Original Article

Can a galacto-oligosaccharide reduce the risk of traveller’s diarrhoea? A placebo-controlled, randomized, double-blind study

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Abstract

Background: Diarrhoea is a common medical problem affecting travellers to Asia, Africa and Latin America. The use of prophylactic antimicrobial agents may increase the risk of contracting resistant bacteria. Findings indicate that oligosaccharides, i.e. carbohydrate chains of 3–10 monosaccharides, reduce the risk of diarrhoea.

Methods: We performed a placebo-controlled, double-blind study of a galacto-oligosaccharide, B-GOS (Bimuno®, Clasado Ltd, Milton Keynes UK), vs placebo for participants travelling to countries with a high/intermediate risk of diarrhoea for 7–15 days. The participants ingested 2.7g of B-GOS daily from 5 days prior to departure throughout the travel period, and returned a questionnaire, with a diarrhoea log, after their return. The case definition of diarrhoea was three or more loose stools per day.

Results: Of 523 enrolled subjects, 334 travellers managed to comply per protocol (PP), 349 followed the protocol at least until the onset of diarrhoea (conditionally evaluable, CE), and 408 followed the protocol with fewer than 5 days of deviance from the protocol (intention to treat, ITT). There was a significant reduction of diarrhoea incidence in the PP group (odds ratio = 0.56, P = 0.03), while the effect in the CE group was non-significant (OR = 0.65, P = 0.08). No significant effect was found during the first 7 days after starting with B-GOS, but from day 8 there was a significant effect in both the PP and CE groups (OR = 0.47, P = 0.02 and OR = 0.53, P = 0.03, respectively). The entire effect was seen in 1-day (i.e. self-limiting) diarrhoea (PP: OR = 0.25, P = 0.004). There was no effect on duration or the number of bowel movements during diarrhoea. The severity of diarrhoea was not affected.

Conclusions: B-GOS reduces the risk of diarrhoea lasting 1 day. The protection seemed to start after a week of treatment with B-GOS. Strict compliance is crucial. The treatment is environmentally friendly and without adverse effects.

Key words: Diarrhoea, galacto-oligosaccharide, traveller’s diarrhoea, randomized clinical trial

Background

Traveller’s diarrhoea (TD) is the most common medical complaint among travellers. The World Health Organization (WHO) defines diarrhoea as ‘the passage of three or more loose or liquid stools per day (or more frequent passage than is normal for the individual)’. The syndrome of TD is more narrowly defined by some authors as ‘three or more loose stools during 24 hours plus at least one additional symptom, such as abdominal cramps, tenesmus, nausea, vomiting, fever, or faecal urgency’. Travellers’ individual dietary precautions do not appear to reduce the risk of TD. Prophylactic use of drugs with an antibacterial effect (fluoroquinolones and rifaximin) is effective. However, consumption of antibiotics to treat TD has been identified as an independent risk factor for colonization with extended-spectrum
beta-lactamase-producing Enterobacteriaceae; therefore, unnecessary use of antibiotics during travel should be discouraged.\textsuperscript{5,6} There are many different causative agents of TD,\textsuperscript{7} and the development of a universal TD vaccine thus seems unlikely. The only vaccine marketed as a TD vaccine in some countries is the cholera vaccine Dukoral\textsuperscript{®}, supported by one study.\textsuperscript{7} However, no cholera vaccine has been established as a general TD vaccine.\textsuperscript{3–11} Therefore, new approaches for preventing TD are needed.

Oligosaccharides, i.e. chains of three to ten monosaccharides, are non-digestible substances found in a wide range of food items. Fructo-oligosaccharides (FOS) occur in tomatoes, asparagus, onion and wheat, and galacto-oligosaccharides (GOS) are present in human milk.\textsuperscript{12} There is evidence that oligosaccharides may protect against diarrhoea with different aetiologies. Morrow et al. found an association between the content of human milk oligosaccharides in mothers’ milk and children’s risk of diarrhoea.\textsuperscript{13} One in vitro study has shown that human milk oligosaccharides and a GOS reduces the attachment capability of Entamoeba histolytica trophozoites and E. histolytica cytotoxicity to the human colon adenocarcinoma HT-29 cell line.\textsuperscript{14} Cummings et al. tested an FOS vs placebo, finding diarrhoea in 19.5% of the placebo group and 11.2% of the FOS group, but the numbers did not reach statistical significance (P = 0.08).\textsuperscript{15}

B-GOS (Bimuno\textsuperscript{®}, Clasado Ltd, Milton Keynes UK) is a trade mark (‘B’ stands for Bifidobacterium). It is a GOS produced by an enzymatic process (transgalactosylation) using an enzyme from Bifidobacterium bifidum NCIMB 41171 and lactose as a substrate.\textsuperscript{16} Bimuno\textsuperscript{®} galacto-oligosaccharides are generally recognized as safe for use in conventional food and beverage products.\textsuperscript{17} Searle et al. found that B-GOS reduced the invasion of Salmonella typhimurium in human colonic cells and murine ligated ileal loops \textit{in vitro}, and prevented colonization in internal organs of BALB/c mice after oral challenge.\textsuperscript{18}

There is only one double-blind, placebo-controlled study addressing the possibility that B-GOS may prevent TD. Drakoularakou et al. found that the incidence of traveller’s diarrhoea was 19/81 (23.4%) in the treatment group after ingestion of B-GOS vs 30/78 (38.5%) in the placebo group, indicating a 39% reduction in the risk of TD (P < 0.05%). However, the mechanism of action is not understood.\textsuperscript{19} The aim of our study was to assess the effect of B-GOS on the incidence of diarrhoea in healthy travellers.

\textbf{Materials and Methods}  
We conducted a parallel-group, randomized, double-blind, placebo-controlled study in healthy travellers. A total of 655 volunteers (Figure 1) were recruited between June 2014 and May 2016 among patients at the Oslo Travel Clinic (Reiseklinikken), the largest vaccination clinic in Norway, with 10 000 travel medicine consultations annually. Eligible patients were healthy, ≥16 years of age, planning a trip for 7–15 days to countries with an intermediate or high risk of TD, i.e. more than 8% risk,\textsuperscript{20} and willing to give informed consent to participate in the study. We included travellers to countries of the former Soviet Union, the Middle East, Asia (except Japan), Africa (except South Africa), Oceania (except Australia and New Zealand), Latin America and the Caribbean islands. The exclusion criteria were: lactose intolerance, any acute or chronic intestinal disease, current abdominal discomfort (including the perception of having three or more loose stools per day), current use of pre- or probiotics, diseases that might affect immune responses, and ongoing medication with antibiotics. The exclusion criteria were modified from the protocol (available at http://www.reiseklinikken.no/B-GOS\textunderscore protocol.pdf) by adding ‘including the perception of having three or more loose stools per day’, as we interpreted this as a current abdominal discomfort, and adding ‘diseases that might affect the immune response’, as those with e.g. immune diseases and diabetes could not be considered as ‘healthy travellers’. Travellers with diseases that, whether on their own or due to their treatment, do not affect the risk of TD were considered as healthy in this context.

Participants were randomly assigned to two groups with an equal probability of receiving active treatment or placebo. The manufacturer delivered the study preparation with eight different letters: four representing B-GOS and four representing placebo. The letters were listed consecutively on the registration sheet, and each new participant was consequently added to the next place on the list. The active ingredient was B-GOS at a dose of 0.9 g per pastille. In the placebo pastilles, B-GOS was replaced with maltodextrine, and the appearance of the blister package was identical to that of the study product. The pastilles themselves had different colour, but only the supplier knew which were B-GOS and which were placebo. The randomization code was kept by the supplier and was not disclosed to the research group until the data collection process was terminated.

Prior to enrolment eligible patients were given a detailed information sheet explaining the rationale and purpose of the study, the fact that it was double blind, how to take the pastilles and what was expected from them. After consent was given, we registered the date of birth, gender, use of Dukoral\textsuperscript{®} and atovacquon-proguanil, destination(s) and travel period. Participants who travelled together were independently randomized, but we registered those who were travelling together. After allocation, the subjects received a questionnaire that was asked to be returned 1 week after the trip (Figure 2). The questionnaire included a diarrhoea log to register days with diarrhoea and stomach pain, as well as the number of bowel movements per day. The participants were instructed to start taking three pastilles once daily from 5 days prior to departure, including the departure day, and were directed to continue throughout the journey, even if they developed diarrhoea. Rescue treatment with antibiotics, motility-regulating drugs and probiotics did not lead to exclusion. The end points defined in the protocol were: incidence of diarrhoea (according to the WHO-definition),\textsuperscript{2} duration of diarrhoea, fever, number of bowel movements during diarrhoea, and incidence of pathogens in returned travellers who still had diarrhoea. As volunteers who said they normally had three loose stools per day were excluded from enrolment, the case definition of diarrhoea in the study was three or more loose stools (as perceived by the participants) per day. The more narrow definition of TD\textsuperscript{1} was not a primary end point of the study, but cases could be identified based on the questionnaire responses concerning the associated symptoms (Figure 2). Adverse effects were also registered in the questionnaire.
**Clinical Monitoring**

As the participants were healthy travellers, they did not need any routine clinical follow-up while travelling. The questionnaire contained the email address and mobile phone number of the principal investigator, in case of adverse events. All participants were offered a free consultation at our clinic after their return if they still had diarrhoea. The examination included taking faecal samples for bacteriological culture for *Salmonella*, *Shigella*, *Yersinia* and *Campylobacter* and PCR for pathogenic *Escherichia coli* (ETEC, EHEC, EPEC and EIEC) and intestinal protozoa.

**Statistics**

Based on a TD incidence of 30% and a postulated 25% effect of B-GOS, a sample size of 800 was estimated to be adequate to achieve statistically significant results with $\alpha = 0.05$. As recruitment was much slower than predicted, a Standard Operational Procedure was developed during the study to decide whether the recruiting could be stopped earlier i.e. whether a significant effect of B-GOS on diarrhoea incidence could be shown with the data collected thus far. The procedure, which was to be performed only once during the study, implied that the significance level for testing the effect of B-GOS on diarrhoea incidence in this study was reduced to $\alpha = 0.0395$. The new significance level was found by simulating data analysis by use of Fisher’s exact test, with the requirement that the procedure would not reject a true null hypothesis in more than 5% of the cases. An external statistician performed the procedure on the data and found a $P$-value <0.0395. Consequently, the study was stopped by the end of May 2016.
A logistic regression analysis was performed for each end point except for duration and number of bowel movements, which were analysed by use of Wilcoxon’s Rank Sum Test. Logistic regression was chosen in order to enable comparison with previous studies, and because travel durations were similar in the treatment and placebo groups (Table 1). The inclusion of covariates such as gender, age and destination depended on the result of a model selection process based on the Akaike Information Criterion (AIC). Models with a random effect accounting for a possible correlation between participants traveling together were tested, but these were not found to perform better than the previously described logistic regression models. Finally, the effect of B-GOS on incidence of diarrhoea and stomach pain in the PP and CE groups was retested by fitting Cox proportional hazards regression models, a method which accounts for differences in travel duration. All analyses were performed in the statistical software R.21

Ethics
This study was approved by the Regional Ethics Committee (reference REK 2014/149) and by the Norwegian Medicines Agency (reference 14/03453-16). It was registered as a randomized clinical trial, EUDRACTNR: 2014-000430-27.

Results
Out of 523 enrolled subjects, a total of 334 participants (64%) took the pastilles exactly as instructed or omitted the pastilles on only 1 day, forming the ‘Per protocol’ (PP) group. Among the 81 participants in the PP group who developed diarrhoea, 78 completed the diarrhoea log in the questionnaire. Fifteen participants (nine in the B-GOS group and six in the placebo group) took the pastilles as prescribed, but discontinued the pastilles when they acquired diarrhoea despite pre-travel instructions to continue the medication. As diarrhoea is the main end point of the study, the PP group plus these 15 participants were included in the ‘Conditionally evaluable’ (CE) group (349 participants). In addition, 36 persons started taking the pastilles later than 5 days before departure, three participants forgot to take the pastilles for 2–4 days during their journey, and 20 stopped the medication during travel; these are included in the ‘Intention to treat’ (ITT) group (Figure 1). The baseline characteristics were similar in the B-GOS and placebo groups for the PP, CE and ITT participants, except that there were comparatively more females in the B-GOS group (Table 1).

In the ITT group, no significant effect was found. In the PP group, B-GOS had a statistically significant effect on diarrhoea incidence, with an estimated odds ratio (OR) of 0.56 between the B-GOS and placebo groups (P = 0.03) (Table 2). In the CE group, the estimated OR was 0.65 (P = 0.08). All three analyses included gender as a covariate as this produced lower AIC values. We found no significant difference between B-GOS and placebo regarding the duration of diarrhoea or the number of bowel movements (Table 3). In the PP group, the number of cases lasting only 1 day was reduced in the B-GOS group compared to the placebo group (OR = 0.25, P = 0.004), while the number of cases lasting 2 days or more was non-significantly reduced (Table 3). The average number of bowel movements in those who had diarrhoea for only 1 day was 4.2 in the B-GOS group and 4.7 in the placebo group (NS). The incidence of diarrhoea beginning later than a week after start of ingestion of the

![Figure 2](https://academic.oup.com/jtm/article-abstract/24/5/tax057/4085921/17-December-2018)

Registration form for traveller’s diarrhoea

<table>
<thead>
<tr>
<th>Participant No.</th>
<th>Pastille code</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Name</th>
<th>Date of birth</th>
<th>Destination</th>
<th>Period (Date to date)</th>
</tr>
</thead>
</table>

Diarrhoea = Three or more loose stools per day
- Did you take three pastilles every day from five days prior to arrival until the day you returned? If not, how many did you take? When did you take them?
- Did you notice any adverse effects? If so, what were they?
- Did you take probiotics? If so, which ones?
- Did you have diarrhoea during the stay? Diarrhoea = three or more loose stools per day
- Did you have one or more of the following: blood in the stool, fever, stomach pain, nausea/vomiting?
- Did you consult a medical doctor during the stay?
- Were you admitted to a hospital during the stay?
- Did you use antibiotics?
- Did you use motility-regulating drugs?

Please send this form to Reiseklinikken seven days after return home

If you have diarrhoea, fill in the log:

| Date | No. bowel movements | Fever (Y/N) | Temp. | Stomach main/vomiting (Y/N) | Remarks |

Figure 2. Translation of the questionnaire for the registration of traveller’s diarrhoea. It contained a diarrhoea log, for day to day registration. The original questionnaire is available at [http://www.reiseklinikken.no/diareregistreringsskjema.pdf](http://www.reiseklinikken.no/diareregistreringsskjema.pdf)
pastilles was significantly reduced in the PP and CE groups, with ORs of 0.47 (P = 0.02) and 0.53 (P = 0.03), respectively, while for the ITT group, an OR of 0.65 (P = 0.1) was estimated. There was no significant reduction when the disease started earlier (Table 4). As the PP participants took B-GOS 5 days prior to departure, including the departure day, 7 days after the start of B-GOS would include the first 2–3 days at the destination, depending on the flight schedule.

Cox proportional hazards models showed a hazard ratio (HR) of 0.62 for diarrhoea in those who used GOS vs those who used the placebo (P = 0.039) in the PP group (Figure 3). In the CE group, an HR of 0.72 was estimated (P = 0.11). Gender was included in both models. For diarrhoea lasting only 1 day, an HR of 0.35 was found in the PP group (P = 0.012). For diarrhoea starting later than a week after beginning with pastilles, an HR of 0.50 was estimated for the PP group (P = 0.020), while an HR of 0.56 was found in the CE group (P = 0.032). The HR for stomach pain was estimated to be 0.68 (P = 0.10).

Perceived adverse effects appeared to be most common in the placebo group, but the difference was not statistically significant (Table 5). Ten participants who received B-GOS and 14 who received the placebo complained of an unpleasant or nauseating taste of the pastilles.

Out of 29 patients (15 in the B-GOS and 14 in the placebo group) who had diarrhoea the day after they returned home, only four took advantage of our offer for a free consultation if they had diarrhoea after returning home. All of these patients were in the placebo group. One had enteropathogenic E. coli (EPEC), one had ST-producing enterotoxigenic E. coli (ETEC), one had Campylobacter jejuni, and one had no detectable pathogen.

Gender, travel duration and destination did not appear to influence the adherence, but age class did. Among the participants aged 16–29 years, 48% adhered to the protocol; 30–59 years: 59%; 60+: years: 82%.

### Discussion

Our data showed a significant reduction in the incidence of diarrhoea among the participants who followed the protocol strictly (PP). This is in accordance with the findings of Drakoularakou et al. (2010). The protection was strongest after a week of treatment with B-GOS. The strength of the treatment seems to lie in preventing mild cases, and severity of diarrhoea does not appear to be affected. The treatment regime must be strictly adhered to in order to have results. When we included those who stopped taking pastilles when they acquired diarrhoea (CE), the P-value increased above the significance level (P = 0.08; z = 0.05). As stopping ingestion of pastilles when diarrhoea has started does not affect the person’s risk of acquiring diarrhoea, both PP and CE data are relevant for assessing the effect of B-GOS. The comparatively weaker results compared to those in Drakoularakou et al. (2010) could be due to the differing number of treatment days before departure, i.e. 5 days in our protocol vs 7 days in the protocol of Drakoularakou et al. (2010). Indeed, when we excluded from our analyses the diarrhoea cases that developed within a week after start of ingesting pastilles (i.e. 2–3 days at the destination), a clear effect of B-GOS was found, with P-values well below the significance level in both the PP and the CE groups. In future studies the start of ingesting pastilles should be at least 1 week before departure. Drakoularakou et al. found a significant effect on the duration of diarrhoea, while we did not. They included participants travelling 14–60 days while our participants travelled for 7–15 days. This could mean that a longer time period is required for B-GOS to have an optimal effect.

Our data suggest that B-GOS can prevent 1-day, self-limiting diarrhoea. Some authors have recommended that travellers carry antibiotics for self-treatment, e.g. in CDC’s 2016 Yellow Book. It is well established that early antibiotic treatment will shorten the course of TD. However, several recent publications question or warn against the practice of treating uncomplicated TD with antibiotics because of the risk of selecting resistant bacteria. By preventing cases of diarrhoea lasting 1 day, B-GOS may reduce the use of antibiotics. For diarrhoea

### Table 1. Baseline characteristics of the participants

<table>
<thead>
<tr>
<th></th>
<th>PP GOS N = 167</th>
<th>Placebo N = 167</th>
<th>CE GOS N = 176</th>
<th>Placebo N = 173</th>
<th>ITT GOS N = 206</th>
<th>Placebo N = 202</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender M/F</td>
<td>73/94</td>
<td>84/83</td>
<td>79/97</td>
<td>85/88</td>
<td>97/108</td>
<td>101/101</td>
</tr>
<tr>
<td>Mean age</td>
<td>44.0</td>
<td>43.8</td>
<td>43.3</td>
<td>43.8</td>
<td>42.0</td>
<td>43.2</td>
</tr>
<tr>
<td>Mean travel duration (days)</td>
<td>11.2</td>
<td>11.3</td>
<td>11.2</td>
<td>11.4</td>
<td>11.2</td>
<td>11.4</td>
</tr>
<tr>
<td>Destination, (no. of travellers):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Africa South of Sahara</td>
<td>59</td>
<td>72</td>
<td>63</td>
<td>74</td>
<td>73</td>
<td>87</td>
</tr>
<tr>
<td>Middle East and North Africa</td>
<td>9</td>
<td>10</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Indian subcontinent</td>
<td>27</td>
<td>25</td>
<td>30</td>
<td>26</td>
<td>33</td>
<td>28</td>
</tr>
<tr>
<td>East Asia, Southeast Asia, and Oceania</td>
<td>49</td>
<td>42</td>
<td>51</td>
<td>43</td>
<td>59</td>
<td>53</td>
</tr>
<tr>
<td>Latin America</td>
<td>19</td>
<td>13</td>
<td>19</td>
<td>14</td>
<td>25</td>
<td>17</td>
</tr>
<tr>
<td>Others, unknown and combined</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>6</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Used Dukoral® before travel</td>
<td>34</td>
<td>34</td>
<td>35</td>
<td>35</td>
<td>37</td>
<td>38</td>
</tr>
<tr>
<td>Used atovaquone-proguanil during travel</td>
<td>54</td>
<td>66</td>
<td>58</td>
<td>70</td>
<td>70</td>
<td>82</td>
</tr>
</tbody>
</table>

### Table 2. Effect of B-GOS on the incidence of diarrhoea

<table>
<thead>
<tr>
<th></th>
<th>B-GOS (%)</th>
<th>Placebo (%)</th>
<th>Odds ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP: B-GOS 167 Placebo 167</td>
<td>32 (19.2)</td>
<td>48 (28.7)</td>
<td>0.56</td>
<td>0.03</td>
</tr>
<tr>
<td>CE: B-GOS 176 Placebo 173</td>
<td>41 (23.3)</td>
<td>54 (31.2)</td>
<td>0.65</td>
<td>0.08</td>
</tr>
<tr>
<td>ITT: B-GOS 206 Placebo 202</td>
<td>52 (25.2)</td>
<td>60 (29.7)</td>
<td>0.79</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Number of diarrhoea cases, odds ratios and P-values for the effect of B-GOS on the incidence of diarrhoea in each group. Gender was included in the model.
lasting 2 days or more, and for diarrhoea accompanied with symptoms such as abdominal pain, nausea, vomiting, fever, blood or mucus in stools (i.e. diarrhoea that will significantly impact the quality of the vacation), further research is needed to see if there is an effect of B-GOS.

Gender was included as a covariate in several analyses, as this was the outcome of the model selection process. This inclusion corrects for any bias caused by the imbalance of gender in the baseline characteristics. In general, TD affects both sexes equally.

However, men and women in our study may have shown different behaviour during their travel, making gender a proxy for other, unobserved variables.

The mechanism by which the B-GOS may reduce the risk of diarrhoea is unknown. It has been suggested that increasing the number of beneficial bacteria in the intestine, notably bifidobacteria, through ingestion of B-GOS may reduce the risk of diarrhoea. This is called a prebiotic effect. B-GOS has been shown to increase the number of *Bifidobacterium* spp. in the human colonic micro-flora. However, acute diarrhoea caused by cholera toxin, *Campylobacter*, *Salmonella* and *Shigella* are diseases that start in the small intestine. The increase in bifidobacteria is documented in the colon, not in the small intestine. Furthermore, it is not well documented that an increase in beneficial bacteria can reduce the risk of diarrhoea in persons with a normal intestinal flora. The use of probiotics (e.g. *Saccharomyces
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**Table 3.** Self-reported incidents among the 334 participants who complied strictly per protocol (PP)

<table>
<thead>
<tr>
<th></th>
<th>B -GOS N = 167</th>
<th>Placebo N = 167</th>
<th>Odds ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants who experienced diarrhoea¹</td>
<td>32 (19.2%)</td>
<td>48 (28.7%)</td>
<td>0.56</td>
<td>0.03</td>
</tr>
<tr>
<td>Mean duration of diarrhoea, days²</td>
<td>3.8</td>
<td>2.9</td>
<td>–</td>
<td>0.16⁶</td>
</tr>
<tr>
<td>Mean number of bowel movements during diarrhoea</td>
<td>17.3</td>
<td>13.7</td>
<td>–</td>
<td>0.32²</td>
</tr>
<tr>
<td>Number with diarrhoea 2 days or more³</td>
<td>24</td>
<td>27</td>
<td>0.88</td>
<td>0.67</td>
</tr>
<tr>
<td>Number with diarrhoea 1 day⁴⁵</td>
<td>6</td>
<td>20</td>
<td>0.25</td>
<td>0.004</td>
</tr>
<tr>
<td>Mean number of bowel movements in those who had diarrhoea 1 day</td>
<td>4.2</td>
<td>4.7</td>
<td>–</td>
<td>0.58⁸</td>
</tr>
<tr>
<td>Stomach pain, with or without diarrhoea</td>
<td>30</td>
<td>43</td>
<td>0.64</td>
<td>0.09</td>
</tr>
<tr>
<td>Stomach pain and diarrhoea</td>
<td>22</td>
<td>28</td>
<td>0.75</td>
<td>0.36</td>
</tr>
<tr>
<td>Fever and diarrhoea</td>
<td>4</td>
<td>6</td>
<td>0.66</td>
<td>0.52</td>
</tr>
<tr>
<td>Nausea and diarrhoea</td>
<td>9</td>
<td>16</td>
<td>0.54</td>
<td>0.15</td>
</tr>
<tr>
<td>Blood in the stool and diarrhoea</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Incidence of diarrhoea with additional symptoms⁶</td>
<td>24</td>
<td>32</td>
<td>0.68</td>
<td>0.20</td>
</tr>
<tr>
<td>Use of motility-regulating drugs</td>
<td>12</td>
<td>18</td>
<td>0.64</td>
<td>0.25</td>
</tr>
<tr>
<td>Treatment of diarrhoea with antibiotics</td>
<td>3</td>
<td>2</td>
<td>1.51</td>
<td>0.65</td>
</tr>
<tr>
<td>Consulted medical doctor for diarrhoea</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Odds ratios below 1 indicate lower incidence in the B-GOS group. Odds ratios were estimated by use of logistic regression.

¹Data on duration are available in 165 participants from the B-GOS group and 166 from the placebo group.

²Gender was included in the model.

³Wilcoxon Rank Sum Test.

⁴Stomach pain, fever, nausea and blood in the stool.

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**Table 4.** Comparison of diarrhoea incidence during the first 7 days after starting with the pastilles vs 8 days or later

<table>
<thead>
<tr>
<th></th>
<th>Up to day 7 OR; P-value</th>
<th>Day 8 or later OR; P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PP GOS N = 167</td>
<td>8: 0.66; 0.38 P = 0.47</td>
<td>18: 0.47; 0.02</td>
</tr>
<tr>
<td>Placebo N = 167</td>
<td>12: 33</td>
<td></td>
</tr>
<tr>
<td>CE GOS N = 176</td>
<td>12: 0.92; 0.84 P = 0.53</td>
<td>23: 0.53; 0.03</td>
</tr>
<tr>
<td>Placebo N = 173</td>
<td>13: 38</td>
<td></td>
</tr>
<tr>
<td>ITT GOS N = 206</td>
<td>14: 1.08; 0.84 P = 0.65</td>
<td>31: 0.65; 0.10</td>
</tr>
<tr>
<td>Placebo N = 202</td>
<td>13: 44</td>
<td></td>
</tr>
</tbody>
</table>

In the analyses of cases 8 days or later, all cases during the first 7 days were removed from the data.

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**Figure 3.** Kaplan-Meier plot showing the empirical probability of not having contracted diarrhoea after a given number of days at the travel destination (PP group, genders combined)
Lactobacillus acidophilus

Galdeano and Perdigon similarly fed Bifidobacterium and Streptococcus thermophilus species. Lactobacillus casei

et al. and IFN-$\gamma$ treatment studies, the effect in children should also be addressed. Further studies are needed to determine why oligosaccharides have not found corresponding studies with B-GOS. A second possible mechanism is that oligosaccharides may have changes in the number of bifidobacteria. A second possible mechanism, suggested by Shoaf-Sweeney & Hutkins, is that oligosaccharides may act as decoys for binding microbial adhesions and may prevent infections by inhibiting the microbes from attaching to the intestinal mucosa. This hypothesis would predict an effect from the first day of ingesting B-GOS. We need more data to see whether B-GOS has an effect during the first 7 days (Table 4).

A third possible mechanism is that oligosaccharides may have modulatory effects on the innate immune system, either by themselves or indirectly via changes in the intestinal microbiota. Vulicevic et al. found an increase in the NK cell activity and cytokine IL10 and IL 2 production after using B-GOS for 5 weeks, with an even a stronger effect after 10 weeks; still, no studies have addressed whether these effects protect against TD. Alizadeh et al. fed a GOS to piglets and found an increase in a defensin (pBD2) and secretory IgA compared to the control group. Perdigon et al. (2002) fed mice different species of Lactobacillus and Streptococcus thermophilus, which led to increased levels of TNF$\alpha$ and IFN$\gamma$, as well as of IL-2, IL-4, IL-10 and IL-12, detected in slices from the small intestine, depending on the Lactobacillus species. Galdeano and Perdigon similarly fed mice Lactobacillus casei, and then isolated mononuclear cells from Peyer’s patches and examined histologic slices of the intestinal mucosa. They found an increase in the number of cells in the treated mice that were positive for CD-206 and TLR-2, which are involved in the innate immune system. The effect increased through the first week of treatment for immune cells in the lamina propria and through the first 5 days for Peyer’s patches. We have not found corresponding studies with Bifidobacterium spp. Further studies are needed to determine why oligosaccharides seem to protect against diarrhoea.

Patients with intestinal disease and reduced immune competence could also benefit from using B-GOS before and during travel, but we currently have no data for these categories. In future studies, the effect in children should also be addressed.

It is unlikely that a single prophylactic measure can offer 100% effective protection against TD. Given the condition’s high incidence in travellers, even a modest risk reduction is helpful. B-GOS is currently sold in the UK for 11.99 GBP (16 USD) for 30 pastilles. For a 12-day trip, and starting B-GOS 8 days before the departure day, 60 pastilles would be needed. From the incidence and duration in the B-GOS and placebo groups (Table 3), it can be calculated that the average reduction in number of days with diarrhoea will be 0.13 per treatment, and the number of travellers needed to be treated to prevent 1 day of diarrhoea would be 7.4. The average price for avoiding 1 day with diarrhoea would be 238 USD, which we believe many travellers would consider a fair price for saving a precious day of vacation or business travel. One study has tested Norwegian travellers’ willingness to pay for a hypothetical diarrhoea vaccine that cost 65 USD. The results revealed that 32% would require a 40% risk reduction, and in respondents older than 50 years, 29% would choose to buy the vaccine at that price if it reduced the risk of diarrhoea by 20%. This indicates that a partial reduction of the risk of diarrhoea is an attractive option for many travellers.

The present study has the following limitations: (1) Although the Standard Operational Procedure enabled a controlled termination of the recruitment of participants with respect to diarrhoea incidence in the PP group, it did not consider the CE or the ITT groups, nor did it consider other end points. Consequently, the result for diarrhoea incidence is not robust with the present sample size, shown by the $P$-value in the CE group. A larger sample size might have produced significant results in the CE and ITT groups, as well as for other end points. Further, it is not clear how the significance level of these analyses was affected by the Standard Operational Procedure. For example, stomach pain was not considered in the Standard Operational Procedure, yet is correlated with diarrhoea incidence. The significance level for testing an effect of B-GOS on stomach pain should hence be reduced, but it is not clear by how much. (2) In retrospect, we should have collected stool samples from all participants who had diarrhoea shortly after arrival home in order to allow for sub-analysis by cause of disease. It remains unclear whether the compound is effective against toxins or against invasion of microbes. Future studies should definitely address the aetiology of diarrhoea. However, calculating the effect of B-GOS for different pathogens would likely require a much larger sample size. (3) The low adherence, 349 in the PP group out of 655 randomized volunteers (53%), could influence the quality of the study.

Oligosaccharides may become an important tool in the prevention of diarrhoea, and could lead to a decline in the use of antibiotic treatment for diarrhoea. As there are now two studies indicating an effect, B-GOS may be recommended as a mean to reduce the risk of diarrhoea for travellers. Further studies are needed in order to see whether there is an effect if the compliance is incomplete.

### Table 5. Perceived adverse effects among 523 participants who returned information

<table>
<thead>
<tr>
<th>Effect</th>
<th>B-GOS (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation/hard stool</td>
<td>2 (0.8)</td>
<td>7 (2.7)</td>
</tr>
<tr>
<td>Loose stool</td>
<td>5 (1.9)</td>
<td>7 (2.7)</td>
</tr>
<tr>
<td>Exanthema</td>
<td>3 (1.2)</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>Bloating/flatulence</td>
<td>2 (0.8)</td>
<td>8 (3.0)</td>
</tr>
<tr>
<td>Vomiting/nausea</td>
<td>0</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Stomach pain</td>
<td>0</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>Lost dental filling</td>
<td>2 (0.8)</td>
<td>0</td>
</tr>
<tr>
<td>Fever</td>
<td>0</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Number of persons$^a$</td>
<td>13 (5.0)</td>
<td>28 (10.2)</td>
</tr>
</tbody>
</table>

$^a$One person in the B-GOS group and three in the placebo group reported bloating/flatulence plus another adverse effect.

*Note: One person in the B-GOS group and three in the placebo group reported bloating/flatulence plus another adverse effect.*

boulardii, Lactobacillus acidophilus and Bifidobacterium bifidum) has been shown to have a minor effect, if any, on the risk of diarrhoea. A meta-analysis of probiotic prophylaxis showed a TD Risk Ratio of 0.94, (95% CI 0.87–1.02). Therefore, it seems unlikely that the observed effect of B-GOS is a direct result of changes in the number of bifidobacteria. A second possible mechanism, suggested by Shoaf-Sweeney & Hutkins, is that oligosaccharides may act as decoys for binding microbial adhesions and may prevent infections by inhibiting the microbes from attaching to the intestinal mucosa.

Further studies are needed to determine why oligosaccharides seem to protect against diarrhoea.

Conclusions

Ingesting B-GOS is an environmentally friendly way to reduce the risk of diarrhoea, without adverse effects. It yields a significant reduction in the incidence of diarrhoea that lasts 1 day, while no significant reduction in diarrhoea lasting more than 1 day could be detected. Ingestion should be started at least 1 week before departure. According to our data B-GOS does not
seem to influence the duration of diarrhoea or the number of bowel movements during diarrhoea. Further data are needed to assess the effect of fever and other symptoms associated with traveller’s diarrhoea.

Contributions by the Authors

Gunnar Hasle initiated the study, organized the recruitment of participants and collection of data and wrote the main part of the manuscript.

Ragnhild Raastad participated in the recruitment of participants and made contributions to the writing of the manuscript.

Gunnar Bjune supervised the project and made contributions to the writing of the manuscript.

Pål A. Jenum was responsible for the microbiological analyses and made contributions to the writing of the manuscript.

Lise Heier performed the statistical analyses, wrote the statistical part of the manuscript and commented on all parts of the manuscript.

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Conflict of interest: None declared.

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