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A Randomized, Double Blind, Placebo-Controlled Trial of an Oral Synbiotic (AKSB) for Prevention of Travelers' Diarrhea

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Background. Travelers' diarrhea (TD) is a significant problem for travelers. TD is treatable once it occurs, but few options for prevention exist. Probiotics have been studied for prevention or treatment of TD; however, very few combination probiotics have been studied. Therefore, the purpose of this study was to determine if prophylactic use of an oral synbiotic could reduce the risk of acquiring TD and reduce antibiotic use if TD occurred.

Methods. Healthy subjects traveling to an area of the world with an increased risk of TD were eligible. All subjects received pre-travel counseling and were provided antibiotics and antidiarrheals (loperamide) for use only if TD developed. The subjects were blinded and randomized to take two capsules of placebo or oral synbiotic (a combination of two probiotics and a prebiotic) called Agri-King Synbiotic (AKSB) beginning 3 days prior to departure, daily while traveling, and for 7 days after return. All subjects kept symptom and medication diaries and submitted a stool sample for pathogen carriage within 7 days of return. The study was powered to detect a 50% reduction in the incidence of TD.

Results. Of the 196 adults (over 18 years of age) enrolled in the study, 54.3% were female and 80.9% were younger than 60 years. The study randomized 94 people to the AKSB arm and 102 to placebo. The incidence of TD was 54.5% in the overall group with 55.3% in the AKSB arm and 53.9% in the placebo ($p = 0.8864$). Among the subjects who experienced diarrhea ($n = 107$) there was no significant difference in the proportion of subjects that took antibiotics versus those that did not take antibiotics (35% vs 29%, $p = 0.68$). AKSB was safe with no difference in toxicity between the two arms.

Conclusions. The prophylactic oral synbiotic was safe but did not reduce the risk of developing TD among travelers, nor did it decrease the duration of TD or the use of antibiotics when TD occurred.

Travelers' diarrhea (TD) is associated with significant morbidity and a decrease in quality of life for international travelers.[1] Symptoms of TD are usually self-limited and resolve within a week. It is estimated that 20% to 50% of people traveling to developing areas will develop TD.[2] TD is defined by more than three loose stools per day with or without associated symptoms of fever, nausea, or abdominal pain.[3] It is typically caused by bacterial pathogens such as enterotoxigenic *Escherichia coli*, enteroaggregative *E coli*, *Campylobacter* species, *Shigella* species, or *Salmonella* species. Prevention of TD relies on food and water precautions. Primary prevention of TD using antimicrobials such as fluoroquinolones,[4] rifaximin,[5,6] or non-antibiotic strategies such as bismuth subsalicylate (Pepto-Bismol)[7,8] are effective but are typically reserved for high-risk populations, such as severely immunosuppressed patients. Use of these agents is also restricted owing to cost, emerging antimicrobial resistance, and dosing complexity (eg, bismuth subsalicylate is best taken as two tablets every 6 hours). Travelers are often provided with antimicrobials and loperamide to self-treat severe diarrhea, should it occur. Self-treatment of TD with antibiotics (often fluoroquinolones or azithromycin) reduces the duration of symptoms to 1 to 2 days.[9]

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However, with increasing travel and antimicrobial resistance, it is important to identify non-antimicrobial-based preventive strategies, such as probiotics, to prevent or treat TD.

Probiotics are viable preparations of live microorganisms that can control or inhibit pathogens in the digestive tract while promoting the establishment of the normal beneficial microflora.[10] Probiotics have in general been considered safe.[11] Prebiotics are non-digestible food ingredients that aid the growth of intestinal bacteria.[10] Synbiotics are a combination of a probiotic and a prebiotic. Although probiotic studies for TD prevention have produced conflicting results regarding efficacy, a recent meta-analysis suggests that probiotics significantly prevent TD (RR = 0.85, 95% CI 0.79–0.91, $p < 0.001$).[11] In a previous study, *Saccharomyces cerevisiae* probiotic alone was not effective for TD prevention[12] but *Saccharomyces boulardii* reduced TD in a dose-dependent fashion (>1 million CFU/day) and in specific geographic areas (North Africa and Turkey).[12,13] Probiotics that have been shown to reduce TD include *Lactobacillus rhamnosus* GG,[14,15] Lactinex, *Lactobacillus fermentum* strain KLD (LF-KLD), *Lactobacillus acidophilus* (LA),[16] but the effect is not seen with all probiotics.[11] Given these conflicting results, new probiotics or combinations of probiotics and prebiotics need to be studied for the prevention of TD. We conducted a study to evaluate a synbiotic called Agri-King Synbiotic (AKSB) for TD prevention to see if it could decrease antibiotic use if TD occurred. AKSB has three ingredients: the prebiotic fructo-oligosaccharide (FOS) and two organisms—*Enterococcus faecium* (microencapsulated SF68 called Ventrux ME 30) and *S cerevisiae* strain CNCM I 4444. *Enterococcus faecium* can compete with gram-negative organisms such as *E coli*.[17] *Saccharomyces boulardii* is shown to bind gram-negative bacteria.[18] A phase 1 study in humans showed that AKSB was safe and increased stool enterococcal and saccharomyces growth within 3 days that washed out within 7 days of the last dose (unpublished data, data on file).

We designed a single center, double-blind, placebo-controlled study comparing the prophylactic use of AKSB to placebo in healthy individuals with the primary aim to determine whether AKSB can significantly reduce the incidence of TD in subjects traveling to a TD high-risk area. The secondary objectives were to: (1) demonstrate that AKSB reduces antibiotic use among travelers to these regions, (2) show that AKSB can shorten the number of days of TD, (3) examine the safety of AKSB in this population, (4) evaluate stool pathogen carriage after travel, and (5) examine the viability of AKSB capsules after subjects return from their trips.

Methods

Participants and Subject Eligibility

This randomized clinical trial was conducted between August 2002 and November 2006 at the Mayo Travel and Tropical Medicine Clinic (TTMC) in Rochester, MN, USA. Subjects aged 18 years or above and traveling for 5 to 30 days to a location considered at high risk for TD were eligible for the trial. The high-risk areas were defined as countries in the continents of Africa, South and Central America, and Asia. Individuals traveling to areas other than those listed were not eligible to participate. Additional exclusion criteria included: current use of antibiotic or antidiarrheal medication (ie, Pepto-Bismol, loperamide, etc.) or their use within 2 weeks prior to departure for the trip, a history of inflammatory bowel disease (Crohn's disease or chronic ulcerative colitis), known bowel cancer, congenital or acquired immunocompromised states such as human immunodeficiency virus infection (HIV/AIDS), current or recent chemotherapy or immunomodulating agents (corticosteroids and TNF-α inhibitors), short-gut syndrome, use of oral typhoid vaccine within 48 hours of starting AKSB, pregnancy, ongoing probiotic use, and previous participation in this study. Women of child-bearing age were required to have a negative pregnancy test within 2 weeks of starting the study drug and were counseled not to get pregnant during the study period.

Subjects seen at the TTMC for pre-travel counseling for international travel were screened and offered enrollment into the TD study. All enrolled subjects received standard counseling and education about food and water precautions and self-management of TD. They were also offered antimicrobials (ciprofloxacin, levofloxacin, or azithromycin) to carry with them to treat TD if needed. They were instructed not to use antibiotics prophylactically. The subjects were instructed to continue taking the study drug even if TD developed and were initiating antibiotics and/or loperamide. A letter was provided to the patient to allow carriage of the study drug across international borders. The letter also contained telephone numbers for on-call personnel in case subjects experienced side-effects or had questions during their trip. This trial was approved by the Mayo Clinic Institutional Review Board (IRB) (Protocol 566–02) and all subjects enrolled in this study provided written informed consent.

Dose Selection, Treatment Assignment, Randomization, and Blinding Procedures

Two capsules of AKSB or placebo were ingested daily with food, beginning 3 days prior to travel, throughout the trip, and for 7 days after return. The two capsules could be taken either at once or one twice a day. The AKSB and placebo capsules were identical in color, packaging, and smell. Subjects were allowed to reduce the dose to one capsule per day if they had uncomfortable increase in intestinal gas. They were allowed to increase back to two capsules per day or one capsule twice a day as symptoms dictated. AKSB has three ingredients: a probiotic bacteria (4.5 billion CFU of *Enterococcus faecium*, microencapsulated SF68 or Ventrux ME 30 from Cerbios-Pharma SA, Barbengo/Lugano, Switzerland), a probiotic yeast

(500 million CFU of *S cerevisiae* strain CNCM I 4444 from Lesaffre, Marcq-en-Barœul, France), and a prebiotic (FOS, NutraFlora from GTC Nutrition, Westchester, IL, USA). All doses were recorded daily in a provided diary. Subjects were randomly allocated to receive AKSB or placebo. Randomization was performed in a block of size 4 using a random number generator from SAS software (version 8.0; SAS, Inc., Cary, NC, USA). Investigators, study coordinators, and subjects were blinded to treatment assignment.

Clinical Monitoring

After initiating the study drug, subjects were asked to maintain a daily diary to record details regarding medication compliance, geographic location, and number of loose stools, symptoms, and daily eating habits. Subjects were asked to grade their symptoms (Appendix, Table A1). The study coordinator contacted the patient within 7 days of their return from the trip to monitor for toxicity, study outcomes, and reminded subjects to submit a fresh stool sample within 5–7 days of the last study dose.

Adverse event (AE) monitoring was done via the daily diary and the final phone interview. An AE was defined as any untoward medical occurrence in a study subject exposed to AKSB or placebo. An AE could be any unfavorable and unintended effect (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of AKSB or placebo. Serious adverse events (SAEs) were defined as those that were life-threatening, resulted in hospitalizations of >24-hour duration, or were disabling or resulted in death. All AEs were assessed whether they were possibly, probably, or definitely related to the study drug or not related at all. All SAEs were to be reported to the IRB within 24 hours and all other AEs were summarized in annual reports to the IRB. Unused capsules from subjects on AKSB were returned to Agri-King, Inc. for probiotic viability studies. Subjects received a $50 honorarium for the inconvenience of participating in the study.

Stool Microbiological Analysis

All subjects were asked to submit a fresh stool specimen in a Para-Pak culture and sensitivity vial within 5–7 days of returning home from their trip. The specimens were submitted for culture of enteric pathogens (*Campylobacter* species, *Salmonella*, *Shigella*, *Aeromonas*, and *Yersinia*), enterotoxigenic *E coli* toxin assay, and ova and parasite examination at the Mayo Clinic Microbiology Laboratory. The fecal specimen was inoculated onto selective media designed to inhibit growth of normal bowel flora while allowing growth of the enteric pathogens. The following media were used: sheep blood agar, Hektoen enteric agar, eosin-methylene blue agar, *Campylobacter* agar, cefsulodin-irgasan-novobiocin agar, and the enrichment broth, selenite F. Suspect colonies were identified using conventional biochemical and serologic methods. These tests were performed per standards set by the Clinical and Laboratory Standards Institute. Returned capsules were analyzed for AKSB organisms' post-travel viability (Analab Laboratories, Fulton, IL, USA).

Statistical Analysis

The primary endpoint was the development of diarrhea. Assuming that the frequency of TD is 25% in those receiving placebo, 348 volunteers (174 placebo and 174 AKSB) were required to have an 85% power to detect a 50% reduction in the frequency of TD for the AKSB group (based on a comparison of 25% vs 12.5%, using a two-sided, $\alpha = 0.05$ level test). We planned to over accrue the study by 15% for a total of 400 subjects to allow for patient dropout.

On the basis of the O'Brien-Fleming method for early stopping,[19] an interim analysis occurred after 174 volunteers (87 on each arm) completed the study. Descriptive summaries were reported as median (minimum and maximum) for continuous variables and frequency and percentages for categorical variables within each treatment arm. Comparison of continuous variables was performed using the Wilcoxon Rank Sum test and a comparison of categorical variables was performed using either a Chi-square or Fisher's exact test. Ordered categorical variables were compared using the Cochran Armitage trend test. Kaplan–Meier survival curves for time to onset of diarrhea for AKSB and placebo groups were plotted and compared using a log rank test. All tests were two-sided and p values < 0.05 were considered statistically significant. Analysis was performed using SAS version 9.0 (SAS, Inc.).

Results

Patient Enrollment and Characteristics

A total of 251 subjects met the criteria for entry and were subsequently enrolled in the study (Table 1). Fifty-five subjects dropped out after consent but prior to starting the study drug and 196 provided follow-up data. The most common reasons cited for dropping out were trip cancellation, participation was too inconvenient, and the use of an antibiotic within 2 weeks prior to onset of study. The current analysis is based on 196 subjects (94 in the AKSB and 102 in the placebo arm), including data from the interim analysis of 174 subjects. The median travel duration was 22 days (Table 1). Travel locations per each group are outlined in Table 2. The study enrollment was discontinued based on the results of the interim analysis.

Adherence to Study Drug

The adherence to the study drug was poor and less than expected. On the basis of self-reported adherence recorded in the patient diaries, only 58.1% (114/196) were fully adherent to the given schedule—62.8% (59/94) of AKSB subjects and 53.9% (55/102) of those on placebo ($p = 0.25$). The median duration of days on the study agents was 20.5 and 21 for AKSB and placebo,

Table 1 Comparison of demographic features

	AKSB $n = 94$ (%)	Placebo $n = 102$ (%)	p Value
Sex			
Female	51 (54.3%)	53 (52.0%)	0.76
Age			
<60	76 (80.9%)	74 (72.6%)	0.18
≥60	18 (19.2%)	28 (27.5%)	
Mean (±SD)	48.7 (±12.4)	48.8 (±14.7)	—
Took study drug			
>15 days	91 (97%)	99 (97%)	0.92*
Median (min, max)	20.5 (2, 34)	21 (2, 39)	0.28
Trip duration (days)			
Mean	21.5	22.4	—
Median	20.5	21	—
Minimum	2	2	—
Maximum	34	39	—
SD	5.9	6.5	0.28

*p Value from Cochran Armitage Trend test. Other p values are based on Fisher's exact test for categorical data and Wilcoxon Rank Sum test for continuous data.

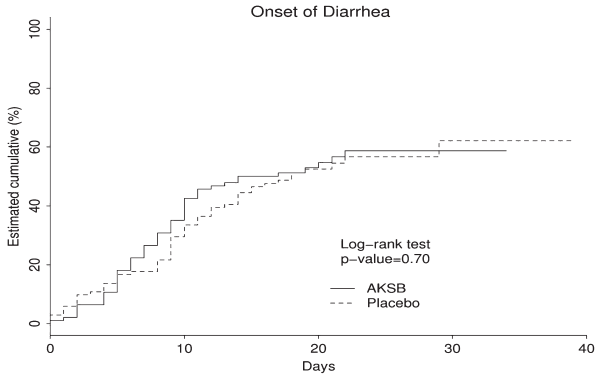

Figure 1 Onset of diarrhea. Kaplan–Meier Survival Estimates for incidence of diarrhea by AKSB versus placebo.

respectively, with 97% (91/94) of subjects on AKSB and 97% (99/102) of those on placebo ($p = 0.92$) staying on drug for at least 15 days.

Clinical Outcomes

Primary Outcome

Of the 196 subjects, 107 (54.5%) subjects reported diarrhea. The incidence of diarrhea was 52 (55.3%) in the AKSB study arm compared to 55 (53.9%) in the placebo arm [p = not significant (NS); Table 3]. Of the 114 subjects in full adherence with the protocol, diarrhea incidence was 31 (52.5%) on the AKSB arm and 27 (49.1%) on the placebo arm (p = NS; Table 3). There was also no statistically significant difference between the time of onset of diarrhea between the two groups ($p = 0.70$; Figure 1). The median time to diarrhea occurrence in the AKSB group was 14 days versus 18 days for the placebo group. In the majority of patients, the diarrhea lasted for three or less days (60% of the patients in AKSB and 80% in placebo arm).

Table 2 Geographic locations traveled in both arms of the study

AKSB	Placebo
Africa*	Afghanistan
Antiqua	Africa*
Aruba	Argentina
Belize	Aruba
Brazil	Asia
Cambodia	Belize
Caribbean	Bolivia
Chile	Brazil
China	Cambodia
Costa Rica	Caribbean
Dominican Republic	Chile
Ecuador	China
Egypt	Cook Islands
Guatemala	Costa Rica
Haiti	Dominican Republic
Honduras	Ecuador
India	Greece
Jordan	Guatemala
Malaysia	Haiti
Mexico	Honduras
Neth.-Antilles	India
Panama	Indonesia
Peru	Jamaica
Singapore	Jordan
Sri Lanka	Korea
Taiwan	Kuwait
Thailand	Malaysia
	Mexico
*Africa	Nepal
Botswana	Paraguay
Kenya	Peru
South Africa	Singapore
Tanzania	Taiwan
Zambia	Thailand
	Turkey
	UAE
	Uruguay
	Vietnam
	*Africa
	Botswana
	Ethiopia
	Kenya
	Mozambique
	Senegal
	Sierra Leone
	South Africa
	Tanzania
	Zambia
	Zimbabwe

Secondary Outcomes

Antibiotic and/or Antidiarrheal Use Within Study Arms. Among the subjects who experienced diarrhea ($n = 107$) there was no statistically significant difference between the proportion of subjects in the AKSB or placebo arms that took antibiotics (ciprofloxacin, levofloxacin, or azithromycin) as provided at the pre-travel consult (35% vs 29%, $p = 0.68$; Table 4). There was no difference

Table 3 Diarrhea incidence in study subjects including those fully adherent versus not fully adherent with the study drug

Diarrhea	AKSB *n*/total (%)	Placebo *n*/total (%)	*p* Value
All subjects	52/94 (55.3)	55/102 (53.9)	0.89
Fully adherent subjects only	31/59 (52.5)	27/55 (49.1)	0.85
Diarrhea duration 3 or less days	31/52 (60)	44/55 (80)	—
Diarrhea duration 4 or more days	12/52 (23.1)	11/55 (20)	—

Table 4 Antibiotic use in all subjects with diarrhea ($n = 107$)

	Treatment group		
Took antibiotics?	AKSB *n* (%)	Placebo *n* (%)	Total
No	34 (65%)	39 71%)	73
Yes	18 (35%)	16 (29%)	34
Total	52	55	107

p Value = 0.68.

Table 5 Antibiotic use in subjects with diarrhea who took loperamide ($n = 49$)

	Treatment group		
Took antibiotics?	AKSB *n* (%)	Placebo *n* (%)	Total
No	9 (41%)	18 (67%)	27
Yes	13 (59%)	9 (33%)	22
Total	22	27	49

p Value = 0.0895.

in antibiotics use in either arm among subjects who reported loperamide (Imodium) use ($n = 49$; Table 5). The number of days with diarrhea was similar in the two groups when all patients were evaluated and also when the analysis was limited to those subjects who were fully adherent to the study protocol.

Safety and AEs of AKSB or Placebo. The minimum and maximum grade for each type of toxicity was recorded for each patient, and frequency tables used to determine toxicity patterns. Toxicities from AKSB or placebo were determined from the symptom diary kept by the subjects and were reviewed with the study nurse at the exit interview. The questions asked at the interview pertained to gastrointestinal or systemic side-effects that one may potentially expect from a probiotic. There was no statistically significant difference between the two arms for all AEs, except for constipation where subjects on AKSB were noted to have less constipation than placebo (Table 6).

Self-reported AEs under the category "other" included free-text comments by participants regarding symptoms and grade. Of the listed symptoms, one subject on AKSB reported a skin rash that was deemed as possibly related, however, not confirmed. One subject on placebo had an asymptomatic elevation of liver function tests after return from the trip. Follow-up liver function tests were normal. Hepatitis serologies were negative. The abnormal liver function values were deemed not related to the study drug.

Table 6 Adverse effects reported

Adverse effect reported	AKSB Total: 94 *n* (%)	Placebo Total 102 *n* (%)	*p* Value*
Mucus or blood in stool	11 (11.7)	8 (7.8)	0.47
Constipation	17 (18.1)	32 (31.4)	0.03
Diarrhea	43 (45.7)	55 (53.9)	0.32
Nausea	34 (36.2)	38 (37.3)	0.88
Flatulence/pass gas	64 (68.1)	71 (69.6)	0.88
Other†	25 (26.6)	34 (33.3)	0.35

*p Value based on Fisher's exact test.
†None of the adverse events reported under "other" were considered possibly, probably, or definitely related to drug except one with rash.

Stool Pathogen Carriage. All returning subjects submitted a stool sample that was evaluated for pathogens by culture (*Campylobacter* species, *Salmonella*, *Shigella*, *Aeromonas*, and *Yersinia*), enterotoxigenic *E coli* toxin assay and ova and parasite. Only 10 of 196 (5%) specimens had a stool pathogen or parasite identified. Of these 10 stool specimens, a bacterial pathogen was identified in seven: *Campylobacter* (five), *Aeromonas* (one), and *Salmonella* (one). The rest had *Endolimax nana* (one) and *Blastocystis hominis* (two). All these subjects were clinically asymptomatic at the time of post-travel stool collection. Of the seven subjects with a bacterial pathogen, three were in the AKSB arm.

Viability of AKSB Synbiotic Capsules After Patient Return From Travel. Leftover capsules were retrieved from 86 (43.8%) participants. Of these, 41 (47.6%) were AKSB synbiotic. Of the 41, 20 (48.8%) had at least five billion total CFU per capsule (range 1.05–8.70E+08) similar to the pre-study viable organisms. Although the total number of organisms decreased in 51.2% of the capsules, approximately half (52%) of those capsules still had more than 1.5 billion organisms per capsule.

Discussion

We conducted a randomized, placebo-controlled trial of a synbiotic to learn if TD could be prevented in healthy subjects traveling to a location where they would be at risk for TD. The incidence of TD was high in this study (54.5%). The study synbiotic, AKSB, did not demonstrate a preventative effect against TD compared to placebo at the interim analysis ($n = 174$) and therefore study was halted. Although adherence to the study was less than expected, we also found no evidence that AKSB could reduce TD incidence in the 114 subjects who were fully protocol adherent. The study drug, AKSB, was found to be safe in all study participants including those older than 60 years ($n = 46$). We

also demonstrated good viability of organisms within unused capsules indicating that the AKSB synbiotic was of high quality. Probiotic studies for the prevention of TD have indeed shown variable results. Briand and colleagues did not find a protective effect with the use of *L acidophilus*,[20] whereas other animal[21,22] and human studies have shown a positive preventative effect of probiotics on TD.[11,14] Similarly, in a recent meta-analysis, only 50% of the randomized clinical trials reported efficacy in the prevention of TD. Efficacy was reported with *S boulardii*, and *L rhamnosus* GG.[11,13–15] Compared to placebo, *S boulardii*[13] decreased the incidence of TD from 39% to 29%–34% but success depended directly on the rigorous use of the preparation and only 1016 of the 3000 (34%) participants completed the study.

Despite the high incidence of TD in our study, only seven subjects demonstrated carriage of a pathogen post-travel. AKSB pill microbiologic assessment showed that the capsules still contained viable organisms although there was a decline in the total CFU of probiotic in approximately half of the pills returned. The medications were not required to be refrigerated but it is possible that travel to high temperature or humid climates may have affected the viability of the organisms.

Limitations of this study include the lack of evidence of protocol adherence because the subjects were traveling and data were collected through self-reporting. Of those that reported compliance only 58.2% were adherent to the protocol. There was no effective way to document reliability of the data entered into the daily diary. As less than half of the participants (43.8%) returned their pill bottles, post-travel pill count was not a reliable measure of compliance. Although there was a lack of protocol adherence, a trend toward benefit would have been expected toward reduction of TD incidence if the synbiotic had a beneficial effect. It is possible that the success of any TD prevention study will be fraught with such problems of compliance. Adherence to the study drugs (and real-life preventive medications) could potentially be increased with the use of individualized schedules, dosettes, and electronic-reminder devices including mobile smart phone-reminder utilization. These have been studied well in the HIV population for drug adherence. TD prevention trials are more likely to be subject to poor compliance based on the fact that most travelers are healthy, do not develop diarrhea, and are potentially in "vacation mode" thereby making it harder for participants to adhere to take daily medications and do documentation. Information collected using the daily diary is also subjected to self-reporting and recall bias, especially if participants did not complete the diaries on a daily basis. TD prevention studies may be better conducted on site (ie, at an international location where risk of TD is high) with better vigil on compliance.

In conclusion, AKSB, a unique synbiotic with *E faecium* (microencapsulated SF68 called Ventrux ME 30) and *S cerevisiae* (along with a growth factor FOS) was not effective in preventing TD, nor in decreasing the duration of TD or the use of antibiotics when TD occurred. AKSB, however, was found to be safe in this study population and should be studied for other potential indications.

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Declaration of Interests

The authors state that they have no conflicts of interest to declare.

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Appendix: Severity grade chart for patients' reference to grade their adverse effects and to document the severity of symptoms

Table A1 Severity chart

1.1 Grade Toxicity	0	1	2	3	4
Loss of appetite	None	Loss of appetite	Oral intake significantly decreased	Requiring IV fluids	Admission to hospital
Mucous and/or blood in stools	None	—	Abdominal pain with mucus and/or blood in stool	Abdominal pain, fever, change in bowel habits, bloating	Admission to hospital
Constipation	None	Requiring stool softener or dietary changes	Requiring laxatives	Resistance to laxatives requiring manual evacuation or enema	Admission to hospital
Diarrhea	None	Increase but less than 4 stools/day over pretreatment	Increase of 4–6 stools/day, or nocturnal stools	Increase of more than 7 stools/day or incontinence; or need for IV fluids for dehydration	Admission to hospital
Dyspepsia/heartburn	None	Mild	Moderate	Severe	Admission to hospital
Flatulence/passing gas	None	Mild	Moderate	Severe	Admit to hospital
Nausea	None	Able to eat	Oral intake significantly decreased	No significant intake, requiring IV fluids	Admission to hospital
Vomiting	None	1 episode in 24 hours over pretreatment	2–5 episodes in 24 hours over pretreatment	More than 6 episodes in 24 hours over pretreatment; or need for IV fluids	Admission to hospital
Cough	None	Occasional	—	—	Admission to hospital
Sore throat	None	Mild	Moderate	Severe	Admission to hospital
Reaction to vaccine	None	Mild local pain	Pain and swelling at injection site	Fever (more than 101° F), rash	Admission to hospital

Instructions to subjects: place number under severity column. Use this scale for abdominal pain, headache, etc.