

## Review Article

# The role of rifaximin in the chemoprophylaxis of travelers' diarrhoea particularly aiming at the first 2 weeks of travel: a meta-analysis of 5 randomized, double-blind, controlled trials

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**Abstract:** The role of rifaximin in travelers' diarrhoea (TD) patients remains effective in major researches and needs further exploration. We pursued one meta-analysis to evaluate the efficiency of rifaximin on TD patients. So a systematic search of integrant databases was performed to identify RCTs comparing the use of rifaximin with placebo in TD patients. Results were expressed as risk ratios with accompanying 95% confidence intervals. This meta-analysis was accomplished with the fixed-effect in accordance with the heterogeneity. Then five studies involving 843 patients conformed our criteria. Rifaximin was associated with a reduction in the occurrence rate of classic travelers' diarrhoea (RR, 0.474; 95% CI, 0.369-0.608), classic travelers' diarrhoea during the first week (RR, 0.309; 95% CI, 0.196-0.487) and second week (RR, 0.477; 95% CI, 0.315-0.723) of travel. Furthermore during the first week of travel, rifaximin has a statistical better effect which directs the start time and duration of rifaximin use.

**Keywords:** Rifaximin, travelers' diarrhoea, travel, meta-analysis

## Introduction

Rifaximin is a semi-synthetic rifamycin derivative and has broad antibacterial spectrum in vitro. And rifaximin undergoes inappreciable systemic absorption (<0.4%), which is used to distinguish from other antibiotics and leads to localized treatment effect. This kind of effect is gut specific and avoids increasing any clinically significant antimicrobial resistance and systemic adverse events [1, 2]. Based on its characteristic above, it has been used effectively in a variety of acute enteric lesions, such as small intestinal bacterial overgrowth, irritable bowel syndrome, hepatic encephalopathy, ulcerative colitis, colonic diverticular disease, and so on [3-5].

Travelers' diarrhoea (TD) is one of the most popular illnesses in people who travel overseas from developed to less-developed countries, such as southern Asia, the Middle East, Africa, Latin America, and so on. And depending on

destination, nearly 20-60% of travelers visiting tropical and subtropical regions encountered TD each year [6]. The foremost reasons that the travelers' diarrhoea could occur in individuals who traveled internationally are poor food and water hygiene [7]. Classic travelers' diarrhoea is defined as the passage of at least three loose or watery stools in 24 hours with one or more enteric infection symptoms of abdominal cramps, fever, nausea, vomiting, or blood in the stool [8]. Generally, the time of six or seven days after arrival is the median time to onset TD. Considering that, a large proportion of affected travelers had to change their plans and suspended their vacation or business trips. Although the diarrhoea could cure spontaneously after three or four days, affected people may encounter continuous diarrhoea or other enteric problems, just like irritable bowel syndrome (IBS), which could last even for years [9]. Among those recent studies, enterotoxigenic *E.coli* (ETEC) is reported to be the predominant pathogen, which is followed by enteroaggrega-

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tive *E.coli* (EAEC), *Campylobacter* spp, *Salmonella* spp and *Shigella* spp [10-12].

Therefore, prevention measures, such as strict food, water, and personal hygiene precautions, are obligatory for potential individuals to avoid TD. As to chemoprophylaxis, lots of prophylactic antibiotics could not be widely recommended for various potential adverse events, for instance, antibiotic resistance [13]. Fluoroquinolone has been proved of its efficacy, and when resistance appears, azithromycin can be considered, but no enough trials had been published on this agent for TD precaution [7]. Nowadays, modest sample size of research evidences had indicated that antibiotic therapy with rifaximin, a poorly absorbed derivative of rifamycin, might be able to protect travelers from travelers' diarrhoea.

Thus, in view of these inconclusive results, we undertook a meta-analysis of published RCTs which were conducted in TD patients to determine whether the use of rifaximin compared with a control could reduce the occurrence rate of TD. In this article, considering the median onset time and duration of TD, detailed analysis had been taken to discuss the preventive effect of rifaximin towards TD and its intensity in different periods of traveling.

### Methods

#### *Search strategy*

PubMed, EMBASE, Cochrane central register of controlled trials, Web of science databases (from inception to February 2014) were searched to identify randomized controlled trials comparing the effectiveness of oral rifaximin to placebo in preventing TD. The organized search strategies covered the following format of search terms: (rifaximin OR rifamycins) with the MeSH terms "travel\* diarrh\*" and "travel". The search was restricted to human subjects and RCTs. The included articles should be published in English. In addition, the reference lists of these studies were further examined manually to identify other potential pertinent trials. This kind of process was performed repeatedly until no additional valuable articles appeared. And expert opinions in the field were collected to identify any missing articles.

#### *Inclusion and exclusion criteria*

The authors singly, independently inspected the results of the above search steps. Rele-

vance of these identified results were screened by reviewing their titles, abstracts, and keywords. When a title or abstract could not be rejected with certainty, the full text article was obtained to examine.

Studies were considered acceptable for inclusion in the meta analysis if they met the following criteria: (1) types of participants: healthy common travelers or military members aged  $\geq 18$  years; (2) type of intervention: rifaximin; (3) type of comparison: placebo; (4) type of study: RCTs; (5) three or more of the following clinical outcomes reported (the first three are necessary): incidence of classic travelers' diarrhoea, incidence of classic travelers' diarrhoea during the first week of travel, incidence of classic travelers' diarrhoea during the second week of travel, incidence of mild travelers' diarrhoea, incidence of antibiotic-treated travelers' diarrhoea, incidence of adverse events.

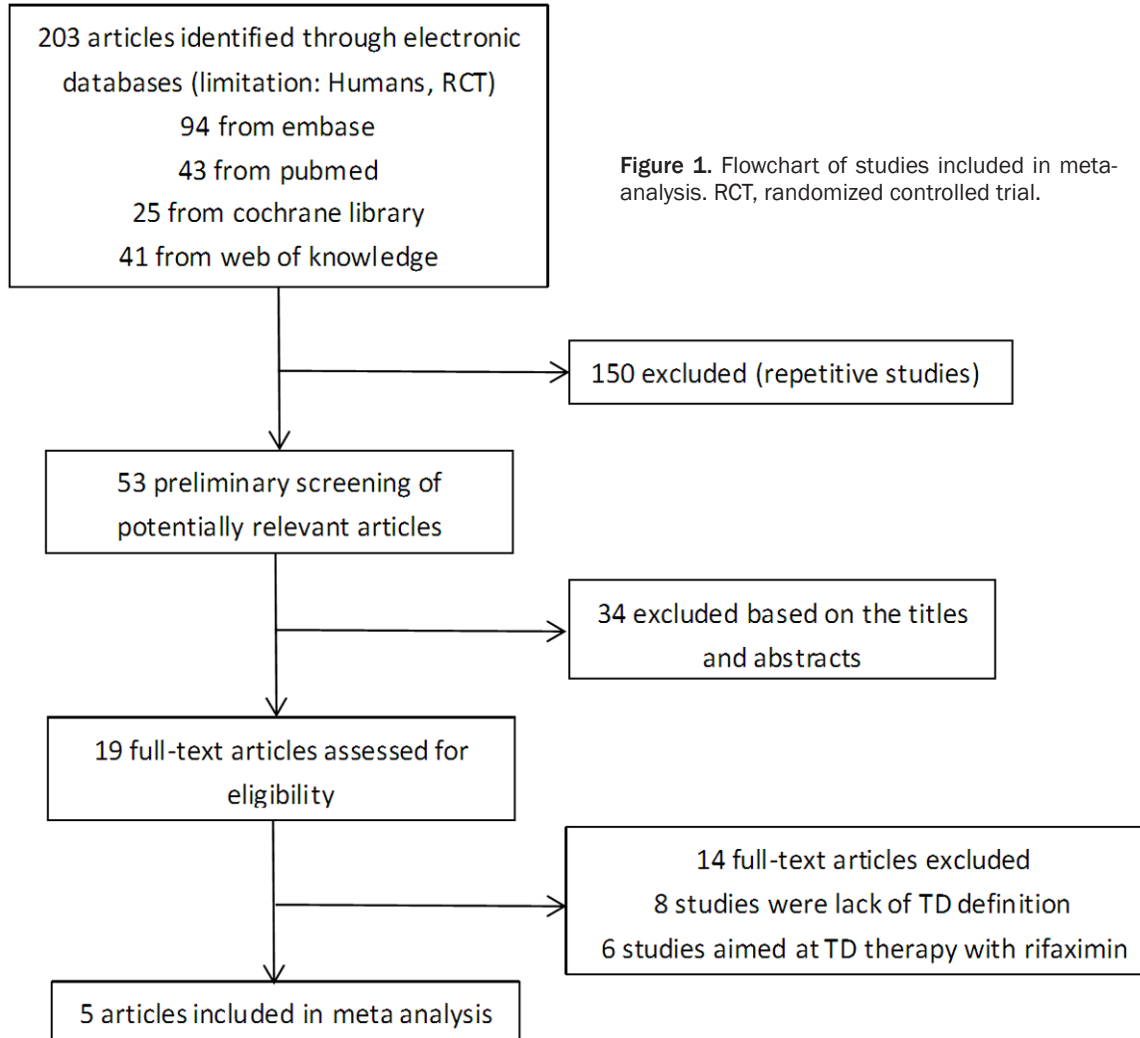
For another, trials were excluded if they (1) were abstracts, letters, or meeting proceedings; (2) had repeated data or did not report outcomes of interest; (3) enrolled objects with other pharmaceutical interruption; (4) enrolled objects who were allergy sufferers or pregnant.

#### *Data extraction and outcome measures*

Two authors independently extracted those requisite data: first author, year of publication, number of patients, population characteristics, study design, setting, rifaximin group (dosage, route, and duration), placebo group, follow-up period, definition of travelers' diarrhoea, incidence of travelers' diarrhoea, and other secondary outcome data. Extracted data were entered into a standardized excel file. Any disagreements were resolved by discussion and consensus.

The primary endpoint was occurrence rate of classic travelers' diarrhoea treated with rifaximin or placebo. Classic travelers' diarrhoea (TD), defined as three or more unformed stools in 24 h, accompanied by one or more of these following enteric symptoms: abdominal pain or cramps, nausea, vomiting, bloating, fecal urgency, bloody stools, fever ( $\geq 37.8^{\circ}\text{C}$ ) or more [14]. Secondary outcomes were occurrence rate of classic travelers' diarrhoea during the first week of travel, occurrence rate of classic travelers' diarrhoea during the second week of travel, occurrence rate of mild diarrhoea (defined as

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one to two unformed stools every 24 h without enteric symptom), occurrence rate of antibiotic-treated travelers' diarrhoea, and occurrence rate of adverse events.

### Quality assessment

For assessing risk of bias, the methodological quality of each trial was evaluated using the evaluation criterion in the Cochrane Handbook 5.1 [15]. The guidelines which consist of these following items describing random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data reporting, selective reporting, and other potential sources of bias (duration, differential destination). Risk of bias for each domain was rated as "high risk" (severely weaken reliability of the results), "low risk" (not seriously impact the results), or "unclear risk".

### Statistical analyses

All statistical analyses were performed using STATA version 12.0 (StataCorp, College Station, TX). Differences were expressed as risk ratios (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes. Heterogeneity of studies was tested by using chi-square test of heterogeneity and the  $I^2$  statistic, which is a quantitative measure of inconsistency across trial results. As a consequence, studies with an  $I^2$  statistic of 25%-50% are considered to have a low degree of heterogeneity, those with an  $I^2$  statistic of 50%-75% have moderate heterogeneity, and those with an  $I^2$  statistic of >75% have high heterogeneity [16]. In a word,  $I^2$  value greater than 50% indicates significant heterogeneity [17]. Generally, a fixed-effects model was used, but when significant heterogeneity ( $P < 0.10$ ,  $I^2 > 50\%$ ) appears, a random-effects

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**Table 1.** Main characteristics of randomized controlled trials included in the meta-analysis

First Author (Year of Publication)	Study Design (Setting)	Population Characteristics	Number in all (rifaximin vs placebo)	Rifaximin Group	Control Group	Follow-up	Primary endpoint
Herbert L. DuPont (2005)	RCT, double-blind (Mexico)	from USA to Mexico	210 (156/54)	200 mg once/twice/3 times daily for 14 days	200 mg 3 times daily for 14 days	3 weeks	the relative risk of developing TD in different period
Francisco Martinez-Sandoval (2010)	RCT, double-blind, multicenter (Mexico)	from USA to Mexico	201 (99/102)	600 mg/d for 14 days	600 mg/d for 14 days	1 week	the RR of developing TD
Adam W. Armstrong (2010)	RCT, double-blind (Turkey)	from USA to Turkey	95 (48/47)	1,100 mg once daily for 2 weeks	1,100 mg once daily for 2 weeks	2 weeks	the RR of developing TD
Jose Flores (2011)	RCT, double-blind, multicenter (Mexico)	from USA to Mexico	98 (50/48)	550 mg/d for 14 days	550 mg/d for 14 days	1 week	the RR of developing TD in different period
Philipp Zanger (2013)	RCT, double-blind (south and southeast Asia)	from Germany to south and southeast Asia	239 (122/117)	200 mg twice daily for a maximum period of 28 days	200 mg twice daily for a maximum period of 28 days	1 week	the RR of developing TD in different period

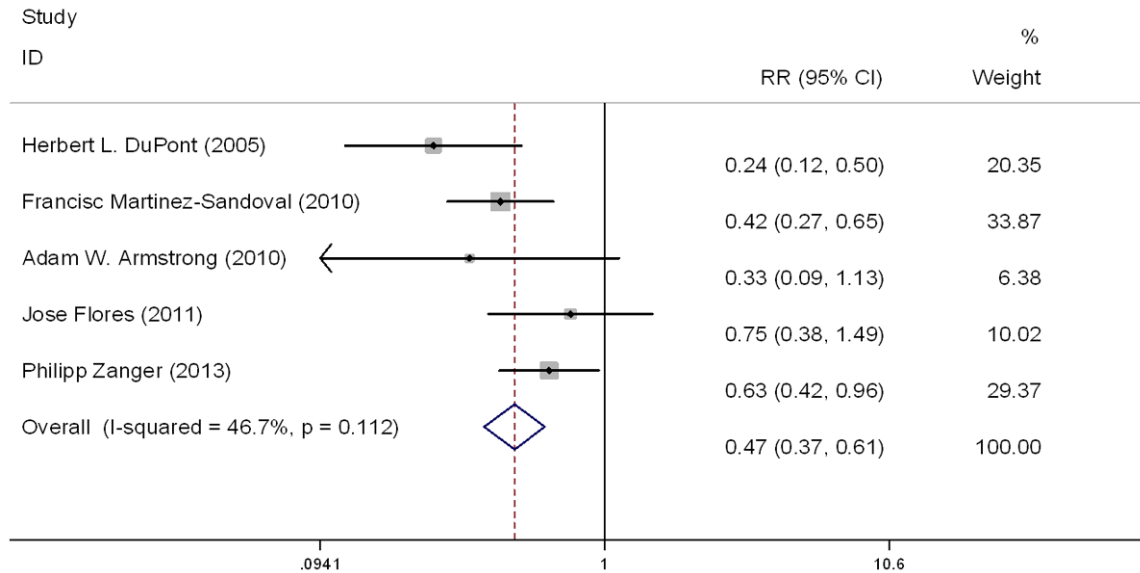
RR, relative risk.

**Table 2.** Outcome data of randomized controlled trials included in the meta-analysis (na, not available)

First Author	Travelers' Diarrhea n/N		First Week		Second Week		Antibiotic-Treated Travelers' Diarrhea n/N		Mild Diarrhea		Adverse Events n/N		E.coli TD	
	R	P	R	P	R	P	R	P	R	P	R	P	R	P
Herbert L. DuPont	7/54	29/54	2/54	17/54	5/52	12/37	2/54	21/54	48/164	40/54	13/54	16/54		
Francisco Martinez-Sandoval	20/99	49/102	9/99	30/102	11/90	19/72	14/99	33/102	NA	NA	81/106	93/104	9/99	18/102
Adam W. Armstrong	3/48	9/47	2/48	8/47	1/46	1/39	0/48	2/47	9/45	8/38	NA	NA		
Jose Flores	11/50	14/48	3/50	5/48	3/47	3/43	NA	NA	11/50	15/48	NA	NA	6/50	2/48
Philipp Zanger	27/122	41/117	6/122	11/117	10/116	17/106	8/122	12/117	NA	NA	112/122	112/117		

R, rifaximin; P, placebo.

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**Figure 2.** Meta-analysis of randomized controlled trials evaluating effect of rifaximin on the incidence of Classic Travelers' Diarrhoea. CI, confidence interval; RR, relative risk.

model should be used. Moreover, numbers needed to treat (NNT) which was figured out as an assisted assessment and stood for the number of patients who should receive rifaximin rather than placebo to prevent any unwished outcome. As patient characteristics, study designs, and other confounding factors were not consistent between studies, we further processed sensitivity analyses to check out possible explanations for heterogeneity and examine the influence of the whole exclusion guidelines on the overall merged evaluation. The presence of publication bias was assessed by using the Egger tests [18]. A  $P$  value  $<0.05$  was judged as statistically significant, except where otherwise specified.

### Results

#### Study Identification and selection

An initial database search identified a total of 203 RCTs of which 150 RCTs were excluded because of repetitive studies, and 34 RCTs were excluded based on the titles and abstracts. The remaining 19 full-text articles were examined for further detailed evaluation in which 8 of them were excluded because they were lack of TD definition and 6 studies aimed at TD therapy with rifaximin. At last, 5 RCTs which met our inclusion criteria were included in the present meta-analysis [19-23]. The flow-

chart of study identification and selection included in the meta-analysis was presented in **Figure 1**.

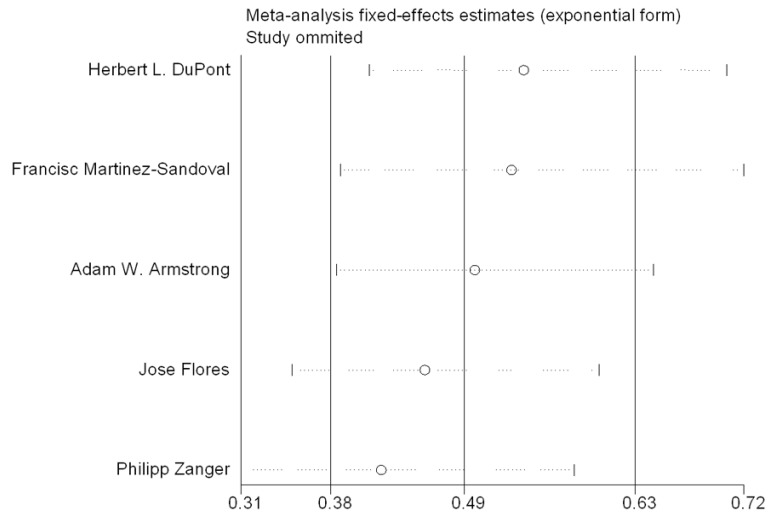
#### Characteristics of the studies

The key characteristics of these 5 RCTs included in this Meta analysis are summarized in **Table 1**, and the outcome data of each inclusive trial are presented in **Table 2**. These studies were published between 2005 and 2013. The study size of the RCT ranged from 95-239 (total 843). Among this 5 RCTs included here, all reported travelers' diarrhoea events, travelers' diarrhoea events during the first week of travel, travelers' diarrhoea events during the second week of travel, 4 reported antibiotic-treated travelers' diarrhoea events and 3 reported adverse events and mild diarrhoea events [19-23]. In one RCT, the test doses of rifaximin were 200 mg qd, bid, and tid. Only the 200 mg tid outcome data were chosen for analysis as 200 mg tid was the test dose of control group and closed to the dosing in other studies [19].

#### Quality assessment

The quality of the included studies was assessed by the evaluation criterion in the Cochrane Handbook 5.1. Of the 5 studies included in the meta-analysis, all were at low

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**Figure 3.** Sensitivity analyses of primary outcome for exploring the potential resource of its heterogeneity.

risk of bias for allocation concealment, incomplete outcome data, blinding of participants and personnel, and blinding of outcome assessment. Two studies were at low risk of bias for random sequence generation, and the other three were unclear [19, 21]. Only one study was at high risk for selective reporting, and the others were low [20] (**Figure 2**).

### Primary outcome

**Incidence of classic travelers' diarrhea:** All 5 RCTs reported classic travelers' diarrhoea in 843 included patients [19-23]. The aggregated results of these studies indicated that the use of rifaximin reduced the incidence of classic travelers' diarrhoea during the whole travel period (5 RCTs; RR, 0.474; 95% CI, 0.369-0.608;  $P < 0.00001$ ; **Figure 3**). The test for heterogeneity was a low degree (test for heterogeneity:  $P = 0.16$ ,  $I^2 = 46.7\%$ ). Subsequently, we performed sensitivity analyses to explore potential source of this low heterogeneity. NNT was five, which represented that every five patients who took rifaximin could prevent one case of classic travelers' diarrhea.

### Secondary outcomes

**Classic travelers' diarrhoea during the first week of travel:** The occurrence rate of classic travelers' diarrhoea during the first week of travel was lower among patients receiving rifaximin than in the control group (5 RCTs; RR, 0.309; 95% CI, 0.196-0.487;  $P < 0.00001$ ; **Fig-**

**ure 4**) [19-23]. There was no evidence of heterogeneity for this secondary outcome ( $P = 0.431$ ,  $I^2 = 0.0\%$ ). And NNT was seven, which represented that one person in every seven patients who took rifaximin could prevent classic travelers' diarrhoea.

**Classic travelers' diarrhoea during the second Week of travel:** All the included 843 patients in five RCTs had the data on the incidence of classic travelers' diarrhoea during the second week of travel comparing rifaximin with placebo group [19-23]. And there was significantly difference between these two groups (5

RCTs; RR: 0.477, 95% CI: 0.315-0.723,  $P < 0.00001$ ; **Figure 5**) and no evidence of heterogeneity ( $P = 0.431$ ,  $I^2 = 0.0\%$ ). Meanwhile, NNT was eleven, which represented that one in every eleven patients who receive rifaximin rather than placebo could avoid classic travelers' diarrhoea.

**Antibiotic-treated travelers' diarrhoea:** 4 RCTs were involved in comparing the incidence of antibiotic-treated travelers' diarrhoea and the statistical results suggested significantly difference between rifaximin group and control group (4 RCTs; RR: 0.359, 95% CI: 0.234-0.552,  $P < 0.00001$ ; **Figure 6**), and low level of heterogeneity ( $P = 0.121$ ,  $I^2 = 48.4\%$ ) [19-21, 23].

### Mild diarrhoea

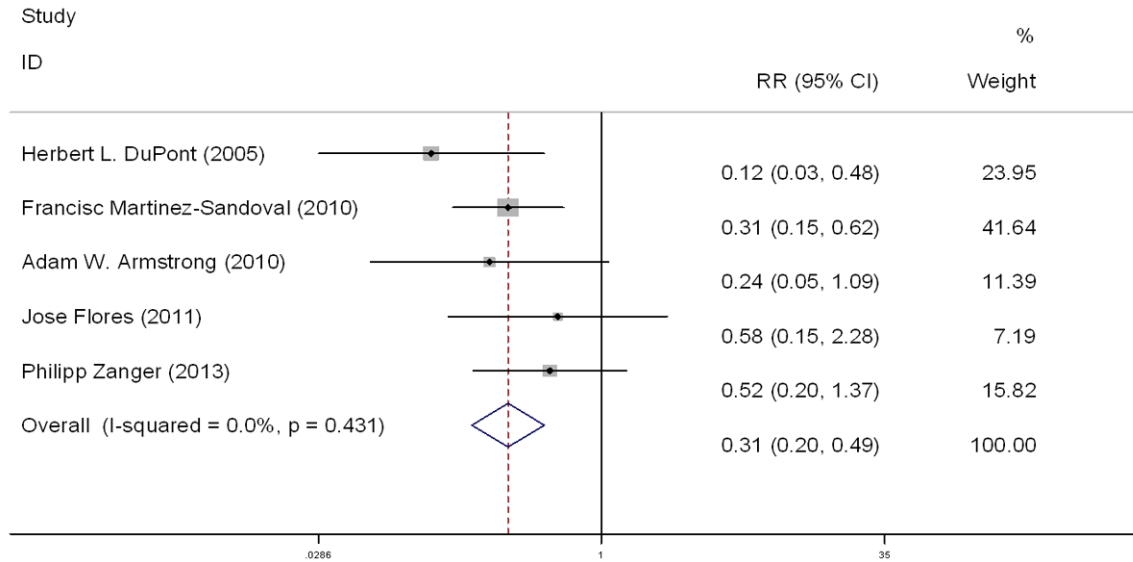
The incidences of mild diarrhea were reported in 3 RCTs and had significantly difference (3 RCTs; RR: 0.570, 95% CI: 0.436-0.745,  $P < 0.00001$ ), but high level of heterogeneity greatly reduced the veracity of this pooled analysis ( $P = 0.001$ ,  $I^2 = 85.7\%$ ) [19-21].

### Adverse events

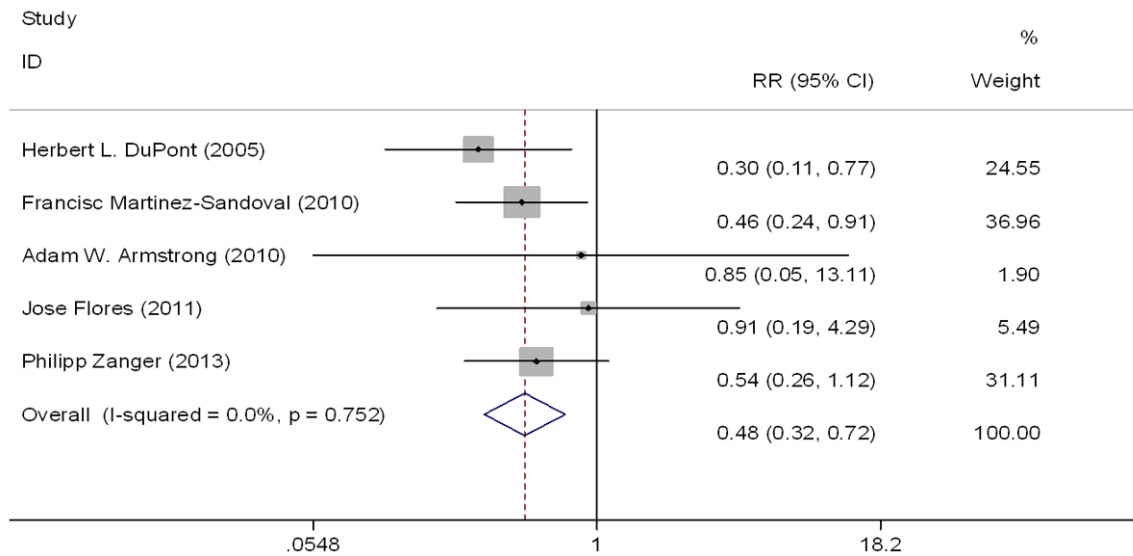
There were 3 RCTs and 282 patients included in counting the occurrence rate of adverse events comparing rifaximin with placebo. The incidence of adverse events was reduced (3 RCTs; RR: 0.905, 95% CI: 0.840-0.975,  $P = 0.009$ ) and low level of heterogeneity ( $P = 0.138$ ,  $I^2 = 49.5\%$ ) [19, 20, 23].



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**Figure 4.** Meta-analysis of randomized controlled trials evaluating effect of rifaximin on the incidence of Classic Travelers' Diarrhoea during the First Week of Travel. CI, confidence interval; RR, relative risk.



**Figure 5.** Meta-analysis of randomized controlled trials evaluating effect of rifaximin on the incidence of Classic Travelers' Diarrhoea during the Second Week of Travel. CI, confidence interval; RR, relative risk.

### Publication bias

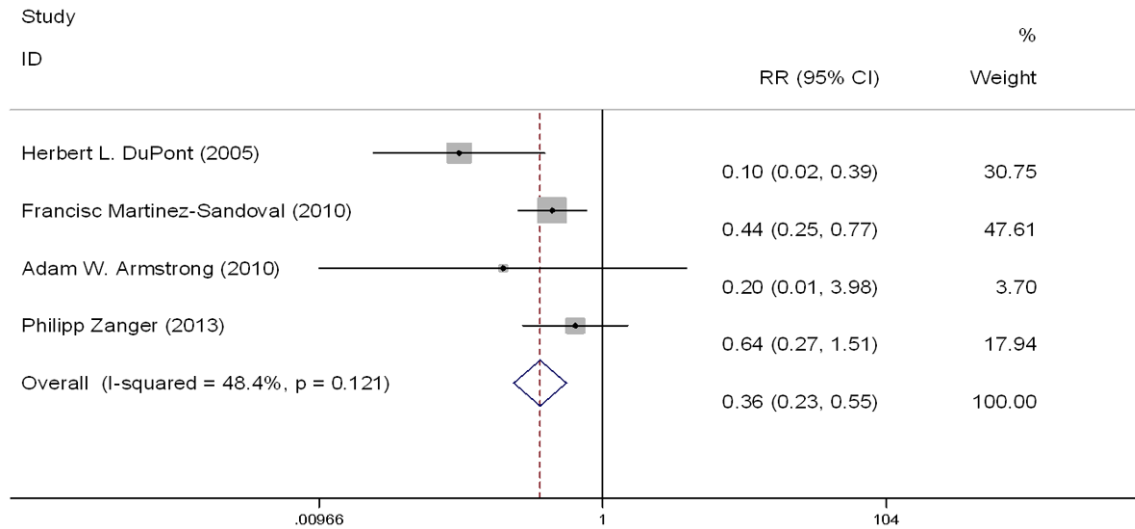
Publication bias had been assessed which included these 5 studies for evaluating the confidence level of meta-analysis (**Figure 7**).

### Discussion

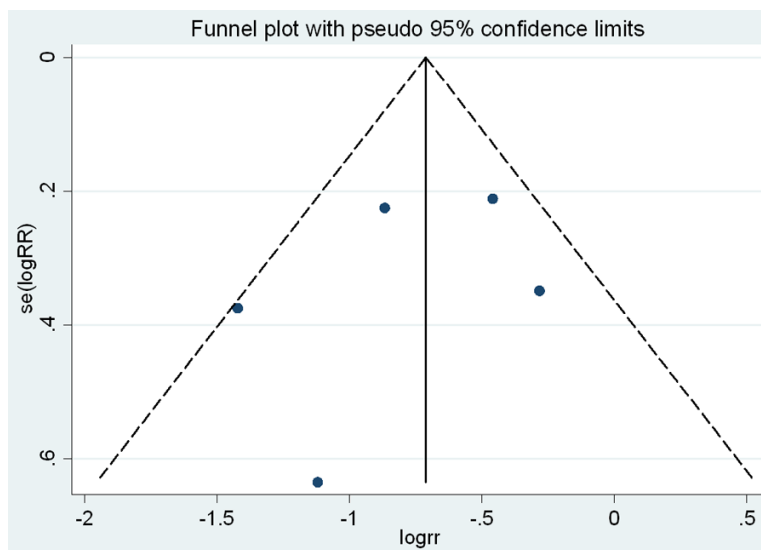
Travelers' diarrhoea occurs frequently in people who traveled to developing countries [24]. Based on what we know, this is not the first

meta-analysis to explore the role of rifaximin as a precaution in TD patients. One systematic review and one meta-analysis had been published in 2012, in which 4 RCTs and 604 patients had been included [25, 26]. However, according to our search results, we found one new eligible RCT which contained 239 patients and published in 2013. Meanwhile, there exists differences between the statistic results of those two foregoing meta-analyses and they all

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**Figure 6.** Meta-analysis of randomized controlled trials evaluating effect of rifaximin on the incidence of antibiotic-treated travelers' diarrhoea. CI, confidence interval; RR, relative risk.



**Figure 7.** Meta-analysis of Publication Bias.

ulations, regimen, and study designs. Actually, these modest number of cases and participators enhanced the possibility that contingency accounted for the results. Our sensitivity analysis suggested that none of the 5 trials were prominent responsible for the heterogeneity. But simply focusing on first week or second week of rifaximin precaution, the rate were 69% and 52%, and none heterogeneity ( $I^2 = 0.0\%$ ). In addition, rifaximin seemed to lower the incidence of antibiotic-treated travelers' diarrhea, mild diarrhea and adverse events than the control group.

didn't go deep into the protective effect of rifaximin in different periods of travelers' diarrhoea. Found on the situation, more meta-analyses are therefore necessary to summarize this issue.

Summarily, the pooled results from the meta-analysis of 5 RCTs using a fixed effects model suggested that the use of rifaximin reduced the incidence of classic travelers' diarrhoea by 53% in TD patients and the heterogeneity was in a low degree ( $I^2 = 46.7\%$ ), which was foreseeably given the differences in characteristics of pop-

As rifaximin is rare systemic absorption and gut specific, which is broad spectrum, semi-synthetic, active against gram-positive bacteria and slightly less active against gram-negative bacteria [27]. As to its mechanism of action, resembling all other members of the rifamycin group, rifaximin specifically restrains bacterial RNA polymerase, but doesn't affect the homologous mammalian enzymes. And due to mutations, bacterial resistance may lead to a change in the structure of the beta subunit of RNA polymerase [28]. But according to former records, rifaximin did not select for apparent resistance



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in various intestinal flora during drug treatment [29]. In short, rifaximin could be theoretically regarded as promising drug to deal with travelers' diarrhoea, since TD was reported to be caused by ETEC, EAEC, *Campylobacter* spp, *Salmonella* spp or *Shigella* spp, which intruded into intestinal canal, but in most trails, the major enteropathogens causing TD were unknown [30]. Meanwhile there existed evidences that rifaximin was a suited choice for *E coli* predomination, but it showed decreased efficacy in potentially invasive pathogens such as *Salmonella*, *Campylobacter*, and *Shigella* [7, 19]. Ignoring the species of enteropathogens and regional difference, exactly referred to the results of our meta-analysis, chemoprevention effect of rifaximin was statistically significant.

As stated above, the effect degrees of first travel week, whole travel period and second travel week were successively decreased. The reason, if we try to explain, might be that people had entered the unqualified standards of hygiene when arriving by practicing contaminated food, water or other public hygiene, which could increase the number of illnesses [31]. Then rifaximin resistance couldn't easily get outburst in the first week compared with other period and enhanced the effect of rifaximin group. And the major infectious enteropathogens of travelers' diarrhea had short incubation period which ensured the cardinality of placebo group. Retrospecting to these five analyzed RCTs, the first dose was ingested in different moments, for instance, the morning of departure, reaching the clinic at enrollment, or even within 72 hours of arrival. In other words, no standardized or uniform medication routine had been applied in rifaximin related research. However, on the basis of our results, it was more efficient that rifaximin had worked when getting to destination, so the morning of departure might be the best choice for the first dose and this could act as guidance for further standardized study and clinic. The most possible reason may be that the initial contact with the susceptible pathogens is the most risky.

As to duration, the vast majority of previous RCTs chose two weeks as study period, but for susceptible population the day of return would be the best deadline. The dosage and frequency of rifaximin or placebo in these five RCTs were totally different, and 600 mg daily or so was mostly used. But concerned with antibiotic

resistance, drug side effects, over confidence in their resistance to enteric infection, we should worry about that this kind of eating pattern might be overly adventurous. Simultaneously, only Mexico, Turkey, south and southeast Asia had been included in this study target. So thinking bravely, optimal daily medication administration and more destinations contained would lead to precise and normative trails in the future.

In conclusion, the current limited evidence suggests that the use of rifaximin would reduce the incidence of travellers' diarrhea, mild diarrhea, and adverse events in TD patients, and furthermore during the first week of travel rifaximin had a statistical better effect. Despite these encouraging findings, the results should be interpreted with caution due to the heterogeneity among study designs. Further large-scale, well-designed RCTs on this topic were still needed. Though rifaximin was commonly considered safe and well tolerated, in such future studies, the safety of rifaximin also should be given more attention.

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### Disclosure of conflict of interest

None.

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