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**Review article: Rifaximin, a minimally absorbed oral antibacterial for the  
treatment of travellers' diarrhoea**

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51 Solvay.  
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59 Dr Viola Andresen has been a speaker and/or advisory board member for Astra Zeneca,  
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## SUMMARY

### Background

Travellers' diarrhoea (TD), a common problem worldwide with significant medical impact, is generally treated with anti-diarrhoeal agents and fluid replacement. Systemic antibiotics are also used in selected cases but these may be associated with adverse effects, bacterial resistance and drug-drug interactions.

### Aim

To review the clinical evidence supporting the efficacy and safety of the minimally absorbed oral antibiotic rifaximin in TD.

### Methods

PubMed and the Cochrane Register of Controlled Clinical Trials (to January 2010) and International Society of Travel Medicine congress abstracts (2003–2009) were searched to identify relevant publications.

### Results

A total of 10 publications were identified. When administered three times daily for 3 days, rifaximin is superior to placebo or loperamide and at least as effective as ciprofloxacin in reducing duration of illness and restoring wellbeing in patients with TD, both with and without identification of a pathogen, as well as in *Escherichia coli* infection causing diarrhoea.

Rifaximin demonstrates only minimal potential for development of bacterial resistance and for cytochrome P450-mediated drug-drug interactions, and its tolerability profile is similar to that of placebo.

### Conclusions

When antibiotic therapy is warranted in uncomplicated TD, rifaximin may be considered as a first-line treatment option due to its favourable efficacy, tolerability and safety profiles.

**Key words:** antibiotic, enteropathogen, minimal absorption, rifaximin, travellers' diarrhoea

## BACKGROUND

Travellers' diarrhoea (TD) is a clinical syndrome frequently encountered by individuals (e.g. holidaymakers, business travellers, military personnel) visiting certain regions of the world, particularly the Middle East, Southern Asia, South and Central America, and the developing nations of Africa.<sup>1</sup> The incidence of TD varies between specific locations, ranging between 20% and 90% for these regions, and is calculated to affect 15–20 million travellers each year worldwide.<sup>2–4</sup>

TD is characterized by acute diarrhoea, often accompanied by nausea, vomiting, abdominal cramps and fever, due to the translocation of fluid and salts from the vascular to the mucosal side of the gut, where they are lost. The impact of TD involves not only significant morbidity, but also interruption to plans and daily activities.<sup>1–3, 5, 6</sup> In the majority of cases, symptoms last 3–4 days;<sup>2, 3</sup> however, in some instances, affected individuals may experience persistent diarrhoea lasting for more than 2 weeks.<sup>7</sup> In addition, more than 10% of people experiencing TD may go on to develop post-infectious irritable bowel syndrome (PI-IBS).<sup>8</sup> The primary causative agents of TD are pathogenic enteric bacteria, most commonly enterotoxigenic *Escherichia coli* (ETEC), enteroaggregative *Escherichia coli* (EAEC), *Campylobacter jejuni*, *Salmonella* species and *Shigella* species.<sup>9–12</sup> However, prevalence of the bacteria causing TD differs between geographical locations and up to 40% of TD cases are of unknown aetiology, even after comprehensive microbiological evaluation.<sup>6, 10, 13</sup>

Following anti-diarrhoeal agents and fluid replacement, treatment of TD includes empiric broad-spectrum oral antibiotic therapy. The goal of treatment is to achieve a rapid resolution of diarrhoea, in order to minimize disruption to planned activities, with only a short course of treatment, and to minimize person-to-person spread of TD.<sup>9, 14</sup> A systematic review of clinical studies (completed up to the year 2000) has concluded that antibiotic therapy for TD is associated with a reduction in frequency of unformed stools passed at 24-hour intervals (i.e. severity) and a significantly increased likelihood (around six-fold) of achieving resolution of

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3 diarrhoea and other symptoms (clinical cure) within 72 hours of treatment initiation, versus  
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5 no treatment (placebo).<sup>15</sup> However, there are differences in efficacy between antibiotic  
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7 agents.<sup>11</sup>  
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11 In addition to broad-spectrum activity against a range of bacterial enteropathogens and  
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13 efficacy against the symptoms of TD, other factors should be considered when selecting an  
14  
15 appropriate antibacterial treatment. These include specific targeted activity at the infection  
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17 site/**poor systemic absorption**,<sup>16</sup> plus a low potential for side effects,<sup>10, 15</sup> drug interactions<sup>1</sup>  
18  
19 and development of antibacterial resistance.<sup>9</sup>  
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23 Many antibacterials, such as the fluoroquinolones, are well absorbed into the systemic  
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25 circulation after oral administration.<sup>17, 18</sup> This may be associated with an increased risk of  
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27 systemic adverse effects, most commonly dizziness and headache, and more rarely, hepatic  
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29 dysfunction or psychiatric adverse effects.<sup>18-21</sup> In addition, resistance to fluoroquinolone  
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31 antibacterials among many of the pathogenic bacteria causing TD, such as ETEC, *C. jejuni*,  
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33 *Shigella* species and *Salmonella* species has been reported in many countries around the  
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35 world, thus limiting their utility.<sup>22-26</sup> Resistance of faecal *E. coli* and *Shigella* isolates from  
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37 subjects with TD to other (older) antibacterials, such as trimethoprim-sulfamethoxazole (**co-**  
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39 **trimoxazole**), tetracycline, chloramphenicol and ampicillin is well-documented and these  
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41 agents are no longer considered an appropriate treatment for TD.<sup>13, 24, 26-28</sup> Notably, the  
42  
43 percentage of resistant enteric bacterial isolates has increased over time, including those  
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45 resistant to more than one class of antibacterial agent.<sup>23, 29</sup>  
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51 Antibacterials that are not absorbed into the systemic circulation have demonstrated efficacy  
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53 as antidiarrhoeal agents, and may be associated with a more favourable safety/tolerability  
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55 profile, due to their minimal systemic exposure.<sup>10</sup> **Rifaximin** is a minimally absorbed oral  
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57 antibacterial available in several countries around the world for the treatment of acute  
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59 bacterial diarrhoea. The *in vitro* inhibitory potency of rifaximin against the majority of  
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bacterial pathogens responsible for TD (**ETEC, EAEC, *Shigella* and *Salmonella* species, *C.***

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3 *difficile*) has been demonstrated in a number of studies.<sup>26, 30-33</sup> Importantly, all the MIC<sub>90</sub>  
4 values for rifaximin against these bacteria are several times lower than the concentrations of  
5 rifaximin excreted in the faeces and therefore achieved within the gut.<sup>30, 34</sup> However, due to  
6 its poor systemic absorption, rifaximin is unlikely to be effective against invasive bacterial  
7 strains responsible for TD.  
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15 Bacterial resistance to rifaximin is low, and long-term monitoring of the faeces of study  
16 participants has demonstrated that the small number of rifaximin-resistant bacterial strains  
17 observed following treatment disappear from the gut rapidly (1–2 weeks) after treatment  
18 discontinuation.<sup>35</sup> Resistance of *C. difficile* strains to rifaximin is also uncommon.<sup>36</sup>  
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25 Interest in the prevention of TD is increasing due to an increase in the number of individuals  
26 visiting tropical and developing countries, the high rates of TD among such visitors and post-  
27 diarrhoea complications such as PI-IBS. A recent systematic review of the literature states  
28 that prevention consists of avoiding food and beverages that may potentially be  
29 contaminated, plus chemoprophylaxis with bismuth salts, probiotics or selected antibiotics,  
30 such as fluoroquinolones.<sup>37</sup> Specific groups of travellers who should be considered as  
31 candidates for chemoprophylaxis include those with underlying chronic medical illnesses, a  
32 known susceptibility to diarrhoea and previous TD.  
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43 In this paper we review the literature supporting the efficacy and safety of rifaximin in the  
44 treatment and prevention of TD.  
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## METHODS

References for this review were identified by searches of PubMed and the Cochrane Register of Controlled Clinical Trials to January 2010 using the terms 'rifaximin' and 'diarrhoea/diarrhea' (with no language restrictions). Reference lists from review articles were also checked for additional papers. In addition, abstracts from the congresses of the International Society of Travel Medicine (ISTM; 2003 to 2009) were also searched. All articles containing clinical data concerning the efficacy and safety of rifaximin in TD were reviewed by the authors (including randomized controlled trials, observational studies, case reports and meta-analyses).

## RESULTS

### Studies identified

From the literature searches, a total of 122 articles were identified. Following review of the abstracts by the authors, 10 were selected for further review.<sup>31, 38-46</sup> From the ISTM abstracts, 3 were selected, but on review the information contained in these had subsequently been published in full. The articles discounted were primarily reviews containing no new clinical data or studies examining the *in vitro* antimicrobial activity of rifaximin.

### Efficacy of rifaximin for the management of travellers' diarrhoea

The clinical efficacy of rifaximin in the treatment of TD has been evaluated in a number of clinical trials (Table 1). In an early study performed in Mexico, US students suffering from TD were randomized to receive one of: rifaximin 200 mg, 400 mg or 600 mg (all TID), or co-trimoxazole 160 mg/800 mg twice-daily (BID) for 5 days.<sup>38</sup> Median time to last unformed



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3 stool (TLUS; i.e. time from start of treatment to resolution of diarrhoea) was similar for  
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5 rifaximin 400 mg TID, rifaximin 600 mg TID and co-trimoxazole. Improvement in diarrhoea at  
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7 24 hours after treatment initiation was achieved by slightly fewer patients receiving rifaximin,  
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9 compared with patients receiving co-trimoxazole. However, at 48 hours, these percentages  
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11 had increased in all groups but were higher for rifaximin 200 mg TID and 600 mg TID than  
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13 co-trimoxazole. In all patients receiving rifaximin, 20 were positive for pathogens (ETEC,  
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15 *Shigella*, *Salmonella*, *Cryptosporidium* or *Campylobacter* species were identified in pre-  
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17 treatment stool samples) and this was reduced by 80% after treatment, compared with  
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19 organism eradication for 100% of pathogens with co-trimoxazole. However, all  
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21 enteropathogens were eradicated with rifaximin 200 mg TID.  
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26 [Table 1 to be inserted near here]  
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29 In a separate randomized, double-blind, double-dummy study, US students visiting Mexico  
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31 or Jamaica received either rifaximin 400 mg BID or ciprofloxacin 500 mg BID, for 3 days.<sup>31</sup>  
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33 Median TLUS was comparable for rifaximin and ciprofloxacin. At 72 hours after treatment  
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35 initiation, similar high percentages of patients receiving rifaximin or ciprofloxacin had  
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37 achieved a clinical cure. No statistically significant differences between treatments were  
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39 observed.  
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43 In a multicentre study involving 380 individuals with TD in Guatemala, Mexico and Kenya,  
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45 rifaximin 200 mg TID and 400 mg TID were compared with placebo over a 3-day treatment  
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47 period.<sup>39</sup> Median TLUS was significantly lower in both rifaximin groups than in the placebo  
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49 group. Clinical cure (wellness; defined as 48 h with no unformed stools and no fever; or 24 h  
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51 without watery stools, maximum 2 soft stools and no clinical symptoms) was achieved at  
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53 Day 5 in similar proportions of patients receiving rifaximin 200 mg TID or rifaximin 400 mg  
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55 TID; both were significantly superior to placebo. Improvement in diarrhoea (defined as the  
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57 passage of ≤50% stools during a 24-hour period versus baseline) was achieved at 48 hours  
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59 by significantly more patients in the rifaximin 200 mg TID group than in the placebo group. At  
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3 72 hours, these percentages had increased in both treatment arms but the difference  
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5 between rifaximin 200 mg TID and placebo remained significant. Although the percentages  
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7 of patients achieving improvement with rifaximin 400 mg TID were numerically higher than  
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9 those with placebo, the difference was not statistically significant.

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12 A subsequent analysis from this study investigated the efficacy of rifaximin in TD caused by  
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14 EAEC in the subgroup of patients (n=43) who remained ill during the study (5 days after  
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16 initiation of therapy).<sup>40</sup> For this population, median TLUS was significantly shorter for those  
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18 receiving rifaximin (22 h; 95% CI: 15–25 h) than those receiving placebo (72 h; 95% CI:  
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20 20–72 h) (p=0.03). For those patients remaining ill during the study and for whom no  
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22 pathogenic cause of TD was identified, similar results were obtained. Median TLUS was  
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24 shorter for those receiving rifaximin (33 h; 95% CI: 19–47 h) than those receiving placebo  
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26 (52 h; 95% CI: 40–78 h), but this difference was not statistically significant.

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29 In a separate randomized, double-blind, double-dummy study, 399 individuals with TD in  
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31 Mexico, Guatemala, India or Peru received 3 days of treatment with rifaximin 200 mg TID,  
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33 ciprofloxacin 500 mg BID, or placebo.<sup>41</sup> Median TLUS was significantly less for both rifaximin  
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35 and ciprofloxacin versus placebo, but there were no differences between the active  
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37 treatments. Median TLUS was also significantly reduced with rifaximin versus placebo in the  
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39 subgroups of patients with diarrhoeagenic *E. coli* but without invasive pathogens, and also in  
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41 those where a pathogen was not identified. There were no differences between active  
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43 treatments for achievement of clinical cure. Across all pathogens identified, eradication rates  
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45 were significantly higher for ciprofloxacin versus rifaximin and placebo.

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48 A post-hoc analysis of pooled data from the previous two studies was performed in order to  
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50 assess the efficacy of rifaximin 200 mg TID versus placebo against TD with no pathogens  
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52 identifiable from stool samples. Median TLUS in this subgroup was 33 h with rifaximin versus  
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54 68 h with placebo (p=0.0015), and a significantly greater proportion of patients achieved  
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56 clinical cure with rifaximin than with placebo (77% versus 61%; p=0.01).<sup>42</sup>

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3 The efficacy of rifaximin monotherapy (200 mg TID for 3 days) has been compared with that  
4 of loperamide monotherapy (4 mg initially followed by 2 mg after each unformed stool) and  
5 rifaximin + loperamide in TD, in more than 300 US students visiting Mexico.<sup>43</sup> Rifaximin  
6 monotherapy and combination therapy significantly reduced median TLUS versus  
7 loperamide monotherapy. Clinical cure, defined in this study as TLUS <120 h, was achieved  
8 more frequently with rifaximin monotherapy or combination therapy than with loperamide  
9 alone. At the end of Day 1, a greater number of patients receiving combination therapy  
10 reported complete wellness compared with rifaximin monotherapy (odds ratio=2.51; 95% CI:  
11 1.35–4.67) or loperamide monotherapy (odds ratio=1.71; 95% CI: 0.95–3.09).  
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### 27 Rifaximin in the prevention of travellers' diarrhoea

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29 Rifaximin has also been evaluated as a chemoprophylactic agent. In a placebo-controlled  
30 study, 219 US adults received a 2-week course of rifaximin 200 mg/day, 200 mg BID or 200  
31 mg TID on their arrival in Mexico.<sup>44</sup> Significantly more individuals receiving placebo than  
32 rifaximin experienced TD during this time. Overall, a protection rate of 72% against TD with  
33 rifaximin was observed (p<0.001). The incidence of ETEC-related TD was reduced by 83%  
34 for rifaximin versus placebo.  
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43 A separate randomized, double-blind, placebo-controlled trial involving 210 travellers to  
44 Mexico compared rifaximin 600 mg OD to placebo over a 14-day period. Those receiving  
45 rifaximin were significantly less likely to develop TD compared with those receiving  
46 placebo.<sup>45</sup>  
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### Bacterial resistance to rifaximin in travellers' diarrhoea

In the placebo-controlled trials evaluating the efficacy of rifaximin 200 mg TID and 400 mg TID in individuals with TD, stool samples were collected and investigated for antibacterial resistance.<sup>46</sup> The number of rifaximin-resistant coliforms isolated was low at baseline (pre-treatment) and did not increase significantly at Days 3 or 5. Pre-treatment MIC<sub>90</sub> values for rifaximin against enterococci in all groups were 8–64 µg/ml and these did not change at Day 3, indicating no significant development of resistance during this time period. In the study comparing rifaximin with co-trimoxazole, 39% of ETEC isolates were resistant to TMP. The median MIC for rifaximin against ETEC in this study was 12.5 µg/ml.<sup>38</sup>

### Safety and tolerability of rifaximin in the management of travellers' diarrhoea

In the 10 studies reviewed for this paper, no specific adverse events associated with rifaximin therapy were highlighted.<sup>31, 38–46</sup> When directly compared to ciprofloxacin in patients with TD, rifaximin demonstrates a similar tolerability profile (Table 2). Adverse events were reported for 24–27% of patients receiving each drug, and these were mild and non-specific (headache, constipation, flatulence, vomiting and nausea).<sup>31, 41</sup> In placebo-controlled studies, the tolerability profile of rifaximin was generally similar to that of placebo, in terms of incidences of gastrointestinal adverse events and headache.<sup>39, 41</sup>

When compared with loperamide monotherapy in individuals with TD, rifaximin monotherapy was associated with a lower incidence of abdominal pain/cramps, tenesmus, nausea and vomiting. The odds ratio of vomiting for loperamide versus rifaximin was 4.41 (95% CI: 1.28–15).<sup>43</sup>

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## DISCUSSION

TD is a common problem in many countries and can have a significant negative impact on an individual's wellbeing and activities. Oral antibacterials are conventional therapy for TD (following antidiarrhoeal agents and fluid replacement), but these may be associated with systemic adverse effects, the development of bacterial resistance and drug-drug interactions.

Rifaximin is a virtually non-absorbed oral antibacterial that achieves high concentrations within the intestine, i.e. the site of infection in TD, but is largely undetectable in the systemic circulation.<sup>34, 47, 48</sup> It has demonstrated good potency *in vitro* against the most common non-invasive pathogenic bacteria responsible for TD,<sup>26, 30-33</sup> and its efficacy is therefore consistent across geographical locations. When administered TID for 3 days, rifaximin has demonstrated significantly superior efficacy to placebo or loperamide and comparable efficacy to a systemically absorbed antibacterial, such as ciprofloxacin, in reducing the duration of illness, rapidly restoring wellness in the majority of patients and therefore minimizing the interruption caused by TD. Efficacy is also consistent across subgroups of individuals with diarrhoeagenic *E. coli* and in cases where no pathogen was identified. The evidence available suggests that the potential for bacterial resistance to rifaximin is low. In addition, rifaximin is well-tolerated by individuals with TD with a tolerability profile generally comparable to those of placebo and ciprofloxacin and minimal systemic side effects and a low potential for drug-drug interactions.<sup>49, 50</sup>

There appear to be a number of gaps in the literature for rifaximin in TD. Notably, the studies conducted to date have focused primarily on individuals visiting Central and South America. Further studies should therefore investigate the utility of rifaximin in TD in travellers to the Middle East, Asia and Africa. In addition, no data are currently available to support the efficacy and safety of rifaximin in individuals with TD who are aged <18 years. Furthermore, although the results from a single study suggest favourable efficacy of rifaximin in preventing

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3 TD, this indication needs to be evaluated in larger and more diverse populations, in terms of  
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5 geographical travel destinations. Another consideration is that the majority of clinical trials  
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7 evaluating rifaximin completed to date have been performed by the same group of  
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9 researchers. The results of these therefore need to be confirmed by other researchers.  
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13 In conclusion, the published evidence suggests that rifaximin should be considered as an  
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15 effective and well-tolerated option for the treatment of uncomplicated TD.  
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For Peer Review

## REFERENCES

1. Al-Abri SS, Breeching NJ, Nye FJ. Traveller's diarrhea. *Lancet Infect Dis* 2005; **5**: 349–60.
2. Steffen R, Collard F, Tornieporth N, *et al.* Epidemiology, etiology, and impact of traveler's diarrhea in Jamaica. *JAMA* 1999; **281**: 811–7.
3. Hill DR. Occurrence and self-treatment of diarrhea in a large cohort of Americans travelling to developing countries. *Am J Trop Med Hyg* 2000; **62**: 585–9.
4. Steffen R. Epidemiology of traveler's diarrhea. *Clin Infect Dis* 2005; **41 Suppl 8**: S536–40.
5. Daniels NA, Neimann J, Karpati A, *et al.* Traveler's diarrhea at sea: Three outbreaks of waterborne enterotoxigenic *Escherichia coli* on cruise ships. *J Infect Dis* 2000; **181**: 1491–5.
6. DuPont HL. Systematic review: the epidemiology and clinical features of travellers' diarrhea. *Aliment Pharmacol Ther* 2009; **30**: 187–96.
7. Connor BA. Sequelae of traveler's diarrhea: focus on postinfectious irritable bowel syndrome. *Clin Infect Dis* 2005; **41**: S577–86.
8. Stermer E, Lubezky A, Potasman I, Paster E, Lavy A. Is traveler's diarrhea a significant risk factor for the development of irritable bowel syndrome? A prospective study. *Clin Infect Dis* 2006; **43**: 898–901.
9. Adachi JA, Ostrosky-Zeichner L, DuPont HL, Ericsson CD. Empirical antibiotic therapy for traveler's diarrhea. *Clin Infect Dis* 2000; **31**: 1079–83.
10. Ericsson CD. Travellers' diarrhea. *Int J Antimicrob Agents* 2003; **21**: 116–24.

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11. Tribble DR, Sanders JW, Pang LW, *et al.* Traveler's diarrhea in Thailand: randomized, double-blind trial comparing single-dose and 3-day azithromycin-based regimens with a 3-day levofloxacin regimen. *Clin Infect Dis* 2007; **44**: 338–46.
12. Adachi JA, Jiang Z-D, Mathewson JJ, *et al.* Enteroaggregative *Escherichia coli* as a major etiologic agent in traveler's diarrhea in 3 regions of the world. *Clin Infect Dis* 2001; **32**: 1706–9.
13. Jiang Z-D, Lowe B, Verenkar MP, *et al.* Prevalence of enteric pathogens among international travellers with diarrhea acquired in Mombasa (Kenya), India (Goa), or Jamaica (Montego Bay). *J Infect Dis* 2002; **185**: 497–502.
14. Clarke SC. Diarrheagenic *Escherichia coli* – an emerging problem? *Diagn Microbiol Infect Dis* 2001; **41**: 93–8.
15. De Bruyn G, Hahn S, Borwick A. Antibiotic treatment for travellers' diarrhea (review). *Cochrane Database Syst Rev* 2000; CD002242.
16. DuPont HL, Ericsson CD. Prevention and treatment of traveler's diarrhea. *N Engl J Med* 1993; **328**: 1821–7.
17. Plaisance KI, Drusano GL, Forrest A, Bustamante CI, Standiford HC. Effect of dose size on bioavailability of ciprofloxacin. *Antimicrob Agents Chemother* 1987; **31**: 956–8.
18. Lubasch A, Keller I, Borner K, Koeppe P, Lode H. Comparative pharmacokinetics of ciprofloxacin, gatifloxacin, grepafloxacin, levofloxacin, trovafloxacin, and moxifloxacin after single oral administration in healthy volunteers. *Antimicrob Agents Chemother* 2000; **44**: 2600–3.
19. Carbon C. Comparison of side effects of levofloxacin versus other fluoroquinolones. *Chemotherapy* 2001; **47 Suppl 3**: 9–14.



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3 20. Ball P, Mandell L, Niki Y, Tillotson G. Comparative tolerability of the newer  
4  
5 fluoroquinolone antibacterials. *Drug Saf* 1999; **21**: 407–21.  
6  
7  
8  
9 21. Fluoroquinolones: psychiatric adverse effects. *Prescrire Int* 2008;17: 20.  
10  
11  
12  
13 22. Committee on Infectious Diseases. Policy statement. The use of systemic  
14  
15 fluoroquinolones. *Pediatrics* 2006; **118**: 1287–92.  
16  
17  
18  
19 23. Pickering LK. Antimicrobial resistance among enteric pathogens. *Semin Pediatr*  
20  
21 *Infect Dis* 2004; **15**: 71–7.  
22  
23  
24 24. Isenbarger DW, Hoge CW, Srijan A, *et al.* Comparative antibiotic resistance of  
25  
26 diarrheal pathogens from Vietnam and Thailand, 1996–1999. *Emerg Infect Dis* 2002;  
27  
28 **8**: 175–80.  
29  
30  
31 25. Nelson JM, Smith KE, Vugia D, *et al.* Prolonged diarrhea due to ciprofloxacin-  
32  
33 resistant *Campylobacter* infection. *J Infect Dis* 2004; **190**: 1150–7.  
34  
35  
36 26. Ruiz J, Mensa L, O’Callaghan C, *et al.* In vitro antimicrobial activity of rifaximin  
37  
38 against enteropathogens causing traveler’s diarrhea. *Diagn Microbiol Infect Dis* 2007;  
39  
40 **59**: 473–5.  
41  
42  
43 27. Murray BE, Mathewson JJ, DuPont HL, Ericsson CD, Reves RR. Emergence of  
44  
45 resistant fecal *Escherichia coli* in travellers not taking prophylactic antimicrobial  
46  
47 agents. *Antimicrob Agents Chemother* 1990; **34**: 515–8.  
48  
49  
50  
51 28. Vila J, Gascon J, Abdalla S, *et al.* Antimicrobial resistance of *Shigella* isolates  
52  
53 causing traveler’s diarrhea. *Antimicrob Agents Chemother* 1994; **38**: 2668–70.  
54  
55  
56 29. Sanches Ito CA, Gales AC, Tognim MCB, Munerato P, Dalla Costa LM. Quinolone-  
57  
58 resistant *Escherichia coli*. *Braz J Infect Dis* 2008; **12**: 5–9.  
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30. Sierra JM, Ruiz J, Navia MM, Vargas M, Gascon J, Vila J. In vitro activity of rifaximin against enteropathogens producing traveler's diarrhea. *Antimicrob Agents Chemother* 2001; **45**: 643–4.
31. DuPont HL, Jiang Z-D, Ericsson CD, *et al.* Rifaximin versus ciprofloxacin for the treatment of traveler's diarrhea: A randomized, double-blind trial. *Clin Infect Dis* 2001; **33**: 1807–15.
32. Gomi H, Jiang Z-D, Adachi JA, *et al.* In vitro antimicrobial susceptibility testing of bacterial enteropathogens causing traveler's diarrhea in four geographic regions. *Antimicrob Agents Chemother* 2001; **45**: 212–6.
33. Hecht DW, Galang MA, Sambol SP, Osmolski JR, Johnson S, Gerding DN. In vitro activities of 15 antimicrobial agents against 110 toxigenic *Clostridium difficile* clinical isolates collected from 1983 to 2004. *Antimicrob Agents Chemother* 2007; **51**: 2716–9.
34. Rizzello F, Gionchetti P, Venturi A, *et al.* Rifaximin systemic absorption in patients with ulcerative colitis. *Eur J Clin Pharmacol* 1998; **54**: 91–3.
35. De Leo C, Eftimiadi C, Schito GC. Rapid disappearance from the intestinal tract of bacteria resistant to rifaximin. *Drugs Exp Clin Res* 1986; **12**: 979–81.
36. Marchese A, Salerno A, Pesce A, Debbia EA, Schito GC. In vitro activity of rifaximin, metronidazole and vancomycin against *Clostridium difficile* and the rate of selection of spontaneously resistant mutants against representative anaerobic and aerobic bacteria, including ammonia-producing species. *Chemotherapy* 2000; **46**: 253–66.
37. DuPont HL. Systematic review: prevention of travellers' diarrhea. *Aliment Pharmacol Ther* 2008; **27**: 741–51.

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38. DuPont HL, Ericsson CD, Mathewson JJ, *et al.* Rifaximin: a nonabsorbed antimicrobial in the therapy of traveler's diarrhea. *Digestion* 1998; **59**: 708–14.
39. Steffen R, Sack DA, Riopel L, *et al.* Therapy of travelers' diarrhea with rifaximin on various continents. *Am J Gastroenterol* 2003; **98**: 1073–8.
40. Infante RM, Ericsson CD, Jiang Z-D, *et al.* Enteroaggregative *Escherichia coli* diarrhea in travelers: response to rifaximin therapy. *Clin Gastroenterol Hepatol* 2004; **2**: 135–8.
41. Taylor DN, Bourgeois AL, Ericsson CD, *et al.* A randomized, double-blind, multicenter study of rifaximin compared with placebo and with ciprofloxacin in the treatment of traveler's diarrhea. *Am J Trop Med Hyg* 2006; **74**: 1060–6.
42. DuPont HL, Haake R, Taylor DN, *et al.* Rifaximin treatment of pathogen-negative traveler's diarrhea. *J Travel Med* 2007; **14**: 16–9.
43. DuPont HL, Jiang ZD, Belkind-Gerson J, *et al.* Treatment of traveler's diarrhea: randomized trial comparing rifaximin, rifaximin plus loperamide, and loperamide alone. *Clin Gastroenterol Hepatol* 2007; **5**: 451–6.
44. DuPont HL, Jiang Z-D, Okhuysen PC, *et al.* A randomized, double-blind, placebo-controlled trial of rifaximin to prevent traveler's diarrhea. *Ann Intern Med* 2005; **142**: 805–12.
45. DuPont HL, Ericsson CD, de la Cabada FJ, *et al.* Prevention of travelers' diarrhea with rifaximin – a phase 3 randomized double-blind placebo-controlled trial in U.S. students in Mexico. *Am J Gastroenterol* 2006; **101 Suppl 2**: S197.
46. DuPont HL, Jiang Z-D. Influence of rifaximin treatment on the susceptibility of intestinal Gram-negative flora and enterococci. *Clin Microbiol Infect* 2004; **10**: 1009–11.

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47. Descombe JJ, Dubourg D, Picard M, Palazzini E. Pharmacokinetic study of rifaximin after oral administration in healthy volunteers. *Int J Clin Pharm Res* 1994; **14**: 51–6.
48. Jiang Z-D, Ke S, Palazzini E, Riopel L, DuPont H. In vitro activity and fecal concentration of rifaximin after oral administration. *Antimicrob Agents Chemother* 2000; **44**: 2205–6.
49. Braun Trapnell C, Connolly M, Pentikis H, Forbes B, Bettenhausen DK. Absence of effect of oral rifaximin on the pharmacokinetics of ethinyl estradiol/norgestimate in healthy females. *Ann Pharmacother* 2007; **41**: 222–8.
50. Pentikis HS, Connolly M, Trapnell CB, Forbes WP, Bettenhausen DK. The effect of multiple-dose, oral rifaximin on the pharmacokinetics of intravenous and oral midazolam in healthy volunteers. *Pharmacotherapy* 2007; **27**: 1361–9.

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Table 1. Summary of clinical studies evaluating rifaximin in travellers' diarrhoea

| Study                             | Number of patients/countries visited | Study design                | Rifaximin dose                         | Control group                       | Treatment length | Key results  |
|-----------------------------------|--------------------------------------|-----------------------------|--|-------------------------------------|------------------|--|
| DuPont et al (1998) <sup>38</sup> | 72/Mexico                            | Randomized controlled trial | 200 mg TID<br>400 mg TID<br>600 mg TID | co-trimoxazole<br>160/800 mg<br>BID | 5 days           | <p>Median TLUS:</p> <p>26.3 h for rifaximin 200 mg<br/>40.5 h for rifaximin 400 mg<br/>35.0 h for rifaximin 600 mg<br/>35.0 h for all rifaximin groups (NS vs. co-trimoxazole)<br/>47.0 h for co-trimoxazole</p> <p>Improvement in diarrhoea* at 24 hours<br/>56% for rifaximin 200 mg<br/>44% for rifaximin 400 mg<br/>53% h for rifaximin 600 mg<br/>65% for co-trimoxazole</p> <p>At 48 hours<br/>83% for rifaximin 200 mg<br/>78% for rifaximin 400 mg<br/>89% h for rifaximin 600 mg<br/>76% for co-trimoxazole</p> <p>Eradication rate of enteropathogens<br/>100% for rifaximin 200 mg<br/>60% for rifaximin 400 mg<br/>50% for rifaximin 600 mg<br/>80% for all rifaximin groups</p> |

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|    |                                    |   |                                |   |                       |  |
|----|------------------------------------|---|--------------------------------|---|-----------------------|--|
| 1  |                                    |   |                                |   |                       | 100% for co-trimoxazole  |
| 2  |                                    |   |                                |   |                       |  |
| 3  |                                    |   |                                |   |                       |  |
| 4  |                                    |   |                                |   |                       |  |
| 5  | DuPont et al (2001) <sup>31</sup>  | 187/Mexico<br>and<br>Jamaica              | Randomized<br>controlled trial | 400 mg BID<br>Ciprofloxacin<br>500 mg BID | 3 days                | Median TLUS:<br>25.7 h for rifaximin (95% CI: 20.9–38.0) (NS vs.<br>ciprofloxacin)<br>25.0 h for ciprofloxacin (95% CI: 18.5–35.2)             |
| 6  |                                    |   |                                |   |                       | Clinical cure <sup>†</sup>   |
| 7  |                                    |   |                                |   |                       | 87% for rifaximin (NS vs. ciprofloxacin)   |
| 8  |                                    |   |                                |   |                       | 88% for ciprofloxacin  |
| 9  |                                    |   |                                |   |                       |  |
| 10 |                                    |   |                                |   |                       | Eradication rate for all pathogens   |
| 11 |                                    |   |                                |   |                       | 74% for rifaximin (NS vs. ciprofloxacin)   |
| 12 |                                    |   |                                |   |                       | 88% for ciprofloxacin  |
| 13 |                                    |   |                                |   |                       |  |
| 14 |                                    |   |                                |   |                       | Adverse events:  |
| 15 |                                    |   |                                |   |                       | 31 (33%) for rifaximin   |
| 16 |                                    |   |                                |   |                       | 34 (36%) for ciprofloxacin   |
| 17 |                                    |   |                                |   |                       |  |
| 18 |                                    |   |                                |   |                       |  |
| 19 |                                    |   |                                |   |                       |  |
| 20 |                                    |   |                                |   |                       |  |
| 21 |                                    |   |                                |   |                       |  |
| 22 |                                    |   |                                |   |                       |  |
| 23 |                                    |   |                                |   |                       |  |
| 24 | Steffen et al (2003) <sup>39</sup> | 380/<br>Guatemala,<br>Mexico and<br>Kenya | Randomized<br>controlled trial | 200 mg TID<br>400 mg TID                  | Placebo TID<br>3 days | Median TLUS:<br>32.0 h for rifaximin 200 mg (p=0.0001 vs. placebo)<br>32.9 h for rifaximin 400 mg (p=0.0001 vs. placebo)<br>60.0 h for placebo |
| 25 |                                    |   |                                |   |                       | Clinical cure <sup>†</sup>   |
| 26 |                                    |   |                                |   |                       | 79.2% for rifaximin 200 mg (p=0.001 vs. placebo)   |
| 27 |                                    |   |                                |   |                       | 81.0% for rifaximin 400 mg (p=0.001 vs. placebo)   |
| 28 |                                    |   |                                |   |                       | 60.5% for placebo  |
| 29 |                                    |   |                                |   |                       |  |
| 30 |                                    |   |                                |   |                       | Improvement in diarrhoea* at 48 h <sup>‡</sup>   |
| 31 |                                    |   |                                |   |                       | 87% for rifaximin 200 mg (p=0.007 vs. placebo)   |
| 32 |                                    |   |                                |   |                       | 72% for placebo  |
| 33 |                                    |   |                                |   |                       | At 72 h  |
| 34 |                                    |   |                                |   |                       | 91% for rifaximin 200 mg (p=0.008 vs. placebo)   |
| 35 |                                    |   |                                |   |                       |  |
| 36 |                                    |   |                                |   |                       |  |
| 37 |                                    |   |                                |   |                       |  |
| 38 |                                    |   |                                |   |                       |  |
| 39 |                                    |   |                                |   |                       |  |
| 40 |                                    |   |                                |   |                       |  |
| 41 |                                    |   |                                |   |                       |  |
| 42 |                                    |   |                                |   |                       |  |
| 43 |                                    |   |                                |   |                       |  |
| 44 |                                    |   |                                |   |                       |  |
| 45 |                                    |   |                                |   |                       |  |
| 46 |                                    |   |                                |   |                       |  |
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|----|-----------------------------------|--|--------------------------------|------------|---|--------|--|
| 1  |                                   |  |                                |            |   |        |  |
| 2  |                                   |  |                                |            |   |        |  |
| 3  |                                   |  |                                |            |   |        | 78% for placebo  |
| 4  |                                   |  |                                |            |   |        |  |
| 5  |                                   |  |                                |            |   |        | Drug-related adverse events  |
| 6  |                                   |  |                                |            |   |        | 74 (59.7%) for rifaximin 200 mg  |
| 7  |                                   |  |                                |            |   |        | 88 (69.7%) for rifaximin 400 mg  |
| 8  |                                   |  |                                |            |   |        | 90 (69.8%) for placebo group   |
| 9  |                                   |  |                                |            |   |        |  |
| 10 |                                   |  |                                |            |   |        |  |
| 11 | Taylor et al (2006) <sup>41</sup> | 399/<br>Guatemala,<br>Mexico,<br>India and<br>Peru | Randomized<br>controlled trial | 200 mg TID | Ciprofloxacin<br>500 mg BID;<br>Placebo | 3 days | Median TLUS:<br>32.5 h for rifaximin (p=0.001 vs. placebo; NS vs.<br>ciprofloxacin)<br>28.8 h for ciprofloxacin (p=0.0003 vs. placebo)<br>65.5 h for placebo<br>Risk ratio for rifaximin vs. placebo=1.63 (95% CI:<br>1.21–2.19)<br>Risk ratio for ciprofloxacin vs. placebo=1.89 (95% CI:<br>1.34–2.65) |
| 12 |                                   |  |                                |            |   |        |  |
| 13 |                                   |  |                                |            |   |        |  |
| 14 |                                   |  |                                |            |   |        |  |
| 15 |                                   |  |                                |            |   |        |  |
| 16 |                                   |  |                                |            |   |        |  |
| 17 |                                   |  |                                |            |   |        |  |
| 18 |                                   |  |                                |            |   |        |  |
| 19 |                                   |  |                                |            |   |        |  |
| 20 |                                   |  |                                |            |   |        |  |
| 21 |                                   |  |                                |            |   |        |  |
| 22 |                                   |  |                                |            |   |        | Clinical cure <sup>†</sup>   |
| 23 |                                   |  |                                |            |   |        | 76.6% for rifaximin (p=0.0002 vs. placebo; NS vs.<br>ciprofloxacin)  |
| 24 |                                   |  |                                |            |   |        | 78.2% for ciprofloxacin (p<0.05 vs. placebo)   |
| 25 |                                   |  |                                |            |   |        | 61.4% for placebo  |
| 26 |                                   |  |                                |            |   |        |  |
| 27 |                                   |  |                                |            |   |        |  |
| 28 |                                   |  |                                |            |   |        |  |
| 29 |                                   |  |                                |            |   |        | Eradication rate for all pathogens:  |
| 30 |                                   |  |                                |            |   |        | 61.6% for rifaximin (NS vs. placebo; p=0.001 vs.<br>ciprofloxacin)   |
| 31 |                                   |  |                                |            |   |        | 80.7% for ciprofloxacin (p=0.001 vs. placebo)  |
| 32 |                                   |  |                                |            |   |        | 51.7% for placebo  |
| 33 |                                   |  |                                |            |   |        |  |
| 34 |                                   |  |                                |            |   |        |  |
| 35 |                                   |  |                                |            |   |        | Adverse events:  |
| 36 |                                   |  |                                |            |   |        | 53 (26.6%) for rifaximin   |
| 37 |                                   |  |                                |            |   |        | 25 (25.0%) for ciprofloxacin   |
| 38 |                                   |  |                                |            |   |        | 24 (24.0%) for placebo   |
| 39 |                                   |  |                                |            |   |        |  |
| 40 |                                   |  |                                |            |   |        |  |
| 41 |                                   |  |                                |            |   |        |  |
| 42 |                                   |  |                                |            |   |        |  |
| 43 |                                   |  |                                |            |   |        |  |
| 44 |                                   |  |                                |            |   |        |  |
| 45 |                                   |  |                                |            |   |        |  |
| 46 |                                   |  |                                |            |   |        |  |
| 47 |                                   |  |                                |            |   |        |  |

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| 1  |                                   |            |                                |            |                |   |
| 2  |                                   |            |                                |            |                |   |
| 3  | DuPont et al (2007) <sup>43</sup> | 311/Mexico | Randomized<br>controlled trial | 200 mg TID | Loperamide     | 3 days  |
| 4  |                                   |            |                                |            | 4 mg initially | Median TLUS:  |
| 5  |                                   |            |                                |            | and then 2     | 32.5 h for rifaximin (p=0.0019 vs.loperamide)               |
| 6  |                                   |            |                                |            | mg after       | 27.3 h for rifaximin-loperamide (p=0.0019 vs. loperamide)   |
| 7  |                                   |            |                                |            | each           | 69.0 h for loperamide                                       |
| 8  |                                   |            |                                |            | unformed       | Clinical cure: <sup>§</sup>                                 |
| 9  |                                   |            |                                |            | stool          | 77% for rifaximin   |
| 10 |                                   |            |                                |            |                | 75% for rifaximin-loperamide                                |
| 11 |                                   |            |                                |            | Rifaximin      | 58% for loperamide  |
| 12 |                                   |            |                                |            | and            | Odds ratio for rifaximin and rifaximin vs. loperamide=1.76  |
| 13 |                                   |            |                                |            | loperamide     | (95% CI: 1.26–4.70)   |
| 14 |                                   |            |                                |            | combination    |   |
| 15 |                                   |            |                                |            | therapy        | Mean number of unformed stools passed during illness:       |
| 16 |                                   |            |                                |            |                | 6.23 for rifaximin (p=0.004 vs. rifaximin-loperamide)       |
| 17 |                                   |            |                                |            |                | 3.99 for rifaximin-loperamide                               |
| 18 |                                   |            |                                |            |                | 6.72 for loperamide (p=0.002 vs. rifaximin-loperamide)      |
| 19 |                                   |            |                                |            |                |   |
| 20 |                                   |            |                                |            |                | Eradication rate of all pathogens:                          |
| 21 |                                   |            |                                |            |                | 76% for rifaximin   |
| 22 |                                   |            |                                |            |                | 68% for rifaximin-loperamide                                |
| 23 |                                   |            |                                |            |                | 67% for loperamide  |
| 24 |                                   |            |                                |            |                | Odds ratio for rifaximin vs. loperamide=1.56 (95% CI:       |
| 25 |                                   |            |                                |            |                | 0.84–2.89)  |
| 26 |                                   |            |                                |            |                | Odds ratio for rifaximin vs. rifaximin-loperamide=1.49 (95% |
| 27 |                                   |            |                                |            |                | CI: 0.80–2.76)  |
| 28 |                                   |            |                                |            |                |   |
| 29 |                                   |            |                                |            |                |   |
| 30 |                                   |            |                                |            |                |   |
| 31 |                                   |            |                                |            |                |   |
| 32 | <b>Prevention</b>                 |            |                                |            |                |   |
| 33 |                                   |            |                                |            |                |   |
| 34 | DuPont et al (2005) <sup>44</sup> | 219/Mexico | Randomized<br>controlled trial | 200 mg OD  | Placebo        | 2-week  |
| 35 |                                   |            |                                | 200 mg BID |                | prophylaxis   |
| 36 |                                   |            |                                | 200 mg TID |                | Occurrence of TD  |
| 37 |                                   |            |                                |            |                | 12.0% for rifaximin 200 mg OD (p<0.001 vs. placebo)         |
| 38 |                                   |            |                                |            |                | 19.2% for rifaximin 200 mg BID (p<0.001 vs. placebo)        |
| 39 |                                   |            |                                |            |                | 13.0% for rifaximin 200 mg TID (p<0.001 vs. placebo)        |
| 40 |                                   |            |                                |            |                | 14.7% for all rifaximin groups (p<0.001 vs. placebo)        |
| 41 |                                   |            |                                |            |                | 53.7% for placebo   |
| 42 |                                   |            |                                |            |                |   |
| 43 |                                   |            |                                |            |                |   |
| 44 |                                   |            |                                |            |                |   |
| 45 |                                   |            |                                |            |                |   |
| 46 |                                   |            |                                |            |                |   |
| 47 |                                   |            |                                |            |                |   |



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ETEC pathogens after treatment  
7.1% for rifaximin groups  
40.7% for placebo

|   |                                   |            |                                |           |         |                       |   |
|---|-----------------------------------|------------|--------------------------------|-----------|---------|-----------------------|---|
| 1<br>2<br>3<br>4<br>5<br>6<br>7<br>8<br>9<br>10<br>11<br>12<br>13<br>14<br>15<br>16<br>17<br>18<br>19<br>20<br>21<br>22<br>23<br>24<br>25<br>26<br>27<br>28<br>29<br>30<br>31<br>32<br>33<br>34<br>35<br>36<br>37<br>38<br>39<br>40<br>41<br>42<br>43<br>44<br>45<br>46<br>47 | DuPont et al (2006) <sup>45</sup> | 210/Mexico | Randomized<br>controlled trial | 600 mg OD | Placebo | 2-week<br>prophylaxis | Occurrence of TD<br>20.0% for rifaximin 600 mg OD (p<0.0001 vs. placebo)<br>48.0% for placebo |
|---|-----------------------------------|------------|--------------------------------|-----------|---------|-----------------------|---|

BID: twice daily; CI: confidence interval; ETEC: enterotoxigenic *Escherichia coli*; NS: non-significant; OD: once daily; TD: travellers' diarrhoea; TID, three times a day; TLUS: time to last unformed stool

\*defined as the passage of 50% or fewer stools during a 24-hour period versus baseline

†wellness; defined as 48 h with no unformed stools and no fever; or 24 h without watery stools, maximum 2 soft stools and no clinical symptoms

‡percentages for 400 mg rifaximin not provided

§defined as TLUS <120 h

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**Table 2. Adverse events with rifaximin and ciprofloxacin a randomized, double-blind, controlled trial in travellers' diarrhoea<sup>41</sup>**

|                   | Rifaximin 200 mg TID<br>(n=199) (%) | Ciprofloxacin 500<br>mg BID (n=100) (%) | Placebo BID<br>(n=100) (%) |
|-------------------|-------------------------------------|---|----------------------------|
| Any adverse event | 26.6                                | 24.0                                    | 25.0                       |
| Headache          | 8.0                                 | 5.0                                     | 9.0                        |
| Constipation      | 4.0                                 | 8.0                                     | 5.0                        |
| Flatulence        | 2.0                                 | 2.0                                     | 3.0                        |
| Rectal tenesmus   | 2.0                                 | 1.0                                     | 1.0                        |
| Dizziness         | 1.0                                 | 2.0                                     | 2.0                        |
| Vomiting          | 1.0                                 | 2.0                                     | 1.0                        |
| Nausea            | 0.5                                 | 2.0                                     | 1.0                        |