Author's response to reviews

Title: Inconvenience due to travelers' diarrhea: a prospective follow-up study

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Author's response to reviews: see over
We thank the reviewers for their constructive comments. In the revised manuscript we have tried to answer the reviewers to best of our ability and we have changed the text accordingly.

Comments in black, response in blue, changes in red

Reviewer's report
Title: Inconvenience due to travelers' diarrhea: a prospective follow-up study
Version: 1 Date: 21 May 2011
Reviewer: Robert Steffen
Reviewer's report:
Essentially this is a well-conceived and very well-presented report on the impact of TD. The authors use an unusual definition for TD, in most papers at least one additional symptom is a requirement — but they included also the 'classic TD' definition. The response rate of 52% is a bit low, but acceptable for such a study.

MAJOR COMPULSORY REVISIONS: none

MINOR ESSENTIAL REVISIONS
1) Do Dutch people understand the word 'tenesmus' or did you explain?
   Thank you for your comments. We asked two separate questions: 1. "Did you have abdominal cramps" ('Heeft u buikkrampen gehad?') and 2. "Did you have fecal urgency?" ('Heeft u hevige aandrang gehad?'). In the manuscript we used ‘tenesmus’ to describe the answers to the second question. On revision, we think that ‘fecal urgency’ is a more correct translation. Throughout the manuscript we have changed ‘tenesmus’ into ‘fecal urgency’.

2) Add definition on 'two weeks stay' — any two weeks, first two weeks?
   We have now specified that we mean ‘any two weeks stay’.

3) Add definition of one day incapacitation: #24 hours, or one 'daylight day'?
   We have now specified that we mean ‘one daylight day’.

4) Add definition on cumulative incidence
   By cumulative incidence we mean: the incident number of cases in relation to the size of the population ('cumulative incidence' or 'incidence proportion' or more traditionally 'attack rate'). We chose not to use the term 'attack rate', because it may be confused with a person-time incidence rate. However, the term 'cumulative incidence' can also be confusing because it also relates to another quantity. Throughout the manuscript we now have used the term 'incidence proportion' and have added a definition in the method section.

DISCRETIONARY REVISIONS
1) Strongly suggest in Background, line 11 to add the reference on the Expert Review on TREATMENT of TD by DuPont, particularly as you have ref. 11 the review on PREVENTION.

2) Staying in luxury hotels as risk factor is no real surprise (probably mentioned in Steffen et al.'Jamaica', JAMA 1999: our interpretation is that more elaborate food bears more risks, e.g. may also be arranged with fingers.
Thank you for your comment. In the JAMA article in 1999 you describe that tourists with full board (3 meals included) had a higher probability of diarrhea. It is probably fair to say that hotels offering full board are mostly classified as luxury hotels. We have added a sentence to the discussion: “Alternatively, staying in luxury hotels may be associated with consumption of more elaborate food which bears more risks [13].”

3) You might mention that increasingly there is concern about buying antibiotics abroad, many being false.
We have added a sentence to the introduction: “Another argument in favor of prescribing stand-by antibiotics for travelers is that there is an increasing concern about purchasing antibiotics abroad, many being false.”

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:
Yes, I have been or still am PI in studies on prevention and treatment of TD in India (Intercell, DrFalk Pharma) and I have received honoraria for lectures by Johnson&Johnson, Santarus, Salix.
Reviewer’s report
Title: Inconvenience due to travelers' diarrhea: a prospective follow-up study
Version: 1 Date: 10 June 2011
Reviewer: Mark Riddle
Reviewer’s report:
- Major Compulsory Revisions
1. Authors should report the statistical package used to conduct all analyses and describe the statistical significance level (alpha) used.
   We have added to the Methods section which statistical package was used: “All analyses were done using PASW Statistics, version 18.0, IBM®. Statistical significance was defined as a p-value <0.05.”

2. It would be helpful to describe the differences in demographic features between the total population, the population meeting inclusion criteria and those completing informed consent. This is important to help the reader ascertain the generalizability of the sample to the overall travel population from which they were drawn. Any differences should be commented on in the results and in the discussion in terms of the implications that such differences might have on the applicability of the results.
   Healthy adults who visited the travel clinic and intended to travel to the (sub)tropics were invited to take part by way of an informative letter. The letter was attached to a standard intake form that clients fill out before their appointment at the travel clinic. All who read the letter were asked to fill out an accompanying answer card that provided three options: (i) yes I want to participate, (ii) no I do not want to participate, (iii) I am not eligible to participate. Exclusion criteria were: travel duration of more than two months, use of systemic immunosuppressive medication, history of Inflammatory Bowel Disease or insulin dependent diabetes mellitus. 1000 Travelers read the informative letter of which 776 were eligible to participate. Of the 224 people who were not eligible to participate, travel duration in excess of two months was the most common exclusion criterion. 406 Travelers took part and 370 travelers refused to participate. We do not have demographic- or travel-related information regarding the 370 travelers who did not want to participate. Sixteen participants were lost to follow-up. Their demographic features were similar to those of the total population. We have added a sentence to the discussion: “Furthermore, the response rate was 50%. The demographic features of those who refused to participate may be different.”

3. For relative comparison it would be of interest to describe the health care utilization frequencies for travelers with non-travelers’ diarrhea related illness. Comparing such measures of disease severity compared to other common travel related illnesses are helpful.
   In the last part of the second questionnaire, we asked the travelers whether they had experienced any non-travelers’ diarrhea related illness and if so to specify their illness. We did not inquire about severity or health care utilization frequencies for these illnesses.

4. Recommend statistically evaluating TD illness characteristics that had an affect of the objective degree of inconvenience. (Table 3)
   As recommended by the reviewer we have added a logistic regression model evaluating which symptoms best predicted incapacitation due to travelers’ diarrhea. “The following symptoms independently increased the odds of incapacitation due to TD: stool frequency, nausea and fever (Table 4).”
5. In design of the study, a unique question was asked to the subject before travel and after travel in regards to a hypothetical scenario of a travelers’ diarrhea illness and the subject’s assessment of the impact of such illness. Interestingly, subjects who contracted TD during their travel stated the impact of future TD during travel would be lesser compared to those that did not experience TD during travel. Surprisingly this was also true for those who had to alter their plans or were forced to stay in doors. On the face of it, this calls into the validity of the question in its intended measurement. Particularly, among those who had to alter their plans or stay indoors due to illness, this would be. Perhaps it could be understood in the context of the individual having experienced such a disease, is less apprehensive. Sort of a parallel would be how nervous one might be when they first go to the dentist, but having been to the dentist, future trips, while as uncomfortable, would not seem so bad. While the authors attempted to evaluate perceptions of impact, such efforts should be secondary to those objective measures such as change in activities, having to seek care, or missing important parts of their itinerary. Subjective assessments of inconvenience are just that, and can introduce problems when looking at them as primary outcomes. Would recommend that the authors explore more in depth the validity and value of such an assessment and how this fits into context of the objective data on impact. I believe the authors could offer further though and explanation for the findings beyond, “...TD is less of a nuisance than one might expect.”

Thank you for your comment. Travelers who did not experience TD were very consistent in their pre- and post-travel answer regarding the perception of TD. This shows that the question as such is valid. Subjects who contracted TD during their travel stated the impact of future TD during travel would be lesser compared to those that did not experience TD during travel. The referee is correct in pointing out that it could mean that people are less apprehensive about TD once they have experienced it. Although we had expected such a finding for those with mild TD we did not expect this for those who had more severe and incapacitating TD. We have added a sentence to add nuance to the discussion. “Although this finding may simply mean that travelers are less apprehensive about problems they have faced before, it suggests that TD is less of a nuisance than travelers expect beforehand.”

6. The first statement in the discussion is that conventional definitions of TD include a spectrum of illness that is of a mild nature and does not warrant treatment or vaccination efforts. This statement is not well substantiated and is dismissive of a large body of research that has described both the individual health, economic and societal impact of such illnesses based on the current TD definitions used. The authors should spend more effort substantiating such an assertion or remove such a statement. It is particularly of concern

On this point we have to disagree with the reviewer. The definition of ‘classic TD’ we have used and the incidence proportion (i.e. attack rate) of TD as well as the magnitude of the objective impact of TD we have found in our study is similar to that reported in other studies. This means that the severity of TD in our population was very similar to that in most other studies. The finding that a large proportion of cases of TD was objectively mild in our study (i.e. mild symptoms, no incapacitation), is also true for many other studies. The main point we make is that the use of well-established definitions of TD leads to a loss of nuance. The incidence proportion of TD is often simply stated as being around 40%. Vaccination or stand-by antibiotic prescription is probably of limited value for mild cases of TD which make up a sizeable proportion of the 40%. This has important implications. It leads to an overestimation of the target population for such interventions, and an underestimation of
the benefit of such interventions for objectively severe (‘real’) TD.

7. No mention of the potential impact of the sample population and generalizability to the results is discussed. This is a major limitation to this study given that 39% of travelers from this clinic were used to base the results and conclusions of this study. Generalizability is a significant concern and results need to be put in context of such with appropriate caveats.

We like to point out that the conclusions of this study were based on the results of 390 of 776 eligible travelers (50%) and that the response rate of those who consented to participate was 96% (390/406); 224 travelers did not meet the inclusion criteria. We have added a sentence to the discussion in the paragraph on generalizability: “Furthermore, the response rate was 50%. The demographic features of those who refused to participate may be different.”

- Minor Essential Revisions
  1. There are issues with spelling, punctuation and grammar throughout. Though relatively minor, they are distracting none-the-less and should be corrected. Too numerous to enumerate here.

We have corrected a number of errors and now use US-English throughout the manuscript.

2. Drop Table 4.

We have dropped table 4 as suggested by the reviewer.

- Discretionary Revisions
  None.

What next?

We suggest that a future study should investigate to what extent routine stand-by antibiotic prescription impacts on the subjective and objective degree of inconvenience due to TD as well as the incidence of chronic gastro-intestinal complaints. This could be done by randomizing a similar group of travelers at the pre-travel consult, either to receive a stand-by antibiotic prescription or not.

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- Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest

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- An article whose findings are important to those with closely related research interests

Quality of written English

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- Needs some language corrections before being published

Statistical review

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- No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests

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I declare that I have no competing interests’ below.

Open peer review

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Submission of this report is taken as confirmation that you are happy for your
signed report to be posted on the BMC Infectious Diseases website as part of the pre-publication history of this article.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests' below.
Reviewer's report
Title: Inconvenience due to travelers' diarrhea: a prospective follow-up study
Version: 1 Date: 7 June 2011
Reviewer: Blaise Genton
Reviewer's report:
This paper addresses an important and yet fairly unexplored issue which is the degree of inconvenience of TD. This paper is original and important in terms of shaping appropriate pre-travel recommendation for prevention and treatment of TD. The methodology is appropriate, the results clearly stated and the interpretation correct. The results on incidence and risk factors concur with previous studies on the topic which confirms the generalization of the findings. It is a very interesting perspective that contrasts with usual statement form experts, mainly from the USA, that are poorly evidence-based in terms of real-life conditions.
All 9 questions asked to the reviewers by BMC when reviewing the work can be answered by Yes.
There is no major compulsory revision to perform.

There are some minor issues to tackle during revision:

Abstract:
- Add denominator ‘390/776 eligible’ travelers
We have added the denominator ‘390 of 776 eligible travelers’.

- The last sentence is vague and should be more focused. The preventive measures (in terms of advice) should always be given to the travelers. The terms ‘therapeutic measures’ are too vague and should be changed for more precision such as ‘stand-by antibiotic prescription’ since this is the relevant output of this study.
We have changed the sentence as suggested. “We suggest that a future study should investigate to what extent routine stand-by antibiotic prescription impacts on the subjective and objective degree of inconvenience due to TD as well as the incidence of chronic gastrointestinal complaints. This could be done by randomizing a similar group of travelers at the pre-travel consult, either to receive a stand-by antibiotic prescription or not.”

Background:
- Add a sentence that most of the studies were efficacy studies made in selected populations and selected destinations.
Thank you for your suggestion. We struggled to find an appropriate place to add this sentence. Although it is a valid point which may limit the generalizability of efficacy studies, it does fit well into the introduction of this study.

Methodology:
- page 7 end of first paragraph: replace ‘illnesses’ with ‘health problems’ and put all of them in plurals.
We have changed the sentence as suggested. “102 travelers (102/390; 26%) reported non-travelers’ diarrhea related health problems:”

Discussion:
- Before last line of page 9: Which activities have been cancelled? This is an
interesting finding to report. Participants provided narrative answers. It is difficult to categorize and report these answers in the manuscript. 53 travelers were incapacitated due to TD. This is what they reported:

- Activities had to be in the vicinity of a toilet.
- Altered travel plans, took it easy
- Cancelled a boat trip
- Cancelled part of programmed activities and refrained from eating for one day.
- Cancelled work for five days
- Cancelled work, remained in bed for three days
- Could not travel to the next hotel, delayed plans
- Delayed an excursion
- Early night (n=2)
- Less excursions, stayed in vicinity of hotel
- Missed one week of study.
- Reduced busy schedule
- Remained at hotel for one day, participated in a tour the next day, fainted during the tour.
- Remained at hotel near to toilet
- Remained at or near accommodation (n=2)
- Remained in bed (n=7)
- Remained indoors (n=10)
- Remained indoors for one day and cut short a hiking trip the next day
- Remained indoors. Returned to the hotel one day earlier than planned
- Shorter hikes
- Skipped a few activities
- Skipped dinner and evening program
- Skipped dinner, had an early night
- Skipped excursion (n=4)
- Skipped shopping for 2 days and swimming for 3 days
- Took it easy (n=8)

- There should be more emphasis on the implications of the study findings in terms of appropriateness of stand-by antibiotic prescription.

Thank you for your comment. As we discuss, no studies have assessed to what extent early antibiotic treatment significantly impacts on the subjective and objective (i.e. incapacitation) degree of inconvenience due to TD. Is the well-established reduction in the severity and duration of diarrhea clinically relevant? This is an important question, but one that we cannot answer with the data. This study was designed to measure the degree of inconvenience due to TD. We cannot conclude whether routine stand-by antibiotic prescription does or does not reduce morbidity in a relevant manner. The main point we make is that the use of well-established definitions of TD leads to a loss of nuance. The incidence proportion of TD is often simply stated as being around 40%. Vaccination or stand-by antibiotic prescription is probably of limited value for mild cases of TD which make up a sizeable proportion of the 40%. This has important implications. It leads to an overestimation of the target population for such interventions, and possibly an underestimation of the benefit of such interventions for objectively severe ('real') TD.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:
I declare that I have no competing interests