Effect of *Lactobacillus rhamnosus* LGG® and *Bifidobacterium animalis* ssp. *lactis* BB-12® on health-related quality of life in college students affected by upper respiratory infections

Tracey J. Smith1*, Diane Rigassio-Radler1, Robert Denmark2, Timothy Haley3,4 and Riva Touger-Decker1

1Department of Nutritional Sciences, University of Medicine and Dentistry of New Jersey, School of Health Related Professions, 65 Bergen Street, Room 157, Newark, NJ 07101, USA
2Department of Interdisciplinary Studies, University of Medicine and Dentistry of New Jersey, School of Health Related Professions, 65 Bergen Street, Room 110B, Newark, NJ 07101, USA
3Adjunct Faculty, University of Medicine and Dentistry of New Jersey, School of Health Related Professions, Newark, NJ 07101, USA
4Office of Medical Support and Oversight, US Army Research Institute of Environmental Medicine, Kansas Street, Building 42, Natick, MA 01760, USA

(Submitted 7 March 2012 – Final revision received 6 August 2012 – Accepted 6 August 2012 – First published online 1 October 2012)

**Abstract**

College students are susceptible to upper respiratory infections (URI) due to inadequate sleep, stress and close living quarters. Certain probiotic strains modulate immune function and may improve health-related quality of life (HRQL) during URI. The present study recruited apparently healthy college students and assessed the effect of probiotics on HRQL outcomes (i.e. self-reported duration, symptom severity and functional impairment of URI) in those who developed URI. Missed school and work days due to URI were also considered. Subjects (n 231) were apparently healthy college students living on campus in residence halls at the Framingham State University (Framingham, MA, USA), and were randomised to receive placebo (n 117) or probiotic-containing powder (daily dose of minimum 1 billion colony-forming units of each *Lactobacillus rhamnosus* LGG® (LGG®); *Bifidobacterium animalis* ssp. *lactis* BB-12® (BB-12®); n 114) for 12 weeks. Subjects completed The Wisconsin Upper Respiratory Symptom Survey-21 to assess HRQL during URI. The final analyses included 198 subjects (placebo, n 97 and probiotics, n 101). The median duration of URI was significantly shorter by 2 d and median severity score was significantly lower by 34 % with probiotics v. placebo (P<0·001), indicating a higher HRQL during URI. Number of missed work days was not different between groups (P=0·429); however, the probiotics group missed significantly fewer school days (mean difference = 0·2 d) compared to the placebo group (P=0·002). LGG® and BB-12® may be beneficial among college students with URI for mitigating decrements in HRQL. More research is warranted regarding mechanisms of action associated with these findings and the cost–benefit of prophylactic supplementation.

**Key words:** Probiotics; Respiratory tract infections; Common cold; *Lactobacillus; Bifidobacterium*

College students may be at increased risk for upper respiratory infections (URI) compared to the general adult population due to a multi-stressor environment, characterised by inadequate sleep and psychological stress(3–5). Additionally, many live in residence halls or alternative group housing (e.g. sorority or fraternity houses)(6), which facilitates the transmission of viruses from one student to another(5). The negative consequences of URI in the present population are missed school days, missed work days, compromised academic performance, burden on the healthcare system and related costs.(2,6–8) There is no evidence that over-the-counter (OTC) drugs have any effect on the duration of the viral infection, and they offer only marginal benefits with regard to alleviation of symptoms.(9–12) Further, OTC drugs may have unwanted side effects, such as drowsiness(11), xerostomia (dry mouth)(11), nervousness(11), irritability(11), difficulty sleeping(11,12) and elevated blood pressure(11,12).

Duration and severity of URI symptoms and functional impairment in response to symptoms contribute to health-related quality of life (HRQL)(13,14). HRQL is subjectively

**Abbreviations:** AE, adverse events; BB-12®, *Bifidobacterium animalis* ssp. *lactis* BB-12®, LGG®, *Lactobacillus rhamnosus* LGG®, OTC, over-the-counter; PI, principal investigator; URI, upper respiratory infections; WURSS-21, Wisconsin Upper Respiratory Symptom Survey-21.

*Corresponding author:* Dr T. J. Smith, email smitht9@umdnj.edu
assessed by the patient(15), and most simply defined as the component of overall quality of life that is determined primarily by the person’s health and that can be influenced by clinical interventions(15). For example, Linder & Singer(16) demonstrated that various aspects of HRQOL were negatively affected during URI, such as physical functioning, bodily pain, vitality, social functioning and mental health. Thus, there is interest in strategies that can improve HRQOL in persons suffering from URI.

One such strategy to improve HRQOL during URI may involve probiotics, defined by the WHO as ‘live organisms which when administered in adequate amounts confer a health benefit on the host’(17). Prior research studies have demonstrated the ability of certain probiotic strains to modulate immune function(18–25). Upper respiratory symptoms result from the inflammatory response of the host towards the virus, not from the viruses themselves(26). Therefore, immune system adaptations by probiotics may reduce the severity and duration of symptoms via modulation of the inflammatory response to the virus, thus having a positive impact on HRQOL during URI. *Bifidobacterium animalis* ssp. *lactis* BB-12® (BB-12®) and *Lactobacillus rhamnosus* LGG® (LGG®) are two particular probiotic strains that may be helpful, according to prior research which showed benefits on immune function in healthy adults(19–25) and URI outcomes in children(27–29). However, there is no published research investigating the effect of LGG® and BB-12®, or other probiotic strains, on HRQOL during URI, taking into account symptom severity and functional impairment, both important factors of HRQOL.

The primary objective of the study was to assess the effect of probiotics on HRQOL during URI in college students living on campus in residence halls at the Framingham State University, Framingham, MA. Measures of HRQOL were investigated during URI, including self-reported duration, severity of symptoms and functional task impairment. Secondary objectives included self-reported missed school and work days due to URI. It was hypothesised that the probiotics group would have a higher HRQOL during URI episodes, as reflected by shorter duration and lower severity scores, compared to the placebo group.

### Experimental methods

#### Study design

The present research study was a prospective, randomised, double-blind, placebo-controlled trial. Daily, for 12 weeks (February–May 2011), subjects were asked to consume probiotics or placebo and complete the Wisconsin Upper Respiratory Symptom Survey-21 (WURSS-21)(30) to assess HRQOL during URI. The Wilson & Cleary(13) HRQL conceptual model provides a framework for indirectly assessing the impact of probiotics on HRQL during URI episodes. Probiotics may directly have an impact on biological and physiological variables (the first stage of the continuum), which will indirectly affect symptoms, functionality, general health perceptions and ultimately overall quality of life (the final stage of the continuum). The present study focused on the impact of probiotics on symptoms (duration and severity of symptoms) and functionality during URI. Once per week, subjects were also asked to complete the weekly questionnaire to assess missed school and work days. Subjects completed all of the aforementioned surveys via the online application, ‘Survey Monkey’ (http://www.surveymonkey.com). Subjects met with the study staff once every 2–3 weeks (to accommodate the academic calendar) during the spring 2011 semester to obtain their supply of probiotics/placebo. The present study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects/patients were approved by The University of Medicine and Dentistry of New Jersey (Newark, NJ) and the Framingham State University (Framingham, MA) Institutional Review Boards. Written informed consent was obtained from all subjects. Participants received up to $100 in the form of shopping gift-cards for study participation. The Clinicaltrials.gov identifier is NCT01657643.

### Participants

All students living on campus in residence halls at the Framingham State University in January 2011 were invited to participate in the study. Study briefings (22 January 2011 to 10 February 2011) consisted of an oral explanation of all study procedures and risks, after which time the interested students were asked to sign the informed consent form. Participants were excluded from participation if: (1) their driver’s license or state identification card indicated that they were under 18 years of age or over 25 years of age; (2) they experienced chronic perennial allergies (such as allergies to dust or mould); (3) they were pregnant; (4) they had been diagnosed with medical conditions affecting immune function (e.g. asthma, chronic fatigue syndrome and HIV); or (5) they had acute pancreatitis, were undergoing treatment for cancer or were taking immunosuppressive drugs for an autoimmune disease or post-transplant. Participants were asked to refrain from consuming non-study-related dietary supplements containing probiotics (e.g. Culturelle®) and yogurts with high probiotic content (e.g. DanActive™ or Activia™) during the study, as well as any other dietary supplements which may have an effect on immune function (e.g. Airborne®, Echinacea and quercitin). Participants were reminded of dietary restrictions weekly via the online questionnaire.

### Randomisation

Participants were assigned a unique study identification number in the order in which they were enrolled in the study. Specifically, participant numbers were assigned in numerical order (starting with the number 001), based on the order in which the signed consent form was returned to the principal investigator (PI). The randomisation list was generated by the PI using an internet-based random number generator (GraphPad Random Number Generator, 2005), wherein participants were randomised to sticks labelled either ‘2930’ or ‘3220’ based on their unique study identification number. The PI was blinded as to which four-digit code represented probiotics or placebo. A person who was not part of the
study staff (i.e. student health services coordinator at the Framingham State University) maintained the randomisation list and the codes indicating placebo or probiotics assignment.

**Intervention**

The intervention was administered as a daily dose of a strawberry-flavoured powder (5 g), and was packaged in a small foil ‘stick’. Each probiotic stick contained a minimum of 1 billion (or $10^9$) colony-forming units each of LGG® and BB-12® in powder form (Chr. Hansen A/S), which was confirmed before, and within 2 weeks of, study completion. Subjects were advised to store their probiotics/placebo sticks in a cool, dry location (<21°C), and to consume only one stick per d.

**Blinding**

The packaging and contents of the placebo sticks were identical in taste and appearance to the probiotics stick, but did not contain any probiotics. Chr. Hansen A/S manufactured the probiotics and placebo sticks, and labelled each stick with a four-digit number code (2930 or 3220) to identify placebo or active. The PI, study staff and study participants were blinded. The blinding code was provided to the PI after the data cleaning and statistical analysis were completed.

**Baseline demographic characteristics and anthropometrics**

Baseline data were collected within approximately 1 week of the subjects’ consent, after subjects were enrolled and randomised. The following self-reported demographic data were collected via a self-administered questionnaire: sex, age, year in school, race and ethnicity. Criteria for reporting race and ethnicity were based on guidelines from the National Institutes of Health.

**Primary outcome: health-related quality of life**

The WURSS-21 was used to determine if a study participant was suffering from a URI and, subsequently, his/her HRQL during the course of the URI. The WURSS-21 is composed of one global severity item, one global change item, ten symptom-based items and nine functional status items. All subjects answered question no. 1 of the WURSS-21, ‘How sick do you feel today?’ each day during the data collection period. The participant was prompted to answer the remaining twenty questions if, and only if, they did not answer ‘not sick’ to question no.1. A URI episode was recorded if the participant answered affirmatively to question no. 1, 2 d in a row. If a participant reported a URI episode within 7 d of recovering from a previous URI episode (indicated by answering ‘no’ to question no. 1, 2 d in a row), then this episode was considered part of the previous infection.

If a participant indicated that he or she could not access a survey due to technological issues, study staff communicated with the participant to determine whether or not they were suffering from a URI. If the participant indicated that he or she was ‘not sick’, the PI manually completed the survey for him or her on the day in question. If a participant indicated that he or she ‘had a cold’, and was unable to complete the survey, the PI recorded that the participant had a URI on the day in question and this datum was included the analyses; however, remaining WURSS-21 data regarding symptom severity and functionality were considered missing.

Two HRQL scores were generated from the WURSS-21. The first HRQL score was related to duration of the URI episode. Self-reported duration of a URI episode was determined using responses to question no. 1 on the WURSS-21. Start of illness was indicated by an affirmative response to question no. 1, 2 d in a row, while the end of illness was indicated by a negative response to question no. 1, 2 d in a row. Duration was calculated from the first day of an affirmative response up to (but not including) the first day of a negative response. The second HRQL score, generated from the WURSS-21, assessed both symptom severity and functional status, and was expressed in terms of AUC, which was ascertained by adding daily WURSS scores (the possible response range was 0–153 per d) across all days of the illness.

**Secondary outcomes: missed school and work days**

Subjects self-reported via the Weekly Questionnaire if they missed any school or work (including an internship or practicum) as a consequence of a URI, and the subsequent number of missed school or work days.

**Compliance**

Subjects received an email and text message daily (7 d/week including weekends and holidays) containing a link to the day’s survey and a reminder to take their probiotics/placebo and complete the survey. Daily, subjects were asked to send a text message or email to a designated mobile phone number or email address, respectively, stating that they had taken their probiotics/placebo and completed the survey(s). Study staff followed-up with all subjects who had not sent a text message or email by approximately 19.00 hours each day. Compliance with the probiotics/placebo and questionnaire(s) was recorded daily. Participants were considered ‘compliant’ if they consumed their probiotics/placebo at least five times the week before and during an URI.

**Sample size calculation**

Sample size estimates were made using SamplePower (release 2.0, SPSS Inc.) paired t test (mean = 0) procedure. The present study aimed to detect a 30% improvement in HRQL (i.e. symptom severity/functional status score) during URI episodes in response to probiotics vs. placebo, based on published literature. Considering an effect magnitude of 93 points, a standard deviation of 250 points and a set at 0.025 (one-tailed), ninety URI per group were required to have 80% power in detecting a significant difference between groups. The present study sought to enrol 175 participants in each group to compensate for an estimated 15% attrition rate and 60% URI infection rate.
**Reporting of adverse events**

At the start of the study, participants were provided with the contact information for the PI and asked to communicate any health/medical issues that occurred during the data collection period, regardless of whether or not medical care was sought. Additionally, participants were queried by the PI every 2 to 3 weeks during the data collection period when they were resupplied with probiotics/placebo.

**Statistical analysis**

Statistical analysis was completed using IBM SPSS statistical software version 19.0 (IBM Corporation) for analysis. All available data were included in the analyses, regardless of compliance with probiotics/placebo and attrition; for example, if a subject withdrew from the study at week 8, all cases of URI that occurred prior to attrition were included in the analyses. Descriptive statistics were obtained for continuous variables and frequencies were calculated for categorical variables. Normal distribution of continuous variables was assessed using the Shapiro–Wilk statistic and visual inspection of histograms. Differences between the probiotics and placebo groups were determined using the Mann–Whitney U test (non-parametric equivalent of the independent samples t test), as data were not normally distributed. For categorical variables, the differences between the probiotics and placebo groups were analysed using the $\chi^2$ test. The Bonferroni adjustment was applied to primary outcomes related to HRQL (i.e. duration of URI and symptom severity/functional status score) and significance was established at $P \leq 0.001$.

**Results**

**Subject disposition and compliance with the intervention**

Fig. 1 depicts the recruitment and retention of subjects throughout the study. Of the 231 subjects who initially enrolled, 86% ($n = 198$; placebo, $n = 97$, 49% and probiotics, $n = 101$, 51%) attended the baseline testing session and consumed at least one dose of placebo or probiotics and were included in the statistical analysis. Of these 198 subjects, the retention rate was 91% ($n = 180$; placebo, $n = 85$, 47% and probiotics, $n = 95$, 53%). Compliance with probiotics/placebo was 94%, wherein probiotics/placebo were consumed at least five times the week before and during a URI in 157 of URI cases (placebo, $n = 78$ cases and probiotics, $n = 79$ cases).

**Baseline characteristics**

The median age of all participants was 19 years (range 18–24 years). Baseline characteristics (Table 1) were non-significantly different between the placebo and probiotic groups.

**Fig. 1.** Flow diagram of study participation. * Of the twenty subjects who did not receive the placebo, one participant indicated that they had decided not to participate and the remaining nineteen participants were lost to follow-up. † Of the thirteen participants who did not receive the probiotics, two participants indicated that they had decided not to participate and the remaining eleven participants were lost to follow-up. ‡ Reasons for discontinuation: withdrawn due to new medication ($n = 1$); withdrawn due to health issues related to prior medical diagnosis ($n = 1$); withdrew due to burden of study activities ($n = 6$); withdrew due to gas/bloating ($n = 3$); withdrew due to hospitalisation related to major reconstructive knee surgery ($n = 1$). § Reasons for discontinuation: withdrawn due to withdrawal from the university ($n = 1$); withdrew due to burden of study activities ($n = 5$).
Primary outcome: health-related quality of life

Available data for HRQL outcomes are shown in Table 2. Of the 167 URI cases reported during the data collection period (placebo, n 83 cases and probiotics, n 84 cases), duration was calculated for 158 cases and severity was calculated for 143 cases due to missing data.

Health-related quality of life outcomes are presented in Table 3. URI duration was 33% (2 d) longer in the placebo group compared to the probiotics group (\(P=0.001\), one-tailed) and severity scores were 34% (30 points) higher for the placebo group compared to the probiotics group (\(P=0.0003\), one-tailed). Significantly fewer days of illness and significantly lower severity scores indicate a higher HRQL in the probiotics group compared to the placebo group.

Secondary outcomes: missed work and school days

In the total sample (n 198), nineteen missed work days (10%; placebo, n 11, 58% and probiotics, n 8, 42%) and forty-nine missed school days (25%; placebo, n 34, 69% and probiotics, n 15, 31%) were reported. A total of 94% of subjects (n 186; placebo, n 92, 50% and probiotics, n 94, 51%) indicated that they did not miss any work due to URI, and the number of missed work days did not differ significantly between the placebo group (median = 0; range = 0–3) and the probiotics group (median = 0; range = 0–2), \(P=0.429\) (one-tailed). The majority of subjects (n 171, 86%; placebo, n 79, 46% and probiotics, n 92, 54%) indicated that they did not miss any school due to URI. The number of missed school days was significantly higher for the placebo group (median = 0; range = 0–4) compared to the probiotics group (median = 0; range = 0–3), \(P=0.002\) (one-tailed).

Adverse events

There were no significant differences between groups for adverse events (AE), and no serious AE were reported. A total of forty-three AE were reported during the study period (Table 4). Of the forty-three reported AE, diarrhea or vomiting was the most commonly reported among 198 subjects who consumed at least one dose of placebo or probiotics (n 22, 11%; placebo, n 10, 45% and probiotics, n 12, 55%). Increased flatulence and bloating were the second most common AE, occurring in approximately 4% of the 198 subjects who consumed at least one dose of placebo or probiotics (n 7; placebo, n 4, 57% and probiotics, n 3, 43%).

Discussion

The present study investigated the effect of a probiotic powder containing both LGG® and BB-12® (10^9 colony-forming units of each strain) on HRQL during URI in college students living on campus in residence halls. Results related to HRQL (the primary outcome) were positive: duration of URI was significantly shorter and URI severity scores were lower in the probiotics group compared to the placebo group. Additionally, the number of missed school days was significantly higher for the placebo group compared to the probiotics group. The majority of subjects did not miss any work or school due to URI. Adverse events, such as diarrhea or vomiting, were reported, but no serious adverse events were observed. The study findings indicate that probiotics may improve HRQL during URI in college students.
Table 2. Available data for primary outcome: components of health-related quality of life
(Number of subjects and percentages)

<table>
<thead>
<tr>
<th></th>
<th>Total sample (n 198)</th>
<th>Placebo (n 97)</th>
<th>Probiotics (n 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-reported duration of URI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Self-reported severity of URI*</td>
<td>158 95</td>
<td>79 50</td>
<td>79 50</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probiotics</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

URI, upper respiratory infection.
* Total severity score took into account symptom severity and functional status during URI.

Table 3. Primary outcome: components of health-related quality of life*
(Mean values and standard deviations; medians, ranges and 95 % confidence intervals)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>Range</th>
<th>95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration (d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sample (n 198)</td>
<td>6.36</td>
<td>5.00</td>
<td>4.80</td>
<td>2–25</td>
<td>5.6, 7.1</td>
</tr>
<tr>
<td>Placebo (n 97)</td>
<td>7.11</td>
<td>6.00*</td>
<td>5.07</td>
<td>2–25</td>
<td>6.0, 8.3</td>
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<tr>
<td>Probiotics (n 101)</td>
<td>5.58</td>
<td>4.00a</td>
<td>4.41</td>
<td>2–21</td>
<td>4.6, 6.6</td>
</tr>
</tbody>
</table>

Total severity score†

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>Range</th>
<th>95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sample (n 198)</td>
<td>127.87</td>
<td>66</td>
<td>164.69</td>
<td>5–832</td>
<td>100.7, 155.1</td>
</tr>
<tr>
<td>Placebo (n 97)</td>
<td>157.30</td>
<td>88*</td>
<td>183.39</td>
<td>6–801</td>
<td>113.3, 201.4</td>
</tr>
<tr>
<td>Probiotics (n 101)</td>
<td>100.43</td>
<td>58*</td>
<td>140.88</td>
<td>5–832</td>
<td>67.8, 133.1</td>
</tr>
</tbody>
</table>

a,b Median values with unlike superscript letters were significantly different between the probiotics and placebo group (duration, $P<0.001$ and severity, $P=0.0003$).
* Health-related quality of life, as reflected by duration and total severity score.
† Total severity score took into account symptom severity and functional status during upper respiratory infection.
British Journal of Nutrition

Probiotics and health-related quality of life

P. L. reuteri ATC probiotic strain, that fewer subjects missed work in response to a different BB-12 own or only in combination. The external validity of the warranted to determine if the strains are effective on their observations reported in the literature. Further research is findings. However, these assumptions were based on clinical when they were not under the influence of OTC medicine participants were asked to consider their symptoms study; however, this potential confounder was minimised as no data were collected regarding work commitments. however, it is also possible that subjects may not have had classes scheduled on days that they were sick. Although the probiotics group missed significantly fewer school days compared to the placebo group (15 v. 34 d, respectively), the effect magnitude was small (0-2 d). Future studies are needed to confirm or refute these findings.

The present study did not detect any significant differences between groups in terms of missed work days due to a URI. These findings are contrary to Tubellius et al. (40), who found that fewer subjects missed work in response to a different probiotic strain, L. reuteri ATCC55730 v. placebo (26 v. 11%, P=0.01). However, the authors (40) did not differentiate between sick days due to gastrointestinal illness and respiratory tract infections. In the present study, differences between groups may not have been detected for missed work days either because few students worked (possibility of a type II error) or because students were highly motivated to earn money. However, these possibilities cannot be confirmed, as no data were collected regarding work commitments.

The use of OTC medicine was not monitored in the present study; however, this potential confounder was minimised as participants were asked to consider their symptoms when they were not under the influence of OTC medicine (e.g. upon waking). Missing survey data, and assumptions with regard to missing survey data, further limit the study findings. However, these assumptions were based on clinical observations reported in the literature. Further research is warranted to determine if the strains are effective on their own or only in combination. The external validity of the study is further limited to the population studied, and additional research is needed to determine if LGG® and BB-12® are effective for limiting decrements in HRQL during URI in other populations (e.g. athletes), as immune response to URI may be different (41–43).

Lactobacillus may be contraindicated in persons with serious underlying diseases and/or with immunosuppression, based on documented cases of lactobacillalaemia, Infectious endocarditis and liver abscess (44–48). Besselink et al. (49) reported that a multi-strain probiotics preparation increased the risk of bowel ischaemia in persons with acute pancreatitis; however, there has been debate as to whether the probiotics were indeed responsible for this negative outcome (50). Although these conditions may be unlikely in college students, they should still be given consideration when educating consumers and health care practitioners, when applying the present study’s findings in practice and conducting future research. Although the present study showed positive results, a cost–benefit analysis is warranted before a widespread supplementation of LGG® and BB-12® is implemented in the present population. Factors in this equation would be the cost of supplementation itself, healthcare costs, cost of OTC medication use, lost wages and lost productivity at work and school.

Conclusion

The findings from the present study suggest that the combination of LGG® and BB-12® may be beneficial for mitigating decrements in HRQL during URI in college students living on campus in residence halls. Further studies are needed to determine if the combination of LGG® and BB-12® is beneficial for preserving absences from school during URI.

Acknowledgements

The present study was funded by Chr Hansen A/S (Hoersholm, Denmark). Chr Hansen A/S provided the probiotics and placebo products, and provided input towards the study design and final report. However, the company had no involvement in data collection, analysis or interpretation. The authors declare no conflicts of interest. T. J. S designed the study, coordinated data acquisition, performed the statistical analysis and drafted the manuscript. D. R.-R., R. T.-D., R. D. and T. H. made substantial contributions to study design and critically revised the manuscript for intellectual content. The authors wish to thank study subjects and research assistants from the Framingham State University, Framingham, MA (USA).

Table 4. Adverse events in the total sample and by group*
(Number of subjects and percentages)

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Adverse events (both groups) (n=198)</th>
<th>Adverse events (placebo group) (n=97)</th>
<th>Adverse events (probiotics group) (n=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total n</td>
<td>%†</td>
<td>n</td>
</tr>
<tr>
<td>Diarrhoea and/or vomited</td>
<td>22</td>
<td>11-1</td>
<td>10</td>
</tr>
<tr>
<td>Increased flatulence/bloating</td>
<td>7</td>
<td>3-5</td>
<td>4</td>
</tr>
<tr>
<td>Urinary tract infection‡</td>
<td>3</td>
<td>1-5</td>
<td>3</td>
</tr>
<tr>
<td>Bacterial respiratory infection‡</td>
<td>5</td>
<td>2-5</td>
<td>1</td>
</tr>
<tr>
<td>Ear infection‡</td>
<td>2</td>
<td>1-0</td>
<td>0</td>
</tr>
<tr>
<td>Appendectomy‡</td>
<td>1</td>
<td>0-5</td>
<td>1</td>
</tr>
<tr>
<td>Eczema‡</td>
<td>1</td>
<td>0-5</td>
<td>0</td>
</tr>
<tr>
<td>Knee injury</td>
<td>2</td>
<td>1-0</td>
<td>1</td>
</tr>
</tbody>
</table>

* Includes subjects who consumed at least one dose of placebo or probiotics (n=198).
† Percentages in this column are representative of subjects who consumed at least one dose of placebo or probiotics (n=198).
‡ These adverse events were diagnosed by a medical doctor.
References

35. Winkler P, de VM, Laue C, et al. (2005) Effect of a dietary supplement containing probiotic bacteria plus vitamins and


