Effectiveness of rifaximin in prevention of diarrhoea in individuals travelling to south and southeast Asia: a randomised, double-blind, placebo-controlled, phase 3 trial

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Summary

Background Travellers' diarrhoea causes substantial acute and long-term morbidity. Chemoprophylaxis with fluoroquinolones or rifaximin is effective in prevention of diarrhoea in individuals travelling to Latin America and Africa. Little evidence is available to support the protective effect of antimicrobial drugs in south and southeast Asia, where enteroinvasive and antibiotic-resistant bacteria cause a substantial proportion of diarrhoeal episodes. We aimed to assess the effectiveness of rifaximin in prevention of diarrhoea in individuals travelling to south and southeast Asia.

Methods We did this double-blind, placebo-controlled, single-centre, parallel-group, clinical trial in Tübingen, Germany, between Nov 12, 2009, and Sept 3, 2012. Individuals aged 18–64 years who were planning a 6–28 day journey to south and southeast Asia were randomly assigned (1:1), according to a randomisation list (permuted block size of eight) generated by an independent statistician, to receive placebo or rifaximin 200 mg tablets twice daily. All members of the study team, including investigators, those assessing outcomes, and data analysts, were masked to treatment allocation. The primary endpoint was time to the first episode of classic travellers' diarrhoea, defined as three or more loose stools in 24 h, accompanied by one or more enteric symptoms. Analyses were by intention to treat and per protocol. This study is registered with ClinicalTrials.gov, number NCT00979056.

Findings We randomly assigned 258 participants to rifaximin (n=129) or placebo (n=129), of whom 239 (93%) returned a completed diary and were included in the primary effectiveness analysis. 48 (41%) of 117 participants in the placebo group and 30 (25%) of 122 in the rifaximin group reported classic episodes of travellers' diarrhoea. From departure to 7 days after return, rifaximin provided 48% protection (95% CI 16–68) by lowering the incidence of travellers' diarrhoea from 1·99 (1·50–2·64) per 100 person-days in the placebo group to 1·04 (0·72–1·48) in the intervention group (incidence rate ratio 0·52, 95% CI 0·32–0·84; p=0·005). The number needed to treat was 5·70 (95% CI 3·44–16·69) to prevent one case of classic travellers' diarrhoea during the first 3 weeks of follow-up. The per-protocol analysis essentially corroborated the findings from the intention-to-treat analysis. We recorded one serious adverse event in a participant in the rifaximin group who had grade 3 right lower quadrant abdominal pain 72 h after the last intake of study drug. The complaints were considered unlikely to be related to use of the drug.

Interpretation Rifaximin is moderately effective in prevention of diarrhoea in individuals travelling to south and southeast Asia. Similar studies are needed to inform travellers and practitioners about the effectiveness of this drug at other popular destinations.

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Introduction

Every day, an estimated 40 000 individuals travelling from industrialised to low-income and middle-income countries have acute diarrhoea,[1] making enteric infections the most common travel-related ailment and the main reason for post-travel consultations.[2] Although most episodes of diarrhoea are mild and affect the traveller for only 3–5 days,[3] a third of patients report an acutely incapacitating disease,[1] and 3–14% develop chronic functional gastrointestinal disorders such as irritable bowel syndrome.[4,5]

Since the late 1950s, antibacterial compounds have been proposed for the prevention of enteric infections abroad, well before many of the microbiological causes involved had been identified.[6] Since then, findings from 12 clinical trials showed 58–100% protective effectiveness of various antibiotic compounds.[7] Although no other intervention confers a similar level of protection,[7] the preventive use of antibiotics against travellers' diarrhoea has been discouraged because of possible side-effects and the potential for stimulation of bacterial resistance to drugs needed for the treatment of extraintestinal infections.[8] Instead, present practice is to inform individuals travelling to high-risk destinations about the prompt symptomatic self-treatment of diarrhoea, and to prescribe antibiotics for severe episodes.[7,9] By contrast, chemoprevention is restricted to travellers with an important mission or comorbidities that increase the risk of complications.[7,9]

One approach to circumvent systemic side-effects is to use poorly absorbed compounds with negligible systemic bioavailability. Rifaximin—a poorly absorbed rifampicin derivative—has been proposed as a safe alternative for chemoprevention of travellers' diarrhoea, on the basis of

its broad antimicrobial range, high faecal concentrations, and good protective effect.[10,11] Rifaximin use seems justified in view of the large number of clinical trials that have assessed the drug as safe when used in various indications.[12] However, for effectiveness against travellers' diarrhoea, present evidence has little generalisability.[10,13] Two trials that showed rifaximin to be effective have been done in individuals travelling to Guadalajara, Mexico, where non-invasive enterotoxigenic *Escherichia coli* are the main cause of diarrhoea.[14,15] One further study from Mexico did not show any protection.[16] One trial of US military personnel deployed in Turkey suggested a beneficial effect, but did not reach significance.[17] So far, no studies have convincingly shown rifaximin's preventive effect in regions where a substantial proportion of enteric episodes are caused by enteroinvasive bacteria such as *Salmonella* spp, *Shigella* spp, and *Campylobacter* spp.[10]

Because of the poor absorption of rifaximin and its negligible concentrations in tissues and fluids, use of the drug for protection against bacteria invading the mucosa might not be suitable. These doubts seem justified on the basis of findings from one trial showing rifaximin to be inferior to ciprofloxacin in treatment of diarrhoea caused by enteroinvasive bacteria.[18] However, Taylor and colleagues reported that volunteers given rifaximin were fully protected against experimentally administered *Shigella flexneri*[19]—a finding that strongly supports the notion that rifaximin, because of extremely high concentrations reached in the gut lumen,[11] is nevertheless capable of preventing invasive enteric infections. Clearly, and as shown by others before,[7,10,13,15] trials of individuals travelling to south and southeast Asia, where the risk of invasive enteric infections is high, are needed to establish the effectiveness of rifaximin for prevention of travellers' diarrhoea in regions where *E coli* is not the major pathogen. Most importantly, such knowledge is crucial to inform debates about whether rifaximin should replace fluoroquinolones as the drug of choice for chemoprevention of travellers' diarrhoea,[7,9,20] and whether its advent should "encourage more liberal use of chemoprophylaxis in preventing illness among international travelers".[21] We assessed the effectiveness of rifaximin in prevention of diarrhoea in individuals travelling to south and southeast Asia.

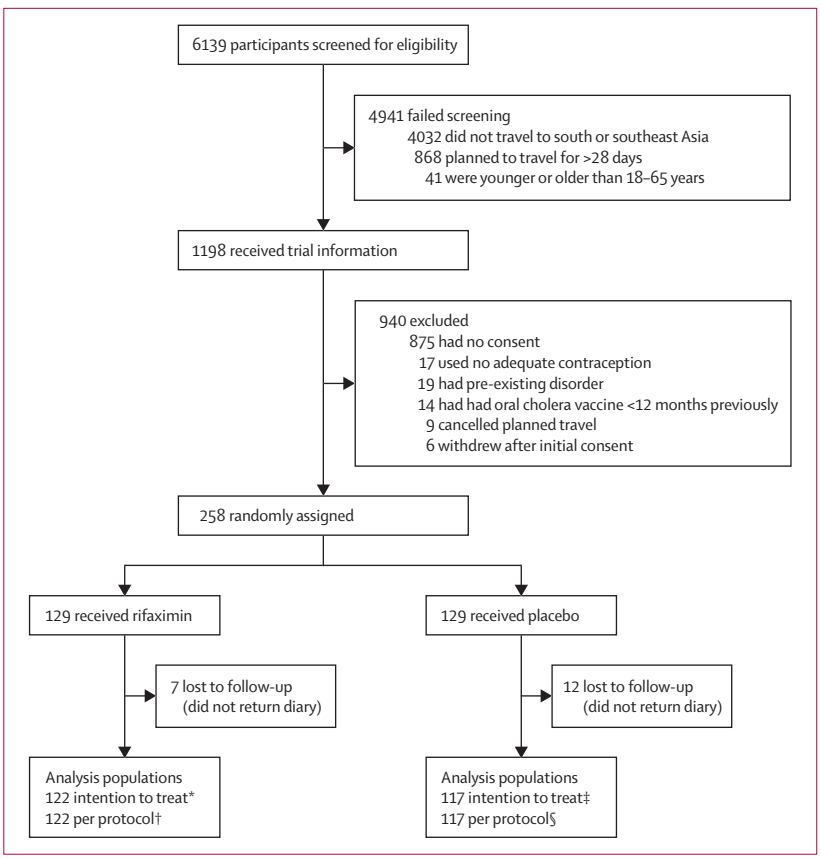

Figure 1: **Trial profile**
*Contributing 2897 days at risk after exclusion of post-travel period of participants travelling for more than 28 days and who were still at risk on day 28 (n=5). †Contributing 2684 days at risk after censoring of observations for concurrent antibiotic use (n=6), loperamide use (n=2), missed intake of two or more tablets in a row (n=6), and discontinuation because of adverse events (n=3) or travel longer than 28 days (n=3). ‡Contributing 2412 days at risk after exclusion of post-travel period of participants travelling for more than 28 days and who were still at risk on day 28 (n=4). §Contributing 2104 days at risk after censoring of observations for concurrent antibiotic use (n=7), loperamide use (n=5), missed intake of two or more tablets in a row (n=6), and discontinuation because of adverse events (n=2) or travel longer than 28 days (n=2).

Methods

Study design and participants

We did this randomised, double-blind, placebo-controlled, single-centre, clinical trial in Tübingen, Germany, between Nov 12, 2009, and Sept 3, 2012. Individuals consulting the University of Tübingen travel clinic for pre-travel advice, who planned to travel to one or more countries in south or southeast Asia for 6–28 days, and who had a predictably high risk of travellers' diarrhoea at the time of recruitment,[1] were invited to participate. Exclusion criteria were age younger than 18 years or older than 64 years; absence of adequate contraception; pregnancy; lactation; known intolerance to rifamycins or lactose; pre-existing disorders or pharmacotherapy associated with a change in stool frequency, consistency, or the propensity to develop gastrointestinal symptoms (eg, inflammatory bowel disease); and oral vaccination with whole-cell plus recombinant cholera toxin B subunit vaccine (Dukoral, Crucell, Sweden) within 12 months before enrolment.

The protocol was filed with the German Federal Institute for Medicines and Medical Devices (EudraCT number 2007-003986-42) and approved by the Ethics Committee of the University of Tuebingen Medical School (number 272/2007AMG1). All participants provided written informed consent. This trial is registered with ClinicalTrials.gov, number NCT00979056.

Randomisation and masking

An independent statistician generated a randomisation list with permuted blocks of eight, which was used to

	Rifaximin (n=122)	Placebo (n=117)
Baseline		
Women	66 (54%)	58 (50%)
Age	29 (24–37)	28 (26–36)
Days of travel	22 (16–26)	21 (17–26)
Irritable bowel syndrome	8 (7%)	15 (13%)
Itinerary		
1 country	99 (81%)	97 (83%)
>1 country	23 (19%)	20 (17%)
Round trip	100 (82%)	96 (82%)
Destination*		
India	51 (33%)	38 (26%)
Thailand	32 (21%)	38 (26%)
Cambodia	11 (7%)	15 (10%)
Indonesia	15 (10%)	11 (8%)
Vietnam	11 (7%)	12 (8%)
Laos	8 (5%)	8 (5%)
Sri Lanka	7 (5%)	6 (4%)
Other†	20 (13%)	19 (13%)
Purpose		
Vacation	105 (86%)	102 (87%)
Business	11 (9%)	12 (10%)
Other	6 (5%)	3 (3%)
Accommodation		
Outdoor	2 (2%)	4 (3%)
Guesthouse or lodge	65 (53%)	65 (56%)
Middle-class hotel	34 (28%)	24 (21%)
Luxury hotel	12 (10%)	14 (12%)
Apartment or house	9 (7%)	10 (9%)
Follow-up		
Lost to follow-up‡	7/129 (5%)	12/129 (9%)
Premature stop§	7 (6%)	2 (2%)
Unplanned travel >28 days	8 (7%)	5 (4%)
Missed ≥2 consecutive tablets¶	6 (5%)	10 (9%)
Missed >2 tablets overall‖	14 (12%)	15 (13%)
New-onset irritable bowel syndrome	8/111 (7%)**	8/95 (8%)**

Data are n (%), median (IQR), and n/N. *155 destinations in the rifaximin group and 147 in the placebo group because of more than one destination per participant. †Burma (n=10), Nepal (n=10), Malaysia (n=9), Philippines (n=8), Bangladesh (n=2). ‡Did not return diary. §Reasons in the rifaximin group were gastrointestinal adverse events (one obstipation, two vomiting, two diarrhoea) and other adverse events (one fever, one skin rash), and in the placebo group were other adverse events (one epistaxis, one allergic reaction). ¶On the basis of self-reported intake. ‖On the basis of the number of returned tablets and with an assumption of intake of two tablets per day at risk. **On the basis of participants who provided post-travel questionnaires and who had no irritable bowel syndrome at baseline.

***Table 1*: Baseline, travel, and follow-up characteristics**

produce numbered containers of tablets of placebo and study drug that were identical in appearance. The containers were allocated successively and in the sequence of enrolment; thus, participants were randomly assigned in a 1:1 ratio to receive rifaximin 200 mg or placebo. All members of the study team, including investigators, those assessing outcomes, and data analysts, at the travel clinic were masked to treatment allocation.

Procedures

Participants were asked to take rifaximin 200 mg (Alpha Wasserman, Bologna, Italy) or placebo tablets (Catalent Pharma Solutions, Schorndorf, Germany) every 12–18 h from the morning of departure to the evening of their return to Germany, preferably with a meal. Participants received a container with 60 tablets (56 for a maximum travel period of 28 days, plus four tablets to compensate for anticipated losses), a thermometer, and a structured diary. While abroad and 7 days after travel, participants documented on various measures and symptoms at two times: (1) every 12 h, on intake of study drug, number and consistency of passed stools, enteric symptoms (pain or cramps, nausea, vomiting, bloating, urgency, bloody stools), and rectal body temperature when feeling ill; and (2) every 24 h, on other complaints, type and dosage of self-medication, health-care consultations, and whether or not they were bedridden. Complaints were graded by intensity, as not disturbing at all (mild, grade 1), disturbing but not preventing daily activities (moderate, grade 2), or preventing daily activities (severe, grade 3). Participants were informed to stop the study drug once an episode of classic travellers' diarrhoea, as defined as primary outcome in the protocol, had occurred, and were counselled on the adequate self-treatment of this ailment. Furthermore, structured, self-administered questionnaires for the diagnosis of irritable bowel syndrome according to ROME III criteria[22] were issued at enrolment and via email 6 months after return. Participants had to return the remaining tablets together with the completed diary by mail, free of charge. All participants were advised to consult the University of Tübingen travel clinic if they felt ill on return.

Our primary outcome was time to the first episode of classic travellers' diarrhoea, defined as three or more unformed stools in 24 h together with at least one of the following enteric symptoms during and 7 days after travel: abdominal pain or cramps, nausea, vomiting, bloating, urgency, bloody stools, or fever of 37·8°C or more rectally. Secondary outcomes were the incidence of first episodes of classic or moderate diarrhoea (moderate defined as one to two unformed stools with at least one enteric symptom, or three or more unformed stools with no accompanying symptom) with enteric symptom of grade 3 or grade 1–3; incidence of first episodes of classic, moderate, or mild diarrhoea (mild defined as one to two unformed stools every 24 h without enteric symptom); and incidence of irritable bowel syndrome 6 months after travel. Exploratory outcomes were defined after masked review of the dataset, and were time to first episode of relevant travellers' diarrhoea, defined as any diarrhoea that led to self-medication or the consultation of health-care facilities; time to first episode of loperamide use; time to first episode of antibiotic intake of any cause;

	Rifaximin (n=122)		Placebo (n=117)		IRR (95% CI)	Effectiveness (95% CI)	p value*
	Events per person-days	Incidence per 100 person-days (95% CI)	Events per person-days	Incidence per 100 person-days (95% CI)			
Classic travellers' diarrhoea							
Travel and post-travel period†	30/2897	1·04 (0·72 to 1·48)	48/2412	1·99 (1·50 to 2·64)	0·52 (0·32 to 0·84)	48% (16 to 68)	0·005
Travel period	25/2269	1·10 (0·74 to 1·63)	45/1934	2·33 (1·73 to 3·12)	0·47 (0·28 to 0·79)	53% (21 to 72)	0·002
Week 1 of travel	6/840	0·71 (0·32 to 1·59)	13/790	1·65 (0·96 to 2·83)	0·43 (0·14 to 1·22)	57% (–18 to 86)	0·08
Week 2 of travel	10/717	1·39 (0·75 to 2·59)	18/611	2·95 (1·86 to 4·68)	0·47 (0·20 to 1·08)	53% (–8 to 80)	0·05
Week 3 of travel	6/472	1·27 (0·57 to 2·83)	11/399	2·76 (1·53 to 4·98)	0·46 (0·14 to 1·36)	54% (–27 to 86)	0·12
Week 4 of travel	3/240	1·25 (0·40 to 3·88)	3/134	2·24 (0·72 to 6·94)	0·56 (0·07 to 4·17)	44% (–76 to 93)	0·4
South Asia‡§	11/1089	1·01 (0·56 to 1·82)	20/699	2·86 (1·85 to 4·43)	0·35 (0·23 to 0·85)	65% (15 to 77)	0·004
Southeast Asia§¶	14/1180	1·19 (0·70 to 2·00)	25/1235	2·02 (1·37 to 3·00)	0·59 (0·28 to 1·17)	41% (–15 to 72)	0·09
Post-travel period	5/628	0·80 (0·33 to 1·91)	3/478	0·63 (0·20 to 1·95)	1·27 (0·25 to 8·17)	–21% (–88 to 75)	0·7
Secondary outcomes							
Classic or moderate travellers' diarrhoea (grade 3)	35/2833	1·24 (0·89 to 1·72)	55/2264	2·43 (1·87 to 3·16)	0·51 (0·32 to 0·79)	49% (21 to 68)	0·002
Travel period	30/2237	1·34 (0·94 to 1·92)	52/1835	2·83 (2·16 to 3·72)	0·47 (0·29 to 0·76)	53% (24 to 71)	0·0005
Classic or moderate travellers' diarrhoea (grade 1–3)	70/2164	3·23 (2·56 to 4·08)	78/1772	4·40 (3·53 to 5·50)	0·73 (0·52 to 1·03)	27% (–3 to 48)	0·06
Classic, moderate, or mild travellers' diarrhoea	91/1622	5·61 (4·57 to 6·89)	98/1277	7·67 (6·30 to 9·35)	0·73 (0·54 to 0·98)	27% (2 to 46)	0·04
Exploratory outcomes							
Relevant travellers' diarrhoea	23/2992	0·77 (0·51 to 1·16)	40/2541	1·57 (1·15 to 2·15)	0·49 (0·28 to 0·84)	51% (16 to 72)	0·006
Loperamide use	12/3160	0·38 (0·22 to 0·67)	27/2786	0·97 (0·66 to 1·41)	0·39 (0·18 to 0·80)	61% (20 to 82)	0·006
Antibiotic use‖	8/3246	0·25 (0·12 to 0·49)	12/2932	0·41 (0·23 to 0·72)	0·60 (0·21 to 1·60)	40% (–38 to 79)	0·3
Health-care contact (travel period)‖	3/2505	0·12 (0·04 to 0·37)	7/2333	0·30 (0·14 to 0·63)	0·40 (0·07 to 1·75)	60% (–43 to 93)	0·2
Fever‖	13/3162	0·41 (0·24 to 0·71)	17/2900	0·59 (0·36 to 0·94)	0·70 (0·31 to 1·54)	30% (–35 to 69)	0·3
Bedridden‖	17/3107	0·55 (0·34 to 0·88)	16/2892	0·55 (0·34 to 0·90)	0·99 (0·47 to 2·09)	1% (–52 to 53)	1·0

We did all analyses for the complete observation period (ie, including 7 days after travel), unless otherwise indicated. IRR=incidence rate ratio. *From log-rank test. †Primary analysis. ‡India, Nepal, Bangladesh, and Sri Lanka. §$p_{interaction}$=0·18. ¶Thailand, Malaysia, Indonesia, Vietnam, Cambodia, Philippines, Burma, and Laos. ‖Of any cause (ie, not restricted to events taking place in association with travellers' diarrhoea).

Table 2: **Intention-to-treat analysis**

time to first health-care consultation abroad for any reason; time to all-cause fever; and time to first episode of all-cause bedridden states.

Statistical analysis

In the primary effectiveness analysis, we compared diarrhoea-free survival with the log-rank test and a modified intention-to-treat approach that included all available information except for the post-travel observation period of participants who had unexpectedly extended their journey beyond the maximum period of 28 days. This approach was decided after a masked review of trial data to account for the fact that these participants might not have taken the adequate amount of study drug. Primary and secondary outcomes were also analysed by per protocol—ie, after right-censoring of observations for the first of the following competing risks: antibiotic intake, loperamide intake, missing more than two tablets in a row, premature stopping of study medication, and a travel period of longer than 28 days. We excluded episodes of diarrhoea that took place during the day of the first intake of the study drug from all effectiveness analyses because they were considered to be incubating when the participant entered the study.

Kaplan-Meier curves were constructed and compared with the log-rank test. We identified incidence per days of observation for each treatment group and compared rates by calculating the incidence rate ratio (IRR; rate in rifaximin group/rate in placebo group), the preventive efficacy (1–IRR), and respective exact 95% CIs. We used cox regression to adjust the hazard ratio for differences in participant characteristics at baseline. We calculated the number needed to treat with methods described by Altman and Andersen,[23] with use of survival probabilities and standard errors at day 21 of follow-up. We assessed the safety of rifaximin by calculating the proportion of participants with at least one particular adverse event and with at least one symptom in a given anatomic region or functional system from intake of the first tablet until 7 days after return from abroad. We regarded complaints reported in association with episodes of diarrhoea as adverse events. For interpretation, we used a significance level of 5% for

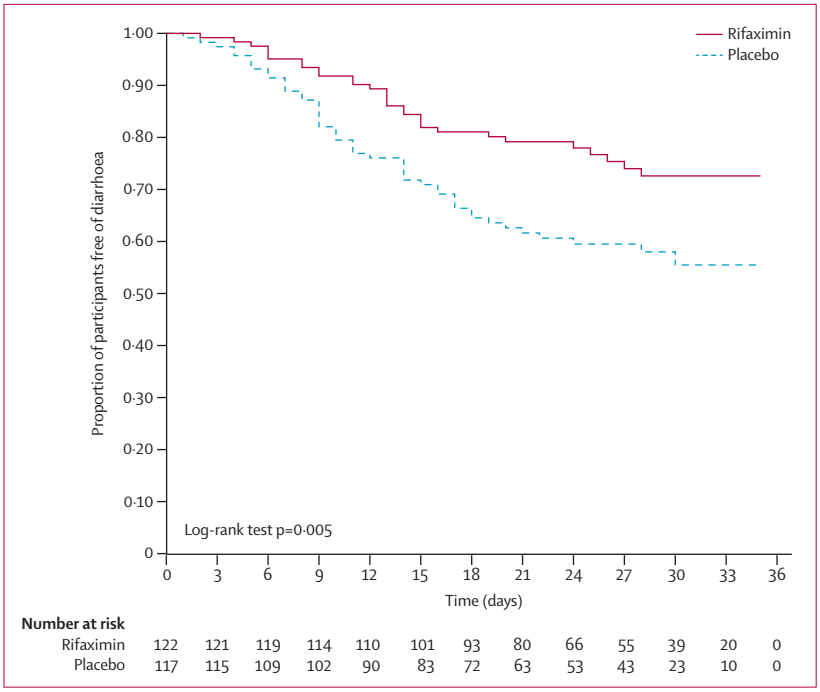

Figure 2: **Classic diarrhoea-free survival in travellers during a 6–28 day journey to south and southeast Asia and 7 days after return**
Intention-to-treat analysis.

the primary analysis and 1% for secondary, exploratory, and safety analyses to minimise the chance of type I error with multiple outcomes.

With an assumption that rifaximin confers 60% protection[15] by lowering the incidence of classic travellers' diarrhoea from 2·0 per 100 person-days in the placebo group[24,25] to 0·8 per 100 person-days in the rifaximin group, and with the assumption of an average of 14 days of travel per participant and a loss to follow-up of 10%, we calculated that 258 participants would have to be randomised to achieve 80% power to detect an effect at a 5% significance level.

Role of the funding source

The trial was started, sponsored, and undertaken, and data analysed, by the investigators. The funding source had no role in study design or data analysis. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. We randomly assigned 258 participants to rifaximin (n=129) or placebo (n=129), of whom 239 (93%) returned a completed diary and were included in the primary effectiveness analyses. 14 (74%) of the 19 individuals who did not return a diary could be contacted and were well. At baseline, individuals in the placebo group reported ROME III criteria for irritable bowel syndrome more often than did those in the rifaximin group; otherwise, demographic and travel characteristics were similar between groups (table 1).

	Rifaximin (n=122)		Placebo (n=117)		IRR (95% CI)	Effectiveness (95% CI)	p value*
	Events per person-days	Incidence per 100 person-days (95% CI)	Events per person-days	Incidence per 100 person-days (95% CI)			
Primary outcome							
Classic travellers' diarrhoea	27/2684	1·01 (0·69 to 1·47)	41/2104	1·95 (1·43 to 2·65)	0·52 (0·31 to 0·86)	48% (14 to 69)	0·009
Travel period	22/2146	1·03 (0·68 to 1·56)	39/1719	2·27 (1·66 to 3·11)	0·45 (0·26 to 0·78)	55% (22 to 74)	0·002
Week 1 of travel	6/832	0·72 (0·32 to 1·61)	11/758	1·45 (0·80 to 2·62)	0·50 (0·15 to 1·47)	50% (–32 to 85)	0·15
Week 2 of travel	10/686	1·46 (0·78 to 2·71)	17/542	3·14 (1·95 to 5·05)	0·46 (0·19 to 1·07)	54% (–7 to 81)	0·05
Week 3 of travel	5/425	1·18 (0·49 to 2·83)	10/321	3·12 (1·68 to 5·79)	0·38 (0·10 to 1·21)	62% (–18 to 90)	0·06
Week 4 of travel	1/203	0·49 (0·07 to 3·50)	1/98	1·02 (0·14 to 7·24)	0·48 (0·006 to 37·90)	52% (–97 to 99)	0·6
South Asia†	9/1035	0·87 (0·45 to 1·67)	16/633	2·53 (1·55 to 4·13)	0·34 (0·17 to 0·87)	66% (13 to 83)	0·006
Southeast Asia‡	13/1111	1·17 (0·68 to 2·02)	23/1086	2·12 (1·41 to 3·19)	0·55 (0·26 to 1·14)	45% (–12 to 74)	0·09
Post-travel period	5/538	0·93 (0·39 to 2·23)	2/385	0·52 (0·13 to 2·08)	1·79 (0·29 to 18·79)	–44% (–95 to 71)	0·3
Secondary outcomes							
Classic or moderate travellers' diarrhoea (grade 3)	31/2644	1·17 (0·82 to 1·67)	48/1997	2·40 (1·81 to 3·19)	0·49 (0·30 to 0·78)	51% (22 to 70)	0·002
Travel period	27/2121	1·27 (0·87 to 1·86)	46/1647	2·79 (2·09 to 3·73)	0·46 (0·27 to 0·75)	54% (25 to 73)	0·0006
Classic or moderate travellers' diarrhoea (grade 1–3)	64/2062	3·10 (2·43 to 3·97)	71/1579	4·50 (3·56 to 5·67)	0·69 (0·48 to 0·98)	31% (2 to 52)	0·03
Classic, moderate, or mild travellers' diarrhoea	86/1584	5·43 (4·39 to 6·71)	91/1151	7·91 (6·44 to 9·71)	0·69 (0·50 to 0·93)	31% (7 to 50)	0·02

IRR=incidence rate ratio. *From log-rank test. †India, Nepal, Bangladesh, and Sri Lanka. ‡Thailand, Malaysia, Indonesia, Vietnam, Cambodia, Philippines, Myanmar, and Lao.

Table 3: **Per-protocol analysis**

For the entire travel and post-travel period, risk of classic travellers' diarrhoea was greater in participants in the placebo group than in those in the rifaximin group (table 2). Estimates of protection against classic travellers' diarrhoea were higher in the first 3 weeks of travel than in the fourth week (table 2) of travel. Protection with rifaximin was numerically more effective in individuals who travelled to south Asia, but we noted no evidence of interaction between the effectiveness of rifaximin and subregion (p=0·18). In the week after return from the journey, incidence of classic travellers' diarrhoea was similar between the two groups (figure 2). Adjustment of the primary analysis for differences in the distribution of irritable bowel syndrome at baseline led to a slight attenuation of rifaximin's protective effect against classic travellers' diarrhoea (crude hazard ratio [HR] 0·53, 95% CI 0·33–0·84, protective effectiveness 47%, 95% CI 16–67%; p=0·007; adjusted HR 0·55, 0·35–0·87, protective effectiveness 45%, 13–65%; p=0·01). The number needed to treat was 5·70 (95% CI 3·44–16·69) to prevent one case of classic travellers' diarrhoea during the first 3 weeks of follow-up.

Rifaximin showed similar protective effectiveness against an outcome combining the first episode of either moderate travellers' diarrhoea accompanied by severe symptoms or a classic episode accompanied by symptoms of any grade (table 2). We noted less protection when endpoint definitions were more relaxed (table 2). A per-protocol analysis of primary and secondary outcomes corroborated the findings from the intention-to-treat analysis (table 3).

Further exploratory analyses showed that rifaximin conferred 51% protection against any type of diarrhoea that led to self-medication or health-care consultation (table 2). Furthermore, the risk of loperamide use was 2·6 times higher in participants in the placebo group

	Rifaximin		Placebo		p value*
	Adverse events (n=570)	Participants with ≥1 event (n=122)	Adverse events (n=501)	Participants with ≥1 event (n=117)	
Adverse events	..	112 (92%)	..	112 (96%)	0·2
Deaths	0	0	0	0	NA
Serious events	1 (<1%)†	1 (<1%)	0	0	0·3
Grade 3 events	59 (10%)	36 (30%)	74 (15%)	51 (44%)	0·02
Gastrointestinal events					
Abdominal pain	136 (24%)	66 (54%)	152 (30%)	76 (65%)	0·09
Bloating	121 (21%)	57 (47%)	100 (20%)	55 (47%)	1·0
Nausea	62 (11%)	42 (34%)	85 (17%)	57 (49%)	0·025
Stool urgency	39 (7%)	26 (21%)	48 (10%)	34 (29%)	0·2
Vomiting	20 (4%)	19 (16%)	23 (5%)	19 (16%)	0·9
Obstipation	33 (6%)	18 (15%)	21 (4%)	16 (14%)	0·8
Heartburn‡	2 (<1%)	1 (<1%)	12 (2%)	7 (6%)	0·03
Bloody stools	3 (<1%)	3 (3%)	1 (<1%)	1 (<1%)	0·3
Any gastrointestinal event (grade 3)§	38 (7%)	27 (22%)	53 (11%)	40 (34%)	0·04
Non-gastrointestinal event					
Headache	96 (17%)	53 (43%)	83 (17%)	45 (39%)	0·4
URTI‡	38 (7%)	26 (21%)	17 (3%)	12 (10%)	0·02
Fever ≥37·8°C	24 (4%)	18 (15%)	34 (7%)	23 (20%)	0·3
Sensation of heat	19 (3%)	14 (12%)	22 (4%)	20 (17%)	0·2
Drowsiness	17 (3%)	11 (9%)	18 (4%)	13 (11%)	0·6
Musculoskeletal‡	10 (2%)	9 (7%)	15 (3%)	11 (9%)	0·6
Urogenital‡¶	9 (2%)	9 (7%)	2 (<1%)	2 (2%)	0·04
Vertigo‡	8 (1%)	7 (6%)	6 (1%)	6 (5%)	0·8
Skin‡	10 (2%)	6 (5%)	9 (2%)	8 (7%)	0·5
Insomnia‡	3 (<1%)	3 (3%)	3 (<1%)	2 (2%)	0·7
Eye‡	2 (<1%)	2 (2%)	1 (<1%)	1 (<1%)	0·6
Any non-gastrointestinal event (grade 3)§	21 (4%)	18 (15%)	21 (4%)	17 (15%)	1·0

Data are n (%), unless otherwise indicated. NA=not applicable. URTI=upper respiratory-tract infection. *χ^2 test comparing proportion of participants with one or more events between groups. †24-year-old woman complaining about grade 3 right lower quadrant abdominal pain with onset 72 h after last intake of rifaximin. ‡Unsolicited adverse events. §Defined as events preventing daily activities. ¶After exclusion of eight adverse events that were described as typical menstrual cramps and classified as unlikely to be associated with the intervention, the distribution of individuals with at least one potentially related urogenital adverse event was three (3%) in the rifaximin group and none in the placebo group (p=0·09).

Table 4: **Adverse events and other safety markers**

Panel: Research in context

Systematic review

The authors of a Cochrane systematic review and meta-analysis[10] searched PubMed and Embase to April, 2012, for randomised, double-blind, placebo-controlled trials of the effectiveness of either poorly absorbed rifaximin or systemically bioavailable fluoroquinolones (ie, norfloxacin and ciprofloxacin) with the MeSH terms "travel* diarrh*" and "travel", restricted to articles about human beings published in English. 11 studies were included in the systematic review and nine in the meta-analysis. Only two of the 11 studies assessed the protective effectiveness of antimicrobials in individuals travelling to Asia: one study[26] of ciprofloxacin in 21 participants on an expedition in Nepal did not define travellers' diarrhoea and was thus excluded from the meta-analysis, and one[27] of 62 individuals travelling to Africa, Latin America, and Asia showed norfloxacin to be protective, but did not state the distribution of destinations between intervention groups rendering inferences about its effectiveness in prevention of diarrhoea in individuals travelling to Asia impossible. To identify further trials of the prophylactic use of antimicrobials for chemoprevention of diarrhoea in Asia, we reviewed the references of two expert reviews of the historic[6] and more recent[7] evidence-base for prevention of travellers' diarrhoea and did a PubMed search for those years that had elapsed since the publication of these reviews in 2005, and 2009, with the same strategy as the Cochrane review. We identified one additional study[28] that assessed 63 Peace Corps volunteers in Thailand and noted a 59% non-significant protection in those given doxycycline (p=0·12).

Interpretation

This study is the first, adequately powered, double-blind, placebo-controlled trial providing convincing evidence of the effectiveness of any type of antimicrobial drug, whether systemic or non-absorbable, in prevention of diarrhoea in individuals travelling to south and southeast Asia. Our study population represents 28% (239 of 843) of individuals ever studied in a randomised clinical trial of rifaximin as a prophylactic drug for travellers' diarrhoea. Our findings show moderate protection when rifaximin was used at destinations in south and southeast Asia and under less controlled conditions than in previous trials.[15] Similar evidence supporting the effectiveness of other immunoprophylactic or chemoprophylactic interventions against diarrhoea in travellers to this region is almost absent,[7] and emerging resistance to fluoroquinolones in enteroinvasive bacteria in Asia[29,30] prohibits the extrapolation of previous studies that showed the preventive effectiveness of ciprofloxacin and norfloxacin against travellers' diarrhoea elsewhere.[7,10] Therefore, our data support the use of rifaximin in individuals visiting south and southeast Asia who need protection against diarrhoea for reasons other than advanced immunosuppression and in whom the systemic bioavailability of traditionally advocated fluoroquinolones bears an increased risk of adverse reactions without proven additional benefit.

than in those in the rifaximin group (table 2). Rifaximin had a protective effect on all-cause fever, health-care consultations, and antibiotic consumption, albeit non-significant; we noted no effect on all-cause bedriddenness (table 2). 6 months after return from travel, eight (7%) of 111 participants in the rifaximin group and eight (8%) of 95 in the placebo group (p=0·7) newly fulfilled ROME III criteria for the diagnosis of irritable bowel syndrome.

No deaths occurred during the observation period (table 4). Overall, we recorded one serious adverse event in a 24-year-old woman who had grade 3 right lower quadrant abdominal pain 72 h after the last intake of rifaximin (table 4). This participant was observed for two nights in a hospital in Germany for suspected appendicitis. The complaints resolved without specific treatment and were considered unlikely to be related to the study drug. Overall, the proportion of individuals reporting one or more adverse events was similar between groups; however those complaining about adverse events that prevented daily activities (grade 3) were more often assigned to placebo (table 4). This difference was due to an excess of participants reporting at least one grade 3 gastrointestinal adverse event in the placebo group, whereas participants with at least one severe non-gastrointestinal adverse event were similarly distributed between groups (table 4). Irrespective of intensity, participants given rifaximin reported fewer episodes of nausea, abdominal pain, and heartburn than did those given placebo (table 4). Non-gastrointestinal adverse events of any intensity were similarly distributed between groups (table 4).

Discussion

Rifaximin 200 mg twice daily reduced classic diarrhoea in individuals travelling to south and southeast Asia and provided a similar protective effect against diarrhoeal episodes that led to self-medication or health-care consultation. Effectiveness was greatly reduced against endpoints that included mild or moderate episodes. Additionally, loperamide use was lower with rifaximin than placebo. The absence of an effect of rifaximin on new-onset irritable bowel syndrome could be attributable to inadequate power to detect a true difference. Larger studies are needed to assess the role of anti-diarrhoeal chemoprophylaxis in prevention of post-infectious irritable bowel syndrome.

This study is the first adequately powered, double-blind, placebo-controlled trial describing the effectiveness of an antibiotic in prevention of diarrhoea in travellers to south and southeast Asia (panel). We noted lower effectiveness than did DuPont and colleagues who reported 72% protection in their pivotal trial of rifaximin for prevention of travellers' diarrhoea in Mexico.[15] This comparison suggests that rifaximin confers less protection in regions where enteroinvasive pathogens are more prevalent than in Mexico. Although our study was not designed to explicitly identify pathogen-specific protection by rifaximin, this interpretation is supported by findings from stool examinations that identified enteroinvasive bacteria in eight of 20 participants presenting ill for post-travel care at our clinic. Among these, we identified *Campylobacter* spp in four of ten participants in the rifaximin group compared with two of ten in the placebo group. Furthermore, we noted a trend towards lower overall effectiveness of rifaximin in individuals travelling to southeast Asia than in those visiting south Asia. In view of other findings showing that *Campylobacter* spp are two to four times more often the cause of travellers' diarrhoea in southeast Asia than south Asia,[2,31] and that the values for 90% minimum inhibitory concentration of rifaximin for *Campylobacter* spp are significantly higher than those of other enteroinvasive bacteria,[32] these observations suggest that rifaximin 200 mg twice

daily is not sufficient to fully protect travellers against campylobacter-associated enteritis. Further study of the pathogen-specific protective effect of rifaximin in people travelling to south and southeast Asia is needed to substantiate this notion and to explore the potential of improved protection at high doses or when using alternative dosing schedules.

Differences in trial design might have contributed towards the substantially increased preventive effect of rifaximin reported previously.[15] In DuPont and colleagues' trial, compliance of participants was optimised through daily follow-up visits and presence of the study team at a predefined destination, thus reducing poor adherence and its attenuating effect. Moreover, in that study the intervention was restricted to 14 days. By contrast, we included travellers to various destinations in Asia, often on round trips, and for up to 28 days. Because of these design characteristics, our estimate of protection is probably a good indication of rifaximin's effectiveness on a trip to south and southeast Asia in real-life conditions. Similar studies in individuals travelling to Africa and Latin America are needed to inform travellers and practitioners in travel medicine about the effectiveness of rifaximin at other popular destinations.

The preventive use of rifaximin for up to 28 days was safe. The excess of upper respiratory-tract infections in the rifaximin group is likely to be a chance finding on the basis that no previous study has reported a similar association and no plausible biological link exists between rifaximin intake and the occurrence of respiratory-tract infections. Nevertheless, investigators of future studies should be cautious and solicit for upper respiratory-tract infections in analyses of rifaximin.

In the absence of similar evidence for fluoroquinolones, our data support the use of rifaximin to prevent diarrhoea in people travelling to south and southeast Asia who need such protection,[9] but in whom the systemic bioavailability of traditionally advocated fluoroquinolones is unlikely to be of additional benefit. However, chemoprophylaxis with rifaximin confers only moderate protection against diarrhoea in travellers to south and southeast Asia; thus, more effective interventions are needed.

Contributors

PZ and PGK had the initial idea for the study. PZ developed the protocol, had sponsor responsibilities, and applied for funding. JG and DN. recruited participants and supported PZ and MG in the everyday management of the trial. PZ and PGK analysed the dataset and drafted the manuscript, which was revised by all authors.

Conflicts of interest

We declare that we have no conflicts of interest.

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