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Original Article

A prospective study of travellers' diarrhoea: analysis of pathogen findings by destination in various (sub)tropical regions

T. Lääveri¹, K. Vilkmann^{1,2}, S.H. Pakkanen³, J. Kirveskari⁴, A. Kantele^{1,2,5,6,*}¹ Inflammation Center, Division of Infectious Diseases, Helsinki University Hospital, Finland and University of Helsinki, Finland² Aava Travel Clinic, Medical Centre Aava, Helsinki, Finland³ Department of Bacteriology and Immunology, University of Helsinki, Finland⁴ Department of Bacteriology, Helsinki University Hospital Laboratory (HUSLAB), Finland⁵ Cliniicum, University of Helsinki, Finland⁶ Unit of Infectious Diseases, Department of Medicine/Solna, Karolinska Institutet, Stockholm, Sweden

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ABSTRACT

Objectives: Eighty million travellers visiting (sub)tropical regions contract travellers' diarrhoea (TD) each year, yet prospective data comparing the prevalence of TD pathogens in various geographical regions are scarce. Our recent study using modern molecular methods found enteropathogenic (EPEC) and enteroaggregative (EAEC) *Escherichia coli* to be the most frequent pathogens, followed by enterotoxigenic *E. coli* (ETEC) and *Campylobacter*. We revisited our data to compare the findings by geographical region. **Methods:** A total of 459 prospectively recruited travellers provided stool samples and completed questionnaires before and after visiting destinations in various geographical regions. A multiplex quantitative real-time PCR assay was used to analyse *Salmonella*, *Yersinia*, *Campylobacter jejuni*/*Campylobacter coli*, *Shigella*, *Vibrio cholerae*, EPEC, EAEC, ETEC, enterohaemorrhagic *E. coli* and enteroinvasive *E. coli*.

Results: TD was contracted by 69% (316/459) of the subjects; EPEC and EAEC outnumbered ETEC and *Campylobacter* in all regions. Multiple pathogens were detected in 42% (133/316) of the samples. The proportions of all pathogens varied by region. The greatest differences were seen for *Campylobacter*: while relatively frequent in South Asia ($n = 11$; 20% of the 55 with TD during travel) and Southeast Asia (15/84, 15%), it was less common in East and West Africa (5/71, 7% and 1/57, 2%) and absent in South America and the Caribbean (0/40).

Conclusions: EPEC and EAEC outnumbered ETEC and *Campylobacter* everywhere, yet the proportions of pathogen findings varied by region, with ETEC and *Campylobacter* rates showing the greatest differences. The high frequency of multibacterial findings in many regions indicates a need for further investigation of the clinical role of each pathogen. **T. Lääveri, Clin Microbiol Infect 2017;•:1**

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Introduction

Travellers' diarrhoea (TD) accounts for more than 80 million cases each year [1]. It is not only the disease most commonly encountered by travellers to (sub)tropical destinations [2,3] but also the most common health complaint at posttravel consultations [2,4]. Bacterial pathogens are known to predominate as aetiologic agents. However, the pathogen remains unidentified in up to half of cases [5,6]. Over the past decade the field of TD research has experienced a renaissance, with new molecular methods covering a larger variety of pathogens than traditional approaches. However,

few data are available comparing the incidence of the various pathogens by geographical area.

Until recently, enterotoxigenic *Escherichia coli* (ETEC) has been reported to outnumber all other pathogens causing TD in most regions [5,6], with the exception of Southeast Asia (Thailand), where *Campylobacter* has been considered the primary pathogen [5–9]. Studies using modern molecular methods have decreased the proportion of unexplained TD cases to only 4% to 24% [10–12]. These investigations have also revealed diarrhoeagenic *E. coli* (DEC) to be even more prevalent than previously thought. The rates for enteropathogenic *E. coli* (EPEC) and enteroaggregative *E. coli* (EAEC) have been at least as high as those for ETEC even after visiting Central America [11,13], South Asia [10] or Africa [10,12,14], where earlier findings have been predominated by ETEC. Other bacterial pathogens such as *Shigella*,

* Corresponding author. A. Kantele, Inflammation Center, Division of Infectious Diseases, Helsinki University Hospital, POB 348, FIN-00029 HUS, Finland.
E-mail address: anu.kantele@hus.fi (A. Kantele).

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Salmonella spp., enteroinvasive and enterohaemorrhagic *E. coli* (EIEC and EHEC respectively), *Aeromonas* spp., *Plesiomonas shigelloides*, *Arcobacter* spp., enterotoxigenic *Bacteroides fragilis* and *Vibrio* spp. have been detected less frequently [5,6].

We found only a handful of reports providing data on TD pathogens by region in a single study using modern molecular methods. EPEC has only been covered in a few investigations. Moreover, EAEC prevalence data among travellers to Southeast Asia and East Africa remain virtually nonexistent.

In our prospective study of 459 Finnish travellers, we applied multiplex quantitative real-time PCR (qPCR) methodology to analysis of various TD pathogens by region, seeking to challenge the current understanding of regionally predominant pathogens.

Materials and methods

Study population and recruitment

The participants for this prospective study were initially enrolled at the Travel Clinic of Aava Medical Centre, Helsinki, Finland, over a 12-month period in 2009–2010 before their journey outside the Nordic countries for more than four nights. Of the 526 volunteers, 459 (63%) completed questionnaires and provided stool samples before and after travel (Supplementary Fig. S1). Ethical approval was obtained from the ethics committee of the department of medicine at Helsinki University Hospital. All study subjects provided written informed consent. We earlier reported the findings of resistant *Enterobacteriaceae* [15] and travel-related health problems [3] in the same volunteers. Recently we described the stool pathogens of 382 travellers who did not use antimicrobials [16].

Definition of TD

TD was defined according to World Health Organization criteria as passage of loose or liquid stools more frequently than is normal for the individual (<http://www.who.int/topics/diarrhoea/en/>). Severe TD was defined as six or more diarrhoeal stools per day, TD accompanied by fever or haemorrhagic stools, or TD requiring hospitalization.

Questionnaires

The pretravel questionnaire included demographic data and information on possible diarrhoeal symptoms at the time of the first faecal sample. The posttravel questionnaire assessed the travel itinerary, diarrhoeal and other symptoms, and medications during or immediately after travel.

Travel destinations

The countries visited were grouped into regions as modified from the United Nations classification: South Asia; Southeast Asia; East Asia; North Africa and Middle East; East Africa; West Africa (Western and Middle Africa); Southern Africa; Latin America (South and Central America and the Caribbean); and Europe, Australia and North America. The 37 travellers (8%) who visited more than one region were grouped by longest stay; 16 (43%) of these visited Europe or the United States on their way to the (sub)tropics. This report focuses on the five most popular destinations: South Asia, Southeast Asia, East Africa, West Africa and Latin America.

Collection and laboratory analysis of stool samples

Briefly, stool samples were collected before departure and from the first (or second) stool passed after returning home as swabs in

Copan M40 Transystem tubes (Copan Diagnostics, Brescia, Italy) and mailed in special boxes, reaching the laboratory within 1 to 3 days. Once the samples arrived, total nucleic acids were extracted using the standard semiautomated protocol of easyMAG (bio-Mérieux, Marcy l'Etoile, France). The analyses were carried out with a multiplex qPCR method [1] which covers the following pathogens: *Campylobacter jejuni* and *Campylobacter coli*, *Salmonella* spp., *Yersinia*, *Vibrio cholerae*, EPEC, EAEC, ETEC, EHEC and EIEC/*Shigella* spp. Here we focus on the findings of pathogens found to associate with ongoing TD symptoms discussed in our previous report (EPEC, EAEC, ETEC and *Campylobacter*) [16].

Statistical analysis

Statistical analyses were carried out by SPSS 22 (IBM SPSS, Chicago, IL, USA).

The chi-square test or binary logistic regression analysis was used to compare categorical variables when applicable. A binomial regression model was used to obtain profile likelihood confidence intervals (CIs) for the proportions of different pathogens in geographical regions; in cases when computation did not converge, asymptotic Wald CIs were used. Statistical significance was determined as either 95% CIs not overlapping, or ranging only either above or below 1.

Results

Demographic data and occurrence of TD

Background data on the travellers and their travels are shown in Supplementary Table S1. TD was reported by 316 travellers (69%). At the time of the posttravel stool sample, 143 (31%) reported having ongoing symptoms, 173 (38%) reported that symptoms had already resolved and 143 (31%) were asymptomatic through the entire journey. Seventy-two (16%) reported having taken antimicrobial medications during travel. TD was most common among those who visited South Asia (55/69, 80%), Southeast Asia (84/108, 79%) and East Africa (71/96, 74%), while 67% (57/85) of those who travelled to West Africa and 60% (24/40) to Latin America reported TD (Supplementary Table S2). There were no significant differences between regions in the severity of TD (severe vs. nonsevere TD, p 0.118; data not shown).

Pathogen findings in stool samples of all 459 travellers

Nineteen (4%) of 459 pretravel samples were positive for bacterial pathogens; only one subject with EPEC reported mild diarrhoeal symptoms. An analysis of the posttravel stool samples of all 459 subjects (Table 1) revealed EPEC ($n = 194$; 42%) and EAEC (192; 42%) to be the most common pathogens, outnumbering both ETEC (88; 19%) and *Campylobacter* (31; 7%). EHEC was identified in 37 (8%), *Salmonella* in 11 (2%) and EIEC/*Shigella* in six (1%) stool samples. *Vibrio cholerae* and *Yersinia* were not detected. Two or more types of bacterial pathogens were found in 168 (37%) of all posttravel faecal samples; 57 (12%) had three or more pathogens.

EPEC, EAEC, ETEC and *Campylobacter* findings in stool samples of travellers to five regions

The findings of EPEC, EAEC, ETEC and *Campylobacter* in relation to symptoms among travellers to South Asia, Southeast Asia, East Africa, West Africa and Latin America are presented in Supplementary Table S2 and in Figs. 1–3. Pathogen findings from countries with more than ten visitors are presented in Supplementary Table S3.

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