Global Etiology of Travelers’ Diarrhea: Systematic Review from 1973 to the Present

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Abstract. Fifty-one published studies of travelers’ diarrhea (TD) were examined to look for regional differences in pathogens identified. Enterotoxigenic E. coli was detected in 1,678/5,518 (30.4%) of TD cases overall, with rates in Latin America/Caribbean (L. America), Africa, south Asia, and Southeast Asia of 1,109/3,302 (33.6%), 389/1,217 (31.2%), 153/499 (30.6%), and 36/500 (7.2%), respectively (P < 0.001). Other significantly regional differences were seen for enteropathogenic E. coli, diffusely adherent E. coli, Campylobacter, Shigella spp., Salmonella, Aeromonas spp., Plesiomonas, Vibrios, rotavirus, noroviruses, Giardia, and Entamoeba histolytica. The regional differences in pathogen identification identified will serve as a baseline for antimicrobial therapy recommendations and vaccines strategies.

INTRODUCTION

Travelers’ diarrhea (TD) is the most common illness of international travelers bound for developing regions of the world where substandard hygienic conditions exist. The average rate of TD among persons entering into the high-risk regions of Latin America, Southern Asia, and Africa from industrialized countries is 40%, a rate unchanged in >50 years.1–5 A potential key to developing a strategy for disease control and prevention is determination of cause of enteric illness. Until 1970, the etiology of TD was obscure.6 During a remarkable 2-year time period in the early 1970s, major advances in the microbiology of acute diarrhea occurred when enterotoxigenic Escherichia coli,7 Campylobacter,8 rotavirus,9 and Norwalk virus10 were identified as causes of human illness. Soon thereafter, it was shown that bacterial enteropathogens were the most common class of agents causing TD, with enterotoxigenic Escherichia coli (ETEC) being the most common etiologic agent.11 It was also shown that antibacterial drugs shortened the illness related to TD.12 In the modern era, vaccines are in development against ETEC to prevent TD.13,14

We review published studies on the cause of TD, carried out since the important bacterial and viral agents were identifiable. The aim of the review was to look at the etiology of TD by region of the developing world and to determine changes in frequency of enteropathogens causing TD over the three decades of study. The review was designed to provide baseline information that would allow identification of treatment and chemoprophylaxis strategies and to help determine the potential value of ETEC vaccines based on the frequency and geographic distribution of ETEC diarrhea within the larger group of TD.

MATERIALS AND METHODS

All studies on the etiology of TD listed by PubMed and Medline Ovid and published since 1973 were reviewed using the following key words: etiology of traveler’s diarrhea; travelers’ diarrhea; and acute diarrhea of travelers. Additionally, the extensive files maintained by the corresponding author were reviewed. The definition of TD was passage of one or more unformed stools in 24 hours with at least one sign or symptom of enteric infection, including fever, abdominal cramps or pain, nausea, vomiting, tenesmus, or fecal urgency. In most of the studies, enrollment criteria included passage of at least three unformed stools in 24 hours together with an enteric sign or symptom. The study divided the cases into geographic settings where the TD occurred including 1) Latin America and the Caribbean (L. America); 2) Africa; 3) South Asia; 4) Southeast Asia; and 5) multiple or unspecified developing regions (unspecified).

Inclusion criteria of the articles reviewed: 1) studies of the etiology of TD when microbiology methods seemed to be appropriate for the organism(s) under study; 2) when travelers were studied for multiple bouts of diarrhea, etiology information only for the first episode of illness was included; and 3) studies of TD where the duration of stay of travelers was 40 days or less.

During the review of published literature, the data extracted included country of origin of the travelers, the regions being visited, the year of data collection for the study, the age of the traveler, the number of study participants, the duration of stay, the number of persons acquiring TD, and identification of enteropathogens.

The statistical analyses were performed using StataCorp 2007 (Stata Statistical Software Release 10; StataCorp, College Station, TX). Regional differences for pathogens were compared using the Fisher exact test. We studied variation in ETEC isolation rate in each group over a period of time from 1970 to 2004 using two-way scatterplots. We tested correlation between ETEC and year of study in each group separately.

RESULTS

In 51 published studies between 1973 and 2008, 57 different groups of travelers were evaluated for etiology of diarrhea. In one study, four different travel groups were evaluated, and in four, two travel groups each were included. In Table 1, the various studies and references are identified by decade carried out. For studies bridging a time period (e.g., 1989–1990), they are included in the later time period (e.g., 1990–1999). In Table 1, the number of studies carried out and the number of subjects included per time period of review are provided.

The total population with TD included in this review was 30,884 persons studied in 57 separate travel groups. For L. America, there were 24 travel groups comprising 3,302
persons with TD studied over the years of the study. For Africa, the number of study groups was 10, with TD occurring in 1,217 persons with TD studied over the years of the study. For Africa, there were no studies carried out in the 2000s. For Africa or L. America.


evaluated developing regions, 13 study groups including 25,302 persons with TD provided information on enteropathogens. One of the studies to many but unspecified regions included 23,215 persons.15

Table 2 shows the combined study groups by major host country region and by pathogen identified in cases of TD. To be included in this analysis, the agent had to have been sought in the study population in at least one study. Significant differences in geographic occurrence of the pathogen under study are provided in Table 2. The identification rate was significantly different when comparing the three major geographic regions for all pathogens other than enteroinvasive E. coli (EIEC), enterohemorrhagic (Shiga toxin-producing) E. coli (EHEC), and Cryptosporidium (see Table 2 for P values).

The most common pathogen identified overall was ETEC, which was found in 1,678/5,518 (30.4%) of the subjects studied. ETEC was most frequently identified in travelers to L. America and Africa, found in 1,109 of 3,302 (33.6%) and 380 of 1,217 (31.2%) subjects in the two locations, respectively. ETEC was found in 153/499 (30.6%) in south Asia and in 36/500 (7.2%) in Southeast Asia (P < 0.001; see Table 2 and Figure 1).

EAEAC was the second most commonly identified enteropathogen found in 202/1,060 (19.0%) of the subjects studied. EAEAC was isolated in 166 of 689 (24.1%) travelers with diarrhea while traveling in L. America. EAEAC was identified in 33 of 206 (16.0%) of travelers with diarrhea developing while traveling in South Asia. EAEAC was relatively infrequently encountered in subjects with TD acquired in Africa; it was found in 3 of 165 (1.8%; P < 0.001). Campylobacter was more often found in Asia compared with L. America and Africa. Shigella spp. were most commonly found in TD cases occurring in Africa compared with Asia, whereas Salmonella spp. were more often identified in TD cases occurring in Asia than in Africa or L. America. Aeromonas spp. were more often found in Asia and Africa than L. America, and Plesiomonas spp. were more often found in Asia than the other study areas. Vibrios (non-cholera and cholera) were more common also in Asia than in the other study groups. Noroviruses and rotavirus were

Table 1
Summary of 51 published studies providing data on the etiology of TD in 30,984 persons as part of 57 study populations by region visited and decade of study, 1973–2004

<table>
<thead>
<tr>
<th>Region</th>
<th>Year of study</th>
<th>Number study groups/number subjects with TD</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>1973–1979</td>
<td>3/40</td>
<td>35,57,58</td>
</tr>
<tr>
<td></td>
<td>1990–1999</td>
<td>3/700</td>
<td>37,54,62</td>
</tr>
<tr>
<td></td>
<td>2000–2004</td>
<td>None</td>
<td>NA</td>
</tr>
<tr>
<td>South Asia</td>
<td>1973–1979</td>
<td>None</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>1980–1989</td>
<td>None</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>1990–1999</td>
<td>1/293</td>
<td>24,37,54,63–65</td>
</tr>
<tr>
<td></td>
<td>2000–2004</td>
<td>1/206</td>
<td>56</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>1973–1979</td>
<td>2/200</td>
<td>66,67</td>
</tr>
<tr>
<td></td>
<td>1980–1989</td>
<td>2/26</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>1990–1999</td>
<td>5/438</td>
<td>24,37,54,63–65</td>
</tr>
<tr>
<td></td>
<td>2000–2004</td>
<td>None</td>
<td>NA</td>
</tr>
<tr>
<td>Unspecified</td>
<td>1973–1979</td>
<td>2/36</td>
<td>69,70</td>
</tr>
<tr>
<td></td>
<td>2000–2004</td>
<td>1/863</td>
<td>78</td>
</tr>
</tbody>
</table>

Seven studies with overlapping decades were included in the later time period (e.g., 1989–1990 would be included in the time period 1990–1999).
more often found in L. America and Africa and less common in Asia. *Giardia* and *E. histolytica* were found more commonly in Asia than the other study groups.

In Figure 2 the percentage isolation of ETEC by year and region of study is provided in a scatterplot. A decreasing ETEC rate for TD cases was observed for travelers to L. America (negative correlation coefficient, 0.41; \( P = 0.036 \)) and Africa (negative correlation coefficient, 0.54; \( P = 0.10 \)) over the years of the study. A non-significant increasing percentage of ETEC-associated diarrhea was seen among the cases of TD occurring in South Asia (negative correlation coefficient, 0.55; \( P = 0.09 \)). Correlation testing showed a decreasing trend for *Shigella* identification rate (data not shown) during the years of the study in L. America (correlation coefficient = 0.46; \( P = 0.023 \)). All the non-ETEC, non-*Shigella* pathogens failed to show significant trends (increases or decreases) over the years of the study.

**DISCUSSION**

This systematic review summarized what is known about the geographic variation of enteropathogens as etiologic agents of TD. The studies have taken place in a limited number of regions of the developing world. Insufficient studies of the incidence of TD and the relative importance of specific enteropathogens among international travelers to various world regions are presently available.

ETEC was found to be the most common organism isolated in all geographic regions in the review. The various studies suggest that the percentage isolation of ETEC may be decreasing over the years of the study in L. America and Africa. The rate of ETEC infection seems to be high in South Asia (India), whereas limited studies suggest that it remains low in Southeast Asia.

Two ETEC vaccines are being developed for use as a preventive against TD. The first is inactivated whole cells of *Vibrio cholerae* strains (WC) combined with recombinant binding subunit of cholera toxin (Dukoral, Oxford, UK). The binding subunit of cholera toxin is closely related to the binding portion of the heat labile enterotoxin (LT) of ETEC. The vaccine is given in two oral doses, providing short-term protection against ETEC diarrhea.\(^{14,16}\) Dukoral is marketed in 50 countries including Canada and the European Union but not in the United States. The second vaccine being developed consists of purified LT that is administered transcutaneously as a patch, leading to brisk serum anti-IgG LT neutralizing antibodies\(^{17}\) and protection against moderate to severe ETEC diarrhea\(^{18}\) and clinically important TD.\(^{19}\) Immunoprophylaxis aimed at ETEC infection seems to be a viable way to reduce enteric infection, and LT preparations may provide protection against TD, beyond that caused by LT-producing ETEC strains.\(^{14,18}\) Based on this study, it would seem that an ETEC vaccine would have its greatest value for persons traveling to Latin America, Africa, and South Asia where ETEC is prevalent. Additional study is needed to determine the importance of ETEC in Southeast Asia.

Non-ETEC diarrhea-producing *E. coli* may be responsible for an important proportion of TD. Unfortunately they have been sought in a limited number of studies. From this study, EAEC strains seem to be important causes of TD worldwide. This group of heterogeneous pathogens\(^{20,21}\) have been found in all major regions of the world,\(^{22}\) although there has been limited study outside L. America. Enteropathogenic *E. coli* (EPEC) have been detected in subjects with TD in each of the five studies in which they were examined. Diarrhea caused by diffusely adherent *E. coli* (DAEC) were sought in four studies (Table 2) and found to be associated with illness. Additional studies with DAEC are needed.

**Campylobacter** was most commonly associated with TD occurring in Asia. Not only has *Campylobacter* been found to be important as a cause of TD occurring in Asia, but ciprofloxacin-resistant strains seem to be commonly encountered in Asia.\(^{23-25}\) Other enteropathogens that seem to be more common in Asia include Vibrios (cholera and non-cholera), *Giardia*, and *E. histolytica*. Previous studies have identified *Giardia* and *Cyclospora* in travelers and expatriates to Nepal.\(^{4,5}\)

A remaining problem in TD is the high percentage (40–50%) of pathogen-negative diarrhea, despite thorough microbiology evaluation. Antibacterial therapy has been shown in multiple studies to shorten the illness associated with pathogen-negative TD,\(^{12,26,27}\) suggesting that undetected bacterial enteropathogens are responsible for a large percentage of this illness. PCR-based detection methods have identified ETEC\(^{28-30}\) and other diarrhea-producing *E. coli* including DAEC\(^{30,31}\) in the undetected pathogen group when conventional methods of detection were used. Noroviruses have not been routinely sought in TD studies and clearly explain
a measure of this illness. More research is needed on the subject of etiology of pathogen-negative diarrhea.

The major limitation of this review is that the study depended on the existing published studies using different methods of organism detection and different definitions. Also, the review did not control for improving technologies for microbiological detection over the years of the study, limiting the validity of organism comparisons between regions. The methods of detection have steadily improved over the years of the study. Polymerase chain reaction–based methods used in more recent years have increased pathogen detection. However, the strength of the study is that a total review of published studies has not taken place in recent years.

This study confirms the importance of bacterial enteropathogens as causes of TD, explaining the remarkable effectiveness of antibiotic drugs in the prevention and therapy of TD.

We recommend more comprehensive studies of TD using the same diagnostic procedures in multiple geographic regions over the same time period as developed by Steffen and others during 1996–1998. This is likely to be a dynamic field requiring that improved methods of surveillance be developed.

Received October 3, 2008. Accepted for publication December 20, 2008.

Acknowledgment: The authors thank Judith Dunn, PhD, for providing statistical guidance.

Financial support: Discretionary funds from the University of Texas–Houston School of Public Health were used to support this study.

Disclaimer: The authors have no conflicts to declare.

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REFERENCES


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