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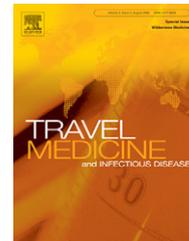
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# Meta-analysis of probiotics for the prevention of traveler's diarrhea<sup>☆</sup>

Lynne V. McFarland<sup>a,b,\*</sup>

<sup>a</sup>Department of Health Services Research and Development, VA Puget Sound Health Care System, S-152, Metropolitan Park West, 1100 Olive Way, Suite 1400, Seattle, WA 98101, USA

<sup>b</sup>Department of Medicinal Chemistry, University of Washington, Seattle, WA 98195, USA

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## KEYWORDS

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## Summary

**Background:** Traveler's diarrhea (TD) is a common health complaint among travelers. Rates of TD can range from 5% to 50%, depending on the destination. The use of probiotics for this disease remains controversial. The objective of this study was to compare the efficacy of probiotics for the prevention of TD based on published randomized, controlled clinical trials.

**Methods:** PubMed, Google Scholar, metaRegister, NIH registry of clinical trials and Cochrane Central Register of Controlled Trials were searched from 1977 to 2005, unrestricted by language. Secondary searches of reference lists, authors, reviews, commentaries, associated diseases, books and meeting abstracts. Inclusion criteria included: randomization, controlled, blinded, efficacy trials, in humans, peer-reviewed journals. Exclusion criteria were: pre-clinical, safety, phase 1 studies in volunteers, reviews, duplicate reports, trials of unspecified probiotics, trials of prebiotics, and inconsistent outcome measures.

**Results:** Twelve of 940 screened studies met the inclusion and exclusion criteria. The pooled relative risk indicates that probiotics significantly prevent TD (RR = 0.85, 95% CI 0.79, 0.91,  $p < 0.001$ ).

**Conclusion:** Several probiotics (*Saccharomyces boulardii* and a mixture of *Lactobacillus acidophilus* and *Bifidobacterium bifidum*) had significant efficacy. No serious adverse reactions were reported in the 12 trials. Probiotics may offer a safe and effective method to prevent TD.

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\*Tel.: +206 277 1095; fax: +206 764 2935.

E-mail address: [Lynne.McFarland@med.va.gov](mailto:Lynne.McFarland@med.va.gov).

## Introduction

TD is a common health problem among travelers. Every year 12 million cases of TD are reported.<sup>1</sup> Rates for TD vary from areas of high incidence (over 50%) such as to northern Africa, Latin America, the Middle East and Southeast Asia to areas of low incidence (5–10%) such as North America, northern Europe, Australia, New Zealand and the United Kingdom.<sup>2–5</sup> However, it is worth noting that TD can strike even “presumed safe” destinations.

TD is acquired by ingestion of fecally contaminated food, water or other liquids. High-risk foods include raw or undercooked meats and seafood, unpeeled raw fruits and vegetables. Tap water, ice, non-pasteurized milk and other dairy products also can be of high risk. The riskiest sources of contaminated food are street vendors, farmers markets and small restaurants.<sup>6</sup>

The incubation period (time from exposure to the contaminated food or liquid to the beginning of symptoms) usually is 2–3 days. The major symptom is diarrhea (4–6 loose, watery or bloody bowel movements/d). The duration of TD usually is 2–6 days, if untreated. Other common symptoms are abdominal cramps and nausea. Vomiting and fever are less common.<sup>3,7</sup> In up to 15% of cases, diarrhea may be prolonged (1 week to 1 month or, rarely, up to one year) and may be associated with repeated bouts of abdominal cramping, malaise, nausea, fever or muscle pain. Traveler’s diarrhea may be especially hazardous for children due to severe dehydration and in people who are frail or immunocompromised.<sup>6,8,9</sup> Other complications of TD include changes in travel plans (35% of 784 surveyed tourists), economic losses to the traveling public (cancelled trips, delays, changed tickets), and economic losses to the host country and its tourist-related industries.<sup>2</sup>

TD usually is experienced by individual travelers, but outbreaks of TD involving large groups of people also occur. Most at risk are groups visiting developing countries, passengers on cruise ships, Peace Corps or other voluntary health teams.<sup>6,10–13</sup> Traveler’s diarrhea was found to be the common prevalent non-combat medical condition (29%) in military troops on short-term missions.<sup>14,15</sup>

Most (80–85%) cases of TD are due to bacterial pathogens (Enterotoxigenic *Escherichia coli*, Enteroaggregative *E. coli*, *Campylobacter jejuni*, *Shigella* species, *Salmonella* species, *Vibrio parahemolyticus*, *Plesiomonas shigelloides*, *Aeromonas hydrophila*, *Yersinia enterocolitica*, *Vibrio cholerae*). The most common cause of bacterial TD is one of the seven types of diarrheagenic *E. coli*.<sup>16,17</sup> Other less frequent causes of TD are viruses (Norwalk or Rotavirus) and parasites (*Entamoeba histolytica*, *Giardia lamblia*, *Cyclospora*, *Cryptosporidium*). Sometimes the cause cannot be determined.

The best strategy to prevent TD is education and avoiding contaminated foods and liquids. As easy as this sounds, most tourists do not follow these guidelines.<sup>3</sup> Their focus usually is on their vacation and not food safety. Tourists often engage in riskier behaviors at exotic destinations than at home.

Traditional medications taken to prevent TD include bismuth subsalicylate and prophylactic antibiotics. Bismuth subsalicylate (the active ingredient in Pepto-Bismol) is best when taken with food four times daily. Prolonged use over 3 weeks is not recommended and this medication cannot be

taken by everyone. Bismuth subsalicylate frequently is not effective as a preventive agent because of non-compliance. To be effective, travelers must ingest 6–8 tablets/d and many fail to do so. Prophylactic antibiotics are also not recommended for TD as the etiologies of TD varies widely and the concern over antibiotic resistance by overuse of antibiotics overweighs the potential benefits.<sup>6</sup>

One of the most promising is the use of probiotics for the prevention of various types of diarrhea.<sup>18</sup> Use of probiotic microorganisms lowers dependence on antibiotics, is relatively inexpensive and is well tolerated, even for prolonged use.

One of the reasons tourists become susceptible to illness is travel can disrupt the body’s normal defense mechanisms against infections. Stress, jet lag, unfamiliar foods and water and disrupted body rhythms can disturb the normally protective bacteria in the intestines. These protective bacteria usually fight off disease-causing bacteria and viruses by “colonization resistance.” Colonization resistance is a barrier effect that prevents attachment and colonization by harmful microorganisms.<sup>19</sup> Probiotics are a promising therapeutic strategy for diseases that involve a disruption of normal microflora as they act by inhibiting pathogen attachment, enhancing the immune response and assisting in re-establishing normal microflora.<sup>20</sup>

## Methods

### Objective

The objective of this meta-analysis is to assess the efficacy and safety of probiotics for the prevention of TD.

### Criteria for study selection

Abstracts of all citations and retrieved studies were reviewed and rated for inclusion. Full articles were retrieved if specific treatments were given to either prevent or treat the disease of interest. Inclusion criteria include: randomized, controlled, blinded efficacy trials in humans published in peer-reviewed journals. Exclusion criteria include: pre-clinical studies, safety studies only, case reports or case series, phase 1 studies in volunteers, reviews, duplicate reports, trials of unspecified probiotics, trials of prebiotics, not in the disease being studied, or inconsistent outcome measures. External and internal validity is strengthened by including only randomized, controlled trials.

### Outcomes and definitions

The primary outcome for this study is diarrhea occurring during travel, which was not present at trip origin and not due to a pre-existing chronic intestinal condition. Documentation of diarrhea is based on clinical assessment and self-report of symptoms and is defined as  $\geq 3$  loose stools/d for at least 2 days or  $\geq 5$  loose stools/48 h.<sup>2,21</sup>

## Data sources

PubMed and Google Scholar were searched from 1977 to 2005 for articles unrestricted by language. Non-English articles were translated. Three on-line clinical trial registers were searched: Cochrane Central Register of Controlled Trials ([www.cochrane.org](http://www.cochrane.org)), metaRegister of Controlled Trials ([www.controlled-trials.com/mrct](http://www.controlled-trials.com/mrct)) and National Institutes of Health ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)). Secondary and hand searches of reference lists, authors, reviews, commentaries, associated diseases, books and meeting abstracts also was performed. Six search terms for randomized controlled trials (RCT), human, blinding, phase 2, phase 3, efficacy were combined with 15 terms for probiotics. Search terms included probiotic\*, microflora, antibiotics, *Clostridium difficile*, colitis, PMC, diarrhea, *Saccharomyces*, *Lactobacill\**, *Bifidobacter\**, *Enterococc\**, *Bacill\**, VSL#3, symbiotic\*, Lactinex. Search strategies were broad-based initially, then narrowed to the disease of interest.<sup>22</sup> The procedure for this meta-analysis was designed as suggested by Egger et al. and MOOSE guidelines using clearly delineated parameters, a priori inclusion and exclusion criteria and standardized data extraction methods.<sup>23–25</sup>

## Data extraction

Information on study design, methods, interventions, outcomes, adverse effects and treatments was extracted from each article. Data on patient inclusion and exclusion criteria, number of completed subjects, attrition, treatment dose and duration, and outcome was extracted into a standardized table. In some cases, the primary or secondary author was contacted for data not reported in the original article. The data abstraction was completed individually, but verified using historic searches with two other researchers for previous review articles.<sup>20,26</sup> A few trials had multiple probiotic arms. Each probiotic arm was compared to a control group separately.

## Assessment of methodological quality

Studies that met the inclusion criteria were graded for quality using a scale reported by the US Preventive Services Task Force.<sup>27</sup> Quality of evidence is rated from 1 to 3 (poor, fair and good) based on randomization, study design, sample size, generalizability, study biases and outcome assessment. Study quality was not integrated with the model weights, as trials of poor quality were excluded from review and this practice is not uniformly recommended.<sup>28</sup> Weights for this analysis are based solely on sample sizes.

## Statistical analysis

Statistical analysis was performed using Stata software version 8.1 (Stata Corporation, College Station, Texas). Relative risks with 95% confidence intervals were computed as summary statistics. Heterogeneity across trials was evaluated using Cochran *Q* test based on pooled relative risks by the Mantel–Haenszel method. If the studies were homogeneous, a fixed-effects model was used and a pooled relative risk was calculated with the Mantel–Haenszel

method for fixed effects. If the studies were heterogeneous a random effects was employed and a pooled relative risk was calculated using the DerSimonian and Laird method.<sup>29</sup> A funnel plot as well as an adjusted rank correlation test using the Egger method were used to assess publication bias.<sup>23,30</sup> *P* values less than 0.05 were considered significant.

## Results

### Overview of included studies

The literature search yielded 940 citations on probiotics, of which 37 relating to TD were selected from retrieval. Twelve (32%) probiotic treatments from seven of the 37 screened articles met inclusion criteria and provided data on 4709 enrolled subjects (Table 1).<sup>31–37</sup> The number of patients in each of these studies was generally large (median, 310; range 50–832 subjects).

### Excluded studies

Of the TD studies, 25 failed to meet one or more of the inclusion criteria. Most were reviews or commentaries ( $n = 19$ ), preclinical or Phase 1 safety studies ( $n = 3$ ). Three trials that passed initial screening were excluded (Table 2), as one tested a prebiotic only with no probiotic component,<sup>38</sup> one had no control group,<sup>39</sup> and one used a different outcome measure (days of diarrhea).<sup>40</sup>

### Study quality

The quality of the studies is presented in Table 1, indicating generally good methodological quality. Most studies of poor quality were excluded from the data extraction in the preliminary steps of this study.

### Efficacy studies

Of the 12 randomized, controlled treatments providing adequate data regarding efficacy, six (50%) trials reported significant prevention of TD for the probiotic in their trial, with two trials having multiple treatment arms, as shown in Table 1.<sup>31,32,34,36</sup> One study found a trend ( $p = 0.07$ ) for efficacy<sup>37</sup> and five other treatments did not find a significant difference between probiotic and control groups, with two trials having multiple treatment arms.<sup>31,33,35</sup> When the 12 randomized controlled treatments were pooled and weighted by their study sizes, the relative risk was 0.85 (95% CI 0.79, 0.91,  $p < 0.001$ ), as shown in Fig. 1. As no significant heterogeneity was found ( $X^2 = 18.9$ , 12 degrees of freedom,  $p = 0.09$ ), a fixed-effects model was used for the meta-analysis. There was no significant publication bias found, as shown by the funnel plot in Fig. 2 or by the rank correlation test ( $z = -0.96$ ,  $P = 0.34$ ).

### *Saccharomyces boulardii*

*Saccharomyces boulardii* is a lyophilized yeast packaged in capsules and is widely available in Europe, South America, Africa, Sweden and Mexico and in the USA (as a dietary

**Table 1** Efficacy of various probiotics for the prevention of traveler's diarrhea from 12 randomized treatment arms.

N	Type of tourists, to destination	Probiotic	Dose/d	Treatment duration	Follow-up	Probiotic-treated		Control group		Weight	Quality	Reference
						# Failed	# Cured	# Failed	# Cured			
832	Austrian, hot climates	SB	$5 \times 10^9$	3 wk	0	143 (34)	283	173 (43)	233	17.1	3	Kollaritsch, 1989 <sup>31</sup>
805	Austrian, hot climates	SB	$1 \times 10^{10}$	3 wk	0	127 (32)	272	173 (43)	233	16.5	3	Kollaritsch, 1989 <sup>31</sup>
713	Austrian, varied	SB	$5 \times 10^9$	3 wk	0	121 (34)	231	141 (39)	220	13.4	3	Kollaritsch, 1993 <sup>32</sup>
664	Austrian, varied	SB	$2 \times 10^{10}$	3 wk	0	87 (29)	214	141 (39)	220	12.4	3	Kollaritsch, 1993 <sup>32</sup>
50	US, Mexico	Lactinex	$4-7 \times 10^9$	8 Days	3 wk	9 (35)	17	7 (29)	17	0.7	2	Pozo-Olano, 1978 <sup>33</sup>
245	US, varied	LGG	$2 \times 10^9$	1-3 wk	0	5 (3.9)	121	9 (7.4)	110	0.9	2	Hilton, 1997 <sup>34</sup>
202	Soldiers to Belize	LA	$2 \times 10^{11}$	3 wk	1 wk	26 (25.7)	75	24 (24)	77	2.3	3	Katellaris, 1995 <sup>35</sup>
181	Soldiers to Belize	LF KLD	$2 \times 10^{11}$	3 wk	1 wk	19 (23.8)	61	24 (24)	77	2.0	3	Katellaris, 1995 <sup>35</sup>
94	Danish to Egypt	Mix1	$3 \times 10^9$	2 wk	0	20 (43)	27	33 (71)	14	3.2	2	Black, 1989 <sup>36</sup>
319	Austrian, hot climates	LA	$2 \times 10^{8-9}$	3 wk	0	82 (53)	72	78 (47)	87	7.3	3	Kollaritsch, 1989 <sup>31</sup>
756	Finnish, Turkey	LGG	$2 \times 10^9$	2 wk	0	153 (41)	220	178 (46.5)	205	16.9	3	Oksanen, 1990 <sup>37</sup>
Vaccine trial												
310	Austrian, to hot climates	Mix2	Dead	3 wk	0	85 (50)	84	70 (46)	71	7.3	3	Kollaritsch, 1989 <sup>31</sup>

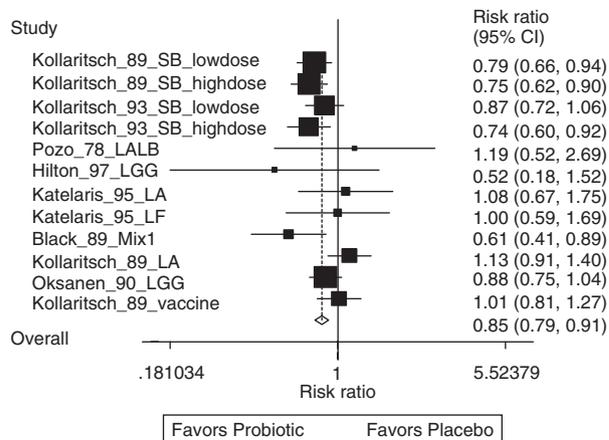
Abbreviations: N, number of subjects with evaluable outcome; SB, *Saccharomyces boulardii*; Lactinex, *L. acidophilus* and *L. bulgaricus*; LGG, *Lactobacillus rhamnosus* GG; LA, *Lactobacillus acidophilus*; LF, *Lactobacillus fermentum* KLD; Mix1, *L. acidophilus*+*L. bulgaricus*+*Bifidobacterium bifidum*+*Streptococcus thermophilus*; Mix2, heat killed *Salmonella*+*Shigella*+*E. coli*.

**Table 2** Excluded studies of probiotics or prebiotics from meta-analysis.

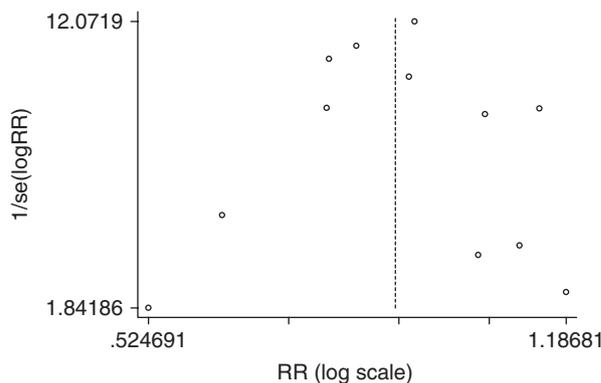
N	Subjects	Probiotic	Dose/d	Treatment duration	Follow-up	Probiotic-treated		Control group		Reason excluded	Reference
						# Failed	# Cured	# Failed	# Cured		
244	UK to varied, prevention	FOS	10 g	4 wk	0	45 (38)	72	58 (45.7)	69	Prebiotic only, no probiotic	Cummings, 2001 <sup>38</sup>
95	Adults with TD	SB	8 × 10 <sup>9</sup> (428 mg)	5 Days	0	0 <sup>a</sup>	95 (100%)	No	Controls	Open trial, no controls	Kirchhelle, 1996 <sup>39</sup>
43	Tourists with TD in Tunisia	SB	1 × 10 <sup>10</sup> (500 mg)	5 Days	0	2.1 Days diarrhea <sup>a</sup>		1.4 Days diarrhea		Outcome not consistent with other studies	Bruns, 1995 <sup>40</sup>

Abbreviations: SB, *Saccharomyces boulardii*; FOS, fructooligosaccharide; TD, traveler's diarrhea; nd, no data.

<sup>a</sup>p < 0.05.



**Figure 1** Forest plot of 12 randomized, controlled treatments for the prevention of traveler's diarrhea by probiotics. Abbreviations: SB = *S. boulardii*, Lactinex = *L. acidophilus* and *L. bulgaricus*, LGG = *L. rhamnosus* GG, LA = *L. acidophilus*, LF = *L. fermentum* KLD, Mix1 = *L. acidophilus*+*L. bulgaricus*+*B. bifidum*+*S. thermophilus*, Mix2 = heat killed *Salmonella*+*Shigella*+ *E. coli*.



**Figure 2** Funnel plot of 12 randomized, controlled trials for the prevention of traveler's diarrhea by probiotics.

supplement). This yeast is non-pathogenic and has been used to treat diarrhea while maintaining an excellent reputation for safety. *S. boulardii* achieves high concentrations in the intestine within 3–4 days, does not permanently colonize the intestine and is quickly cleared from the colon (within 4–6 days) after the yeast has been discontinued.<sup>18,41</sup>

Two randomized, controlled trials have been done with *S. boulardii* that included a total of four different probiotic treatment arms. Kollaritsch et al. enrolled 1231 Austrian tourists traveling to hot climates and randomized them to either one of two doses of *S. boulardii* (250 or 500 mg/d) or placebo for 3 weeks.<sup>31</sup> The treatment was started 5 days prior to the trip and continued through the duration of the trip. Traveler's diarrhea developed in 43% given placebo, but in significantly fewer given either 250 mg/d of *S. boulardii* (34%) or 500 mg/d (32%). No adverse reactions were noted. No further follow-up was done once the travelers returned home. A second study by Kollaritsch et al. was done with 3000 Austrian tourists traveling to northern Africa, the Middle East and Far East.<sup>32</sup> Tourists were given either a low dose of *S. boulardii* (250 mg/d), or a high dose of *S. boulardii* (1 g/d),

or a placebo, then diarrheal symptoms were recorded. The treatment was started 5 days prior to the trip and continued through the duration of the trip (mean of 3 weeks). Only 1016 (34%) completed the study. *S. boulardii* significantly reduced TD in a dose-dependent manner. Patients treated with placebo had a higher frequency (39%) of TD compared to both the low dose of *S. boulardii* (34%) and the high dose of *S. boulardii* (29%) groups. Efficacy of *S. boulardii* was more pronounced in some destinations (North Africa, 24% for 1 g/d *S. boulardii* versus 44% placebo) compared to others (South America, 33% for both 1 g/d *S. boulardii* and placebo). More TD was found in group tours (50%) and individuals on vacation (29–36%) than in business travelers (3%). There was no difference in the incidence of TD by the type of hotel. No significant side effects were reported.

### Lactobacilli probiotics

Seven randomized controlled trials tested various types of *Lactobacilli* (*L. rhamnosus* strain GG, *L. acidophilus*, *L. bulgaricus* and *L. fermentum* for TD (Table 1). *L. rhamnosus* GG originally was isolated in humans, is resistant to bile and acid, binds to intestinal cells, produces several microbe-fighting substances and has been studied in blinded clinical trials.<sup>42</sup> *L. rhamnosus* GG usually is taken as powder contained within a capsule or as a fermented milk product (Valio Dairies, Helsinki, Finland). *Lactobacillus* GG is widely available both in Europe and in the USA, it is sold as a dietary supplement. Other *Lactobacilli* probiotics have shown promise in preventing other types of diarrhea (pediatric, acute adult and inflammatory bowel disease) and were considered candidates for TD.<sup>18,20</sup>

Oksanen et al. enrolled 820 Finnish travelers going to one of two cities in Turkey and randomized them to either *L. rhamnosus* GG ( $2 \times 10^9$  organisms/d) or placebo.<sup>37</sup> The treatment was started 2 days before the 1 or 2 week trip and continued for the trip duration. Most ( $n = 756$ , 92%) completed a questionnaire during the plane ride home about any illnesses during their trip. Overall, 41.0% given *L. rhamnosus* GG developed TD and a similar number given placebo developed TD (46.5%,  $p = 0.07$ ). Interestingly, the effect of the probiotic was more pronounced in one city than the other. Among tourists going to Alanya, Turkey, for 1 week, 17 (24%) given *L. rhamnosus* GG developed TD, while significantly more 30 (39.5%) given placebo developed diarrhea ( $p = 0.04$ ). If the trip to Alanya lasted for 2 weeks, there was no longer a significant difference between the probiotic group (47%) and the controls (66%,  $p = 0.1$ ). In the tourists going to Marmaris, Turkey, 68 (38.9%) given *L. rhamnosus* GG developed TD and 74 (42.3%) given placebo developed TD ( $p > 0.05$ ). This study did not propose a reason why *L. rhamnosus* GG seemed to work in one city and not the other, but this may have been due to different pathogens in one area or because the placebo group going to Marmaris was slightly older. No side effects related to the probiotic were reported.

Hilton et al. enrolled 400 adult patients seen at a travel and immunization center who were traveling from the USA to a variety of developing countries for 1–3 weeks.<sup>34</sup> Tourists were randomly assigned to either *L. rhamnosus* GG ( $2 \times 10^9$  organisms/d) or placebo. The treatment began 2 days prior

to departure and continued throughout the trip. Most (61%) completed the trial, but 155 were excluded due to non-compliance ( $n = 142$ ) and 13 were false starts (cancelled trips). The risk of developing TD was significantly lower in the group taking *L. rhamnosus* GG (3.9%) compared to the group taking placebo (7.4%,  $p = 0.05$ ). No serious side effects were observed in the treatment group.

Another treatment arm of the trial by Kollaritsch et al. included 319 tourists randomized to either *L. acidophilus* ( $2 \times 10^9$  organisms/d) or placebo, starting on the day of departure and continuing during the trip.<sup>31</sup> Traveler's diarrhea occurred as frequently in the tourists treated with *L. acidophilus* (53%) as those given placebo (47%),  $p > 0.05$ .

Katellaris et al. enrolled 282 soldiers going to Belize and randomized them to one of three groups: *L. acidophilus*, *L. fermentum* strain KLD or placebo.<sup>35</sup> The treatments were started 1 day prior to departure and continued for 3 weeks. The soldiers were followed for an additional week for delayed symptoms. There were no significant differences in the frequency of TD among those receiving *L. acidophilus* (25.7%), *L. fermentum* KLD (23.8%) or placebo (24%). No adverse reactions were noted.

Based on the concept that the healthy colon functions effectively due to the multiple types of normal microflora residing within, another tactic using mixtures of different probiotic strains, instead of relying upon a single type of bacteria or yeast was investigated. Pozo-Olano et al. randomized 50 travelers going to Mexico to either Lactinex (a mixture of *L. acidophilus* and *L. bulgaris*) or placebo.<sup>33</sup> The treatment was begun 2 days before departure in one group and within 2 days of arrival for another group and continued for 8 days. Travelers were followed for an additional 3 weeks. There was no significant difference in the frequency of TD in the group given the probiotic mixture (37% for those started prior to travel and 29% started at arrival) and those given placebo (29%). No adverse reactions were reported.

However, another probiotic mixture showed better effectiveness. Black et al. enrolled 94 Danish tourists going on a 2 week trip to Egypt and randomized them to either a mixture of probiotics (*L. acidophilus*, *L. bulgaricus*, *B. bifidum*, and *Streptococcus thermophilus*) or a placebo.<sup>36</sup> The dose of probiotic or placebo was started 2 days prior to travel to allow the probiotic to colonize the intestinal tract, and the treatment was continued until the last day of travel. Significantly fewer tourists given the probiotic mixture developed TD (43%) compared to those given the placebo (71%,  $p < 0.001$ ). No adverse reactions were noted during this study.

Another treatment arm of the trial by Kollaritsch et al. included 310 tourists randomized to either a vaccine made of three heat-killed bacteria (*Salmonella*, *Shigella* and *E. coli*) or placebo, starting 10 days prior to departure and continued during the trip.<sup>31</sup> Traveler's diarrhea occurred as frequently in the tourists treated with vaccine (50%) as those given placebo (46%),  $p > 0.05$ .

### Adverse events

Most 10 (83%) of the 12 trials presented data on adverse reactions, but two trials did not.<sup>33,36</sup> In 10 trials, no serious

adverse reactions including bacteremia or fungemia were associated with the probiotic treatments. One study reported abdominal cramping was associated with 2% of the subjects taking *L. rhamnosus* GG.<sup>34</sup>

## Discussion

This meta-analysis found probiotics are safe and effective for the prevention of TD. The pooled risk estimate found that 85% of TD cases were prevented by probiotics. The main advantage of probiotic therapy for this type of disease that is mediated through changes in intestinal microflora in response to exposures incurred during travel is that they are therapeutically active but they do not disrupt the re-establishment of the protective normal microbial flora.

An important consideration when drawing conclusions from meta-analyses is that potential biases may be present due to publication bias. Sutton et al. reviewed 48 meta-analyses and found 30 (63%) made no reference to publication bias or reported funnel plots.<sup>43</sup> In this meta-analysis, publication bias was minimized by conducting extensive searches through multiple databases and receiving original data from the authors. In addition, the funnel plot and adjusted rank correlation test indicated there is no significant publication bias in this data set.

Contradictory results from randomized trials may arise from differences in study populations, type of probiotic being investigated or differences in probiotic doses and duration of treatment. For TD, additional factors may influence the efficacy including trip destination, probiotic potency during travel, medication compliance, and behaviors of the traveler. The populations in these trials were diverse in that they were from several different countries and no descriptions of age or other demographic data were provided, so a comparison between the trials was not able to be done. The advantage of selecting a non-restrictive study population is that they may represent tourists in general.

Another source of heterogeneity for probiotic trials is the type of probiotic itself. Significant differences in effectiveness have been reported for different species and strains of similar species of bacteria and yeasts.<sup>20,44</sup> Unfortunately, many trials only report the genus and species and do not provide strain designations. Grouped by the type of probiotic and adjusted for differences in study sample size, 3 (75%) of the *S. boulardii* treatment arms were significantly protective of TD, but only one (13%) of the Lactobacilli trials was protective. Whether this was due to the type of probiotic chosen or other influences must be considered.

The differences in the results may have been due to sub-therapeutic doses of probiotics ( $<10^{10}$  organisms/d). In trials for TD, eight (67%) of the trials used what would be considered currently as sub-therapeutic doses in other diseases such as the prevention of antibiotic-associated diarrhea,<sup>45</sup> but there was no significant dose effect on the rate of TD. Two trials found a lower rate of TD as the dose of *S. boulardii* was increased, but there was no significant dose-response effect.<sup>31,32</sup>

The differences in the trial results may have been due to trials failing to provide the probiotic during the entire period of susceptibility when normal intestinal microflora is

becoming re-established (usually 6–8 weeks).<sup>19</sup> All trials gave the probiotic during the trips, which ranged from 8 days to 3 weeks. There is no significant effect of treatment duration on efficacy. As only two studies followed returning tourists, the occurrence of delayed onset TD was not reported. Delayed cases of TD have been reported.<sup>46</sup> It would be interesting for future studies to document the frequency of delayed TD and whether a longer course of probiotics would be effective.

Inconsistent efficacy results may also be due to the viability and stability of the probiotic product. Probiotics that are lyophilized are stable at room temperature (such as *S. boulardii* and *L. rhamnosus* GG), but some products require refrigeration (such as Lactinex). This presents a difficulty for travelers, as constant refrigeration is seldom possible, thus a loss of product potency may decrease the efficacy of these types of products. Only one study confirmed the probiotic viability at the end of the study, but did not report the result.<sup>35</sup> The importance of probiotic viability is seen with trials that used killed preparations and found no protective effect.<sup>31</sup>

Another limitation to these trials is that there was a difference in compliance with the treatment. Although most trials had low attrition, one study lost 39% due to non-compliance<sup>34</sup> and another had 66% drop out due to a variety of reasons.<sup>32</sup> Katelaris et al. reported that 24% of their enrolled population had less than 90% compliance with their treatments.<sup>35</sup> All three of these trials with poor compliance did not find a significant protective effect for the probiotic.

Efficacy also was found to vary by travel destination in several trials. Rates of TD in tourists given *S. boulardii* were lower in tourists traveling to Africa (50% protection) than to India (no protection).<sup>31</sup> A follow-up study also found lower rates of TD in Africa (24% *S. boulardii*) than in other destinations such as South America (33%).<sup>32</sup> In a study of tourists traveling to Turkey, protection by *L. rhamnosus* GG was found to be higher in one city (48% TD in Alanya) than in another (56% TD in Marmaris).<sup>37</sup> Interestingly, the rates of TD in the placebo treated were higher in Alanya (66%) than in Marmaris (52%), so the difference in efficacy was not solely due to the destination.

The safety of probiotics should also be considered. Although case reports and case series of bacteremia and fungemia have been reported in the literature, no incidents occurred in patients enrolled in the 12 trials reviewed for this meta-analysis. Caution should be exercised for patients who are severely ill and receiving nutrition or antibiotics through a potentially open portal (catheter or nasogastric tube). Infrequent blood-stream infections have been reported, most probably due to contamination of the environment as the probiotic capsule is opened at bedside and mixed with food.<sup>47</sup> Rare complications including endocarditis and liver abscess have been associated with *L. rhamnosus* GG use.<sup>48,49</sup> Bacteremia and fungemia have been associated with probiotics, but respond well to antibiotics or anti-fungal medications.<sup>26,50,51</sup>

The value of a meta-analysis is that it provides a tool to combine studies with the above differences and arrive at a pooled estimate of the efficacy of different probiotics. Probiotics may be a safe and effective strategy to prevent TD, but continued research is warranted.

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