Traveling hosts and pathogens; Epidemiology of travel-related infections
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Diarrhea among long-term travelers: high attack rates and highest incidence in the beginning of travel.

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Diarrhea among long-term travelers: high attack rates and highest incidence in the beginning of travel.
Abstract

Background
We estimated the attack and incidence rate (AR and IR) of first and multiple episodes of travelers’ diarrhea (TD), and examined TD risk factors, symptoms and (self)treatment.

Methods
A mono-center prospective study was performed among immunocompetent Dutch long-term travelers 18 years and older. Participants kept a weekly travel diary, recording itinerary, gastrointestinal symptoms, physician visits during a diarrheal episode, and (self)treatment.

Results
Of 592 travelers, TD AR was 83%, IR for first episodes 1.5/100 travel days. In total, 1146 episodes were recorded. Risk factors for a first episode included: travel to Asia, female sex, younger age, holiday as travel purpose. Risk factors for having multiple episodes included: female sex, younger age, travel to Asia. IR of first TD episodes significantly decreased from 1.7 to 0.8 and 0.4, and the mean IR for all episodes significantly decreased from 1.5 to 1.0, to 0.7 episodes/100 travel days in the 1st, 2nd and 3rd quarter. Of first episodes 18% was defined as ‘febrile/dysenteric’, of subsequent episodes 17%. Antibiotic treatment was obtained for 119 episodes.

Conclusion
Most long-term travelers acquire TD at least once: typically a self-limiting, ‘watery’ disease without requiring antibiotic treatment. First quarter of travel showed the highest quarterly TD IR.
Background

Travelers from industrialized regions going to developing countries frequently report health problems, of which travelers’ diarrhea (TD) is the most common infectious disease (1). TD therefore remains an important travel-associated disease among the approximately 80 million travelers who annually travel from industrialized to developing countries (2). If TD affects 20-60% (3-7) of these 80 million travelers, an estimated 16-48 million persons will experience TD every year.

Numerous studies have assessed TD among short-term travelers (travel <13 weeks) with attack rates varying from 20-60% (3-7), and also demonstrated that around 90% of TD episodes occur within the first two weeks of travel (4;8). Little is known about TD among long-term travelers (travel ≥13weeks). A few studies assessed health risks among expatriates, Peace Corps Volunteers, and military personnel, and showed longer travel duration to be associated with increased or persistent health risks, including travelers’ diarrhea (9-12). This was also found in a retrospective study in 2002 among Israeli travelers (mean duration of travel 14.7 weeks) (13). Another retrospective study in 2005 among long-term travelers (travel >2 months) to India showed a relatively high TD attack rate of 83% (14). In addition, travelers with a travel duration of >6 months visiting GeoSentinel clinics upon return more frequently suffered from gastrointestinal diseases than short-term travelers, but sought treatment less often for ingestion transmitted diseases (15).

Although a persistent risk for diarrheal episodes exists for up to 2 years of travel (11), it is also assumed that longer travel duration is associated with developing immunity for TD (8-10). Immunity development is also suggested in a study regarding Panamanian tourists traveling to Mexico by Ryder et al (16). Different isolation rates of pathogens found in the study may be explained by varying immunity to enteropathogens endemic in Panama. They also found that higher socio-economic status was directly correlated to TD suggesting that higher socio-economic groups may be less exposed to enteric pathogens in their home country, and thus more susceptible to TD. Steffen et al demonstrated that visiting a tropical country in the 6 months prior to a trip, protected against TD during that trip (17), and Cobelens et al even found travelers with a history of travel >12 months to have a reduced risk for TD (18). Also, risk for diarrhea can change over time because of behavior changes, and travelers can acquire different infections over time (more bacterial infections with shorter travel duration).
versus more parasitic infections with longer duration) (19).
This prospective study among long-term travelers is, to our knowledge, the first of its kind. We estimated the attack rate and incidence rate of first and subsequent TD episodes and studied the severity of episodes, (self) treatment, and risk factors for TD in a cohort of immunocompetent, long-term travelers to tropical and subtropical countries.

Methods

Study population
A mono-center prospective study was performed among persons attending the Public Health Service Amsterdam travel clinic from December 2008 to September 2011. All immunocompetent persons 18 years and older and of western ethnicity were eligible if they were planning to travel for 13-52 weeks to one or more (sub) tropical countries. These countries were categorized in regions and continents according to the definition of regions by the United Nations (20). Those who reported a history of functional gastrointestinal disorders were excluded. All participants were seen by a physician or nurse specialised in travel medicine. Based on Dutch national traveler’s health advice guidelines (21), they received oral and written information regarding the avoidance of travel-related diseases including diarrhea, such as having good personal hygiene and sanitary conditions and avoiding unsafe water and food. They were also advised to carry an antimotility agent and oral rehydration solution.
According to the guidelines, a cholera vaccine was not advised. Antibiotics are only prescribed as stand-by treatment for TD to those at increased risk and cannot be purchased without a prescription in the Netherlands. Thus, a prescription was not provided to this cohort of immunocompetent travelers.

Ethics Statement
Study protocol was approved by the Medical Ethics Committee of the Academic Medical Center Amsterdam (MEC 08/064). Participants were included after informed and written consent.
Survey methods

A standard questionnaire in Dutch or English was used to collect data before departure on socio-demographics, travel history, and purpose of travel (tourism, work, or education). Participants were given a digital thermometer (Huikeshoven Medical, Tiel, the Netherlands) and asked to take their temperature if they felt feverish. They were also asked to keep a structured travel diary, recording their itinerary, signs of disease such as gastrointestinal symptoms (fever, vomiting, diarrhea, and bloody or mucous stools and/or other symptoms as they occurred), physician visits during a diarrheal episode, and possible (self) treatment. To encompass incubation periods of diarrhea, participants made weekly diary entries from the first week of travel to 1 week after their return. Diaries were filled out on paper or digitally, and travelers received a weekly email as a reminder to do so. Travel duration was recorded as the total weeks spent in areas meeting the inclusion criteria. All participants were seen between 2 to 6 weeks after return; a registered nurse or physician then checked the diary in the presence of the participant. At that visit, participants received a gift voucher of 40€ for completing the study.

Definitions

TD was defined as the passage of three or more loose stools during a 24-hour period with or without additional symptoms (5;22). Participants reported diarrhea in the weekly diary when they had at least one day of TD in that week. A diarrheal episode was considered new when at least one week free of diarrhea between subsequent episodes was reported in the diary. Episodes were classified as either ‘watery’ (without fever and/or bloody or mucous stools) or ‘febrile/dysentery’ (TD with self reported bloody or mucous stools and/or symptoms of fever). Fever was recorded if the temperature was 38°C or higher (confirmed by thermometer) during a diarrheal episode.

Data analysis

Data analysis was performed with SPSS version 19.0.0.1 (2010, IBM, Somers, USA) and Stata statistical software, version 11 (Statacorp, College Station, USA). Variables were summarised categorically in proportions, or by median and interquartile range (IQR). Travel destination was treated as a variable with three categories. Attack rates (AR) were calculated by dividing the number of persons reporting one or more TD episodes by the total number of
persons at risk. As follow up time of individuals can be different, we also calculated incidence rates per 100 travel days of first episodes by dividing the number of first episodes by the total number of travel days in which participants were at risk for a first episode. Crude incidence rates for multiple episodes were calculated by dividing the total number of episodes by the total person-days of travel. Univariable and multivariable Poisson regression models with the logarithm of person-days-of-travel as offset value, were used to examine the effect of covariates (including gender, age, travel purpose, destination, and history of travel to a developing country) on the number of TD episodes. In the multivariable model, a backward stepwise approach was chosen to ensure inclusion of predictors involved in suppressor effects. Outcomes were expressed as incidence rate ratios (IRRs) with 95% confidence intervals. A p-value < 0.05 was considered statistically significant. To estimate variation over time in both the incidence of first episode of TD as well as the mean incidence of TD episodes per 100 travel days, we examined 12-weekly (henceforth quarterly) consecutive incidence rates in travelers.

Results

Study population

Between December 2008 and September 2011 682 subjects who intended to travel between 13-52 weeks to (sub) tropical countries provided informed consent. Of these, 80 (12%) were excluded upon completion of the study: 42 had their travel arrangements changed, and 38 were lost to follow-up. For this study we excluded another 10 subjects with pre-existing functional gastrointestinal disorders. The remaining 592 formed the study population (Table 1). The median age was 25 years (Interquartile range [IQR] 23-30); 26 for men, 25 for women). The majority were tourists traveling for holiday (386, 65%); 35% traveled for work, training, or study. The median travel duration was 20 weeks (IQR 16-25). The most frequently visited continent was Asia (44%); 37% traveled to Latin America and 19% to Africa. Most of the 592 travelers had visited subtropical and tropical countries before (465, 79%).
Table 1: Characteristics of a prospective cohort of 592 long-term travelers from the Netherlands to (sub) tropical countries, December 2008 - September 2012

<table>
<thead>
<tr>
<th>Total</th>
<th>592</th>
</tr>
</thead>
</table>

**Sex**
- Male: 211 (36%)
- Female: 381 (64%)

**Age, years, median**
- 25 (23-30)

**Age group, years**
- 18-30: 443 (75%)
- 30-46: 124 (21%)
- >46: 25 (4%)

**Purpose of travel**
- Holiday: 386 (65%)
- Work, training or study: 206 (35%)

**Travel duration, weeks, median**
- 20 (16-25)

**Travel duration, weeks in quarters**
- 12: 9 (0.8%)
- 13-24: 742 (65%)
- 25-36: 276 (24%)
- ≥37: 119 (10%)

**Previous travel to a developing country**
- Never: 127 (21%)
- Yes: 465 (79%)

**Previous travel to a developing country, continents**
- Never: 127 (21%)
- 1: 221 (37%)
- 2: 151 (26%)
- 3: 93 (16%)

**Primary destination**
- Asia and Oceania: 262 (44%)
- Latin America: 220 (37%)
- Africa: 110 (19%)

**Number of countries visited**
- 1 country only: 106 (18%)
- 2 or 3 countries: 145 (24%)
- 4 or 5 countries: 146 (25%)
- 6 or more countries: 195 (33%)

* Interquartile range between brackets
First TD episodes

Of all 592 travelers, 491 (Attack rate (AR) 83%, 95% CI 80-86%) experienced one or more diarrheal episodes (Table 2). The overall incidence rate (IR) for a first TD episode was 1.5 per 100 travel days (95% CI 1.3 - 1.6). Both the attack rate and the incidence rate (IR) for the first episode were highest among travelers to Asia (AR: 87%; IR: 1.9 per 100 travel days [95% CI 1.7 - 2.1]). Independent determinants for a first TD episode included: travel to Asia (Latin America reference), female sex, younger age, and holiday as a travel purpose. Of first episodes, 101 out of 491 (21%) started within the first two travel weeks and 266 (54%) started in the first 5 weeks. The incidence rate of first TD episodes decreased from 1.7 to 0.8 and 0.4 per 100 travel days in the 1st, 2nd and 3rd quarters respectively (Figure 1). No significant differences in traveler characteristics were found over the 12-weekly consecutive quarters.
Table 2: Attack rates, person-time incidence rates and determinants of first TD episodes in a prospective cohort of 592 travelers from the Netherlands to (sub)tropical countries, December 2008 - September 2012

<table>
<thead>
<tr>
<th></th>
<th>Attack rate</th>
<th>Person-days of travel</th>
<th>Incidence rate per 100 travel days (95% CI)</th>
<th>Incidence rate ratio, univariable (95% CI)</th>
<th>p value</th>
<th>Incidence rate ratio, multivariable (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>592</td>
<td>491 (83%)</td>
<td>33678.5</td>
<td>1.5 (1.3 - 1.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>211</td>
<td>168 (80%)</td>
<td>14231</td>
<td>1.2 (1.0 - 1.4)</td>
<td>1.00</td>
<td>0.003</td>
<td>0.028</td>
</tr>
<tr>
<td>Female</td>
<td>381</td>
<td>323 (85%)</td>
<td>19447.5</td>
<td>1.7 (1.5 - 1.9)</td>
<td>1.4 (1.1 - 1.6)</td>
<td>1.3 (1.0 - 1.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.97 (0.95 - 0.98)</td>
<td>&lt;0.001</td>
<td>0.97 (0.95 - 0.98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Purpose of travel</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Holiday</td>
<td>386</td>
<td>330 (85%)</td>
<td>21427</td>
<td>1.5 (1.4 - 1.7)</td>
<td>1.00</td>
<td>0.192</td>
<td>1.00</td>
</tr>
<tr>
<td>Work, training or study</td>
<td>206</td>
<td>161 (78%)</td>
<td>12251.5</td>
<td>1.3 (1.1 - 1.5)</td>
<td>0.9 (0.7 - 1.1)</td>
<td>0.8 (0.6 - 0.99)</td>
<td></td>
</tr>
<tr>
<td><strong>Previous travel to a developing country</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>127</td>
<td>108 (85%)</td>
<td>6519</td>
<td>1.7 (1.4 - 2.0)</td>
<td>1.00</td>
<td>0.202</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>465</td>
<td>383 (82%)</td>
<td>27159.5</td>
<td>1.4 (1.3 - 1.6)</td>
<td>0.9 (0.7 - 1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary destination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>261</td>
<td>228 (87%)</td>
<td>12107</td>
<td>1.9 (1.7 - 2.1)</td>
<td>1.6 (1.3 - 2.1)</td>
<td>1.5 (1.2 - 1.9)</td>
<td></td>
</tr>
<tr>
<td>Latin America</td>
<td>220</td>
<td>174 (79%)</td>
<td>15093</td>
<td>1.2 (1.0 - 1.3)</td>
<td>1.00</td>
<td>&lt;0.001</td>
<td>1.00</td>
</tr>
<tr>
<td>Africa</td>
<td>110</td>
<td>88 (80%)</td>
<td>6495</td>
<td>1.4 (1.1 - 1.7)</td>
<td>1.2 (0.8 - 1.6)</td>
<td>1.3 (0.9 - 1.8)</td>
<td></td>
</tr>
</tbody>
</table>

* CI, Confidence interval

b The geographical continent with the lowest TD attack rate was chosen as the reference category
**Figure 1:** Incidence of first episode of diarrhea per traveler, per quarter

<table>
<thead>
<tr>
<th>Travel quarter (weeks of travel)</th>
<th>qr1</th>
<th>qr2</th>
<th>qr3</th>
<th>qr4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Travelers remaining (N)</td>
<td>592</td>
<td>165</td>
<td>29</td>
<td>7</td>
</tr>
<tr>
<td>Person days of travel (N*t)</td>
<td>24913</td>
<td>7259</td>
<td>1064</td>
<td>287</td>
</tr>
<tr>
<td>First diarrheal episodes during quarter (n)</td>
<td>425</td>
<td>60</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Incidence per 100 travel days (n/(N*t))</td>
<td>1.71</td>
<td>0.83</td>
<td>0.38</td>
<td>0.70</td>
</tr>
<tr>
<td>95% CI (lower)</td>
<td>1.55</td>
<td>0.64</td>
<td>0.12</td>
<td>0.12</td>
</tr>
<tr>
<td>95% CI (upper)</td>
<td>1.87</td>
<td>1.02</td>
<td>0.91</td>
<td>2.30</td>
</tr>
</tbody>
</table>
Multiple TD episodes

A total of 1146 episodes were reported by 491 travelers. Of all 592 travelers, 169 (29%) reported only 1 episode; 145 (25%) 2 episodes, 90 (15%) 3 episodes, 52 (9%) 4 episodes, and 35 (6%) reported 5 or more episodes. Independent determinants for having multiple TD episodes included: female sex, younger age, and travel to Asia (Latin America reference) (Table 3). Most of the subsequent episodes (261 out of 655, 40%) started in the first 12 weeks of travel and all subsequent episodes started within a median duration of 3 weeks (IQR 2-6) after the preceding episode. The mean incidence of all TD episodes decreased from 1.5 to 1.0, to 0.7 episodes/100 travel days in the 1st, 2nd and 3rd quarters respectively; the proportion who were diarrhea free increased through the 1st (28%), 2nd (61%) and 3rd quarter (79%) and the proportion reporting multiple episodes decreased (Figure 2). No significant differences in traveler characteristics were found over the 12-weekly consecutive quarters. In the final quarter, the number of travelers remaining was small and confidence intervals were too wide to comment.
Table 3: Crude incidence rates and determinants of multiple TD episodes in a prospective cohort of 592 travelers from the Netherlands to (sub) tropical countries, December 2008 - September 2012

<table>
<thead>
<tr>
<th></th>
<th>Persondays of travel&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Crude incidence rate per 100 travel days (95% CI)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Crude incidence rate ratio, univariable (95% CI)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>p value</th>
<th>Crude incidence rate ratio, multivariable (95% CI)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>1146</td>
<td>90069</td>
<td>1.3 (1.2 - 1.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>368</td>
<td>33544</td>
<td>1.1 (1.0 - 1.2)</td>
<td>1.00</td>
<td>0.002</td>
<td>1.00</td>
</tr>
<tr>
<td>Female</td>
<td>778</td>
<td>56525</td>
<td>1.4 (1.3 - 1.5)</td>
<td>1.3 (1.1 - 1.4)</td>
<td>1.2 (1.0 - 1.4)</td>
<td>1.2 (1.0 - 1.4)</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td>0.98 (0.97 - 0.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Purpose of travel</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Holiday</td>
<td>735</td>
<td>57477</td>
<td>1.3 (1.2 - 1.4)</td>
<td>1.00</td>
<td>0.846</td>
<td>1.00</td>
</tr>
<tr>
<td>Work, training or study</td>
<td>411</td>
<td>32592</td>
<td>1.3 (1.1 - 1.4)</td>
<td>1.0 (0.9 - 1.1)</td>
<td>0.9 (0.8 - 1.1)</td>
<td>0.9 (0.8 - 1.1)</td>
</tr>
<tr>
<td>Previous travel to a developing country</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>248</td>
<td>17514</td>
<td>1.4 (1.3 - 1.6)</td>
<td>1.00</td>
<td>0.077</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>898</td>
<td>72555</td>
<td>1.2 (1.2 - 1.3)</td>
<td>0.9 (0.8 - 1.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary destination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>539</td>
<td>37989</td>
<td>1.4 (1.3 - 1.5)</td>
<td>1.2 (1.1 - 1.4)</td>
<td>1.2 (1.1 - 1.4)</td>
<td>1.2 (1.1 - 1.4)</td>
</tr>
<tr>
<td>Latin America</td>
<td>397</td>
<td>34650</td>
<td>1.2 (1.0 - 1.3)</td>
<td>1.00</td>
<td>0.012</td>
<td>1.00</td>
</tr>
<tr>
<td>Africa</td>
<td>210</td>
<td>17289</td>
<td>1.2 (1.1 - 1.4)</td>
<td>1.1 (0.9 - 1.3)</td>
<td>1.1 (0.9 - 1.4)</td>
<td>1.1 (0.9 - 1.4)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Traveler had a median of 2 episodes (range 0 – 10). Diarrheal episodes are the total number of episodes in each variable category.

<sup>b</sup> Those who had zero diarrheal episodes contribute to the denominator and are accounted for in the analysis.

<sup>c</sup> CI, Confidence interval.
Figure 2: Mean incidence of all diarrheal episodes in travelers, per quarter

<table>
<thead>
<tr>
<th>Quarter no. (q)</th>
<th>q1</th>
<th>q2</th>
<th>q3</th>
<th>q4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week no.</td>
<td>1-12</td>
<td>13-24</td>
<td>25-36</td>
<td>37</td>
</tr>
<tr>
<td>Travelers remaining (N)</td>
<td>592</td>
<td>586</td>
<td>174</td>
<td>40</td>
</tr>
<tr>
<td>Person days of travel (N)*</td>
<td>48728</td>
<td>30534</td>
<td>6853</td>
<td>2681</td>
</tr>
<tr>
<td>Diarrheal episodes during quarter (n)</td>
<td>761</td>
<td>305</td>
<td>46</td>
<td>32</td>
</tr>
<tr>
<td>Mean incidence per 100 travel days (n/N)*</td>
<td>1.53</td>
<td>1.00</td>
<td>0.70</td>
<td>1.19</td>
</tr>
<tr>
<td>95% CI (lower)</td>
<td>1.45</td>
<td>0.89</td>
<td>0.52</td>
<td>0.83</td>
</tr>
<tr>
<td>95% CI (upper)</td>
<td>1.64</td>
<td>1.12</td>
<td>0.92</td>
<td>1.67</td>
</tr>
<tr>
<td>% Diarrhea free per quarter</td>
<td>28.2</td>
<td>60.6</td>
<td>79.3</td>
<td>47.5</td>
</tr>
<tr>
<td>% with multiple episodes (n2)</td>
<td>39.2</td>
<td>10.2</td>
<td>5.2</td>
<td>17.6</td>
</tr>
</tbody>
</table>
Symptoms
During first TD episodes, ‘watery’ TD occurred in 82% of travelers (402/491), and consequently the proportion of ‘febrile/dysenteric’ TD was 18% (89/491). Of the 89 travelers with ‘febrile/dysenteric’ TD, 72% (64/89) had fever: 52 travelers had fever without bloody and/or mucous stools and 12 travelers fever with bloody and/or mucous stools, with a median temperature of 38.5°C (IQR 38.2 – 39.0). The other 28% (25/89) travelers with ‘febrile/dysenteric’ TD had bloody and/or mucous stools without fever. Of all travelers with a first episode of TD, vomiting was reported by 20% (99/491) and nausea by 7% (32/491). During all subsequent TD episodes no differences in symptoms were found. Of all 1146 episodes, ‘watery’ TD occurred in 82% (943/1146), and ‘febrile/dysenteric’ in 18% (203/1146). The proportion of ‘febrile/dysenteric’ TD was similar among first and subsequent episodes (18% (89/491) and 17% (114/655) respectively (p=0.405).

Treatment
The following treatment was used in the 1146 episodes of TD monitored: no treatment for 611 episodes (53%), an antimotility agent such as loperamide for 375 episodes (33%), oral rehydration solution (ORS) in 285 episodes (25%), and antibiotic treatment in 119 episodes (10%). In 62 of these, a local physician prescribed antibiotics, in 57 they were bought over the counter (Table 4). In 89 of all 1146 (8%) diarrheal episodes, a physician was consulted (in 32/89 (36%) for first episodes and in 57/89 (64%) for subsequent episodes), including 56 with ‘febrile/dysenteric’ diarrhea. Of the 89 episodes in which a physician was consulted, 14 (16%, including 10 with febrile/dysenteric diarrhea) required a (short) hospital admission for a drip and treatment: 6 of these were first episodes (6/491) and 8 were subsequent episodes (8/655).
Table 4: Treatment for TD in a prospective cohort of 592 long-term travelers from the Netherlands to tropical countries, December 2008 - September 2012

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total episodes</th>
<th>1st episode</th>
<th>≥2 episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>watery</td>
<td>febrile/dysentery</td>
</tr>
<tr>
<td>Total</td>
<td>1146</td>
<td>402 (82%)</td>
<td>89 (18%)</td>
</tr>
<tr>
<td>No treatment</td>
<td>611</td>
<td>220 (55%)</td>
<td>30 (34%)</td>
</tr>
<tr>
<td>Antimotilic agents</td>
<td>375</td>
<td>128 (32%)</td>
<td>40 (45%)</td>
</tr>
<tr>
<td>ORS*</td>
<td>285</td>
<td>88 (22%)</td>
<td>36 (40%)</td>
</tr>
<tr>
<td>Antibiotic (over the counter)</td>
<td>57</td>
<td>14 (4%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Antibiotic (prescribed by a physician)</td>
<td>62</td>
<td>3 (1%)</td>
<td>17 (19%)</td>
</tr>
<tr>
<td>Visited local physician for diarrhea</td>
<td>89</td>
<td>8 (2%)</td>
<td>24 (27%)</td>
</tr>
</tbody>
</table>

*ORS, Oral Rehydration Solution
Discussion

In this prospective study among long-term travelers to (sub)tropical countries the attack rate (AR) of travelers’ diarrhea (TD) is high at 83%, with 66% reporting 2 or more episodes while traveling, and the incidence decreased with prolonged travel duration. Compared to short-term travelers (3-7), we found a higher attack rate, most likely due to longer travel duration and therefore longer exposure time. This suggests a persistent risk for TD, which was also suggested by a retrospective study among long-term travelers (mean duration 14.7 weeks) (13), a prospective surveillance study (11), a case-control study (10) among expatriates, and a prospective longitudinal study among Peace Corps Volunteers (9).

The overall incidence rate of 1.5 per 100 travel days (95% CI 1.3 - 1.6) for first TD episodes was lower compared to the IR of 2.49 per 100 travel days (95% CI 2.3 - 2.7) we found in a study among short-term travelers conducted in 2006-2007, or compared to the IR of 3.14 per 100 travel days (95% CI 2.86 - 3.43) observed among short-term travelers from Amsterdam almost 15 years ago (18). It is possible that the incidence of diarrhea among travelers is decreasing because hygienic standards in travel destinations are increasing with increasing prosperity (23). However, because of differences in study design, travelers’ characteristics, and differences in definitions of TD and TD episodes, these results are not directly comparable.

The duration of travel per traveler was variable, and individual travelers experienced between zero and 10 diarrheal episodes. Although we could not directly estimate the trend in incidence per traveler per week of travel, both the incidence rate for a first episode of TD and the mean quarterly incidence of all episodes decreased significantly between the first and second quarter, the proportion who were diarrhea free increased, and the proportion experiencing multiple episodes decreased. This gives the impression of a decrease in the incidence of TD episodes per traveler as their travel progresses, and could suggest the development of immunity for TD during travel, as in previous studies (8-10;16). This decrease could also be due to behavioral change by travelers, by change in kind of infection, or a combination of factors.

Independent determinants for having a first TD episode included: female sex, younger age, holiday as travel purpose, and visiting Asia, and all variables, except for travel purpose,
were also determinants for having multiple episodes. Sex differences in travel-associated
disease and diarrhea, independent of travel duration, have been reported previously (7;23),
but it is unclear if this difference can be explained by women being more susceptible to diar-
rhea, being more likely to report diarrhea, or by travel-related factors, such as different travel
behavior. The association between risk for TD and younger age groups has been reported
previously (4;8;10;13;17;18). Younger persons could have different risk behaviors (17). As the
median age of our cohort is 25 years (IQR 23-30), this could have contributed to the high AR
we found. Asia, and specifically the Indian subcontinent, appears to be the highest risk area.
This is consistent with studies among short-term travelers (4-7;18). The continental (and re-
gional) variations in AR and IR(R) may be due to differences in circulating pathogens (5) and
hygienic standards (24). Altogether, risk factors found for TD among travelers, regardless of
first or subsequent episodes, do not seem to differ by travel duration.

Of all 1146 TD episodes in our study, 203 (18%) were ‘febrile/dysenteric’. According to pre-
vious knowledge (5;7;8), most TD episodes, both first and subsequent episodes, were acute
watery and not invasive. We found no difference in accompanying symptoms of TD between
first and subsequent episodes.

Only in 5% of episodes (57/1146 TD episodes), antibiotics were bought over the counter
during travel, and for 5% (62/1146) were prescribed by local physicians. As our study sho-
wed an overall ‘watery’ course of TD, prescribing antibiotics before travel to all travelers for
the possible high number of diarrheal episodes is, in our opinion, unnecessary and potentially
harmful, as its use for a mild self-limiting disease may have side effects and may increase the
development of resistance of pathogens to antibiotics (25-27).

To our knowledge, this is the first prospective study conducted among long-term travelers.
Because of the prospective design we were able to estimate attack rates and incidence rates
and found a decreasing incidence of TD, at least in the earlier weeks of travel. A strength
of the diary entries is the minimization of recall bias. We asked participants for weekly diary
entries because we expected long-term travelers to better comply with weekly than daily
entries. The diary entries per week also have limitations: we did not ask the participants the
duration of the TD episode in days, nor the exact frequency of stools per 24hr other than
‘more than 3 per day’, which would have allowed us to make more detailed recurrent event
analyses. In addition, we did not ask for the degree of disability travelers experienced.
The absence of exact date of onset and duration of TD episodes and exposure time may
have resulted in an underestimation of the incidence of diarrheal episodes: what was ana-
lyzed as one episode could have been two short episodes in one week, and in estimating crude total incidence, we assumed that the traveler was exposed for their entire trip.

In conclusion, most long-term travelers acquire TD at least once. It is typically a self-limiting, ‘watery’ disease not requiring antibiotic treatment. The first quarter of travel showed the highest incidence for a first episode of TD as well as the highest mean quarterly incidence of all TD episodes.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
SB contributed to the acquisition of the data, analyzed the data and wrote the article. AvdH designed the study, contributed to the article and was guarantor. JW analyzed the data and contributed to the article. GS designed the study and contributed to the article. All authors read and approved the final manuscript.

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References


