older than those assigned to the *L acidophilus* group or the *L acidophilus/B lactis* group, by ~4 to 5 months ($P < .001$). This finding necessitated adjustment for age in subsequent analyses. No significant difference in the distribution of subjects leaving the study was observed (Fig 1). Twenty-four subjects were excluded from the study after originally being assessed for eligibility, for reasons involving compliance. With respect to losing subjects during the study, there was no clear pattern or significant difference between the groups regarding those who withdrew because of

TABLE 1 Baseline Characteristics According to Study Group

Characteristic	Study Group		
	Placebo	<i>Lactobacillus acidophilus</i>	<i>L acidophilus/Bifidobacterium lactis</i>
N, intent to treat	104	110	112
Age, y			
Mean \pm SD	4.1 \pm 0.54	3.7 \pm 0.7	3.8 \pm 0.6
Median	4.2	3.5	4.1
Weight, kg			
Mean \pm SD	17.1 \pm 2.30	18.0 \pm 5.4	16.9 \pm 2.0
Median	17	17	17
Male, n (%)	44 (42.3)	47 (42.0)	53 (48.2)

illness. Fever and runny noses were the 2 dominant reasons for withdrawal, again distributed evenly among the study groups. There was no evidence of significant variations in the distributions of personal reasons according to study group.

General Distribution of Sick Days

When the occurrence of ever being absent was compared according to study

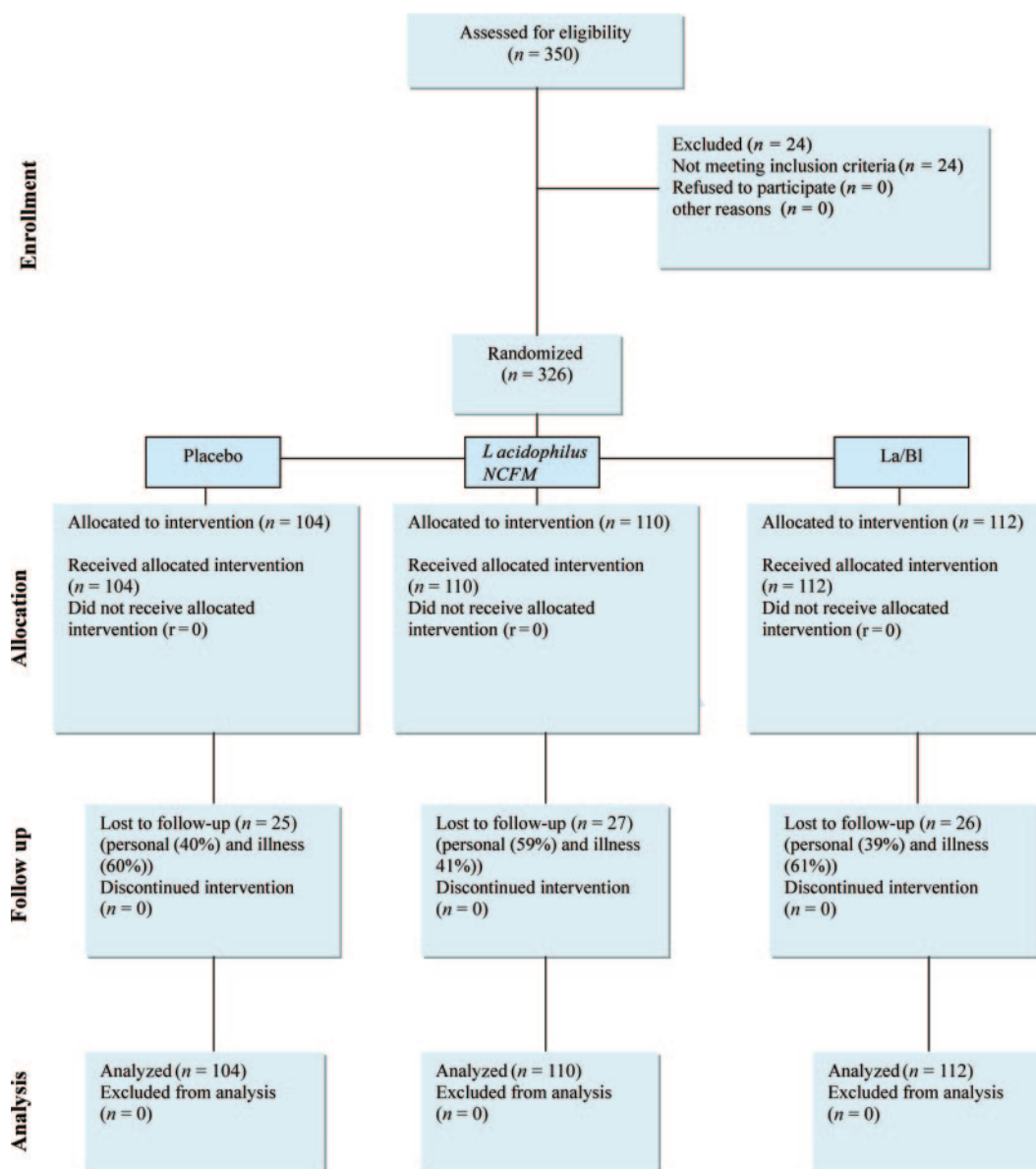
**FIGURE 1**

Diagram showing the flow of participants through each stage of the randomized trial. La/BI, *L acidophilus* NCFM in combination with *B animalis* subsp *lactis* Bi-07.

group, overall there were 91 children (28%) with ≥ 1 day absent. Among the 91 children, 51 belonged to the placebo group (49% of the placebo group) and 20 each to the 1-strain and 2-strain groups (18% of each of the probiotic groups). Analyses of the difference among the groups indicated a significant difference ($P = .02$) between each of the probiotic groups and the placebo group. Statistical significance testing of group differences in total days absent was performed by using analysis of variance techniques, with adjustment for multiple comparisons with Dunnett's method (Table 2). The differences in total days absent between either the 1-strain group or the 2-strain group and the placebo group

were statistically significant ($P = .01$). The differences in the total number of days absent could be as small as .06 or 0.25 days but could be as great as 2.7 or 3.0 days.

Incidence of Influenza-Like Episodes, With Adjustment for Missed Group Child Care Days

The clinical effects of probiotic supplementation on the incidence of fever, rhinorrhea, coughing, or any symptoms and the use of antibiotics were evaluated in pairwise comparisons by using logistic regression analyses (Tables 3 and 4). Subjects in the *L acidophilus* group were found to have significantly lower incidence (Table 3) and odds (Table 4) of having fever and cough,

compared with subjects in the placebo group. Subjects in the *L acidophilus/B lactis* group were found to have significantly lower odds, relative to the placebo group, of having fever (OR: 0.34), cough (OR: 0.44), rhinorrhea (OR: 0.52), or any of these symptoms (OR: 0.55). Furthermore, the incidence of antibiotic use among the probiotic-consuming subjects was significantly lower ($P = .0001$) than that in the placebo group.

Although the ORs for the *L acidophilus/B lactis* group tended to be smaller (lower risk of occurrence) than those for the *L acidophilus* group, this reached statistical significance only when the presence of any symptom

TABLE 2 Multiple Comparison-Adjusted Differences in Total Numbers of Days Absent Among Study Groups

	<i>Lactobacillus acidophilus</i> vs Placebo	<i>L acidophilus/Bifidobacterium lactis</i> vs Placebo	<i>L acidophilus</i> vs <i>L acidophilus/B lactis</i>
No. of days absent, mean (95% confidence interval)	-1.6 (-2.9678 to -0.2489)	-1.4 (-2.7389 to -0.0569)	-0.21 (-1.1502 to 1.5711)
<i>P</i>	.01	.01	

Dunnett's method was used for the multiple-comparison adjustment.

TABLE 3 Six-Month Frequency and Proportion of Ever Experiencing Episode of Influenza-like Symptoms and Antibiotic Use During Intervention, According to Study Group

Symptom/Prescription	<i>n</i> (%)			<i>P</i>		
	Placebo (<i>N</i> = 104)	<i>Lactobacillus acidophilus</i> (<i>N</i> = 110)	<i>L acidophilus/Bifidobacterium lactis</i> (<i>N</i> = 112)	Placebo vs <i>L acidophilus</i>	Placebo vs <i>L acidophilus/B lactis</i>	<i>L acidophilus</i> vs <i>L acidophilus/B lactis</i>
Fever	66 (63.5)	31 (28.2)	18 (16.1)	.0085	.0009	.32
Cough	87 (83.7)	51 (46.4)	33 (29.5)	.027	.005	.44
Rhinorrhea	85 (81.7)	61 (55.5)	35 (31.3)	.68	.03	.088
Antibiotics	57 (54.8)	18 (16.4)	9 (8.0)	.0002	<.0001	.286

An episode was defined as a continuous display of symptoms measured in days (24 hours from the start of a school day). Symptom-free was defined as a continuous period free of symptoms measured in days (24 hours from the start of a school day). Symptoms displayed by a child for part of a day were considered to be experienced for the whole day.

TABLE 4 Six-Month ORs Among Study Groups for Fever, Cough, Rhinorrhea, and Antibiotic Prescription, Adjusted for Age and Time Absent

Group Comparisons	Fever	Cough	Rhinorrhea	Any Symptom	Antibiotics
<i>Lactobacillus acidophilus</i> vs placebo					
OR (95% CI)	0.57 (0.44–0.90)	0.59 (0.39–0.96)	0.93 (0.57–1.49)	1.09 (0.52–2.9)	0.35 (0.15–0.55)
<i>P</i>	.015	.028	.69	.86	.0001
Significant risk reduction, %	43	41	NA	NA	65
<i>L acidophilus/Bifidobacterium lactis</i> vs placebo					
OR (95% CI)	0.34 (0.22–0.63)	0.44 (0.28–0.78)	0.52 (0.34–0.97)	0.55 (0.28–0.99)	0.23 (0.1–0.45)
<i>P</i>	.01	.005	.04	.045	<.0001
Significant risk reduction, %	66	56	48	45	77
<i>L acidophilus/B lactis</i> vs <i>L acidophilus</i>					
OR (95% CI)	0.74 (0.38–1.33)	0.84 (0.46–1.40)	0.65 (0.34–1.11)	0.50 (0.26–0.98)	0.66 (0.29–1.49)
<i>P</i>	.33	.47	.089	.04	.29
Significant risk reduction, %	NA	NA	NA	50	NA

NA indicates not applicable; CI, confidence interval.

was included, because of the higher incidence of rhinorrhea. The incidences of vomiting and diarrhea were low during the study period, and these symptoms were distributed proportionally across the study groups. In the whole cohort, 6 children experienced vomiting and 24 experienced diarrhea. These incidence rates were too low to be influenced by either of the probiotic treatments. Visits to a physician were not significantly different between the 3 treatment groups, with the numbers of patients with ≥ 1 physician visit being 25, 21, and 14 for the placebo, *L acidophilus*, and *L acidophilus/B lactis* groups, respectively.

Symptom Duration

Fever, cough, and rhinorrhea symptom duration (mean \pm SD) during the 6-month study period were 6.5 ± 7.3 days for subjects in the placebo group, 4.5 ± 4.7 days for subjects in the *L acidophilus* group, and 3.4 ± 3.7 days for subjects in the *L acidophilus/B lactis* group (Table 5). To accommodate age discrepancies at baseline (Table 1), symptom duration was also compared for children of similar ages, by modeling the cumulative duration of symptoms as a function of study group and age with linear regression. After this correction, the placebo group had the longest symptom duration, relative to the *L acidophilus/B lactis* group ($P < .001$) and the *L acidophilus* group ($P = .0023$) (Table 5). The age-corrected difference between the 2 probiotic groups indicated a nonsignificantly shorter symptom duration in the *L acidophilus/B lactis* group, compared with the *L acidophilus* group.

DISCUSSION

In the current study, 248 of 326 enrolled children completed a 6-month, double-blind, placebo-controlled, intervention trial. No notable adverse events were attributed to study probiotic

TABLE 5 Symptom Duration According to Study Group During 6-Month Follow-up Period

	Symptom Duration		
	Placebo	<i>Lactobacillus acidophilus</i>	<i>L acidophilus/Bifidobacterium lactis</i>
<i>N</i>	104	110	112
Mean \pm SD, d	6.5 ± 7.3	4.5 ± 4.7	3.4 ± 3.7
Reduction vs placebo, %	NA	31.8	47.7
25th percentile, d	1	1	1
50th percentile, d	4	3	2
75th percentile, d	10	6	5

Cumulative duration of symptoms was modeled by using linear regression as a function of study group and age. Differences reflect the regression coefficients in such models accounting for the effects of age. Age-adjusted differences (mean \pm SD) were as follows: *L acidophilus/B lactis* versus placebo, -3.2 ± 0.76 days ($P < .001$); *L acidophilus* versus placebo, -2.17 ± 0.71 days ($P = .0023$); *L acidophilus/B lactis* versus *L acidophilus*, -1.06 ± 0.81 ($P = .195$).

strains. Probiotic supplementation was found to reduce the incidence and duration of fever, rhinorrhea, and cough and the incidence of antibiotic prescriptions, compared with the placebo group. Compared with the placebo group, the group treated with the 1-strain product exhibited reduced incidence of fever and cough, whereas the group treated with the 2-strain combination exhibited reduced incidence of fever, cough, rhinorrhea, and any symptom. Both treatment groups exhibited significantly reduced symptom duration, compared with the placebo group. Furthermore, both probiotic groups demonstrated significantly reduced antibiotic use, compared with the placebo group.

Probiotics have been investigated widely for health benefits in different disease conditions.^{2-7,10,11} A limited number of studies have shown that prophylactic administration of probiotics can contribute to reduced incidence or duration of illness in healthy subjects. One of the first such studies investigated the effects of *Lactobacillus GG* on children's health status in group child care centers.⁸ However, no significant differences could be observed after correction for age. A study by Weizman et al⁹ compared 2 different probiotics, namely, *Lactobacillus reuteri* (ATCC 55730) and *B animalis* subsp *lactis* Bb-12, independently among 4- to 10-

month-old infants and observed a higher fever incidence in the placebo group. Reduced antibiotic prescriptions were noted in the *L reuteri* group. In contrast to the current study, however, no difference in respiratory symptom incidence was observed in either probiotic group.

A combination of 3 probiotic strains (*Lactobacillus gasseri* PA 16/8, *Bifidobacterium longum* SP 07/3, and *Bifidobacterium bifidum* MF 20/5), along with vitamin and mineral supplementation, was shown to reduce common cold duration and severity^{12,13} but not incidence in healthy adults. Probiotics also were shown to reduce the incidence of diarrhea in children.^{9,14} In the current study, however, the incidence of diarrhea was low and no such effect could be observed. Therefore, the current study is the first to show that probiotic (*L acidophilus* NCFM or a combination of *L acidophilus* NCFM with *B animalis* subsp *lactis* Bi-07) consumption reduced both the incidence and duration of fever, cough, and rhinorrhea symptoms in children. Although the reduced incidence of antibiotic prescriptions for all indications noted in an earlier study⁹ was confirmed, this study is the first to indicate a trend toward more-significant results with a combination versus single-strain preparation. Reducing the need for antibiotic use early in life may have

important benefits (eg, reduced adverse reactions, costs, and risk for antimicrobial resistance development).

Regarding the potential mechanisms through which the reductions in respiratory symptoms and antibiotic usage could be explained, an immune-enhancing effect is a likely explanation, because numerous studies with various probiotic bacteria have demonstrated their ability to modulate immune responses through interactions with toll-like receptors.^{15–17} Winkler et al¹⁸ showed that a probiotic combination combined with vitamins and minerals reduced the duration and severity of common cold symptoms and also enhanced cellular immunity. Importantly, some of the rationale for choosing the strains in this study was based on a demonstrated ability to stimulate dendritic cell regulatory functions.¹⁹

An additional aim of the current study was to establish whether a 1-strain probiotic treatment would perform differently from a 2-strain treatment.

Although treatment with the 1-strain preparation alone was effective, the 2-strain combination produced a more-pronounced effect, especially in the area of rhinorrhea. The mechanism for this synergism is not clear. Perhaps the presence of bifidobacteria in the mouth decreases adherence of certain respiratory viruses to the epithelium. Because this study did not evaluate mucosal colonization or mechanisms, the mechanism for the observed synergism remains speculative.

The potential utility of documented probiotics as a prophylactic therapy against the onset of cold and influenza symptoms may help alleviate the need for medicinal symptom relief. This is especially relevant in light of the recent US Food and Drug Administration Public Health Advisory regarding the use of cough and cold medicines for children <2 years of age²⁰ and the US Food and Drug Administration support of the Consumer Healthcare Products Association voluntary modification of

product labels to state “do not use” for children <4 years of age.²¹ The impact of probiotics in an acute response to signs of illness was not evaluated in this study.

CONCLUSIONS

Daily probiotic dietary supplementation during the winter months was a safe effective way to reduce episodes of fever, rhinorrhea, and cough, the cumulative duration of those symptoms, the incidence of antibiotic prescriptions, and the number of missed school days attributable to illness. *L acidophilus* NCFM alone was effective. There was, however, a trend for a broader protective effect with the combination of *L acidophilus* NCFM and *B lactis* Bi-07.

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