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Health problems and risks encountered among healthy and vulnerable Dutch travelers

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Health problems and risks encountered among healthy and vulnerable Dutch travelers

Jessica Vlot

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Jessica Alexandra Vlot

The studies described in this thesis were performed at the Department of Infectious Diseases of the Leiden University Medical Center, Leiden, the Netherlands.

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Health problems and risks encountered among healthy and vulnerable Dutch travelers

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Prof. dr. C. Schultsz (Amsterdam Universitair Medisch Centrum, locatie AMC)

Dr. M. Croughs (Travel Clinic of Institute of Tropical Medicine in Antwerp (ITM))

Contents

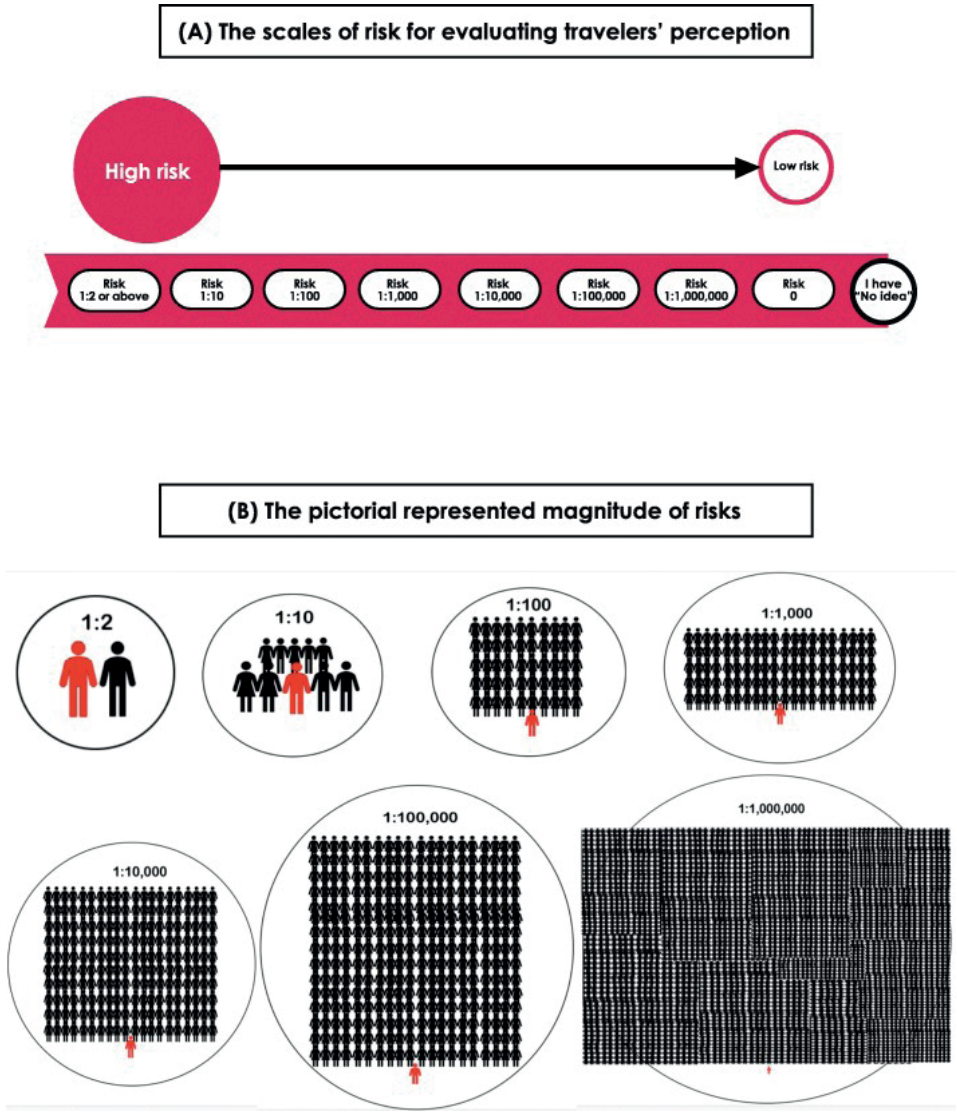
1

General introduction

People are fond of traveling around the globe for leisure, business or other purposes, regardless of their age or health status. In the Netherlands, over 35 million holiday trips were taken, of which 51% were spend outside the country in 2016. This number increased to almost 41 million trips in 2019 with 56% of the trips abroad. [1, 2]

While being abroad, travelers may experience a variety of, mostly self-limiting, travel-related health problems, ranging from infectious diseases to trauma, mental illness or exacerbation of a pre-existing disease. A retrospective study of the Dutch General Practitioners among 600 Dutch travelers revealed that one out of every five Dutch travelers experienced some kind of health complaints while abroad. They strongly advise to be well prepared for the planned journey. [3]

Travel medicine professionals strive to provide travelers with personalized, easy-to-understand risks numbers concerning travel-related health problems. In this way, travelers can make well-informed decisions in adherence to the preventive measures that were advised during the travel health consultation depending on their individual risk thresholds. Compliance with travel health advice while being abroad relies on effective risk communication by the travel health provider and knowledge of the risk perception and risk thresholds of the traveler itself. [4, 5] Hiranrusme et al. demonstrated that images could be a useful tool to enlarge and visualize the risk perception of travel-related health problems in travelers (figure 1). This is particularly the case for 'new' travelers, as experienced travelers often received pre-travel advice(s) in the past. [6] In the Netherlands travelers can contact travel clinics or municipal health services (MHS, in Dutch: GGD) for a pre-travel advice, preferable 4-6 weeks before departure. They receive verbal and written advice and preventive measures concerning various topics, mostly related to infectious diseases, depending on the travel destination(s) that will be visited. Also, the immunization status of the traveler is checked and updated if needed. Guidelines of the foundation named National Coordination Center for Travelers Health Advice (in Dutch: Landelijke Coordinatorcentrum Reizigersadvisering, LCR) are hereby followed. [7] Besides the travel clinic consult, travelers also have other sources for collecting travel information: internet, pharmacies, friends and relatives or travel agencies. The travel health provider should be aware of this as contradictory information can be given, leading to a confused traveler who has less compliance for any preventive measures during travel. [8]



Images reprinted according to Creative Commons Attribution 4.0 International Licence (http://creativecommons.org/licenses/by/4.0/), based on original article "Risk perception of health problems among travelers visiting a travel clinic in Bangkok, Thailand", Hiranrusme T et al, Trop Dis Travel Med Vaccines, 2020; 6:7. https://doi.org/10.1186/s40794-020-00108-0. No changes were made.

Figure 1. Measurement scales used for risk evaluation in Thai and western travelers who received pre-travel advice at the Thai Travel Clinic in 2019.

Travel-related health risks

There are different methods to estimate health risks that can be used, each with their associated advantages and disadvantages. In travel medicine, and also in the research described in this thesis, data is often collected in prospective cohort studies. Associated risk measures reported in cohort studies are incidence rates (i.e. number of new disease cases within a specific at-risk population, expressed per time unit such as per 1,000 travelers per months), or incidence proportions/attack rates (i.e. proportion of at-risk travelers that develops a disease during the foreign journey). Cohort studies are laborious and time-consuming and limited by the fact that most health problems are rare except gastrointestinal complaints and respiratory infections. An alternative option for collecting information is the use of notification data. The number of reported cases among travelers over a specific time period (=numerator) can be compared with the total number of arrivals to a specific destination (=denominator). International registries such as the World Tourism Organization can be used for this purpose. The associated risk measure are case numbers whereby stratification into regions of acquisition can be done. However, under-reporting and under-diagnosis can occur for cases during travel or when a medical diagnosis is missing. [4]

For all types of health-risk estimates it should be kept in mind that travelers are a heterogeneous population. Each traveler is unique and the chance of falling ill depends on many environmental and personal factors such as age, demographics, health status (e.g. comorbidities, medication use), educational level, financial status, and compliance with preventive measures. [4] Travelers to low- or middle-income countries (LOMIC) have higher risk of travel-related morbidity and mortality. In addition, the season of travel (e.g. dry versus rainy season), travel duration, type of journey (e.g. all-inclusive hotels versus low budget hostels), travel purpose (e.g. visiting friends and relatives versus tourism versus medical electives), and risky behavior (e.g. diving, high-altitude hiking) all affect health risks. [9]

In the first part of this thesis we aimed at focusing on health risks and problems and (risk)behavior in specific groups of travelers in order to provide more precise estimates of health risk.

In some cases, travelers require medical assistance while staying abroad, and admission to a foreign hospital or even repatriation to the home country may be necessary. The latter is mostly for medical reasons, but sometimes because of

patient's wishes or high costs of hospital care abroad. Death is the most serious outcome and is often caused by a natural cause (e.g. cardiovascular events) or sustained injuries caused by road traffic accidents, falls, or burns for example. [9-13] Notification data provide an insight on the most serious travel-related health problems that can occur. Regarding travel destinations, these are categorized in geographical regions throughout this thesis, mostly according to the United Nations geographical classification, see figure 2.

In **chapter 2** we explored in a retrospective study how many Dutch travelers received hospital-based care while being abroad or died abroad. We examined the disease burden in a five-year period using data that was retrieved from three medical assistance centers based in the Netherlands and the Dutch Ministry of Foreign Affairs.

Chapter 3 describes the degree of inconvenience of travelers' diarrhea experienced in adult Dutch travelers to (sub)tropical destinations using web-based questionnaires. This is meaningful because many travelers have to deal with gastrointestinal complaints during one of the trips they undertake in their life. Travelers' diarrhea is mostly caused by bacterial pathogens such as *Escherichia coli (E.coli)* and has a mean duration of three to five days. Young children and elderly with diarrhea are more at risk for dehydration. During the pre-travel consult it is therefore important for the travel health provider to highlight preventive measures a traveler can take: good hygienic measures, drinking bottled water that is properly sealed, and avoiding raw and uncooked vegetables, meat and salads. [8, 14] This advice is also summarized in the traditional recommendation "Peel it, cook it, boil it or forget it". Unfortunately this turns out not to be the Holy Grail in practice and travelers still develop health complaints. [15] A travel medical kit should always contain oral rehydration solution (ORS) to prevent dehydration and the antimotility agent loperamide. Antibiotics (i.e. azitromycine or ciprofloxacine) are only prescribed for self-treatment in special groups such as immunocompromised or long-term travelers. Travelers should also be informed when they should visit a physician when having additional complaints (i.e. fever, bloody stools, increased thirst, infrequent/ little urination, or drowsiness) with the diarrhea. [14] In order to get a better understanding of the impact of gastrointestinal complaints, the study in **chapter 3** was performed.

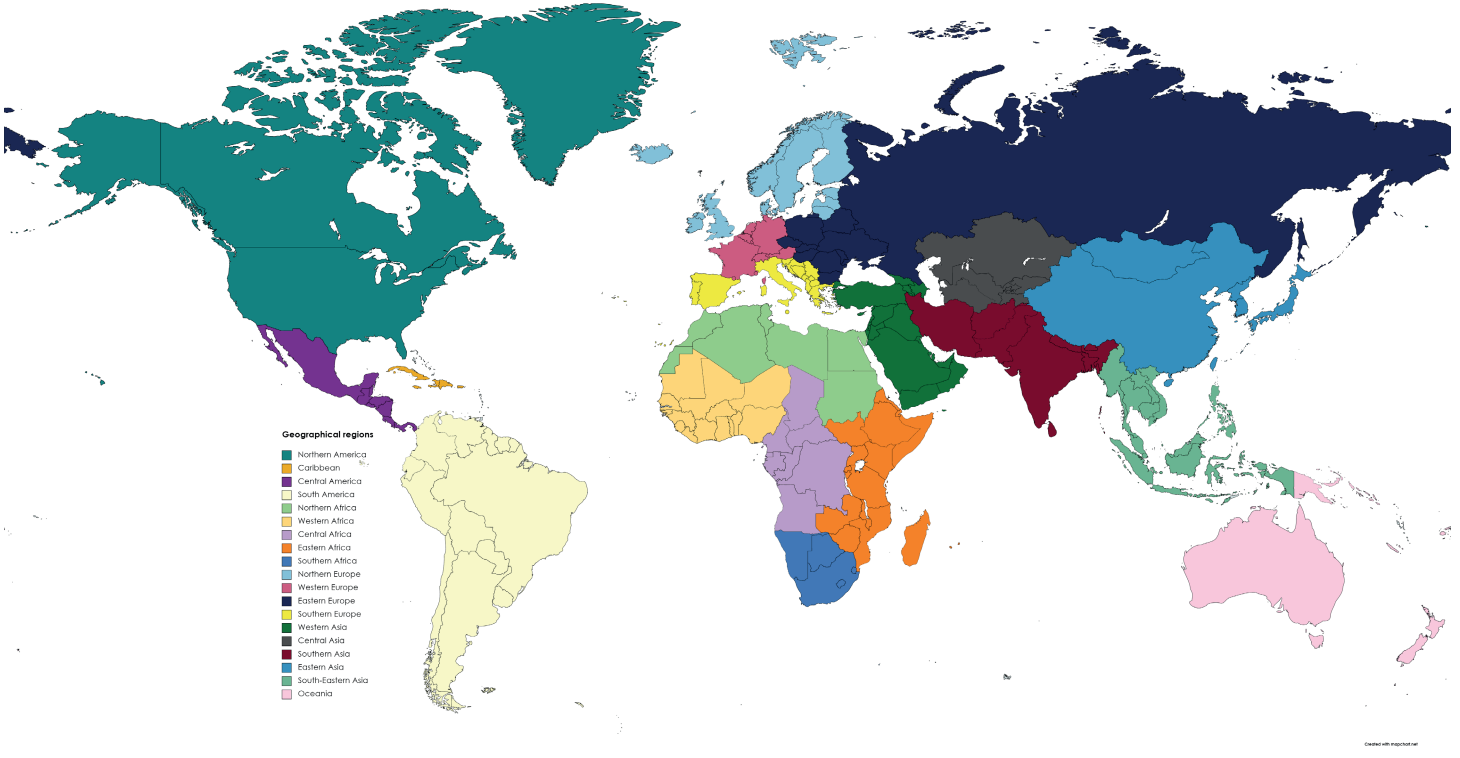


Figure 2. World map according to the geographical regions assigned by the Statistics Division of the United Nations. Data were adopted from https://unstats.un.org/unsd/methodology/m49/. World map is created using https://mapchart.net.

Alongside the “ordinary” travelers, many medical schools offer their students the opportunity to perform an elective abroad. Students often choose for an institution in LOMIC countries and can be exposed to specific work- and travel-related health risks that can have serious impact on their long-term stay abroad. Therefore, we performed a web-based questionnaire study in **chapter 4** that highlights various aspects that Dutch and Belgian medical students may face before, during and after their elective in a LOMIC country, such as pre-travel preparation, culture shock, health problems and post-travel screening for several infectious diseases.

In thirty years, the Dutch population aged older than 65 years increased from 13% in 1990 to 20% in 2019 (n=3,484,216). Of this, 57% of the older Dutch citizens are between 65 and 75 years of age. [16] Travel-related morbidity in this group of travelers is expected to differ from that of younger travelers due to medical, physiological, and behavioral differences.[17-19] Older persons are more susceptible to infections due to waning immunity, impaired immune responses, and limited effectiveness of received pre-travel vaccinations. [20-24]

Chapter 5 contains a study in which we try to identify predictors for the development of (travel-related) morbidity in Dutch travelers aged 60 years and older that needs to be taken into account during the pre-travel consult in their home country. Pre-travel physical performance was measured with hand grip strength and a cognition performance test. Questionnaires and a paper diary were used to register health complaints at different moments. We performed this study since the increase in life expectancy and vitality has led to a growing population of older adults traveling internationally over the past decades. [25]

The second part of this thesis addresses the occurrence of antimicrobial resistance in international travelers.

Antimicrobial resistance (AMR) is a complex health problem and is a growing global public health treat, fueled by the use and misuse of antimicrobial agents. [26] With the lack of new antimicrobials, treatment of common infections may become a challenge, and this can lead to higher morbidity and mortality. [27] For years there was no proper global surveillance system and countries ‘created’ their own routine surveillance that was mainly based on samples that were taken from patients with severe infections. In 2014, the World Health Organization (WHO) started to collect resistance surveillance data from 129 member states. *E. coli* and *Klebsiella pneumoniae* (*K. pneumoniae*) were identified as the main bacterial causes of urinary

tract infections, and a frequent cause of blood stream infections in hospitals and in the community, with resistance against fluoroquinolones and 3rd generation cephalosporins. Due to this resistance, severely ill patients can probably only be treated with expensive and limited available carbapenems. Although carbapenem resistance already have been reported. [26] Antimicrobial Resistance Collaborators across the world generated a world map with raw and modelled estimates for the percentage of pathogen isolates of *E. coli* and *K. pneumoniae* that are drug resistant in 2019, see Figure 3.

Traveling to a high-prevalence area of extended-spectrum beta-lactamase-producing *Enterobacteriaceae (ESBL-E)* or carbapenemase-producing *Enterobacteriaceae* (CP-E) may have a significant impact on the gut flora in travelers up to several months after return. [28] Tängdén et al. was the first who reported on the relationship between international travel and the risk of colonization with ESBL-E in 2010. [29] In the same year, CP-E was reported for the first time in the Netherlands in three travelers who visited Greece and India. [30]

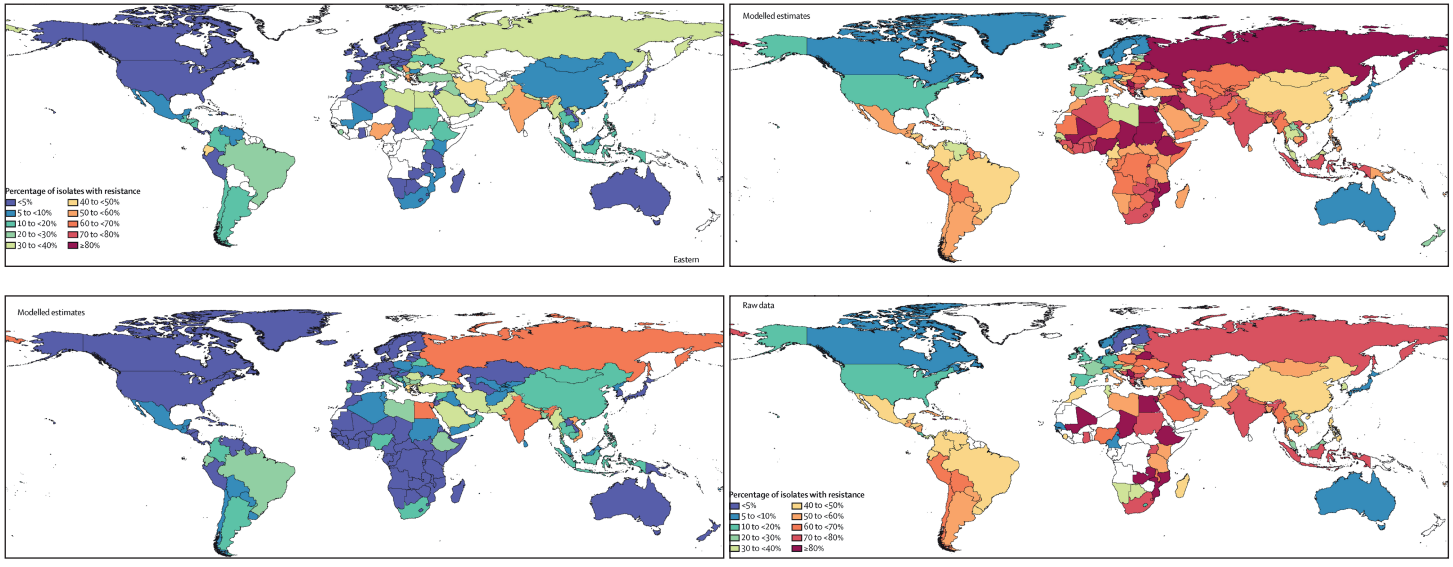
In **Chapter 6** we focus on the acquisition and duration of post-travel rectal carriage of (multi)resistant *Enterobacteriaceae* and on the identification of risk factors in a prospective cohort of Dutch travelers. For this study we were interested in the role of travelers' diarrhea, antibiotic use and the local hygiene- and sanitation level in relation to the spread of resistant organisms such as ESBL-E and CP-E .

In **Chapter 7**, data of the African travelers described in **chapter 6** were combined with comparable data from Finland and another study from the Netherlands to assess colonization rates and risk factors in this specific group of travelers.

The third part of this thesis consists of **chapter 8**, in which the findings are summarized and discussed, and **chapter 9**, which contains a Dutch summary.

A. Third-generation cephalosporin-resistant *E.coli*

B. Fluoroquinolone-resistant *E.coli*



C. Carbapenem-resistant *K. Pneumoniae*

D. Third-generation cephalosporin-resistant *K. Pneumoniae*

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Figure 3. Raw data and modelled estimates for the percentage of *E. Coli* and *K. Pneumoniae* isolates that are resistant by country in 2019. Locations with no raw data or modelled estimates are presented in white.

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PART I

Health problems and (risk) behavior

2

Hospital-based care and/or death followed by repatriation in Dutch travelers: the HAZARD study

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Katie Geary, Perry J.J. van Genderen, Leo G. Visser

Travel Med Infect Dis. 2022 sep-oct;49:102329

Abstract

Background Travelers can experience health problems while abroad. This descriptive study aimed to quantify the disease burden leading to hospital-based care, repatriation or death in Dutch travelers during a stay in a foreign country, including Europe.

Methods Retrospective study of demographic and clinical data from three medical assistance centers (MACs) and the Dutch Ministry of Foreign Affairs on Dutch travelers receiving hospital-based care or who died abroad in the years 2010-2014. Diagnoses were coded according to the International Classification of Diseases (ICD) and classified using the Global Burden of Disease tool.

Results Data was available for 77,741 travelers' incidents: 75,385 medical consultations and 2,356 deaths. Four in five travelers received inpatient care, of which 36% concerned older travelers (65+) who had significantly longer hospital stays. Overall the top three diagnoses were: injuries (29%), infectious diseases (17%), and cardiovascular diseases (17%). Mental illness was reported in nearly 1.5% of the travelers. Incidence proportions were highest in South-Eastern Asia, with enteric infections as most common diagnosis. Injuries and communicable diseases occurred most often in South-Eastern Asia, while non-communicable diseases were mostly reported in South America. One in five travelers who consulted a physician was repatriated back home, mostly on a scheduled flight with or without medical escort. Cardiovascular diseases and injuries were the leading causes of death.

Conclusions Not only communicable diseases, but also injuries and chronic diseases (in particular cardiovascular diseases) frequently affected travelers' health while staying abroad and frequently necessitated hospital-based care. This should be addressed during the pre-travel counseling.

Introduction

Travelers may experience a variety of health problems while being abroad, ranging from infectious diseases, trauma or exacerbation of a pre-existing disease. Most illnesses are self-limiting, but travelers may be hospitalized and may require repatriation (air or ground) to their home country. These situations can be costly for the traveler, as not all costs are always covered by insurance [1, 2]. Incidences of reported health problems in travelers vary between 40%-80% in previous studies [3-6]. Siikamaki et al. reported that Finnish travelers were more frequently hospitalized for infections (49%), than for injuries (18%) or vascular diseases (9%) [6].

The most serious health outcome is death. Frequent causes of death in travelers are natural causes (such as cardiovascular events) and injuries (e.g. motor vehicles, drowning, falls, and burns) [7-11]. Studies report that travelers to low- or middle-income countries (LOMIC) are twice as likely to be involved in a road traffic accident than in their home country as they are more at risk due to unfamiliarity with local traffic [7, 8, 12]. It is relatively uncommon for travelers to die from an infectious disease abroad, partly because serious outcome and death can be effectively prevented (e.g. malaria) or treated (e.g. respiratory tract infections) [6, 7].

Home country-based medical assistance centers (MACs) play a crucial role in case of health problems abroad by providing (medical) support for travelers and their travel companion(s) abroad or their family at home. Depending on the travelers' insurance coverage, MACs provide medical advice, information on quality of local health care, perform medical evacuations and repatriations, and repatriate mortal remains.

Worldwide, there are several data surveillance networks such as the GeoSentinel Surveillance Network [13] and the sub-network European Travel and Tropical Medicine Network (EuroTravNet) [14] that register travel-related morbidity in returning international travelers who present themselves, mostly post-travel, to a participating travel clinic in their home country. However, to our knowledge limited data is available on travelers who received medical help, or even died, during their stay abroad. Therefore, the aim of our descriptive study was to quantify the disease burden leading to hospital-based care, repatriation or death in Dutch travelers during their stay in a foreign country, including Europe. The outcome of this study could be

used as background information to support the risk-based pre-travel health advice worldwide, which ideally should not be restricted to tropical diseases alone.

Material and methods

Study design and participants

We conducted a retrospective study of health problems in Dutch travelers who received medical assistance abroad (HAZARD: HospitAliZAtions, Repatriation and causes of Death among Dutch travelers). Data were collected from the case records of three MACs with an office based in the Netherlands (Eurocross Assistance, Royal Dutch Touring Club [ANWB] and International SOS). Together, these centers cover more than 50% of all insured Dutch residents. We included all pseudonymized case records of all subsequent Dutch travelers who were hospitalized or who died abroad between January 1st, 2010 and December 31st, 2014. We approached the Dutch Ministry of Foreign Affairs (MoFA) to include Dutch nationals who might not appear in the MACs records, for example because of insufficient insurance or death under special circumstances. Only digitally available MoFA data from the years 2013 and 2014 was included.

Available information consisted of demographic (age, gender), travel-related (destination, duration, travel purpose), and medical characteristics (main diagnosis, duration of hospital stay, type of repatriation, medical expenses of repatriation, and cause of death). This data is routinely collected by the MACs during their contact with the traveler and their treating physicians abroad. Exclusion criteria were: travel duration less than three days, travelers with foreign nationality, expatriates, and travelers specifically traveling abroad for medical treatment such as medical tourists and border residents.

Classification of diseases

Reasons for medical assistance and cause of death were coded according to the International statistical Classification of Diseases and related health problems (ICD) of the World Health Organization (WHO) [15]. Both ICD-9 and ICD-10 were used by the MACs. To allow uniform grouping of data from the different MACs, the cause-ICD codes map GBD 2019 of the Global Burden of Disease (GBD) collaborative network

was used. We mainly used three of the four available levels of diseases and injuries of the GBD list (Supplemental Table S1) [16, 17]. If the ICD code was not registered, we retrieved open field texts and classified accordingly. Cases with missing ICD codes and insufficient information in the open text fields or unclear diagnoses were grouped as 'unknown' and 'unclassified symptoms and signs'.

Definitions

Travel destinations were categorized according to geographical regions of the United Nations (UN) Statistics Division (Supplemental Table S2) [18]. Travel duration was categorized in short-term (3 – 30 days) and long-term travel (≥31 days). Purpose of travel was defined as leisure or business. Inpatient care was defined as a hospital admission with at least one overnight stay. Hospital-based care without overnight stay was defined as outpatient care. Air ambulance transportation was defined as all other than regular flights deployed by the MACs in case of a medical indication (i.e. seriously ill patients in need of specialized hospital care in their home country or a very high oxygen demand not feasible on a regular flight) or for logistical reasons (i.e. no other way of transportation possible).

Data processing

The total number of Dutch travelers visiting individual countries during the study period was obtained from the World Tourism Organization (UNWTO). This data was based on arrivals of Dutch travelers at destination countries [19]. Age of the affected traveler was calculated using the year of birth and the date of the incident and categorized as children (0-4 and 5-19 years), young adults (20-39 years), middle-aged adults (40-64 years) and older adults (65 years and above). Travelers who were re-admitted for other medical conditions were counted as separates cases. Incidence proportions of illnesses or injuries were calculated as follows: (nominator: number of cases in the specific GBD group) / (denominator: total number of Dutch travelers visiting the specific UN region between 2010-2014) * 10,000. Type of repatriation was categorized as unescorted flight, escorted by nurse or physician, by air ambulance, by (winter)shuttle flight or by road. To protect commercially sensitive information, data of the participating MACs were merged and analysed jointly.

Statistical analyses

All data were retrieved by the IT department of the respective MACs, pseudonymized and stored in Excel-files. These files were imported into IBM® SPSS® Statistics version 25 (IBM Corp) for analyses. Descriptive statistics and univariable analysis were used where appropriate. Statistical significance was defined as a p-value <0.05. Data of the MoFA is analyzed separately due to different type of travelers.

Ethics

The study was endorsed by the Committee Medical Ethics (CME) of the Leiden University Medical Center (LUMC), Leiden, the Netherlands (registry number C15.067). Written informed consent was not required as the study did not fall under the scope of the Medical Research Involving Human Subjects Act (in Dutch: WMO). The study was registered in the Netherlands Trial Register under NL5377 (NTR5478).

Results

Data from medical assistance centers (MACs)

Over a 5-year period, MACs provided assistance to 76,816 travelers: 75,385 medical consultations and 1,431 deceased travelers without receiving hospital-based care. The number of cases remained relatively constant over the years 2010 to 2014. According to the UNWTO data, the total number of Dutch travelers in this study period was 141,581,550. Demographic and travel characteristics are presented in Table 1.

Characteristics of travelers in need of inpatient and outpatient care

Leisure was the main reason (96%) for travel for the 75,385 travelers. The majority (73%) of trips were short-term. The median age was 56 years (interquartile range (IQR) 35-68 years). Most medical consultations occurred in Europe (particularly Western [France] and Southern Europe [Spain]) and Asia (in particular Western Asia [Turkey] and South-Eastern Asia [Thailand]), which is consistent with the major travel destinations according to the UNWTO data (84% and 9% for Europe and Asia, respectively). The median length of hospital stay was 4 days (IQR 2-7 days). Admission to an intensive care unit was reported in 2,035 travelers (3%). Almost one-fifth of cases received outpatient care (13,791/75,000, 18%). Four out of five

children between 0 and 19 years (81%) were admitted. Gender distribution was equal in outpatient cases, however more male travelers were hospitalized (54% vs 46%, p<0.001) (Table 1).

Burden of disease categories

Almost half of all medical consultations (45%) were for non-communicable diseases, of which 40% was outpatient (Table 1). The top five causes for inpatient treatment were injuries (31%), cardiovascular diseases (19%), digestive system diseases (10%), enteric infections (9%), and respiratory tract infections (RTIs, 7%). For outpatients the top five were injuries (31%), enteric infections (17%, predominantly gastroenteritis), cardiovascular diseases (17%), digestive system diseases (7%, e.g. inguinal hernia, inflammatory bowel diseases, diverticulitis) and other non-communicable diseases (7%, e.g. urinary tract infections, kidney stones, allergic reactions) (Table 2).

For both injuries and communicable diseases the incidence proportions were highest in South-Eastern Asia (3.3 and 6.7 per 10,000 travelers respectively), whilst for non-communicable diseases this was highest in South America (7.8 per 10,000 travelers) (Figure 1, Supplementary Table S3, Supplementary Table S4).

Only a minority of medical consultations (n=746, 1.1%) was due to tropical diseases such as dengue fever (626/746, 84%, mostly in Asia) or malaria (93/746, 13%, mostly in Africa) (Table 2). The incidence for tropical diseases was highest for travelers to Asia (71%, mainly Indonesia and Thailand), followed by the Americas (16%, mainly Surinam) and Africa (11%, mainly Kenya and Ghana). Overall, these travelers were relatively young with a median age of 36 years (IQR 25-58 years). More than 90% of travelers with a tropical disease were admitted to hospital. One traveler died due to cerebral malaria during hospitalization in Ghana (data not shown).

Nine hundred and ninety-one travelers (1.4%) received medical assistance for mental disorders (Table 2), primarily for schizophrenia and delusional disorders (24%), depression (15%), and anxiety (11%). Nearly half of the mental disorders were unspecified (46%). Median age was 42 years (IQR: 30-52 years); more males received medical help (57% vs 43% females). Most of the mental diseases were diagnosed closer to the home country: Germany (13%), France (10%), Belgium (9%), but not all (Turkey 13%, Spain 9% and Morocco 4%) (data not shown).

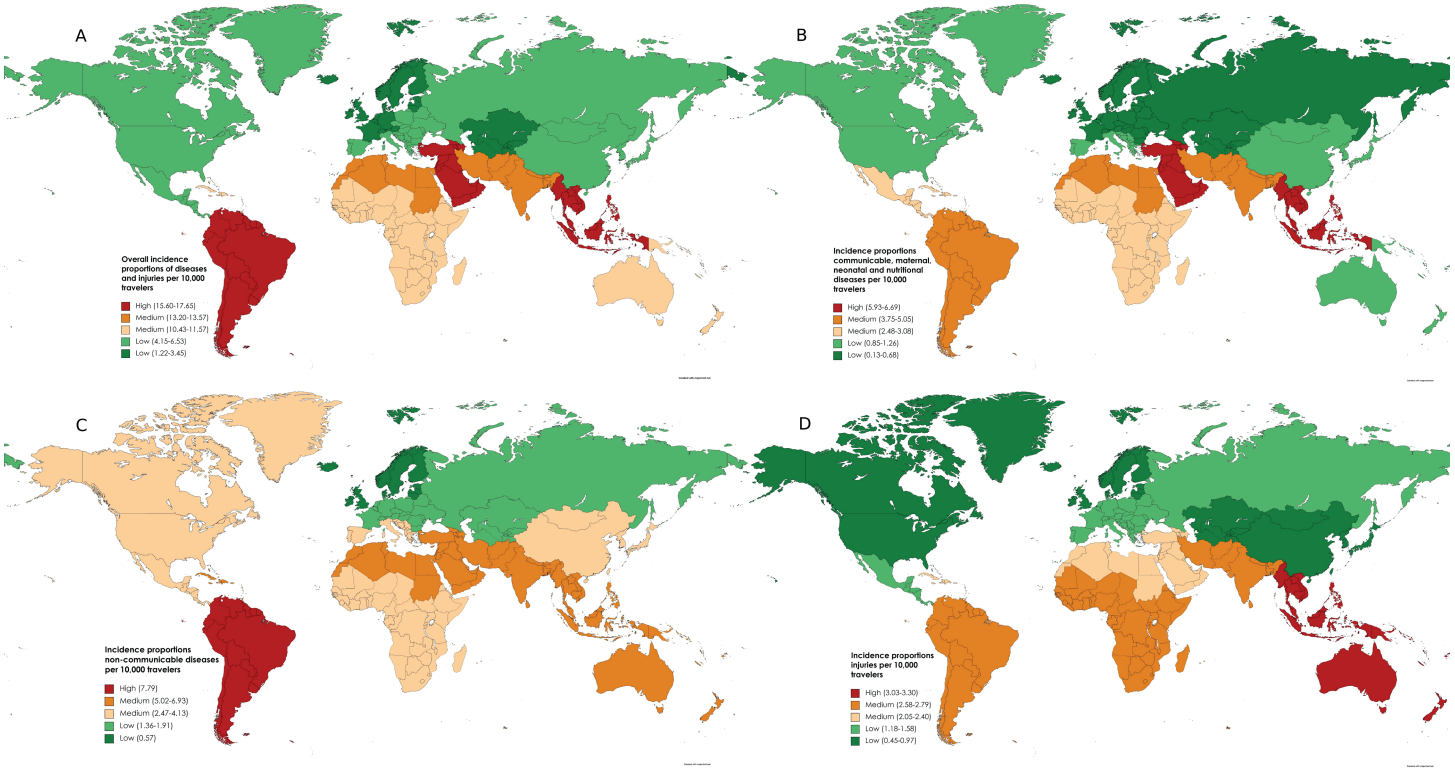

Figure 1 Incidence proportions of diseases and injuries in Dutch travelers between 2010-2014 per UN regions reported by MACs.

Abbreviations: UN, united nations; MACs, medical assistance centers. Data source: Supplementary Table S3 and Supplementary Table S4.

A: Overall incidence proportions of diseases and injuries per 10,000 Dutch travelers; **B**: Incidence proportions of communicable, maternal, neonatal and nutritional diseases per 10,000 travelers; **C**: Incidence proportions of non-communicable diseases per 10,000 Dutch travelers; **D**: Incidence proportions of injuries per 10,000 Dutch travelers.

Almost a third of all travelers (29%) were injured, of which 82% needed inpatient care (Table 1). Injuries were as frequently reported in male (51%) as female travelers (49%). Most injuries were acquired in Europe (77%) and Asia (14%). An identifiable cause was reported for 23% of the injured travelers (5,029/21,755). One in four travelers was involved in a road traffic accident (RTA), either as motor vehicle occupant, motorcyclist or cyclist. Accidental falls were the main reason for unintentional injuries for all destinations (62%) (Table 3). They occurred in and around the accommodation or during sport activities such as winter sports activities, hiking, swimming or horseback riding. One or more fractures were reported in almost 60% of the injuries, and contusions in 5%, including concussion (data not shown). One hundred and sixty-one travelers (161/3,295, 5%) had burns. A minority (232/3,295, 7%) were injured after animal contact (i.e. bites or stings), of which two-thirds in travelers aged 20-59 years. Insect bites and stings (e.g. by wasps or bees) occurred in 106 travelers (46%) and led to local allergic or toxic reactions in almost one-third of these cases. Thirty-five travelers (15%) had contact with venomous animals such as snakes. Thirty-one travelers (13%) were bitten by a dog; half of them concerned older travelers. Hands and arms were the most common bite locations. Three travelers had been exposed to an avalanche: two rockslides (Switzerland and Spain) and one snow avalanche (Austria). Self-harm and interpersonal violence represented 3% of the injuries of which two resulted in death (Table 3).

Older versus younger travelers

Overall the largest groups requiring medical assistance (47%) were travelers aged 20 to 59 years. However, inpatients were older than outpatients (median age 57 vs 51 years, $p<0.001$). Older travelers required longer hospital stay than younger travelers (mean: 6.3 [SD 7.0] vs 4.6 days [SD 6.3] ($p<0.001$) (Table 1).

Older travelers (65+) also differed from younger (65-) travelers in type of diseases for which medical assistance was received: of all reported communicable diseases (excluding maternal and neonatal disorders), only 28% were seen in older travelers. Whereas, RTIs occurred more frequently in the older group (54% vs 28%), the opposite was true for enteric infections (35% vs 58%). Almost one third of the travelers, mainly between 50 and 64 years of age, presented with a cardiovascular

disease. No age difference was seen for involvement in RTAs or unintentional injuries (5% and 18% vs 6% and 16%, respectively). Mental disorders were primarily seen in younger travelers (5% vs 0.7%). (Table 4, Supplementary Table S5). Diseases and injuries among children are presented in Supplemental Table S6.

Direct fatal injuries (without receiving medical assistance) occurred less frequently in older travelers (RTAs 7% vs 25%, unintentional injuries 6% vs 13%, self-harm 0.2% vs 4.2% and interpersonal violence 0% vs 1.1%). More older travelers died following a cardiovascular disease (80% vs 50%). No differences were observed in other causes of death (data not shown).

Repatriation

Twenty percent of travelers receiving medical assistance were repatriated (14,874/75,385), of which at least 90% after inpatient care. Most repatriations were with a scheduled flight without (4,389/14,874, 30%) or with (3,028/14,874, 20%) a medical escort (nurse or physician). Travelers repatriated with a medical escort concerned more males ($p=0.002$), older travelers ($p<0.001$), and for the diagnoses RTIs ($p=0.002$) cardiovascular conditions ($p=0.014$), neoplasms ($p<0.001$), mental disorders ($p<0.001$), chronic respiratory diseases ($p=0.010$), neurological disorders ($p<0.001$), and diabetes and kidney diseases ($p=0.034$). In addition, it mostly concerned travelers from destinations in the Americas ($p=0.021$). Injuries, independently of the cause, are mainly repatriated with a scheduled flight without a medical escort (Supplemental Table 7). A ground ambulance was frequently used for repatriations in Europe. An air ambulance was used in 5% of the repatriations (Table 1), mainly conducted from Europe and the Southern Mediterranean. This type of repatriation was mostly for injured travelers (211/676, 31%) or for non-communicable diseases (365/676, 32%). Older adults accounted for half of the cases (52%) of this repatriation method (data not shown). The exact repatriation type is unknown for about one-third of the cases, although the involved traveler was mostly transported on a stretcher or by adapted seat conditions (e.g. business class instead of economy class for additional leg or arm space).

Cause of death in deceased travelers without receiving hospital-based care

Demographic and travel characteristics are presented in Supplemental Table S8. The leading cause of death were cardiovascular diseases (51%), of which most due to out-of-hospital cardiac arrest (329/724, 45%), myocardial infarction (210/724, 29%), or stroke (64/724, 9%). Injuries were the second largest group (19%), of which most as a result of RTAs (53%, e.g. motor vehicle injuries) or unintentional accidents (35%) (such as accidental falling (43/94, 46%) or drowning (28/94, 30%)). Twenty travelers (20/1,431, 1.4%), mostly males between 20-59 years of age, committed suicide. Seven travelers (7/1,431, 0.5%) were murdered. A minority (19/1,431, 1.3%) died after an infectious disease. Most fatal injuries occurred in 65- travelers. One in-flight death during commercial air travel was reported without reported cause of death (Table 5).

Dutch Ministry of Foreign Affairs

A total of 925 records of deceased Dutch travelers was handled by MoFA in the years 2013 and 2014, including 197 victims (21%) of the MH17 plane crash in eastern Ukraine, Europe in July 2014. The median age of the remaining 728 travelers was 63 years (IQR: 51-71 years); 81% were men. Almost two thirds of all deaths were caused by non-communicable diseases (33%, mostly cardiovascular diseases) or injuries (26%, mostly caused by self-harm). Most deaths occurred in South-Eastern Asia (30%, mainly Thailand [70%] and Philippines [13%]), followed by Western- and Southern Europe (both 15%) (Supplementary Table S9). Three travelers in Africa died of malaria. Fifty-five travelers (8%) committed suicide. Thirty-one travelers (4%) were killed by interpersonal violence. Most of these cases occurred in the Caribbean, South America and Africa (Supplementary Table S10).

Table 1 Demographic and travel characteristics of 75,385 Dutch travelers contacting their MAC while receiving medical assistance and possibly followed by death between 2010 and 2014.

	All cases		Outpatient cases[a]		Inpatient cases[a]	
	N=75,385		N=13,791	(18.4)	N=61,209	(81.6)
General information						
Gender *(N=75,324, information missing N=61)*	*75,324*	*(99.9)*	*13,768*	*(9.8)*	*61,171*	*(99.9)*
Female	35,299	(46.9)	6,880	(50.0)	28,261	(46.2)
Male	40,025	(53.1)	6,888	(50.0)	32,910	(53.8)
Age, *years, median (IQR) (N=75,283, information missing N=102)*	56	(36-68)	51	(29-65)	57	(37-69)
Age group in years *(N=75,348, information missing N=37)*	*75,348*	*(99.9)*	*13,775*	*(99.9)*	*61,188*	*(99.9)*
0-4	1,692	(2.2)	148	(1.1)	1,544	(2.5)
5-19	5,031	(6.7)	1,150	(8.3)	3,865	(6.3)
20-39	14,510	(19.3)	3,532	(25.6)	10,894	(17.8)
40-59	20,697	(27.5)	4,118	(29.9)	16,441	(26.9)
60-64	7,772	(10.3)	1,284	(9.3)	6,451	(10.5)
65-69	8,871	(11.8)	1,340	(9.7)	7,501	(12.3)
70-74	7,282	(9.7)	1,074	(7.8)	6,176	(10.1)
75-79	5,133	(6.8)	643	(4.7)	4,468	(7.3)
80-84	2,860	(3.8)	330	(2.4)	2,509	(4.1)
≥85	1,500	(2.0)	156	(1.1)	1,339	(2.2)
Travel details						
Travel duration *(N=68,167, information missing N=7,218)*	*68,167*	*(90.4)*	*12,119*	*(87.9)*	*55,816*	*(91.2)*
Short-term travel (3-30 days)	49,937	(73.3)	9,738	(80.4)	40,055	(71.8)
Long-term travel (≥31 days)	18,230	(26.7)	2,381	(19.6)	15,761	(28.2)
Purpose of travel *(N=38,485, information missing N=37,410)*	*38,485*	*(51.1)*	*3,243*	*(23.5)*	*35,174*	*(57.5)*
Leisure	36,846	(95.7)	3,084	(95.1)	33,718	(95.9)
Business	1,639	(4.3)	159	(5.2)	1,456	(4.1)
Destination *(N=75,384, information missing N=1)*						
America[b]	*6,081*	*(8.1)*	*1,111*	*(8.1)*	*4,917*	*(8.0)*
Caribbean	1,523	(25.0)	300	(27.0)	1,210	(24.6)
Northern America	2,033	(33.4)	473	(42.6)	1,531	(31.1)
Central America	442	(7.3)	92	(8.3)	347	(7.1)
South America	2,083	(34.3)	246	(22.1)	1,829	(37.2)
Europe[c]	*46,076*	*(61.1)*	*7,234*	*(52.5)*	*38,680*	*(63.2)*
Northern Europe	1,646	(3.6)	221	(3.1)	1,419	(3.7)
Western Europe	24,905	(54.1)	3,669	(50.7)	21,139	(54.7)
Southern Europe	17,897	(38.8)	3,083	(42.6)	14,766	(38.2)

	All cases		Outpatient cases[a]		Inpatient cases[a]	
	N=75,385		N=13,791	(18.4)	N=61,209	(81.6)
Eastern Europe	1,628	(3.5)	261	(3.6)	1,356	(3.5)
Africa[d]	*4,380*	*(5.8)*	*860*	*(6.2)*	*3,492*	*(5.7)*
Northern Africa	3,051	(69.7)	608	(70.7)	2,432	(69.6)
Sub-Saharan Africa	1,329	(30.3)	252	(29.3)	1,060	(30.4)
Asia[e]	*18,423*	*(24.4)*	*4,517*	*(32.8)*	*13,767*	*(22.5)*
Western Asia	11,284	(61.2)	3,516	(77.8)	7,676	(55.8)
Central Asia	11	(0.1)	3	(0.1)	8	(0.1)
South-Eastern Asia	5,656	(30.7)	807	(17.9)	4,821	(35.0)
Eastern Asia	621	(3.4)	72	(1.6)	534	(3.9)
Southern Asia	851	(4.6)	119	(2.6)	728	(5.3)
Oceania[f]	*424*	*(0.6)*	*69*	*(0.5)*	*352*	*(0.6)*
Disease specification according GBD						
Communicable, maternal, neonatal and nutritional diseases	14,955	(19.8)	3,220	(23.3)	11,684	(19.1)
Non-communicable diseases	33,662	(44.7)	5,416	(39.3)	28,057	(45.8)
Injuries	21,755	(28.9)	3,902	(28.3)	17,739	(29.0)
Unclassified symptoms and signs	4,721	(6.3)	1,145	(8.3)	3,549	(5.8)
Unknown	292	(0.4)	108	(0.8)	180	(0.3)
Duration hospital stay *(N=75,000, information missing N=385)*	75,000	(9.5)	13,791	(100)	61,209	(100)
Median (IQR)	3	(2-6)	1	(1-1)	4	(2-7)
Mean (SD)	5,2	(6.6)	1	(0.02)	6,2	(6.9)
Repatriation						
Repatriation performed after receiving medical assistance						
No	59,795	(79.3)	12,252	(88.8)	47,275	(77.2)
Yes	14,874	(19.7)	1,398	(10.1)	13,385	(21.9)
Scheduled flight without medical escort	4,389	(29.5)	556	(39.8)	3,826	(28.6)
Scheduled flight with medical escort	3,028	(20.4)	176	(12.6)	2,840	(21.2)
Air ambulance	676	(4.5)	57	(4.1)	616	(4.6)
(winter)shuttle flight	818	(5.5)	39	(2.8)	779	(5.8)
Ground ambulance	1,697	(11.4)	56	(4.0)	1,641	(12.3)
Method unknown	4,266	(28.7)	514	(36.8)	3,683	(27.5)
Death						
Died after receiving medical assistance	*701*	*(0.9)*	*141*	*(1.0)*	*550*	*(0.9)*
RMR	496	(70.8)	101	(71.6)	392	(71.3)
Buried or cremated locally	205	(29.2)	40	(28.4)	158	(28.7)
Repatriation, unknown level of hospital-based care	18	(0.02)	-		-	

Data are presented as N (%), unless otherwise specified. MAC: medical assistance center; IQR: interquartile range; GBD: global burden of diseases and injuries; RMR: repatriation of mortal remains.

[a] Information about patient status is missing for N=385. Overall total for in- and outpatient columns is therefore N=75,000.

[b] **Caribbean**: Netherlands Antilles N=931 (61%), Dominican Republic N=443 (29%), Cuba N=85 (6%); **Northern America**: United States of America N=1,740 (86%), Canada N=290 (14%); **Central America**: Mexico N=274 (62%), Costa Rica N=85 (19%), Guatemala N=34 (8%); **South America**: Surinam N=1,193 (58%), Peru N=341 (17%), Brazil N=178 (9%)

[c] **Northern Europe**: Norway N=397 (24%), United Kingdom N=311 (19%), Sweden N=281 (17%), Great Britain N=228 (14%), Denmark N=142 (9%), Ireland N=113 (7%), Finland N=74 (5%), Iceland N=29 (2%) Latvia N=24 (2%), Lithuania N=17 (1%), Estonia N=9 (0.6%), Guernsey N=4 (0.2%), Jersey N=1 (0.1%); **Western Europa**: France N=7,140 (32%), Germany N=6,213 (28%), Austria N=5,988 (27%), Belgium N=1,519 (7%), Switzerland N=1,348 (6%), Luxembourg N=168 (1%), Monaco N=33 (0.1%), Liechtenstein N=3 (1%); **Southern Europa**: Spain N=10,306 (62%), Italy N=2,141 (13%), Greece N=1,929 (12%), Portugal N=1,456 (9%), Croatia N=37 (2%), Malta N=170 (1%), Serbia N=115 (0.7%), Bosnia Herzegovina N=77 (0.5%), Slovenia N=73 (0.4%), Andorra N=40 (0.2%), Macedonia N=32 (0.2%), Montenegro N=13 (0.1%), Kosovo N=6 (0.1%), Albania N=4 (0.1%), Gibraltar N=2 (0.1%), Former Yugoslavia N=2 (0.1%); **Eastern Europa**: Poland N=392 (25%), Czech Republic N=318 (21%), Hungary N=304 (20%), Bulgaria N=252 (16%), Russia N=120 (8%), Romania N=83 (5%), Ukraine N=38 (3%), Slovakia N=32 (2%), Belarus N=5 (0.3%), Moldova N=3 (0.2%).

[d] **Northern Africa**: Morocco N=1,835 (62%), Egypt N=883 (30%), Tunisia N=252 (14%), Algeria N=3 (0.1%), Libya N=3 (0.1%), Sudan N=3 (0.1%); **Sub-Saharan Africa**: *Middle Africa*: Angola N=8 (35%), Cameroon N=6 (27%), Congo N=5 (23%), Chad N=1 5%), Equatorial-Guinea N=1 (5%), Gabon N=1 (5%); *Western Africa*: Ghana N=69 (27%), Gambia N=47 (18%), Cape Verde N=38 (15%), Nigeria N=33 (13%), Senegal N=22 (9%), Togo N=15 (6%), Benin N=7 (3%), Burkina Faso N=7 (3%), Ivory Coast N=5 (2%), Sierra Leone N=4 (2%), Guinea N=2 (0.8%), Liberia N=2 (0.8%), Mali N=2 (0.8%), Mauritania N=1 (0.4%), St. Helena N=1 (0.4%); *Eastern Africa*: Kenya N=218 (55%), Tanzania N=37 (9%), Uganda N=33 (8%), Mauritius N=32 (8%), Ethiopia N=22 (6%), Zimbabwe N=10 (3%), Malawi N=9 (2%), Mozambique N=9 (2%),Zambia N=7 (2%), Eritrea N=5 (1%), Burundi N=3 (0.8%), Seychelles N=3 (0.8%), Reunion N=2 (0.5%), Rwanda N=2 (0.5%), Somalia N=2 (0.5%), Madagascar n=1 (0.3%); *Southern Africa*: South Africa N=612 (93%), Namibia N=33 (5%), Botswana N=8 (1%), Swaziland N=2 (0.3%).

[e] **Western Asia**: Turkey N=10,269 (93%), Cyprus N=260 (2%), Israel N=166 (2%), United Arab Emirates N=122 (1.1%), Jordan N=35 (0.3%), Armenia N=30 (0.3%), Lebanon N=23 (0.2%), Iraq N=18 (0.2%), Saudi Arabia N=17 (0.2%), Georgia N=16 (0.1%), Oman N=14 (0.1%), Qatar N=7 (0.1%) Azerbaijan N=5 (0.1%), Syria N=5 (0.1%), Yemen N=4 (0.1%), Kuwait N=4 (0.1%), Bahrein N=2 (0.1%), Palestinian Authority N=1 (0.1%); **Central Asia**: Kazakhstan N=7 (64%), Kyrgyzstan N=2 (18%), Uzbekistan N=1 (9%), Tajikistan N=1 (9%); **South-Eastern Asia**: Thailand N=2,741 (49%), Indonesia N=1,870 (34%), Vietnam N=226 (4%), Malaysia N=22 (4%), Philippines N=215 (4%), Singapore N=171 (3%), Cambodia N=111 (2%), Laos N=13 (0.2%), Myanmar N=6 (0.1%), Nation of Brunei N=3 (0.1%); **Eastern Asia**: China N=322 (52%), Hong Kong N=200 (32%), Republic of Korea N=34 (6%), Japan N=32 (5%), Taiwan N=23 (4%), Mongolia N=6 (1%), Macau N=1 (0.2%), Democratic People's Republic of Korea N=1 (0.2%); **Southern Asia**: India N=398 (47%), Nepal N=174 (20%), Sri Lanka N=116 (14%), Iran N=68 (8%), Pakistan N=37 (4%), Afghanistan N=33 (4%), Bangladesh N=18 (2%), Maldives N=6 (1%).

[f] **Oceania:** Australia N=264 (62.3%), New Zealand N=150 (35.4%), French Polynesia N=3 (0.7%), New Caledonia N=2 (0.5%), Fiji N=2 (0.5%), Cook Islands N=1 (0.2%), Papua New Guinea N=1 (0.2%), Vanuatu N=1 (0.2%)

Table 2 Travelers receiving medical assistance between 2010-2014 presented by the GBD cause list levels one and two and in- or outpatient status reported by MACs.

	All[a]		Outpatient cases		Inpatient cases		Unlabeled cases	
Diagnosis	**N=70,372**	**(93.4)**	**N=12,538**	**(17.8)**	**N=57,480**	**(81.7)**	**N=354**	**(0.5)**
Communicable, maternal, neonatal and nutritional diseases	**14,955**	**(21.3)**	**3,220**	**(25.7)**	**11,684**	**(20.3)**	**51**	**(16.6)**
Enteric infections	7,235	(10.3)	2,174	(17.3)	5,045	(8.8)	16	(4.5)
Respiratory infections and tuberculosis	4,974	(7.1)	691	(5.5)	4,259	(7.4)	24	(6.8)
Maternal and neonatal disorders	986	(1.4)	185	(1.5)	795	(1.4)	6	(1.7)
Other infectious diseases[b]	932	(1.3)	113	(0.9)	816	(1.4)	3	(0.8)
Neglected tropical diseases and malaria	746	(1.1)	44	(0.4)	700	(1.2)	2	(0.6)
Nutritional deficiencies	47	(0.1)	11	(0.1)	36	(0.1)	-	
HIV, AIDS and STI	35	(0.1)	2	(0.02)	33	(0.1)	-	
Non-communicable diseases	**33,662**	**(47.8)**	**5,416**	**(43.2)**	**28,057**	**(48.8)**	**189**	**(61.4)**
Cardiovascular diseases	13,016	(18.5)	2,103	(16.8)	10,865	(18.9)	48	(13.6)
Digestive system diseases	6,612	(9.4)	870	(6.9)	5,720	(10.0)	22	(6.2)
Other non-communicable diseases[c]	3,791	(5.4)	818	(6.5)	2,952	(5.1)	21	(5.9)
Musculoskeletal disorders	1,823	(2.6)	305	(2.4)	1,505	(2.6)	13	(3.7)
Skin and subcutaneous diseases	1,601	(2.3)	243	(1.9)	1,352	(2.4)	6	(1.7)
Chronic respiratory diseases	1,566	(2.2)	211	(1.7)	1,340	(2.3)	15	(4.2)
Neurological disorders	1,361	(1.9)	240	(1.9)	1,118	(1.9)	3	(0.8)
Neoplasms	1,342	(1.9)	157	(1.3)	1,170	(2.0)	15	(4.2)
Mental disorders	991	(1.4)	126	(1.0)	841	(1.5)	24	(6.8)
Diabetes and kidney diseases	794	(1.1)	102	(0.8)	672	(1.2)	20	(5.6)
Sense organ disease	643	(0.9)	196	(1.6)	446	(0.8)	1	(0.3)

	All[a]		Outpatient cases		Inpatient cases		Unlabeled cases	
Diagnosis	**N=70,372**	**(93.4)**	**N=12,538**	**(17.8)**	**N=57,480**	**(81.7)**	**N=354**	**(0.5)**
Substance use disorders	122	(0.2)	45	(0.4)	76	(0.1)	1	(0.3)
Injuries	**21,755**	**(30.9)**	**3,902**	**(31.1)**	**17,739**	**(30.9)**	**114**	**(22.1)**
No clearly identifiable cause	16,726	(23.8)	2,416	(19.3)	14,264	(24.8)	46	(13.0)
Unintentional injuries	3,555	(5.1)	1,098	(8.8)	2,421	(4.2)	36	(10.2)
Road traffic injuries	1,321	(1.9)	347	(2.8)	949	(1.7)	25	(7.1)
Self-harm	43	(0.06)	9	(0.07)	33	(0.06)	1	(0.3)
Interpersonal violence	110	(0.16)	32	(0.26)	72	(0.13)	6	(1.7)

Data are presented as N (%). GBD: global burden of diseases and injuries; MACs: medical assistance centers; HIV; human immunodeficiency virus, AIDS; acquired immunodeficiency syndrome, STI; sexually transmitted infections.

[a] No further subdivision possible for 5,013 cases in various GBD groups: unclassified (N=4,721) and unknown (N=292).

[b] Such as sepsis, meningitis, encephalitis, varicella and herpes zoster and acute hepatitis.

[c] Such as urinary tract infections, kidney stones and allergic reactions.

Table 3 Type of injuries of 21,755 Dutch travelers reported by MACs presented by the GBD cause list levels two and three where possible.

	All[a]		Africa[b]		America[c]		Asia[d]		Europe[e]		Oceania[f]	
Diagnosis	**N=21,755**		**N=853**	**(3.9)**	**N=1,052**	**(4.8)**	**N=2,966**	**(13.6)**	**N=16,773**	**(77.1)**	**N=111**	**(0.5)**
Road traffic injuries	**1,321/5,029**	**(26.3)**	**79/244**	**(32.4)**	**112/378**	**(29.6)**	**196/995**	**(19.7)**	**925/3,386**	**(27.3)**	**9/26**	**(34.6)**
Road injuries	1,262/1,293	(97.6)	77/78	(98.7)	99/100	(99.0)	186/190	(97.9)	891/916	(97.3)	9/9	(100)
Pedestrian road injuries	37	(2.9)	1	(1.3)	4	(4.0)	9	(4.8)	23	(2.6)	-	
Cyclist road injuries	375	(29.7)	3	(3.9)	16	(16.2)	9	(4.8)	346	(38.8)	1	(11.1)
Motorcyclist road injuries	312	(24.7)	10	(13.0)	14	(14.1)	83	(44.6)	205	(23.0)	-	
Motor vehicle road injuries	442	(35.0)	57	(74.0)	61	(61.6)	60	(32.3)	256	(28.7)	8	(88.9)
Undefined	96	(7.6)	6	(7.8)	4	(4.0)	25	(13.4)	61	(6.8)		
Other traffic injuries	31/1,293	(2.4)	1/78	(1.3)	1/100	(1.0)	4/190	(2.1)	25/916	(2.7)	-	
Unintentional injuries	**3,555/5,029**	**(70.7)**	**154/244**	**(63.1)**	**252/378**	**(66.7)**	**763/995**	**(76.7)**	**2,370/3,386**	**(70.0)**	**16/26**	**(61.5)**
Falls	2,034/3,295	(61.7)	69/142	(48.6)	81/244	(33.2)	333/685	(48.6)	1,540/2,209	(69.7)	11/15	(73.3)
Animal contact[g]	232/3,295	(7.0)	15/142	(10.5)	26/244	(10.7)	74/685	(10.8)	115/2,209	(5.2)	2/15	(13.3)
Exposure to forces of nature[h]	209/3,295	(6.3)	14/142	(9.9)	67/244	(27.5)	87/685	(12,7)	40/2,209	(1.8)	1/15	(6.7)
Fire, heat and hot substances[i]	161/3,295	(4.9)	12/142	(8.5)	7/244	(2.9)	28/685	(4.1)	113/2,209	(5.1)	1/15	(6.7)
Environmental heat and cold exposure	150/3,295	(4.6)	10/142	(7.0)	16/244	(6.6)	53/685	(7.7)	71/2,209	(3.2)	-	
Adverse effects of medical treatment	140/3,295	(4.2)	6/142	(4.2)	10/244	(4.1)	27/685	(3.9)	97/2,209	(4.4)	-	
Other unintentional injuries	137/3,295	(4.2)	3/142	(2.1)	12/244	(4.9)	30/685	(4.4)	92/2,209	(4.2)	-	
Foreign body	106/3,295	(3.2)	7/142	(4.9)	7/244	(2.9)	23/685	(3.4)	69/2,209	(3.1)	-	
Poisonings	65/3,295	(2.0)	4/142	(2.8)	8/244	(3.3)	19/685	(2.8)	34/2,209	(1.5)	-	
Drowning	43/3,295	(1.3)	2/142	(1.4)	10/244	(4.1)	8/685	(1.2)	23/2,209	(1.0)	-	
Exposure to mechanical forces	18/3,295	(0.5)	-		-		3/685	(0.4)	15/2,209	(0.7)	-	
Self-harm and interpersonal violence	**153/5,029**	**(3.0)**	**11/244**	**(4.5)**	**14/378**	**(3.7)**	**36/995**	**(3.6)**	**91/3,386**	**(2.7)**	**1/26**	**(3.8)**
Self-harm	43/144	(29.9)	1/11	(9.1)	3/13	(23.1)	6/33	(18.2)	33/86	(38.4)	-	
Interpersonal violence	99/144	(68.8)	8/11	(72.7)	10/13	(76.9)	27/33	(81.8)	53/86	(61.6)	1	(100)
Conflict and terrorism	2/144	(1.4)	2/11[j]	(18,2)	-		-		-		-	

Data are presented as N (%). MACs: medical assistance centers; GBD: global burden of diseases and injuries.

[a] Inpatient cases N=17,739 (81.5%), outpatient cases N=3,902 (17.9%), missing N=114 (0.5%). For N=16,726 travelers (77%) no cause was identified.

[b] Northern Africa N=522 (61.2%), Sub-Saharan Africa N=331 (38.8%).

[c] Caribbean N =289 (27.5%), Northern America N=339 (32.2%), Central America N=80 (7.6), South America N=344 (32.7%).

[d] Western Asia N=1,650 (55.6%), South-Eastern Asia N=1,058 (35.7%), Southern Asia N=175 (5.9%), Eastern Asia N=81 (2.7%), Central Asia N=2 (0.07%).

[e] Western Europe N=11,431 (68.2%), Southern Europe N=4,220 (25.2%), Northern Europe N=602 (3.6%), Eastern Europe N=520 (3.1%).

[f] Australia and New Zealand N=111 (100%).

[g] Of which at least 35 with a venomous animal (Africa N=5, America N=4, Asia N=4, Europe N=18, Oceania N=2): snakes N=20, scorpions N=4, spiders N=3, ocean animals N=3, unspecified N=3 (8%), bees or wasps N=2. Four travelers were bitten by a monkey, one traveler was scratched by a monkey, and four travelers were bitten by a cat.

[h] Travelers experienced atmospheric and hydrostatic pressure-related side effects like decompression illness N=40 (19%) and mountain sickness N=56 (27%).

[i] Location of the burns were known for 75% of the cases (N=121): lower extremities N=42 (34.7%), upper extremities N=26 (21.5%), face, head and neck N=18 (14.9%), multiple regions N=18 (14.9%), trunk N=17 (14.0%).

[j] Bomb attack in Marrakech, Morocco in 2011.

Table 4 Medical assistance presented by the GBD cause list level two categorized by younger (65-) and older (65+) travelers reported by MACs.

	All		65-		65+		Age unknown	
Diagnosis	**N=75,385**		**N=49,702**	**(65.9)**	**N=25,646**	**(34.0)**	**N=37**	**(0.05)**
Communicable, maternal, neonatal and nutritional diseases	**14,955**	**(19.8)**	**10,994**	**(22.1)**	**3,949**	**(15.4)**	**12**	**(32.4)**
Enteric infections	7,235	(48.4)	5,844	(53.2)	1,385	(35.1)	6	(50.0)
Respiratory infections and tuberculosis	4,973	(33.3)	2,845	(25.9)	2,124	(53.8)	4	(33.3)
Maternal and neonatal disorders	986	(6.6)	985	(9.0)	-		1	(8.3)
Other infectious diseases	931	(6.2)	644	(5.9)	286	(7.2)	1	(8.3)
Neglected tropical diseases and malaria	748	(5.0)	629	(5.7)	119	(3.0)	-	
Nutritional deficiencies	47	(0.3)	13	(0.1)	34	(0.9)	-	
HIV, AIDS and STI	35	(0.2)	34	(0.3)	1	(0.03)	-	
Non-communicable diseases	**33,662**	**(44.7)**	**19,484**	**(39.2)**	**14,166**	**(55.2)**	**12**	**(32.4)**
Cardiovascular diseases	13,016	(38.7)	5,763	(29.6)	7,249	(51.2)	4	(33.3)
Digestive system diseases	6,612	(19.6)	4,557	(23.4)	2,053	(14.5)	2	(16.7)
Other non-communicable diseases	3,791	(11.3)	2,547	(13.1)	1,243	(8.8)	1	(8.3)
Musculoskeletal disorders	1,823	(5.4)	1,233	(6.3)	590	(4.2)	-	
Skin and subcutaneous diseases	1,601	(4.8)	1,077	(5.5)	523	(3.7)	1	(8.3)
Chronic respiratory diseases	1,566	(4.7)	800	(4.1)	765	(5.4)	1	(8.3)
Neurological disorders	1,361	(4.0)	984	(5.1)	376	(2.7)	1	(8.3)
Neoplasms	1,342	(4.0)	661	(3.4)	681	(4.8)	-	
Mental disorders	991	(2.9)	889	(4.6)	102	(0.7)	-	
Diabetes and kidney diseases	794	(2.4)	392	(2.0)	402	(2.8)	-	
Sense organ disease	643	(1.9)	463	(2.4)	178	(1.3)	2	(16.7)
Substance use disorders	122	(0.4)	118	(0.6)	4	(0.03)	-	

	All		65-		65+		Age unknown	
Diagnosis	**N=75,385**		**N=49,702**	**(65.9)**	**N=25,646**	**(34.0)**	**N=37**	**(0.05)**
Injuries	**21,755**	**(28.9)**	**15,993**	**(32.2)**	**5,753**	**(22.4)**	**9**	**(24.3)**
No clearly identifiable cause	16,726	(76.9)	12,289	(76.8)	4,432	(77.0)	5	(55.6)
Unintentional injuries	3,555	(16.3)	2,541	(15.9)	1,010	(17.6)	4	(44.4)
Road traffic injuries	1,321	(6.1)	1,019	(6.4)	302	(5.2)	-	
Self-harm	43	(0.2)	41	(0.3)	2	(0.03)	-	
Interpersonal violence	110	(0.5)	103	(0.6)	7	(0.12)	-	
Unclassified symptoms and signs	**4,721**	**(6.3)**	**3,025**	**(6.1)**	**1,693**	**(6.6)**	**3**	**(8.1)**
Unknown	**292**	**(0.4)**	**206**	**(0.4)**	**85**	**(0.3)**	**1**	**(2.7)**

Data are presented as N (%). GBD: global burden of diseases; MACs: medical assistance centers; HIV; human immunodeficiency virus, AIDS; acquired immunodeficiency syndrome, STI; sexually transmitted infections.

Table 5 Cause of deaths without medical assistance presented by the GBD cause list levels one and two categorized by younger (65-) and older (65+) travelers reported by MACs.

	All		65-		65+		Age unknown	
Diagnosis	**N=1,431**		**N=489**	**(34.2)**	**N=601**	**(42.0)**	**N=341**	**(23.8)**
Communicable, maternal, neonatal and nutritional diseases	**26**	**(1.8)**	**10**	**(2.0)**	**8**	**(1.3)**	**8**	**(2.3)**
Respiratory infections and tuberculosis[a]	9	(34.6)	3	(30.0)	5	(62.5)	1	(12.5)
Other infectious diseases[b]	8	(30.8)	2	(20.0)	2	(25.0)	4	(50.0)
Maternal and neonatal disorders[c]	6	(23.1)	4	(40.0)	-		2	(25.0)
Neglected tropical diseases and malaria[d]	2	(7.7)	1	(10.0)	1	(12.5)	-	
Enteric infections	1	(3.8)	-		-		1	(12.5)
Non-communicable diseases	**780**	**(54.5)**	**207**	**(42.3)**	**370**	**(61.6)**	**203**	**(59.5)**
Cardiovascular diseases	724	(92.8)	191	(92.3)	351	(94.9)	182	(89.7)
Neoplasms	31	(4.0)	9	(4.3)	12	(3.2)	10	(4.9)
Digestive system diseases	8	(1.0)	3	(1.4)	1	(0.3)	4	(2.0)
Chronic respiratory diseases	8	(1.0)	-		4	(1.1)	4	(2.0)
Neurological disorders	4	(0.5)	2	(1.0)	1	(0.3)	1	(0.5)
Substance use disorders	1	(0.1)	-		-		1	(0.5)
Diabetes and kidney diseases	2	(0.3)	-		1	(0.3)	1	(0.5)
Other non-communicable diseases	2	(0.3)	2	(1.0)	-		-	
Injuries	**266**	**(18.6)**	**162**	**(33.1)**	**59**	**(9.8)**	**45**	**(13.2)**
Road traffic injuries	142	(53.4)	93	(57.4)	32	(54.2)	17	(37.8)
Road injuries	117	(82.4)	71	(76.3)	30	(93.8)	16	(94.1)
Pedestrian road injuries	8	(6.8)	6	(8.5)	1	(3.3)	1	(6.3)
Cyclist road injuries	11	(9.4)	4	(5.6)	6	(20.0)	1	(6.3)
Motorcyclist road injuries	12	(10.3)	9	(12.7)	1	(3.3)	2	(12.5)

	All		65-		65+		Age unknown	
Diagnosis	**N=1,431**		**N=489**	**(34.2)**	**N=601**	**(42.0)**	**N=341**	**(23.8)**
Motor vehicle road injuries	58	(49.6)	36	(50.7)	11	(36.7)	11	(68.8)
Undefined	28	(23.9)	16	(22.5)	11	(36.7)	1	(6.3)
Other traffic injuries[e]	25	(17.6)	22	(23.7)	2	(6.3)	1	(5.9)
Unintentional injuries	94	(35.3)	49	(30.2)	26	(44.1)	19	(42.2)
Falls	43	(45.7)	20	(40.8)	14	(53.8)	9	(47.4)
Drowning	28	(29.8)	13	(26.5)	7	(26.9)	8	(42.1)
Fire, heat and hot substances	1	(1.1)	1	(2.0)	-		-	
Environmental heat and cold exposure	1	(1.1)	1	(2.0)	-		-	
Exposure to forces of nature	6	(6.4)	5	(10.2)	-		1	(5.3)
Other unintentional injuries	5	(5.3)	4	(8.2)	-		1	(5.3)
Undefined	10	(10.6)	5	(10.2)	5	(19.2)	-	
Self-harm and interpersonal violence	**27**	**(10.2)**	**20**	**(12.3)**	**1**	**(1.7)**	**6**	**(13.3)**
Self-harm (i.e. suicide)	20	(74.1)	16	(80.0)	1	(100)	3	(50.0)
Interpersonal violence[f]	7	(25.9)	4	(20.0)	-		3	(50.0)
No clearly identifiable cause[g]	3	(1.1)	-		-		3	(6.7)
Unclassified symptoms and signs	**22**	**(1.5)**	**10**	**(2.0)**	**11**	**(1.8)**	**1**	**(0.3)**
Unknown	**337**	**(23.5)**	**100**	**(20.4)**	**153**	**(25.5)**	**84**	**(24.6)**

Data are presented as n (%). GBD; global burden of disease; MACs: medical assistance centers.

[a] Pneumonia N=8.

[b] Sepsis N=4, meningitis N=3, blood in lungs N=1.

[c] Premature birth

[d] Malaria N=2, in Thailand and Gambia.

[e] Includes plane crash Tripoli, Libya in 2010 (N=18).

[f] By firearm N=3, by sharp object N=1.

[g] Missing person N=1, death as a result of injuries by an unknown cause N=2.

Discussion

In this large retrospective study we explored the disease burden in over 77,000 Dutch travelers who received hospital-based care abroad or who died before reaching the hospital. Western (33%) and Southern Europe (24%), and Western Asia (15%) were the top three regions where travelers sought medical care. Injuries, cardiovascular diseases, and the classical traveler's diseases (enteric infections and respiratory tract infections (RTIs)) were the leading diagnoses. One in every three medical consultations concerned older travelers (65+). Cardiovascular conditions accounted for half of the causes of death, followed by road traffic accidents (RTAs). Repatriation was necessary for one in five travelers, mostly for non-communicable diseases (e.g. cardiovascular diseases) or injuries.

Our findings regarding the occurrence of enteric infections and RTIs are in line with earlier findings [20-22]. However, our results differ in the associated hospitalization rates for these infectious diseases with respect to a Finnish study with a comparable study design: Finnish travelers were more frequently hospitalized for a RTI than for an enteric infection, while the opposite was seen in our study [20]. Inpatient cases accounted for 82% of our study population and this is much higher than the 16% reported in another Finnish study. In addition, Finnish travelers in need of medical help seemed overall younger than the Dutch [6]. Both studies have a large sample size, so it could be that Finnish travelers with health complaints consulted a physician in an earlier stage than the Dutch and outpatient care sufficed. The majority of medical assistance was provided to Dutch travelers in Western and Southern Europe and Western Asia, whilst top locations were Europe and Eastern Mediterranean and South-Eastern Asia in the Finnish study [6]. More Finnish than Dutch travelers visited Southern Mediterranean countries, and the number of medical consultations is more than twice as high (54% vs 24%). Most of our Western Asia travelers visited Turkey (94%), probably due to the large number of 'visiting friends and relatives' (VFR, as the Turkish-Dutch population is the largest immigrant population in our country) and the huge range of cheap package holidays in the coastal regions. Further comparison of our data with previous studies is limited due to the differences in classifications of key variables, such as the used medical diagnosis classification methods (ICD vs GBD) [6, 20, 23].

Almost a third of all medical consultations were due to an injury, either unintentional or as a result of a RTA. Injuries were mainly sustained in South-Eastern and Southern Asia, Australia and New Zealand. Literature shows that traffic injuries among international travelers consistently accounts for more travel-related morbidity and mortality than infectious diseases [24]. Stewart et al. described that travelers have a more than ten-fold risk of dying from an injury than due to an infection [8]. RTA are reported to be more common in LOMIC-countries and in countries with opposite driving conditions (i.e. left-hand vs right-hand driving). Our data identifies that twice as many cyclists, motorcyclists and pedestrians as motor vehicle occupants were injured, which corresponds with existing literature [8, 9, 24]. Sapsirisavat et al. reported that well-known risk factors such as night-time driving and alcohol use doubled the risk of hospitalization after a RTA [25]. Unfortunately, of all injured travelers in the HAZARD study an identifiable cause was only reported in 23% of the cases. Of these, older travelers (65+) accounted for half (50%) of the reported injured pedestrians in the HAZARD study. This is consistent with the literature that older travelers represent a large group of fatalities among pedestrian victims [24]. In the pre-travel consultation, personal safety (e.g. wearing a seatbelt, renting a vehicle with a qualified driver, wearing a bike helmet, crossing roads safely as a pedestrian) should be emphasized [9, 24]. Dutch travelers can register themselves pre-travel at the information service tool of the MoFA to be informed about (changes in) the local security situation [26]. The Dutch travelers who were killed during the plane crashes in Tripoli, Libya in May 2010 and in Ukraine in July 2017 (MH17) accounted for 1.3% of the deceased travelers of the MACs study population and 21% of the MoFA data, respectively. Due to this exceptional cause of death, the large group of MH17 victims were excluded from the analysis as they would influence the results (e.g. lower the median age as many young families were involved).

Nearly 1.5% of the consultations concerned travelers with a mental illness, mostly receiving medical assistance in countries close to their home country. It is unknown if this condition was pre-existing. Individuals with known or high risk for mental illness can travel, but are strongly advised to discuss their travel plan with a mental health professional [27, 28]. Rofaiel et al. [29] reported that very few mental health patient organizations have pre-travel information available online, while travel can have both negative and positive effects on (mental) health [30]. It is estimated that 10-20%

of all repatriations concerned psychiatric emergencies (e.g. due to a pre-existing illness, a first-time event that is triggered by stress or after experimenting with alcohol or drugs) [31]. In our study, this number of repatriated psychiatric travelers was even higher (29%). The difference could be explained by the fact that most of our cases were repatriated from destinations nearby their home country. For 'far-away' destinations the patient should first have clearance to travel (fit-to-fly) before they can be repatriated as this type of transport can differ from other medical repatriations as it depends partly on the patient's cooperation, and the occurrence of aggressive and/or anxiety behavior, and the willingness of an airline company to transport these patients [31]. Therefore, patients are often accompanied by two (para)medical escorts instead of one. Mental health in travelers is a neglected topic and deserves more research [31, 32].

A relatively small number of Dutch travelers required medical help after suffering from an animal bite (i.e. dogs, cats, monkeys) [33]. Our numbers are lower than the study of Verdoes et al [34]. They reported on 691 Dutch travelers who actively contacted their MAC due to an animal-associated injury in a four-year period (2015 –2019), with most incidents occurring in South-Eastern Asia. This difference can be explained by the fact that Verdoes et al. analyzed all contact moments with the MAC, while the HAZARD study was limited to contacts concerning in- and outpatient care. According to EuroTravNet, exposure to animals accounted for nearly 3% (2,688 / 103,739) of all medical consultations in participating clinics during or after travel between 1998-2018. Most exposures were in Asia (mainly South-East Asia) and involved bites from dogs, monkeys, cats and bats [35].

A small number of travelers (701/75,385, 0.9%) died despite receiving medical help and as expected, cardiovascular diseases and injuries accounted for the largest proportion. This is in line with previous studies [11, 23]. Suicide and interpersonal violence accounted for a small proportion of deaths (n=113).

Twenty percent of the travelers were repatriated after receiving hospital-based care. This number is much higher compared to that in Finnish (4%) [6] and Norwegian travelers (13%) [23]. It is possible that repatriations were not always for medical reasons, but due to patient's wishes or due to high costs of hospital care abroad, (FL, personal communication, 13 July, 2021). According to a study of Greuters et al. [36] 67% of travelers repatriated by aeromedical transportation concerned mainly

older travelers (≥50 years) from Europe (often the Mediterranean) due to cardiovascular diseases. This pattern is also seen in our study.

This study has a number of strengths. First, the multicenter design resulted in one of the largest datasets covering a five-year period. Second, all types of travelers were investigated including children and uninsured Dutch travelers (from MoFA) to generate a broader scope of health-related problems during travel in the Dutch travelers population worldwide. In addition, differences in travel-related diseases between older (65+) and young (65-) travelers could be clearly distinguished. Third, using the Global Burden of Disease Study 2019 cause list resulted in a more comprehensive overview of diseases and injuries than the different versions of ICD. We also believe that the ICD classification has some inaccuracies as it is more focused on the organs involved in a disease instead of the etiological origin: ICD categorizes for example a pneumonia as a respiratory system disease, while the GBD classifies it as a RTI.

This study also has its limitations. First**,** due to high workload of extracting data from the different operating systems not all MAC's in the Netherlands could participate. However, as several large MACs were included this will minimize the chance of bias given the size of the population. Second, the dataset consisted of routinely collected data leading to missing values and/or possible inaccuracies in study variables such as medical diagnosis, travel purpose and length of hospital stay. Records were cross-checked to minimize this where possible. Travelers might have been wrongly classified as 'outpatient' if a traveler died on the day of admission to the hospital. The number of outpatient cases (18%) in the study could therefore be an overestimation. In addition, medical tourism (e.g. dental care, elective surgery or fertility treatment) was excluded in the HAZARD study, but this group of travelers is interesting as these kind of trips can be a risky event since the quality of local healthcare can be different from that in the home country [37]. Third, the UNTWO travel data on Dutch travelers did not include an age distribution, making it impossible to calculate incidence proportions for the different age categories. This could have led to a base rate fallacy. However, we think that overestimation of the incidence proportions in the older age group is unlikely because it is improbable that there were more 65+ than 65- travelers in the UNWTO database. Fourth, the use of databases of MACs databases to assess travel-related health problems abroad, will

skew the data towards more serious health conditions for which hospital-based care is required. Therefore these study results are not representative of the most common health problems in travelers abroad as most illnesses are self-limiting and medical help is not necessary. However, our results do provide a detailed insight on the most severe travel-related health problems. Fifth, no distinction could be made for the specific VFR group of travelers as they might differ in risk-seeking and travel behavior from holiday makers. Seeking pre-travel advice is less common in this group of travelers while they often travel to high-risk environments [38]. In our study, 2% was recorded as VFR, but not all MACs defined this specific group separately leading to an underestimation of the total number VFRs. Sixth**,** information on pre-existing illnesses was not available in the MACs databases. In a study of Wieten et al. 26% of the travelers visiting the travel clinic for pre-travel advice had a medical condition (often cardiovascular); this was doubled in older travelers [39]. However, in a prospective cohort study we found that exacerbations of pre-existing illness as a health problem while being abroad was only rarely reported by older travelers to the tropics [30]. In addition, the post-travel health status of affected travelers was unknown since no (medical) follow up was done by the MAC after discharging from the hospital or after the repatriation. Sometimes travelers needed to be readmitted in a Dutch hospital or rehabilitation facility. It is therefore unknown what the consequences were following the foreign hospitalization, such as the acquisition of multiresistant pathogens [40], resulting in an underestimation of the actual disease burden and associated morbidity. Lastly, due to the mutual contact between the participation MACs it could be possible that more than one center was involved in special cases resulting in a double included record in the dataset. Given the size of the dataset we believe that these few cases do not affect our results.

In practice

Data from the HAZARD project can be considered as a proxy for the incidence proportion of serious health problems experienced by Dutch travelers while traveling abroad. Not only the usual suspects communicable diseases such as RTIs and enteric infections are common, but more importantly injuries and non-communicable diseases, such as cardiovascular diseases, have the largest influence on travelers

health and itinerary. The pre-travel advice should therefore, also for travelers to destinations within Europe, besides the standard infection prevention topics, provide information about adequate travel insurance, considering the possibility of an unplanned exposure to foreign healthcare and personal (road) safety [25, 41-43]. Since injuries are frequently experienced, it would be interesting for MAC's worldwide to expand their current database systems by not only reporting the ICD code, but also record the injury cause instead of the body areas affected. As a result, frequent overviews can be generated with little effort providing important practical information that can be used towards the travelers they represent [23].

List of abbreviations

LOMIC (low- or middle-income countries), MAC (Medical Assistance Center), EuroTravNet (European Travel and Tropical Medicine Network), HAZARD (reasons for HospitAliZAtions, Repatriation and causes of Death among Dutch travelers), ANWB (Royal Dutch Touring Club), MoFA (Dutch Ministry of Foreign Affairs), ICD (International Classification of Diseases), WHO (World Health Organization), GBD (Global Burden of Disease), UN (United Nations), UNWTO (World Tourism Organization), IT (Information Technology), SPSS (Statistical Package for the Social Sciences), CME (Committee Medical Ethics), LUMC (Leiden University Medical Center), IQR (interquartile range), RTI (respiratory infection), RTA (road traffic accident), SD (standard deviation), VFR (visiting friends and relatives).

Ethics approval and consent to participate

The study was endorsed by the Committee Medical Ethics (CME) of the Leiden University Medical Center (LUMC), Leiden, the Netherlands (registry number C15.067). Written informed consent was not required as the study did not fall under the scope of the Medical Research Involving Human Subjects Act (in Dutch WMO). The study was registered in the Netherlands Trial Register under NL5377 (NTR5478).

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Credit authorship contribution statement

Jessica A. Vlot: Conceptualization, Data curation, Formal analysis, Project administration, Visualization, Writing – original draft, Writing – review & editing.
Jim E. van Steenbergen: Conceptualization, Supervision, Writing – review & editing
HAZARD project group: Data curation, Resources, Writing – review & editing.
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Leonardus G. Visser: Conceptualization, Supervision, Writing – review & editing.

Declaration of competing interest

All authors declare that they have no conflicts of interest.

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Supplementary data

Supplementary Table S1 GBD cause list with four levels.

Diagnosis group	GBD Level
Communicable, maternal, neonatal and nutritional diseases	**1**
HIV, AIDS and STI	2
Respiratory infections and tuberculosis	2
Enteric infections	2
Neglected tropical diseases and malaria	2
Other infectious diseases	2
Maternal and neonatal disorders	2
Neonatal disorders	2
Nutritional deficiencies	2
Non-communicable diseases	**1**
Neoplasms	2
Cardiovascular diseases	2
Chronic respiratory diseases	2
Digestive diseases	2
Neurological disorders	2
Mental disorders	2
Substance use disorders	2
Diabetes and kidney diseases	2
Skin and subcutaneous diseases	2
Sense organ diseases	2
Musculoskeletal disorders	2
Other non-communicable diseases	2
Injuries	**1**
Transport injuries	*2*
Road injuries	3
Pedestrian road injuries	4
Cyclist road injuries	4
Motorcyclist road injuries	4
Motor vehicle road injuries	4
Other road injuries	4
Other transport injuries	3
Unintentional injuries	*2*
Falls	3

Diagnosis group	GBD Level
Drowning	3
Fire, heat and hot substances	3
Poisonings	3
Exposure to mechanical forces	3
Adverse effects of medical treatment	3
Animal contact	3
Foreign body	3
Environmental heat and cold exposure	3
Other unintentional injuries	3
Self-harm and interpersonal violence	**2**
Self-harm	3
Interpersonal violence	3
Conflict and terrorism	3
Police conflict and executions	3

GBD: Global burden of diseases and injuries; HIV; human immunodeficiency virus, AIDS; acquired immunodeficiency syndrome, STI; sexually transmitted infections.

Supplementary Table S2 Geographic (sub)regions according to the United Nations (UN) Statistics Division[1].

Geographic (sub)regions
Africa
Northern Africa
Sub-Saharan Africa
Eastern Africa
Middle Africa
Southern Africa
Western Africa
Americas
Latin America and the Caribbean
Caribbean
Central America
South America
Northern America
Antarctica
Asia
Central Asia
Eastern Asia
South-Eastern Asia
Southern Asia
Western Asia
Europe
Eastern Europe
Northern Europe
Southern Europe
Western Europe
Oceania
Australia and New Zealand
Melanesia
Micronesia
Polynesia

UN: United Nations.

Supplementary Table S3 Numbers and incidence proportions of in- and outpatient cases between 2010-2014 per region reported by MACs.

		All[b] N=75,384			Inpatient cases[b] N=61,208			Outpatient cases N=13,791		
Destination	**Total number of Dutch travelers between 2010-2014[a]**	**Cases**		**Incidence proportion - per 10,000 travelers**	**Cases**		**Incidence proportion - per 10,000 travelers**	**Cases**		**Incidence proportion - per 10,000 travelers**
America										
Caribbean	1,407,371	1,523	(2.0)	10.82	1,210	(2.0)	8.60	300	(2.2)	2.13
Northern America	3,510,949	2,033	(2.7)	5.79	1,531	(2.5)	4.36	473	(3.4)	1.35
Central America	676,757	442	(0.6)	6.53	347	(0.6)	5.13	92	(0.7)	1.36
South America	1,335,537	2,083	(2.8)	15.60	1,829	(3.0)	13.69	246	(1.8)	1.84
Europe										
Northern Europe	13,379,112	1,646	(2.2)	1.23	1,419	(2.3)	1.06	221	(1.6)	0.17
Western Europe	72,174,801	24,905	(33.0)	3.45	21,139	(34.5)	2.93	3,669	(26.6)	0.51
Southern Europe	29,035,341	17,897	(23.7)	6.16	14,766	(24.1)	5.09	3,083	(22.4)	1.06
Eastern Europe	3,924,024	1,628	(2.2)	4.15	1,356	(2.2)	3.46	261	(1.9)	0.67
Africa										
Northern Africa	2,311,345	3,051	(4.1)	13.20	2,432	(4.0)	10.52	608	(4.4)	2.63
Sub-Saharan Africa	1,274,397	1,329	(1.8)	10.43	1,060	(1.7)	8.32	252	(1.8)	1.98
Asia										
Western Asia	6,870,985	11,284	(15.0)	16.42	7,676	(12.5)	11.17	3,516	(25.5)	5.12
Central Asia	39,222	11	(0.01)	2.80	8	(0.01)	2.04	3	(0.02)	0.76
South-Eastern Asia	3,204,121	5,656	(7.5)	17.65	4,821	(7.9)	15.05	807	(5.9)	2.52
Eastern Asia	1,443,891	621	(0.8)	4.30	534	(0.9)	3.70	72	(0.5)	0.50
Southern Asia	627,301	851	(1.1)	13.57	728	(1.2)	11.61	119	(0.9)	1.90
Oceania	**366,396**	**424**	**(0.6)**	**11.57**	**352**	**(0.6)**	**9.61**	**69**	**(0.5)**	**1.88**

Date are presented as N (%), unless otherwise specified. MACs: medical assistance centers.

[a] Number of Dutch travelers arriving at the specific destination was obtained from the world tourism organization (UNWTO).

[b] Destination missing for one traveler.

Supplementary Table S4 Numbers and incidence proportions per 10,000 Dutch travelers presented by the GBD cause list level one between 2010-2014 per region reported by MACs.

		All cases			Communicable, maternal, neonatal and nutritional diseases			Non-communicable diseases			Injuries		
Destination	**Total number of Dutch travelers between 2010-2014[a]**	**Cases**		**Incidence proportion - per 10,000 travelers**	**Cases**		**Incidence proportion - per 10,000 travelers**	**Cases**		**Incidence proportion - per 10,000 travelers**	**Cases**		**Incidence proportion - per 10,000 travelers**
America													
Caribbean	1,407,371	1,523	(2.0)	10.82	427	(2.9)	3.03	722	(2.1)	5.13	289	(1.3)	2.05
Northern America	3,510,949	2,033	(2.7)	5.79	310	(2.1)	0.88	1,197	(3.6)	3.41	339	(1.6)	0.97
Central America	676,757	442	(0.6)	6.53	168	(1.1)	2.48	167	(0.5)	2.47	80	(0.4)	1.18
South America	1,335,537	2,083	(2.8)	15.60	594	(3.97)	4.45	1,040	(3.1)	7.79	344	(1.6)	2.58
Europe													
Northern Europe	13,379,112	1,630	(2.2)	1.22	174	(1.2)	0.13	768	(2.3)	0.57	602	(2.8)	0.45
Western Europe	72,174,801	24,905	(33.0)	3.45	2,026	(13.6)	0.28	9,786	(29.1)	1.36	11,431	(52.5)	1.58
Southern Europe	29,035,341	17,897	(23.7)	6.16	3,026	(20.2)	1.04	9,426	(28.0)	3.25	4,220	(19.4)	1.45
Eastern Europe	3,924,024	1,628	(2.2)	4.15	266	(1.8)	0.68	748	(2.2)	1.91	520	(2.4)	1.33
Africa													
Northern Africa	2,311,345	3,051	(4.0)	13.20	866	(5.8)	3.75	1,453	(4.3)	6.29	522	(2.4)	2.26
Sub-Saharan Africa	1,274,397	1,327	(1.8)	10.41	315	(2.1)	2.47	526	(1.6)	4.13	331	(1.5)	2.60
Asia													
Western Asia	6,870,985	11,284	(15.0)	16.42	4,072	(27.2)	5.93	4,760	(14.1)	6.93	1,650	(7.6)	2.40
Central Asia	39,222	11	(0.0)	2.80	2	(0.01)	0.51	7	(0.02)	1.78	2	(0.01)	0.51
South-Eastern Asia	3,204,121	5,656	(7.5)	17.65	2,145	(14.3)	6.69	2,135	(6.3)	6.66	1,058	(4.9)	3.30

		All cases			Communicable, maternal, neonatal and nutritional diseases			Non-communicable diseases			Injuries		
Destination	**Total number of Dutch travelers between 2010-2014[a]**	**Cases**		**Incidence proportion - per 10,000 travelers**	**Cases**		**Incidence proportion - per 10,000 travelers**	**Cases**		**Incidence proportion - per 10,000 travelers**	**Cases**		**Incidence proportion - per 10,000 travelers**
Eastern Asia	1,443,891	621	(0.8)	4.30	123	(0.8)	0.85	366	(1.1)	2.53	81	(0.4)	0.56
Southern Asia	627,301	851	(1.1)	13.57	317	(2.1)	5.05	315	(0.9)	5.02	175	(0.8)	2.79
Oceania	**366,396**	**424**	**(0.6)**	**11.57**	**46**	**(0.3)**	**1.26**	**245**	**(0.7)**	**6.69**	**111**	**(0.5)**	**3.03**

Date are presented as N (%), unless otherwise specified. GBD: global burden of diseases and injuries; MACs: medical assistance centers.

[a] Number of Dutch travelers arriving at the specific destination was obtained from the world tourism organization (UNWTO).

[b] Destination missing for one traveler.

Supplementary Table S5 Medical assistance presented by the GBD cause list level one categorized by age groups reported by MACs.

	All		Communicable, maternal, neonatal and nutritional diseases[a]		Non-communicable diseases[b]		Injuries[c]		Unclassified symptoms and signs		Unknown	
Age groups in years ***(n=75,348, information missing n=37)***	**N=75,348**		**N=14,943**	**(19.8)**	**N=33,650**	**(44.7)**	**N=21,746**	**(28.9)**	**N=4718**	**(6.3)**	**N=291**	**(0.4)**
Younger travelers (65-)	**49,702**	**(66.0)**	**10,994**	**(73.6)**	**19,484**	**(57.9)**	**15,993**	**(73.5)**	**3,025**	**(64.1)**	**206**	**(70.8)**
0-4	1,692	(3.4)	1,015	(9.2)	264	(1.4)	249	(1.6)	157	(5.2)	7	(3.4)
5-9	904	(1.8)	316	(2.9)	195	(1.0)	346	(2.2)	45	(1.5)	2	(1.0)
10-14	1,069	(2.2)	234	(2.1)	266	(1.4)	515	(3.2)	49	(1.6)	5	(2.4)
15-19	3,058	(6.2)	729	(6.6)	908	(4.7)	1,186	(7.4)	217	(7.2)	18	(8.7)
20-24	4,621	(9.3)	1,578	(14.4)	1,320	(6.8)	1,421	(8.9)	288	(9.5)	14	(6.8)
25-29	3,702	(7.4)	1,211	(11.0)	1,022	(5.2)	1,236	(7.7)	214	(7.1)	19	(9.2)
30-34	3,152	(6.3)	984	(9.0)	1,010	(5.2)	973	(6.1)	176	(5.8)	9	(4.4)
35-39	3,034	(6.1)	791	(7.2)	1,119	(5.7)	937	(5.9)	171	(5.7)	16	(7.8)
40-44	3,958	(8.0)	699	(6.4)	1,662	(8.5)	1,340	(8.4)	245	(8.1)	12	(5.8)
45-49	4,820	(9.7)	691	(6.3)	2,090	(10.7)	1,731	(10.8)	289	(9.6)	19	(9.2)
50-54	5,803	(11.7)	854	(7.8)	2,616	(13.4)	1,951	(12.2)	358	(11.8)	24	(11.7)
55-59	6,117	(12.3)	812	(7.4)	2,999	(15.4)	1,940	(12.1)	344	(11.4)	22	(10.7)
60-64	7,772	(15.6)	1,080	(9.8)	4,013	(20.6)	2,168	(13.6)	472	(15.6)	39	(18.9)
Older travelers (65+)	**25,646**	**(34.0)**	**3,949**	**(26.4)**	**14,166**	**(42.1)**	**5,753**	**(26.5)**	**1,693**	**(35.9)**	**85**	**(29.2)**
65-69	8,871	(34.6)	1,281	(32.4)	4,824	(34.1)	2,196	(38.2)	547	(32.3)	23	(27.1)
70-74	7,282	(28.4)	1,109	(28.1)	4,091	(28.9)	1,558	(27.1)	489	(28.9)	35	(41.2)

	All		Communicable, maternal, neonatal and nutritional diseases[a]		Non-communicable diseases[b]		Injuries[c]		Unclassified symptoms and signs		Unknown	
Age groups in years *(n=75,348, information missing n=37)*	**N=75,348**		**N=14,943**	**(19.8)**	**N=33,650**	**(44.7)**	**N=21,746**	**(28.9)**	**N=4718**	**(6.3)**	**N=291**	**(0.4)**
75-79	5,133	(20.0)	842	(21.3)	2,888	(20.4)	1,030	(17.9)	356	(21.0)	17	(20.0)
80-84	2,860	(11.2)	480	(12.2)	1,557	(11.0)	619	(10.8)	195	(11.5)	9	(10.6)
Above 85	1,500	(5.8)	237	(6.0)	806	(5.7)	350	(6.1)	106	(6.3)	1	(1.2)

Data are presented as N (%). MACs: medical assistance centers. HIV; human immunodeficiency virus, AIDS; acquired immunodeficiency syndrome, STI; sexually transmitted infections.

[s] Enteric infections N=7,229 (13.5%), respiratory infections and tuberculosis N=4,969 (9.3%), maternal and neonatal disorders N=986 (1.8%), other infectious diseases N=930 (1.7%), neglected tropical diseases and malaria N=748 (1.4%), nutritional deficiencies N=47 (0.1%), HIV, AIDS and STI N=35 (0.1%).

[b] Cardiovascular diseases N=13,012 (24.3%), digestive system diseases N=6,610 (12.3%), other non-communicable diseases N=3,790 (7.1%), musculoskeletal disorders N=1,823 (3.4%), skin and subcutaneous diseases N=1,600 (3.0%), chronic respiratory diseases N=1,565 (2.9%), neoplasms N=1,342 (2.5%), neurological disorders N=1,360 (2.5%), mental disorders N=991 (1.8%), diabetes and kidney diseases N=794 (1.5%), sense organ disease N=641 (1.2%), substance use disorders N=122 (0.2%).

[c] Unintentional injuries N=3,551 (6.6%), road traffic injuries N=1,321 (2.5%), self-harm and interpersonal violence N=153 (0.3%). No further subdivision possible for remaining 16,721 cases due to unidentifiable cause.

Supplementary Table S6 Medical assistance in children presented by the GBD cause list level one and two reported by MACs.

	All		0-4 years		5-9 years		10-14 years		15-19 years	
Diagnosis	**N=6,723**		**N=1,692**	**(25.2)**	**N=904**	**(13.4)**	**N=1,069**	**(15.9)**	**N=3,058**	**(45.5)**
Communicable, maternal, neonatal and nutritional diseases	**2,294**	**(34.1)**	**1,015**	**(60.0)**	**316**	**(35.0)**	**234**	**(21.9)**	**729**	**(23.8)**
Enteric infections	1,235	(53.8)	413	(40.7)	183	(57.9)	143	(61.1)	496	(68.0)
Respiratory infections and tuberculosis	765	(33.3)	440	(43.3)	114	(36.1)	67	(28.6)	144	(19.8)
Other infectious diseases	145	(6.3)	65	(6.4)	13	(4.1)	19	(8.1)	48	(6.6)
Maternal and neonatal disorders	98	(4.3)	89	(8.8)	-		-		9*	(1.2)
Neglected tropical diseases and malaria	47	(2.0)	7	(0.7)	6	(1.9)	5	(2.1)	29	(4.0)
HIV, AIDS and STI	3	(0.1)	1	(0.1)	-		-		2	(0.3)
Nutritional deficiencies	1	(0.04)	-		-		-		1	(0.1)
Non-communicable diseases	**1,633**	**(24.3)**	**264**	**(15.6)**	**195**	**(21.6)**	**266**	**(24.9)**	**908**	**(29.7)**
Digestive system diseases	620	(38.0)	36	(13.6)	73	(37.4)	141	(53.0)	370	(40.7)
Other non-communicable diseases	284	(17.4)	84	(31.8)	30	(15.4)	30	(11.3)	140	(15.4)
Neurological disorders	173	(10.6)	46	(17.4)	25	(12.8)	27	(10.2)	75	(8.3)
Skin and subcutaneous diseases	139	(8.5)	37	(14.0)	26	(13.3)	16	(6.0)	60	(6.6)
Chronic respiratory diseases	99	(6.1)	41	(15.5)	14	(7.2)	12	(4.5)	32	(3.5)
Cardiovascular diseases	70	(4.3)	3	(1.1)	5	(2.6)	5	(1.9)	57	(6.3)
Mental disorders	53	(3.2)	-		1	(0.5)	4	(1.5)	48	(5.3)
Diabetes and kidney diseases	51	(3.1)	4	(1.5)	7	(3.6)	16	(6.0)	24	(2.6)
Musculoskeletal disorders	47	(2.9)	3	(1.1)	4	(2.1)	5	(1.9)	35	(3.9)
Sense organ disease	41	(2.5)	6	(2.3)	10	(5.1)	7	(2.6)	18	(2.0)
Substance use disorders	39	(2.4)	-		-		-		39	(4.3)
Neoplasms	17	(1.0)	4	(1.5)	-		3	(1.1)	10	(1.1)

	All		0-4 years		5-9 years		10-14 years		15-19 years	
Diagnosis	**N=6,723**		**N=1,692**	**(25.2)**	**N=904**	**(13.4)**	**N=1,069**	**(15.9)**	**N=3,058**	**(45.5)**
Injuries	**2,296**	**(34.2)**	**249**	**(14.7)**	**346**	**(38.3)**	**515**	**(48.2)**	**1,186**	**(38.8)**
No clearly identifiable cause	1,850	(80.6)	195	(78.3)	324	(93.6)	461	(89.5)	870	(73.4)
Unintentional injuries	351	(15.3)	48	(19.3)	20	(5.8)	43	(8.3)	240	(20.2)
Road traffic injuries	71	(3.1)	3	(1.2)	2	(0.6)	10	(1.9)	56	(4.7)
Self-harm	11	(0.5)	3	(1.2)	-		-		8	(0.7)
Interpersonal violence	13	(0.6)	-		-		1	(0.2)	12	(1.0)
Unclassified symptoms and signs	**468**	**(7.0)**	**157**	**(9.3)**	**45**	**(5.0)**	**49**	**(4.9)**	**217**	**(7.1)**
Unknown	**32**	**(0.5)**	**7**	**(0.4)**	**2**	**(0.2)**	**5**	**(2.1)**	**18**	**(2.5)**

Date are presented as N (%), unless otherwise specified. GBD: global burden of diseases and injuries; MACs: medical assistance centers. HIV; human immunodeficiency virus, AIDS; acquired immunodeficiency syndrome, STI; sexually transmitted infections.

*Three child births (mothers were 16, 18 and 19 years old), and six pregnancies with complications (mothers were 17 years [n=2], 18 years [n=2], and 19 years old [n=2]).

Supplementary Table S7 Characteristics of 7,417 repatriations with a scheduled flight, with or without a medical escort.

	All scheduled flights N=7,417		Scheduled flight without medical escort N=4,389		Scheduled flight with medical escort N=3,028		p-value[a]
Gender							p=0.002
Female	3,498	(47.2)	2,136	(48.7)	1,362	(45.0)	
Male	3,918	(52.8)	2,252	(51.3)	1,666	(55.0)	
Unknown			1	(0.02)	-		
Age, *years, median (IQR)*	60	(44-70)	57	(40-78)	65	(51-73)	p<0.001[b]
Age, *years, mean (SD)*	55.7	(19.4)	53.2	(18.4)	59.3	(20.3)	
Age group in years							p<0.001
0-4	65	(0.9)	8	(0.2)	57	(1.9)	
5-19	330	(4.4)	190	(4.3)	140	(4.6)	
20-39	1,178	(15.9)	879	(20.0)	299	(9.9)	
40-59	2,012	(27.1)	1,361	(31.0)	651	(21.5)	
60-64	887	(12.0)	531	(12.1)	356	(11.8)	
65-69	1,006	(13.6)	553	(12.6)	453	(15.0)	
70-74	813	(11.0)	400	(9.1)	413	(13.6)	
75-79	608	(8.2)	289	(6.6)	319	(10.5)	
80-84	340	(4.6)	121	(2.8)	219	(7.2)	
≥85	178	(2.4)	57	(1.3)	121	(4.0)	
Destination							
America	*949*	*(12.8)*	*510*	*(11.6)*	*439*	*(14.5)*	*p=0.021*
Caribbean	232	(24.4)	118	(23.1)	114	(26.0)	p=0.793
Northern America	361	(38.0)	193	(37.8)	168	(38.3)	p=0.188
Central America	75	(7.9)	48	(9.4)	27	(6.2)	p=0.015
South America	281	(29.6)	151	(29.6)	130	(29.6)	p=0.210
Europe	*3,874*	*(52.2)*	*2,298*	*(52.4)*	*1,576*	*(52.0)*	*p<0.001*
Northern Europe	428	(11.0)	282	(12.3)	146	(9.3)	p<0.001
Western Europe	733	(18.9)	522	(22.7)	211	(13.4)	p<0.001
Southern Europe	2,547	(65.7)	1,404	(61.1)	1,143	(72.5)	p<0.001
Eastern Europe	166	(4.3)	90	(3.9)	76	(4.8)	p=0.277
Africa	*536*	*(7.2)*	*321*	*(7.3)*	*215*	*(7.1)*	*p<0.001*
Northern Africa	286	(53.4)	156	(48.6)	130	(60.5)	p=0.124
Sub-Saharan Africa	250	(46.6)	165	(51.4)	85	(39.5)	p<0.001
Asia	*1,951*	*(26.3)*	*1,191*	*(27.1)*	*760*	*(25.1)*	*p<0.001*
Western Asia	902	(46.2)	553	(46.4)	349	(45.9)	p<0.001

	All scheduled flights N=7,417		Scheduled flight without medical escort N=4,389		Scheduled flight with medical escort N=3,028		p-value[a]
Central Asia	3	(0.2)	3	(0.3)	-		-
South-Eastern Asia	824	(42.2)	503	(42.2)	321	(42.2)	p<0.001
Eastern Asia	86	(4.4)	49	(4.1)	37	(4.9)	p=0.196
Southern Asia	136	(7.0)	83	(7.0)	53	(7.0)	p=0.010
Oceania	*107*	*(1.4)*	*69*	*(1.6)*	*38*	*(1.3)*	*p=0.003*
Disease specification according GBD							
Communicable, maternal, neonatal and nutritional diseases	*1,102*	*(14.9)*	*753*	*(17.2)*	*349*	*11.5*	*p<0.001*
Enteric infections	348	(31.6)	290	(38.5)	58	16.6	p<0.001
Respiratory infections and tuberculosis	492	(44.6)	280	(37.2)	212	60.7	p=0.002
Maternal and neonatal disorders	56	(5.1)	43	(5.7)	13	3.7	p<0.001
Other infectious diseases	97	(8.8)	50	(6.6)	47	13.5	p=0.761
Neglected tropical diseases and malaria	102	(9.3)	89	(11.8)	13	3.7	p<0.001
Nutritional deficiencies	4	(0.4)	-		4	1.1	-
HIV, AIDS and STI	3	(0.3)	1	(0.1)	2	0.6	p=0.564
Non-communicable diseases	*3,735*	*(50.4)*	*1,952*	*(44.5)*	*1,783*	*58.9*	*p<0.006*
Cardiovascular diseases	1,514	(40.5)	709	(36.3)	805	45.1	p=0.014
Digestive diseases	762	(20.4)	540	(27.7)	222	12.5	p<0.001
Other non-communicable diseases	249	(6.7)	177	(9.1)	72	4.0	p<0.001
Musculoskeletal disorders	224	(6.0)	132	(6.8)	92	5.2	p=0.008
Skin and subcutaneous diseases	179	(4.8)	131	(6.7)	48	2.7	p<0.001
Chronic respiratory diseases	143	(3.8)	56	(2.9)	87	4.9	p=0.010
Neurological disorders	143	(3.8)	44	(2.3)	99	5.6	p<0.001
Neoplasms	221	(5.9)	71	(3.6)	150	8.4	p<0.001
Mental disorders	178	(4.8)	24	(1.2)	154	8.6	p<0.001
Diabetes and kidney diseases	72	(1.9)	27	(1.4)	45	2.5	p=0.034
Sense organ disease	45	(1.2)	39	(2.0)	6	0.3	p<0.001
Substance use disorders	5	(0.1)	2	(0.1)	3	0.2	p=0.655
Injuries	*2,348*	*(31.7)*	*1,518*	*(34.6)*	*830*	*27.4*	*p<0.001*
No clearly identifiable cause	2,220	(94.5)	1,132	(74.6)	702	84.6	-
Unintentional injuries	78	(3.3)	261	(17.2)	78	9.4	p<0.001
Transport injuries	46	(2.0)	117	(7.7)	46	5.5	p<0.001

	All scheduled flights N=7,417		Scheduled flight without medical escort N=4,389		Scheduled flight with medical escort N=3,028		p-value[a]
Self-harm and interpersonal violence	4	(0.2)	8	(0.5)	4	(0.5)	p=0.248
Unclassified symptoms and signs	*227*	*(3.1)*	*161*	*(3.7)*	*66*	*2.2*	*p<0.001*
Unknown	*5*	*(0.1)*	*5*	*(0.1)*	*0*		-

Date are presented as N (%), unless otherwise specified. IQR: interquartile range, SD: standard deviation, GBD: global burden of diseases and injuries; HIV; human immunodeficiency virus, AIDS; acquired immunodeficiency syndrome, STI; sexually transmitted infections.

[a] P-values were calculated using the Chi-Square test, unless otherwise specified.

[b] Calculated with the Mann-Whitney test.

Supplementary Table S8 Demographic and travel characteristics of 1,431 deceased Dutch travelers without receiving hospital-based care while being abroad between 2010 and 2014 reported by MACs.

	All cases N=1,431	
Gender (n=1090; 76.2%, information missing n=341)		
Female	297	(27.2)
Male	793	(72.8)
Unknown	341	(23.8)
Age, *years, median (IQR)* (n=1,083; 75.6%, information missing n=348)	66	(56-73)
Age group in years (n=1,090; 76.2%, information missing n=341)		
0-4	8	(0.7)
5-19	8	(0.7)
20-39	79	(7.2)
40-59	252	(23.1)
60-64	142	(13.0)
65-69	201	(18.4)
70-74	158	(14.5)
75-79	117	(10.7)
80-84	69	(6.3)
≥85	56	(5.1)
Travel duration (n=1,304; 91.1%, information missing n=127)		
Short-term travel (3-30 days)	899	(68.9)
Long-term travel (≥31 days)	405	(31.1)
Purpose of travel (n=530; 36.4%, information missing n=901)		
Leisure	500	(94.3)
Business	30	(5.7)
Destination		
America	*153*	*(10.7)*
Caribbean	41	(26.8)
Northern America	34	(22.2)
Central America	9	(5.9)
South America	69	(45.1)
Europe	*974*	*(68.1)*
Northern Europe	59	(6.1)
Western Europe	442	(45.4)
Southern Europe	428	(43.9)
Eastern Europe	45	(4.6)

	All cases N=1,431	
Africa	*81*	*(5.7)*
Northern Africa	55	(67.9)
Sub-Saharan Africa	26	(31.1)
Asia	*214*	*(15.0)*
Western Asia	77	(36.0)
Central Asia	2	(0.9)
South-Eastern Asia	114	(53.3)
Eastern Asia	10	(4.7)
Southern Asia	11	(5.1)
Oceania	*9*	*(0.6)*
Australia and New Zealand	9	(100)
RMR	**1,250**	**(87.4)**
Buried or cremated locally	**181**	**(12.6)**

Data are presented as n (%). MACs, medical assistance centers, IQR: interquartile range; RMR: repatriation of mortal remains.

Supplementary Table S9 Characteristics and causes of death of 728 Dutch travelers between 2013 and 2014, recorded by the Dutch MoFa.

	All		Communicable, maternal, neonatal and nutritional diseases		Non-communicable diseases		Injuries		Unclassified symptoms and signs		Unknown		Injuries including MH17[a]	
	N=728		N=36	(4.9)	N=238	(32.7)	N=187	(25.7)	N=27	(3.7)	N=240	(33.0)	N=384	
Gender														
Female	137	(18.8)	2	(5.6)	35	(14.7)	35	(18.7)	7	(25.9)	58	(24.2)	*128*	*(33.3)*
Male	591	(81.2)	34	(94.4)	203	(85.3)	152	(81.3)	20	(74.1)	182	(75.8)	*256*	*(66.7)*
Age in years, *median (IQR)*	63	(51-71)	65	(59-71)	65	(55-72)	51	(32-62)	58	(41-71)	66	(55-75)	*44*	*(25-57)*
0-4	6	(0.8)	1	(2.8	-		3	(1.6)	-		2	(0.8)	*8*	*2.1)*
5-19	4	(0.5)	-		-		3	(1.6)	-		1	(0.4)	*56*	*(14.6)*
20-39	84	(11.5)	-		14	(5.9)	55	(29.4)	6	(22.2)	9	(3.8)	*102*	*(26.6)*
40-59	221	(30.4)	9	(25.0)	73	(30.7)	72	(38.5)	9	(33.3)	58	(24.2)	*147*	*(38.3)*
60-64	93	(12.8)	7	(19.4)	30	(12.6)	20	(10.7)	1	(3.7)	35	(14.6)	*29*	*(7.6)*
65-69	114	(15.7)	8	(22.2)	45	(18.9)	13	(7.0)	2	(7.4)	46	(19.2)	*15*	*(3.9)*
70-74	88	(12.1)	5	(13.9)	36	(15.1)	15	(8.0)	4	(14.8)	28	(11.7)	*20*	*(5.2)*
75-79	55	(7.6)	2	(5.6)	19	(8.0)	3	(1.6)	4	(14.8)	27	(11.3)	*4*	*(1.0)*
80-84	34	(4.7)	2	(5.6)	13	(5.5)	3	(1.6)	-		16	(6.7)	*3*	*(0.8)*
≥85	29	(4.0)	2	(5.6)	8	(3.4)	-		1	(3.7)	18	(7.5)	-	
What happened with the deceased's body														
Repatriation of human remains	262	(36.0)	11	(30.6)	102	(42.9)	74	(39.6)	13	(48.1)	62	(25.8)	*271*	*(70.6)*
Burial overseas	178	(24.5)	10	(27.8)	53	(22.3)	26	(13.9)	7	(25.9)	82	(34.2)	*26*	*(6.8)*
Cremation overseas	83	(11.4)	13	(36.1)	33	(13.9)	10	(5.3)	5	(18.5)	22	(9.2)	*10*	*(2.6)*

	All		Communicable, maternal, neonatal and nutritional diseases		Non-communicable diseases		Injuries		Unclassified symptoms and signs		Unknown		Injuries including MH17[a]	
	N=728		N=36	(4.9)	N=238	(32.7)	N=187	(25.7)	N=27	(3.7)	N=240	(33.0)	N=384	
Body donation to medical science	2	(0.3)	-		-		-		-		2	(0.8)	-	
Unknown	203	(27.9)	2	(5.6)	50	(21.0)	77	(41.2)	2	(7.4)	72	(30.0)	*77*	*(20.1)*
Destination														
America														
Northern America	13	(1.8)	-		1	(0.4)	6	(3.2)	-		6	(2.5)	*6*	*(1.6)*
Caribbean	14	(1.9)	-		3	(1.3)	10	(5.3)	1	(3.7)	-		*10*	*(2.6)*
Central America	9	(1.2)	-		2	(0.8)	3	(1.6)	-		4	(1.7)	*3*	*(0.8)*
South America	28	(3.8)	1	(2.8)	9	(3.8)	10	(5.3)	1	(3.7)	7	(2.9)	*10*	*(2.6)*
Europe														
Northern Europe	18	(2.5)	-		2	(0.8)	11	(5.9)	1	(3.7)	4	(1.7)	*11*	*(2.9)*
Western Europe	111	(15.2)	-		28	(11.8)	41	(21.9)	1	(3.7)	41	(17.1)	*41*	*(10.7)*
Southern Europe	108	(14.8)	2	(5.6)	31	(13.0)	34	(18.2)	2	(7.4)	39	(16.3)	*34*	*(8.9)*
Eastern Europe	39	(5.4)	-		11	(4.6)	12	(6.4)	-		16	(6.7)	*209*	*(54.4)*
Africa														
Northern Africa	24	(3.3)	-		10	(4.2)	2	(1.1)	1	(3.7)	11	(4.6)	*2*	*(0.5)*
Sub-Saharan Africa	36	(4.9)	4	(11.1)	7	(2.9)	14	(7.5)	1	(3.7)	10	(4.2)	*14*	*(3.6)*
Asia														
Western Asia[b]	67	(9.2)	1	(2.8)	38	(16.0)	5	(2.7)	1	(3.7)	22	(9.2)	*5*	*(1.3)*
South-Eastern Asia[c]	216	(29.7)	24	(66.7)	77	(32.4)	29	(15.5)	17	(63.0)	69	(28.8)	*29*	*(7.6)*
Eastern Asia	12	(1.6)	1	(2.8)	6	(2.5)	2	(1.1)	-		3	(1.3)	*2*	*(0.5)*

	All		Communicable, maternal, neonatal and nutritional diseases		Non-communicable diseases		Injuries		Unclassified symptoms and signs		Unknown		Injuries including MH17[a]	
	N=728		N=36	(4.9)	N=238	(32.7)	N=187	(25.7)	N=27	(3.7)	N=240	(33.0)	N=384	
Central Asia[d]	1	(0.1)	-		-		1	(0.5)	-		-		*1*	*(0.3)*
Southern Asia	28	(3.8)	3	(8.3)	13	(5.5)	4	(2.1)	1	(3.7)	7	(2.9)	*4*	*(1.0)*
Oceania														
Australia and New Zealand	4	(0.5)	-		-		3	(1.6)	-		1	(0.4)	*3*	*(0.8)*

Data are presented as N (%). MoFA: the Dutch Ministry of Foreign Affairs, IQR; interquartile range.

[a] Includes victims of the airplane crash MH17 in Ukraine, 2014. Adding up to total N=925.

[b] Mostly Turkey (82%).

[c] Mostly Thailand (70%), Philippines (13%) and Indonesia (8%).

[d] Kazakhstan.

Supplementary Table S10 Causes of death of 461 Dutch travelers according to the Dutch MoFA presented by the GBD cause list level two.

	All N=461	
Communicable, maternal, neonatal and nutritional diseases	**36**	**(7.8)**
Respiratory infections and tuberculosis[a]	23	(5.0)
Other infectious diseases	6	(1.3)
Neglected tropical diseases and malaria[b]	3	(0.7)
HIV, AIDS and STI	2	(0.4)
Enteric infections	1	(0.2)
Maternal and neonatal disorders	1	(0.2)
Non-communicable diseases	**238**	**(51.6)**
Cardiovascular diseases	193	(41.9)
Neoplasms	24	(5.2)
Digestive diseases	9	(2.0)
Substance use disorders[c]	5	(1.1)
Chronic respiratory diseases	4	(0.9)
Diabetes and kidney diseases	2	(0.4)
Other non-communicable diseases	1	(0.2)
Neurological disorders	-	
Injuries	**187**	**(40.6)**
Self-harm and interpersonal violence	87	(18.9)
Conflict and terrorism	1	(1.1)
Self-harm[d]	55	(63.2)
Interpersonal violence	31	(35.6)
Road traffic injuries	57	(12.4)
Road injuries	52	(91.2)
Pedestrian road injuries	2	(3.8)
Cyclist road injuries	9	(17.3)
Motorcyclist road injuries	10	(19.2)
Motor vehicle road injuries	24	(46.2)
Undefined	7	(13.5)
Other transport injuries	5	(8.8)
Unintentional injuries	43	(9.3)
Falls	18	(42.9)
Drowning	10	(23.8)
Other unintentional injuries	5	(11.9)
Fire, heat and hot substances	3	(7.1)

	All N=461	
Exposure to forces of nature	2	(4.8)
Exposure to mechanical forces	2	(4.8)
Environmental heat and cold exposure	1	(2.4)
Foreign body in airway	1	(2.4)

Data are presented as n (%). HIV; human immunodeficiency virus, AIDS; acquired immunodeficiency syndrome, STI; sexually transmitted infections, MoFA: the Dutch Ministry of Foreign Affairs; GBD; global burden of diseases and injuries.

[a] Almost all due to pneumonia; [b] All due to malaria; [c] Drug trafficker (n=1), alcohol addiction (n=3), overdose heroine and morphine (n=1); [d] By hanging, jumping or by overdosing drugs.

References supplementary data

1. United Nations Statistics Division. Composition of macro geographical (continental) regions, geographical sub-regions, and selected econimic and other groupings. http://unstats.un.org/unsd/methods/m49/m49regin.htm

3

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

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Abstract

Background Limited data exist documenting the degree to which travelers are inconvenienced by travelers' diarrhea (TD). We performed a prospective follow-up study at the travel clinic of Leiden University Medical Center in The Netherlands to determine the degree of inconvenience and to determine how experiencing TD affects travelers' perception.

Methods Healthy adults who intended to travel to the (sub)tropics for less than two months were invited to take part. Participants filled out a web-based questionnaire before departure and after returning home. TD was defined as three or more unformed stools during a 24-hour period.

Results 390 of 776 Eligible travelers completed both questionnaires. Participants' median age was 31 years and mean travel duration 23 days. Of 160 travelers who contracted TD (incidence proportion 41%, median duration of TD episode 2.5 days) the majority (107/160, 67%) could conduct their activity program as planned despite having diarrhea. However, 21% (33/160) were forced to alter their program and an additional 13% (20/160) were confined to their accommodation for one or more daylight days; 53 travelers (33%) used loperamide and 14 (9%) an antibiotic. Eight travelers (5%) consulted a physician for the diarrheal illness. When asked about the degree of inconvenience brought on by the diarrheal illness, 39% categorized it as minor or none at all, 34% as moderate and 27% as large or severe. In those who regarded the episode of TD a major inconvenience, severity of symptoms was greater and use of treatment and necessity to alter the activity program were more common. Travelers who contracted travelers' diarrhea considered it less of a problem in retrospect than they had thought it would be before departure.

Conclusion Conventional definitions of TD encompass many mild cases of TD (in our study at least a third of all cases) for which treatment is unlikely to provide a significant health benefit. By measuring the degree of inconvenience brought on by TD, researchers and policy makers may be able to better distinguish 'significant TD' from mild TD, thus allowing for a more precise estimation of the size of the target population for vaccination or stand-by antibiotic prescription and of the benefit of such measures.

Introduction

Travelers' diarrhea (TD) affects 20-50% of travelers from industrialized regions to developing countries [1-3]. Many travel medicine experts recommend loperamide for mild TD and self-administered antibiotic treatment in case of moderate or severe TD [4-6]. Compared with placebo, antibiotics shorten the duration of diarrhea by 0.7-1.5 days and reduce the number of unformed stools per 24 hour time interval by 1.6 on the first day of treatment, 2.1 on the second day, and 1.4 on the third day [7]. No studies exist that have assessed to what extent early antibiotic treatment significantly impacts the subjective and objective (i.e. incapacitation) degree of inconvenience due to TD. The benefit of prescribing all travelers with antibiotics for self-treatment in case of TD should be weighed against the drawbacks. Although side-effects are seldom serious, use of an antibiotic makes a person more susceptible to colonization by drug resistant *Enterobacteriaceae* [8,9]. Furthermore, large-scale use and disposal of antibiotics in the environment induces resistance among pathogens. For these reasons, there are pro- and opponents regarding routine pre-travel prescription of stand-by antibiotics for travelers [10]. An argument favoring routine prescription is that there is an increasing concern about purchasing antibiotics abroad, many being false. A central argument for those who advocate wide-spread use of antibiotics for TD is that it can cause considerable inconvenience, ruin holidays and cause financial loss and that it may cause chronic gastro-intestinal complaints [6,11,12]. A number of studies describe the impact of TD on quality of life and incapacitation [2,3,13-15]. Of those with TD, 20-45% is unable to pursue planned activities for 1 day and the quality of life is affected, mostly with regard to the ability to participate in leisure activities, sexual activity, and the feeling of general well-being [13]. The present prospective follow-up study was designed to determine the degree of subjective and objective inconvenience that Dutch travelers experience when they contract diarrhea during travel to the (sub)tropics. In addition we determined how an episode of TD affects travelers' perception of TD and we explored risk factors.

Methods

Design and study population

This was a single-center prospective cohort study at the travel clinic of Leiden University Medical Center in The Netherlands. It was conducted from March until November 2010. 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: a travel duration of more than two months, use of systemic immunosuppressive medication, a history of inflammatory bowel disease or insulin-dependent diabetes mellitus. Participants were sent two web-based questionnaires via e-mail, the first before departure, and the second a week after returning home. In The Netherlands no formal approval by a medical ethics committee is required for this kind of questionnaire study.

The pre-travel consult was not different for participants than for other travelers. All received a brochure about preventive measures and self-treatment with loperamide and oral rehydration solution in case of TD. In The Netherlands, pre-travel supply of antibiotics for self-treatment in case of TD is restricted to high-risk travelers who are at increased risk of severe infection or dehydration, and to those who travel to remote areas with limited access to health care facilities [16].

Definition of travelers’ diarrhea

In order to avoid misinterpretation we used a straightforward definition of TD. In the questionnaires TD was defined as: the passage of three or more unformed stools during a 24-hour period with or without additional symptoms [14,17]. In the analyses, ‘classic TD’ was defined separately as: the passage of three or more unformed stools during a 24-hour period with one or more symptoms of enteric disease such as nausea, abdominal cramps, vomiting, fever or fecal urgency [18,19].

Questionnaires

The first questionnaire (Q1) consisted of questions on past travel to the tropics, past experience with TD and past inconvenience due to TD. In addition, we surveyed the incidence of diarrhea among participants during a two-month period in The Netherlands and during past travel to the tropics. The second questionnaire (Q2) was sent within a week after returning home and dealt with travel characteristics, the incidence of TD and accompanying symptoms, the use of anti-diarrheal medication, the incidence of other health problems, the incidence of TD among travel companions, health-care use for TD and subjective and objective inconvenience due to TD. The *objective* degree to which TD inconvenienced travelers was measured by asking: "To what extent were you inconvenienced by your episode of diarrhea?". Participants could choose one of the following answers: (i) "I interrupted my journey and returned home due to the diarrhea and abdominal complaints", (ii) "I was ill, I altered my activity program and stayed indoors for one or more days due to the diarrhea and abdominal complaints", (iii) "I altered my activity program due to the diarrhea and abdominal complaints", or (iv) "despite the episode of diarrhea, I could take part in all planned activities". Some travelers may have had more than one episode of TD. All questions concerning symptoms of TD and the degree of inconvenience due to TD pertained to the most severe episode. The *subjective* degree of inconvenience due to TD was measured by asking: "To what degree did you experience inconvenience due to the episode of diarrhea?". Participants could choose from the following answers: (i) "no inconvenience", (ii) "a minor degree of inconvenience", (iii) "a moderate degree of inconvenience", (iv) "a large degree of inconvenience", or (v) "a severe degree of inconvenience". In addition, we explored how an episode of TD during travel changed travelers' own perception of TD. This was done as follows. Before departure we asked: "If you were to contract travelers' diarrhea with fecal urgency and abdominal cramps for three days, how large a problem would you consider this to be?". (i) "no problem", (ii) "a small problem", (iii) "neither a small nor a large problem", (iv) "a large problem", (v) "a very large problem". After returning home all travelers were presented with a similar scenario pertaining to a hypothetical future travel. We thought that the answer to this question would change in travelers who had contracted TD and would remain the same in those who had not. The overall direction in which the answer changes, reflects how experiencing an episode

of TD influences the perception of TD. We piloted the questionnaire among travelers, acquaintances and staff of the department of Clinical Epidemiology at Leiden University Medical Center.

Data editing

Travel destination was categorized according to the United Nations (UN) International Migrant Stock [20]. Travel destination was also categorized according to the UN Human Development Index (HDI) value (0 to 1) and UN HDI category (high, medium, low) [21]. The HDI is based upon indicators of life expectancy, education and living standards. If a participant visited more than one country, the HDI value of the country with the lowest HDI was used. In regression analyses, continuous variables that were not linearly associated with the dependent variable were categorized based on exploratory analyses of the continuous data in small categories to see at which values of the continuous variable the regression coefficient changed.

Sample size

The sample size was based on the rule of thumb that 10 cases are needed for each covariate that is introduced in a logistic regression model [22]. Based on an assumed incidence proportion (i.e. the incident number of cases in relation to the size of the population) for TD of 25% we estimated that 400 travelers were needed to be able to introduce a maximum of 10 separate covariates in a logistic regression analysis.

Regression analyses

In a prediction model we explored which variables significantly increased the odds of contracting classic TD. Categorical variables were analyzed with χ^2-tests and continuous variables with t-tests. Variables with $p < 0.2$ were entered in a multiple logistic regression model based on maximum likelihood estimation. Interaction terms were not entered in the model to prevent overfitting and because interaction was deemed unlikely. Cook's distance values, leverage values and standardized residuals were examined to detect cases that might be influencing the model disproportionately. Variance inflation factors were examined to test whether any covariates were highly collinear. The relative strength of each covariate in the final regression model was determined by computing the delta in Nagelkerke R^2 when

one covariate was deleted and by dividing delta by the final model's Nagelkerke R^2. In another logistic regression analysis restricted to travelers who had TD, we explored which person- and travel characteristics predicted incapacitation due to TD. In a third model we explored which symptoms predicted incapacitation due to TD. All analyses were done using PASW Statistics, version 18.0, IBM®. Statistical significance was defined as a *p*-value <0.05.

Results

Study population and travel characteristics

At our travel clinic 776 of 1,000 travelers fulfilled the inclusion criteria of which 406 provided informed consent (response rate 52%). Of the 224 people who were not eligible to participate, travel duration in excess of two months was the most common exclusion criterion. Three hundred and ninety travelers completed both the pre- and post- travel questionnaire (follow-up rate 96%) (Figure 1). The median age was 31 years (IQR 24-50 years). The majority was female (65%), and had completed higher education (62%) (i.e. a Bachelor degree). Person- and travel characteristics are described in Table 1 and 2. Tourism was the main reason for travel and South-eastern Asia was visited most frequently (31%). The mean travel duration was 23 days (range 4-57 days). At the pre-travel consult, 27 travelers (7%) received a stand-by antibiotic prescription (ciprofloxacin or azitromycin). In total 335 travelers (86%) carried treatment for TD in their travel-kit, mainly loperamide (282/390; 72%), oral rehydration solution (229/390; 59%) or activated carbon (83/390; 21%).

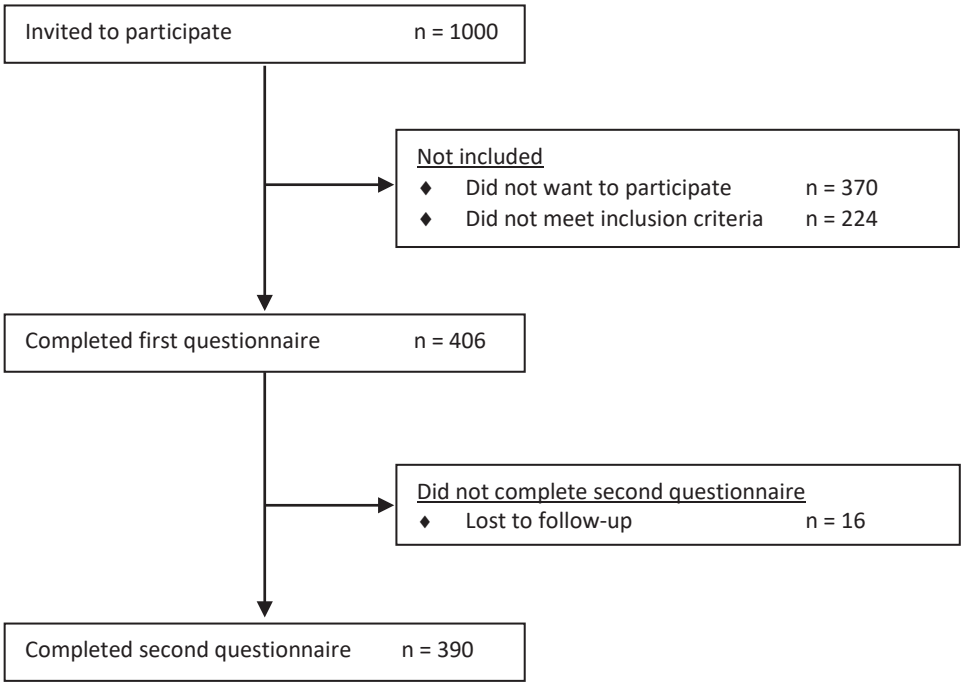

Figure 1. Flowchart of participants in the study of inconvenience due to travelers' diarrhea.

Travelers' diarrhea: incidence, symptoms, treatment and risk factors

One hundred sixty travelers (160/390, 41%) (26% per any two weeks of stay) contracted TD. Of these 160 travelers with TD, 16 did not have any accompanying symptom of enteric disease such as nausea, abdominal cramps, vomiting, fever or fecal urgency, making the incidence proportion of classic TD 37% (144/390). The overall TD Incidence Rate (IR) was 1.78 cases per 100 person days of travel (pdt). IRs were highest for travelers to Northern-Africa (3.95/100 pdt) and South-central Asia (2.55/100 pdt) (Table 2). Most affected travelers had typical symptoms: watery stools (138/160, 86%), fecal urgency (114/160, 71%) and abdominal discomfort (123/160, 77%) (Table 3). The diarrheal episode lasted a median of 2.5 days (IQR 1-2.5 days). Sixty-five of 160 travelers with TD (41%) started treatment with an anti-motility agent or an antibiotic: 26% (41/160) used loperamide only, 4% (6/160) activated carbon only, 3% (4/160) used both loperamide and activated carbon and 9% (14/160) used an antibiotic, of whom most (9/14; 64%) used the antibiotic in combination with an anti-motility agent.

Table 1 Travel characteristics and risk factors for travelers' diarrhea in a cohort of 390 Dutch travelers.

Characteristic	All n = 390	Classic TD n = 144	No TD n = 246	Univariate OR [95% CI]	*p*-value	Multivariate OR [95% CI]	Relative contribution of each characteristic to the model's R^2 (%)
Gender, female[1]	253 (65)	98 (68)	155 (63)	1.25 [0.81-1.93]	0.31		
Age					<0.001		18.6
18-34 years	217 (56)	102 (71)	115 (47)	1.0		1.0	
≥35 years	173 (44)	42 (29)	131 (53)	0.36 [0.23-0.56]		0.38 [0.23-0.65]	
Use of an antacid[2]	24 (6)	14 (10)	10 (4)	2.54 [1.10-5.88]	0.03	2.95 [1.14-7.60]	6.8
Born in the tropics[3]	19 (5)	5 (3)	14 (6)	0.60 [0.21-1.69]	0.33		
Traveled to the tropics in the preceding 5 years[4]	251 (64)	91 (63)	160 (65)	0.92 [0.60-1.42]	0.71		
Mean travel duration - *days* (SE)	22.9 (0.65)	25.6 (1.2)	21.4 (0.7)	1.03 [1.01-1.04]	0.002	1.02 [0.99-1.04]	2.7
Travel destination, Human Development Index					0.02		10.6
High	79 (20)	18 (13)	61 (25)	1.0		1.0	
Medium	219 (56)	90 (63)	129 (54)	2.36 [1.31-4.27]	0.004	2.29 [1.22-4.33]	
Low	92 (24)	36 (25)	56 (23)	2.18 [1.11-4.27]	0.02	2.51 [1.19-5.33]	
Main travel purpose[5]							
Holiday	236 (61)	89 (62)	147 (60)	1.09 [0.72-1.66]	0.69		
Visit friends/relatives	55 (14)	13 (9)	42 (17)	0.48 [0.25-0.93]	0.03	0.56 [0.27-1.19]	3.3
Business/professional	32 (8)	5 (4)	27 (11)	0.30 [0.11-0.81]	0.02	0.31 [0.11-0.88]	7.6
Study	51 (13)	29 (20)	22 (9)	2.57 [1.41-4.67]	0.002	1.16 [0.56-2.40]	0.2
Volunteer work	16 (4)	8 (6)	8 (3)	1.75 [0.64-4.77]	0.27		
Type of travel[6]							
Self-arranged, not backpacking	170 (44)	56 (39)	114 (46)	0.74 [0.49-1.12]	0.15	1.17 [0.68-2.01]	0.4
Backpacking	85 (22)	44 (31)	41 (17)	2.20 [1.35-3.58]	0.002	1.89 [0.96-3.70]	4.5
Organized group travel	108 (28)	37 (26)	71 (29)	0.85 [0.54-1.36]	0.50		
Other	27 (7)	7 (5)	20 (8)	0.58 [0.24-1.40]	0.23		

Characteristic	All n = 390	Classic TD n = 144	No TD n = 246	Univariate OR [95% CI]	*p*-value	Multivariate OR [95% CI]	Relative contribution of each characteristic to the model's R^2 (%)
Type of accommodation[7]							
Luxury hotel only	98 (25)	43 (30)	55 (22)	1.48 [0.93-2.36]	0.10	2.94 [1.64-5.29]	18.2
Budget hotel only	95 (24)	34 (24)	61 (25)	0.94 [0.58-1.52]	0.79		
Camping (tent/camper)	26 (7)	9 (6)	17 (7)	0.90 [0.39-2.07]	0.80		
Holiday home	15 (4)	5 (4)	10 (4)	0.85 [0.28-2.53]	0.77		
Stayed with friends or relatives	12 (3)	3 (2)	9 (4)	0.56 [0.15-2.10]	0.39		
Stayed with locals	13 (3)	8 (6)	5 (2)	2.84 [0.91-8.84]	0.07	2.91 [0.80-10.55]	3.4
Combination of the above†	131 (34)	42 (29)	89 (36)	0.73 [0.47-1.13]	0.16		
Diarrheal episode 2 months prior to departure*					**0.003**		
No	195/251 (78)	61/91 (67)	134/160 (84)	1.0			
Yes	56/251 (22)	30/91 (33)	26/160 (16)	2.54 [1.38-4.65]			
Subjective susceptibility for travelers' diarrhea*					**0.12**		
Never	104/251 (41)	33/91 (36)	71/160 (44)	1.0	0.47		
Sometimes	121/251 (48)	44/91 (48)	77/160 (48)	1.23 [0.71-2.14]	0.04		
Often/always	26/251(10)	14/91 (15)	12/160 (8)	2.51 [1.05-6.02]			

Data are presented as n (%), unless otherwise stated. OR: odds ratio; SE: standard error of the mean; CI: confidence interval. *P*-values based on χ^2-tests for categorical variables and t-tests for continuous variables. Variables with $p < 0.2$ were included in the multivariate logistic regression model. Reference category: [1]male gender, [2]no use of an antacid, [3]born in The Netherlands, [4]not having traveled to the tropics in the preceding 5 years, [5]not the specified travel purpose, [6]not the specified type of travel, [7]not having stayed in the specified type of accommodation. †Not included in the multivariate model because it is not a uniform category. *Not included in the multivariate logistic regression model because subjects who had not traveled to the tropics in the past 5 years had missing values for these variables. Model: constant = 0.19, Nagelkerke's $R^2 = 0.22$, Hosmer and Lemeshow test for goodness of fit $p = 0.4$.

Table 2 Travelers' diarrhea, cumulative incidences and incidence rates for 390 Dutch travelers.

Travel destination	Travelers - *n*	TD cases - *n*	TD cumulative incidence - % (SE)	Mean travel duration - days	TD Incidence rate - per 100 pdt (SE)
Northern Africa	17	7	41 (12.3)	10.4	3.95 (1.47)
South-central Asia	31	16	52 (9.1)	20.2	2.55 (0.63)
Central America and Caribbean	24	11	46 (10.4)	18.9	2.42 (0.72)
South-eastern Asia	121	61	50 (4.6)	22.5	2.25 (0.28)
Eastern Africa	57	25	44 (6.6)	23.4	1.88 (0.37)
Central Africa	7	3	43 (20.2)	23.4	1.83 (1.05)
Central and Western Asia	32	8	25 (7.8)	14.3	1.75 (0.61)
Western Africa	15	7	47 (13.3)	28.6	1.63 (0.61)
Southern Africa	15	4	27 (11.8)	23.1	1.16 (0.58)
Eastern Asia	36	11	31 (7.8)	29.4	1.04 (0.31)
South America	46	7	15 (5.4)	26.4	0.58 (0.22)
All travelers	401†	160	41 (2.4)	22.4	1.78 (0.14)

pdt: person days of travel; SE: standard error. †11 participants travelled to more than one destination. NOTE: Incidence rates were not corrected for the time to first episode of TD or for the number of episodes of TD.

Five travelers who used an antibiotic (5/14, 36%) had been prescribed the antibiotic at the pre-travel consult. Loperamide was started a median of 1 day (IQR 0-2 days) after onset of symptoms. Antibiotics were started later (median 3 days after onset of symptoms; IQR 2-5 days). In total eight travelers (8/160; 5%) consulted a physician for the diarrheal illness of whom two (2/160; 1%) were admitted to hospital in Africa with fever, diarrhea, vomiting and dehydration. One hundred and two travelers (102/390; 26%) reported non-travelers' diarrhea related health problems: 13 vomiting without diarrhea, 11 abdominal discomfort or loose stools that did not fit the definition of TD, 6 constipation, 24 a respiratory tract infection, 19 a skin or eye infection, 3 a urinary tract infections, 2 fever (1 unknown cause, 1 malaria), 12 headache or tiredness, and 12 some other health problem.

The following variables independently increased the odds of contracting TD: younger age, use of an antacid, longer travel duration, lower Human Development Index of the country that was visited, backpacking as type of travel and staying in luxury hotels. Travelers whose main travel purpose was to visit friends/relatives or who traveled for business/professional reasons had reduced odds for contracting

TD. Nagelkerke's R^2 was 0.22, which means that the model accounted for 22% of the variance in TD (Table 1).

Inconvenience due to travelers' diarrhea

Although most travelers (107/160; 67%) could conduct their activity program as planned despite having diarrhea, 21% (33/160) were forced to alter their program and an additional 13% (20/160) were confined to their accommodation for one or more daylight days (median 1 day; IQR 1-2 days). When asked about the degree of inconvenience brought on by the diarrheal illness, 39% (63/160) categorized it as minor or none at all, 34% (54/160) as moderate and 27% (43/160) as large or severe. Severity of symptoms was greater and use of treatment and necessity to alter the activity program were more common in those who were incapacitated due to TD (Table 3). In a logistic regression model, restricted to travelers who contracted TD, none of the person- or travel-characteristics was significantly (p <0.05) associated with incapacitation due to TD. The following symptoms independently increased the odds of incapacitation due to TD: stool frequency, nausea and fever (Table 4).

Table 3 Characteristics of the episode of travelers' diarrhea for 160 Dutch travelers, stratified by the objective degree of inconvenience.

Objective degree of inconvenience - *n* (%)	**Conducted program as planned 107/160 (67%)**	**Forced to alter program 33/160 (21%)**	**Confined to accommodation 20/160 (13%)**	**Total 160 (100%)**
Stool frequency - *n* (%)				
3 stools/day	64 (60)	11 (33)	1 (5)	76 (48)
4-5 stools/day	35 (33)	15 (46)	8 (40)	58 (36)
6-10 stools/day	7 (7)	6 (18)	9 (45)	22 (14)
> 10 stools/day	1 (1)	1 (3)	2 (10)	4 (3)
Watery stools, duration - *n* (%)				
No watery stools	20 (19)	1 (3)	1 (5)	22 (14)
1 day	37 (35)	11 (33)	4 (20)	52 (32)
2-3 days	31 (29)	14 (42)	8 (40)	53 (33)
4-7 days	10 (9)	5 (15)	5 (25)	20 (13)
> 7 days	9 (8)	2 (6)	2 (10)	13 (8)
Fecal urgency, duration - *n* (%)				
No fecal urgency	38 (36)	8 (24)	-	46 (29)
1 day	30 (28)	10 (30)	7 (35)	47 (29)
2-3 days	22 (21)	10 (30)	6 (30)	38 (24)
4-7 days	11 (10)	3 (9)	1 (5)	15 (9)
> 7 days	6 (6)	2 (6)	6 (30)	14 (9)
Abdominal cramps, duration - *n* (%)[†]				
No abdominal cramps	32 (30)	3 (9)	2 (10)	37 (23)
1 day	32 (30)	11 (33)	4 (20)	47 (29)
2-3 days	30 (28)	12 (36)	6 (30)	48 (30)
4-7 days	9 (8)	5 (15)	4 (20)	18 (11)

Objective degree of inconvenience - *n* (%)	**Conducted program as planned 107/160 (67%)**	**Forced to alter program 33/160 (21%)**	**Confined to accommodation 20/160 (13%)**	**Total 160 (100%)**
> 7 days	4 (4)	2 (6)	4 (20)	10 (6)
Nausea, duration - *n* (%)				
No nausea	82 (77)	13 (39)	4 (20)	99 (62)
1 day	17 (16)	9 (27)	6 (30)	32 (20)
2-3 days	6 (6)	8 (24)	6 (30)	20 (13)
4-7 days	1 (1)	2 (6)	3 (15)	6 (4)
> 7 days	1 (1)	1 (3)	1 (5)	3 (2)
Vomiting - *n* (%)*	13 (12)	12 (36)	7 (35)	32 (20)
Fever - *n* (%)	6 (6)	8 (7)	11 (55)	17 (11)
Treatment - *n* (%)				
Loperamide	29 (27)	11 (33)	14 (70)	54 (34)
Activated carbon	3 (3)	6 (18)	2 (10)	11 (7)
Antimicrobial agent	3 (3)	6 (18)	5 (25)	14 (9)
Subjective degree of inconvenience - *n* (%)				
None/Minor	58 (54)	5 (15)	-	63 (39)
Moderate	33 (31)	13 (39)	8 (40)	54 (34)
Large/Severe	16 (15)	15 (46)	12 (60)	43 (27)

* 13 additional travelers who did not have diarrhea reported vomiting; †10 additional travelers who did not have travelers' diarrhea according to the definition, reported abdominal cramps.

Table 4 Logistic regression model evaluating which symptoms best predicted incapacitation due to travelers' diarrhea.

Characteristic	All with TD n = 160	Conducted program as planned n = 107	Incapacitated n = 53	Univariate OR [95% CI]	p-value	Multivariate OR [95% CI]
Stool frequency					**<0.001**	
3 stools/day	76 (48)	64 (60)	12 (23)	1.0		1.0
4-5 stools/day	58 (36)	35 (33)	23 (43)	3.51 [1.56–7.88]		2.05 [0.77-5.43]
> 5 stools/day	26 (16)	8 (8)	18 (34)	12.0 [4.26-33.8]		4.84 [1.40-16.8]
Abdominal cramps					**0.005**	
No abdominal cramps	37 (23)	32 (30)	5 (9)	1.0		1.0
1 -3 days	95 (59)	62 (58)	33 (62)	3.41 [1.21-9.57]		1.86 [0.55-6.34]
> 3 days	28 (18)	13 (12)	15 (28)	7.39 [2.22-24.5]		2.64 [0.62-11.3]
Fecal urgency[1]	114 (71)	69 (65)	45 (85)	3.10 [1.32-7.25]	0.009	0.93 [0.32-2.70]
Nausea[2]	61 (38)	25 (23)	36 (68)	6.95 [3.35-14.4]	<0.001	4.38 [1.70-11.3]
Vomiting[3]	32 (20)	13 (12)	19 (36)	4.04 [1.80-9.06]	0.001	0.96 [0.32-2.91]
Fever[4]	25 (16)	6 (6)	19 (36)	9.41 [3.47-25.5]	<0.001	5.65 [1.80-17.7]

TD: travelers' diarrhea; OR: odds ratio; CI: confidence interval. *P*-values based on χ^2-tests for categorical variables. Variables with $p < 0.2$ were included in the multivariate logistic regression model. Reference category: [1]no fecal urgency, [2]no nausea, [3]no vomiting, [4]no fever. Model: constant = 0.06, Nagelkerke's $R^2 = 0.42$, Hosmer and Lemeshow test for goodness of fit $p = 0.7$.

Before departure, we surveyed the incidence of diarrhea among participants during a two-month period in The Netherlands; 22% answered that they had an episode of diarrhea according to our definition of (travelers') diarrhea. The normal stool pattern of these participants may come close to fulfilling our definition of TD, making these participants more likely to report TD during travel without significant inconvenience. Therefore, we performed a sensitivity analysis in which we excluded these participants. This did not cause a major change in the results. In the remaining subset 62% could conduct their activity program as planned, 27% were forced to alter their program and 10% were confined to their accommodation. In another sensitivity analysis restricted to 144 participants with classic TD, 65% could conduct their activity program as planned, 22% were forced to alter their program and 14% were confined to their accommodation.

Before departure all travelers were asked the following question: "If you were to contract travelers' diarrhea with fecal urgency and abdominal cramps for three days, how large a problem would you consider this to be?". After returning home all travelers were presented with a similar scenario. Table 5 shows that the distribution of participants' answers did not shift in those who did not contract TD ($p = 0.6$, Wilcoxon signed rank test for two-related samples, comparison of the distribution of two variables). However, those who did contract TD tended to consider TD a smaller problem when asked the question upon return than they had thought it would be prior to departure ($p < 0.001$). Surprisingly, even the participants who were forced to alter their planned activities ($p = 0.01$) and the participants who were forced to stay indoors ($p=0.03$) tended to consider TD less of a problem when asked the question upon return than they had thought it would be before departure.

Table 5 How did an episode of travelers' diarrhea (TD) influence travelers' perception of TD? The expected amount of subjective inconvenience due to travelers'' diarrhea before and after travel is stratified by whether travelers had TD.*

	Travelers who had TD N=160		Travelers who did not have TD N=230	
	Before departure	**After returning**	**Before departure**	**After returning**
No problem - *n* (%)	1 (1)	11 (7)	1 (0.4)	3 (1)
A small problem - *n* (%)	22 (14)	42 (26)	50 (22)	53 (23)
Neither a small nor a large problem - *n* (%)	51 (32)	56 (35)	61 (27)	57 (25)
A large problem - *n* (%)	69 (43)	49 (31)	99 (43)	99 (43)
A very large problem - *n* (%)	17 (11)	2 (1)	19 (8)	18 (8)

*Participants were presented with the following scenarios: *Before departure:* If you were to contract travelers'' diarrhea during the coming journey, with a duration of three days accompanied by urgency and abdominal cramps, how large a problem do you think this would be for you? *After returning*: If you were to make the exact same journey in the future and you were to contract travelers'' diarrhea with a duration of three days accompanied by urgency and abdominal cramps, how large a problem do you think this would be for you?

Discussion

This study was specifically designed to measure the degree of inconvenience brought on by TD. We found that approximately one-third of travelers who contracted TD were forced to change their activity program or stay indoors, which is in line with other reports [2,3,13-15]. Two travelers were even admitted to hospital. Two-thirds did not need to change their activity program and a sizeable proportion (39%) said that the episode of TD caused only minor inconvenience. Those who reported minor inconvenience seldom used an anti-diarrheic agent meaning that the reported degree of inconvenience in this subgroup was not significantly influenced by treatment. As it is to be expected, the severity of symptoms was greater in those who regarded the episode of TD a major inconvenience. The travelers' perception of TD changed based on the current experience. Travelers who contracted TD considered it less of a problem in retrospect than they had thought it would be before departure. Surprisingly, this was even true for those who were forced to change their plans and for those who had to stay indoors. 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.

Most risk factors for contracting TD were in line with recent reports. Unexpectedly, we found that staying in luxury hotels increased the odds for contracting TD. Travel duration for participants who stayed in luxury hotels was shorter and they were more likely to have traveled to high risk destinations, such as Indonesia and Egypt (data not shown). Residual confounding due to incomplete adjustment for destination and for the time to the first episode of TD may account for (part of) the unexpected association between accommodation in luxury hotels and TD. Alternatively, staying in luxury hotels may be associated with consumption of more elaborate food which bears more risks [13].

This study has a number of strengths. First, participants were recruited before departure. This way we aimed to limit the chance of preferentially selecting travelers with more severe TD who may be more inclined to respond to a questionnaire taken after the facts. Secondly, surveying travelers both before- and after travel, enabled analysis of how travelers' perception of TD changed depending on whether or not TD was contracted during travel. Thirdly, nearly all participants completed both

questionnaires, further limiting the chance of bias. Lastly, we measured both the objective and subjective degree of inconvenience. Participants' reporting of both kinds of inconvenience was consistent, which shows that the data are robust. The study also has limitations. First, although we piloted the questionnaire among travelers, acquaintances and epidemiologists, questions could have been misinterpreted. To limit the chance of misinterpretation, participants could contact us by e-mail in case of any ambiguity. We also provided ample opportunity for participants to further specify their answers. For example, those who reported that they had to change their activity program or remain indoors due to TD were requested to describe which activities were cancelled. Secondly, the normal stool pattern of some participants may come close to fulfilling the definition of TD, making these participants more likely to report TD without significant inconvenience. This may have led to an underestimation of the inconvenience associated with 'real TD'. However, two sensitivity analyses in which such participants were excluded did not yield different results. Therefore it is unlikely that we underestimated the inconvenience associated with TD during the stay abroad. Thirdly, many travelers used an anti-motility agent or an antibiotic to treat TD. It stands to reason that the degree of inconvenience would have been larger if nobody had used treatment and would have been smaller if all had used treatment. Lastly, TD incidence rates were not corrected for the time to the first episode of TD or for the number of episodes. This may have inflated incidence rates for destinations for which travel duration was longer than average and deflated incidence rates for destinations for which it was shorter than average.

Most cases of TD in this study fitted the classic definition of TD. Overall incidence rates and risk factors were in line with recent reports [1,3,13,14,23]. These aspects increase the generalizability of this study. Some aspects limit the generalizability. Firstly, the study population consisted mainly of Dutch born nationals. Dutch people may be more inclined to await the natural course of a self-limiting illness than travelers from other countries [24]. This could influence the way in which they perceive TD as a problem. However, such cultural differences would probably not impact the objective degree of inconvenience. Secondly, participants were recruited at our travel clinic. The results may not be representative of travelers who do not seek health-related travel advice before travel. Furthermore, the response rate was 50%. The demographic features of those who refused to participate may be different.

Lastly, although the majority of visitors to our hospital based travel clinic can be classified as 'general travelers', relatively more hospital employees and (bio)medical students visit our travel clinic compared with other out-of-hospital based travel clinics.

Conclusion

This study shows that conventional definitions of TD encompass many cases of mild TD (in our study at least a third of all cases) for which vaccination or antibiotic treatment is unlikely to provide a significant health benefit. By measuring the degree of inconvenience brought on by TD, researchers and policy makers may be able to better distinguish 'significant TD' from mild TD, thus allowing for a more precise estimation of the size of the target population for vaccination or stand-by antibiotic prescription and of the benefit of such measures. 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.

List of abbreviations

TD: Travelers' diarrhea, UN: United Nations, HDI: Human Development Index.

Competing interests

None.

Authors' contributions

DS and JV were involved in the study design, in data collection, in the analysis and interpretation of the data and in drafting the article. LV was involved in the study design, in the interpretation of the data and in drafting the article. All authors gave final approval to the manuscript.

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4

Travel preparation and health risks in Dutch and Belgian medical students during an elective in low- or middle-income countries: a prospective self-reporting cohort study

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Abstract

Background Medical schools offer students the opportunity to perform international electives. This study aimed to assess health risks among medical students, to tailor institutional guidelines.

Methods Multicenter study at Dutch and Belgian universities, among medical students who visited low- or middle-income countries. Students completed four questionnaires: once before the elective and two weeks, three- and six months after return.

Results Data was complete for 479 students (follow-up rate 84%). Most traveled to Surinam (29%) and South-Africa (14%). Half of the students encountered difficulties in adapting to local culture. Almost 40% visited malaria endemic countries. Nearly all (87%) used chemoprophylaxis as prescribed. Definite needle-stick or splash injuries were reported by 7%. All were dealt with adequately in accordance with national guidelines. However, less than half of 24 possible incidents were handled adequately. Two-and-a-half percent had unprotected sex with a new partner. The incidence of travelers' diarrhea (TD) was 46%. In those with TD, the incidence of post-travel new-onset abdominal complaints was 3%. Three percent were involved in a minor traffic accident , 18% were injured during leisure activities, 5% were threatened or experienced physical violence. Only half of the students visiting a highly endemic country were screened for tuberculosis post-travel. For schistosomiasis this was 6%.

Conclusions Students abroad are exposed to medical and non-medical challenges, which should be addressed during pre-travel counseling. Contact details of a professional back home should be provided, so students can confer in case of problems while abroad. Lastly, we recommend a centrally organized post-travel health check.

Introduction

Teaching global health is an important part of medical education. It enhances doctors' knowledge of global burden of disease, tropical diseases, ethnicity-related health issues and health care systems in other countries [1, 2]. Many medical schools offer the opportunity to perform an elective abroad. Students often choose electives in low- or middle-income countries (LOMIC), where they are exposed to specific work- and travel-related health risks, such as needle-stick injuries, traffic accidents and travelers' diarrhea (TD). Visiting LOMIC countries is also associated with a higher risk of contracting infectious diseases, such as tuberculosis (TB), malaria, helminths and colonization with multidrug-resistant bacteria [3-7]. Psychological stressors and culture shock are frequently reported in post-travel health surveys as well [8].

Adequate pre-travel counseling can reduce morbidity in travelers [9, 10]. Several studies have assessed pre-travel preparation and health risks in (medical) students during an elective abroad [8, 11-22]. These are mainly single-center questionnaire studies performed upon return from an elective, which limits the generalizability and increases the chance of recall bias. By performing a prospective multicenter international study, combining pre- and post-travel data from Dutch and Belgian universities, we provide unique insight into pre-travel advice, health risks and post-travel care. This data can be used to optimize care for students who perform an elective in LOMIC countries.

Material and methods

Study design

For this prospective multicenter study, medical students planning an elective abroad were recruited from three Dutch universities (Leiden University [July 2010-May 2016], VU University Amsterdam [May 2013-November 2016], University of Groningen [July 2013- March 2016]) and two Belgian universities (University of Leuven [January 2014- February 2016] and Ghent University [February 2015-December 2016]). We focused on students visiting LOMIC countries defined as countries where hepatitis A is endemic. Students following multiple electives abroad could participate only once.

Eligible students were identified when they registered at the international office of their university in order to receive study credits for the future elective abroad. Travel- and contact information was gathered by the coordinator for internationalization of the Directorate of Education and Study Programmes in Leiden and was periodically sent to the investigators. Two weeks before departure all eligible students were invited to take part in the study by an e-mail, sent on behalf of the contact person at the local international office. A monetary incentive was given to optimize the response rate.

Survey

The study consisted of four web-based questionnaires, which were to be filled out two weeks before departure (Q1), and two weeks (Q2), three months (Q3), and six months after returning home (Q4). Web links to the e-questionnaires were sent by e-mail, NetQPremium (NetQ Netherlands B.V., Utrecht, the Netherlands). The questionnaires concerned pre- and post-travel health status, health risks and post-travel health checks (e.g. TB, Methicillin-resistant Staphylococcus Aureus, and schistosomiasis). Information on questionnaire items is summarized in Supplementary Table S1. Those who did not complete a questionnaire received up to four weekly reminders. If a questionnaire was not completed by the due date of the next questionnaire, participation in the study ended.

Definitions

TD was defined as the passage of three or more unformed stools during a 24-hour period with or without additional symptoms like abdominal cramps, nausea, vomiting or fever. Fever was defined as a body temperature ≥38°C. Travel destination was categorized in six regions (Table 1). Assisting during surgeries or deliveries, suturing, placing an intravenous catheter and performing phlebotomy were considered invasive procedures due to an increased risk of exposure to blood-borne viral infections. Needle-stick injury was defined as an accidental skin puncture with a sharp medical instrument which has potentially been in contact with human body fluids; a splash injury as an accidental spraying of body fluids onto mucocutaneous surfaces. Some students reported that they were uncertain whether an event that

they had experienced could be classified as a true needle-stick or splash injury. These events were classified as possible needle-stick or splash injuries.

Data processing

An elective was considered to be clinical when invasive procedures could be performed. For privacy reasons only year of birth was recorded. LCR guidelines (National Travel Advice Coordination Center) were used to classify the countries that were visited as TB-, malaria- and schistosomiasis endemic areas [11]. HIV prevalence data was obtained from the WHO [12]. Culture shock was measured using an adapted version of a questionnaire developed by Mumford. Four questions were scored 2, 1 or 0, according to decreasing severity [13]. Additionally, sum scores for the cohort and the continents were calculated. Chronic abdominal discomfort was defined as discomfort or pain, unrelated to menstrual bleeding, for ≥3 days per month during more than six months. Pre- and post-travel diarrhea was defined as loose, mushy or watery stool for ≥3 days per month during the last three months.

Statistical analyses

All data were exported directly from the NetQ server into IBM® SPSS® Statistics version 23.0 for analyses. Data was only analyzed for students who had completed all four questionnaires. Anonymization was done by using unique study numbers. Descriptive statistics and univariable analysis were used to analyze the data where appropriate. Statistical significance was defined as a p-value <0.05.

Ethics

The study was endorsed by the Committee Medical Ethics (CME) of the Leiden University Medical Center, Leiden, the Netherlands (registry number P11.046). They decided that the study does not fall under the scope of the Medical Research Involving Human Subjects Act (in Dutch: WMO). Participants provided digital informed consent by completing the first questionnaire.

Results

Over a six-year period, 1178 students fulfilled the inclusion criteria. Fifty-six students had already left for their elective and could not be invited to participate, leaving 1122 eligible students. The response rate was 51% (572/1122) and the follow-up rate was 84% (479/572), with 479 students completing all questionnaires (see Supplementary Figures S1 and S2). The majority (80%) was Dutch.

Student and travel characteristics

Participants were predominantly female (76%) with a median age of 24 years (interquartile range (IQR) 23-25). The most popular destinations were South America (in particular Surinam) and Africa (in particular South-Africa). The median time spent abroad was 67 days (range 24-234 days). Belgian students stayed abroad significantly longer than Dutch students: median 91 days versus 61 days. Two-thirds combined their elective with a holiday in the same region. This was more common among Dutch students. Belgian students only went on elective during the masters' program, whereas 10% of Dutch students was still in their bachelor program. The majority conducted a clinical (78%) or pre-clinical elective (13%). Most popular specialties were gynaecology/obstetrics (44%) and pediatrics (38%). Every student was vaccinated against hepatitis B as part of the regular medical curriculum. Four students did not know their antibody titer (1%).

Students themselves were responsible for obtaining pre-travel health and safety advice. The majority (93%) did so, mainly at a travel clinic. More than 90% of students had access to internet within 30 minutes of their accommodation with sufficient mobile phone reception to connect with family and friends. Most accommodations were equipped with basic facilities such as running water and sanitation and 38% had air-conditioning. Electricity was mostly available around the clock; although not always in Africa (37%) and Asia (28%) (see Supplementary Table S2).

Culture shock

Students staying in Central America had the highest culture shock mean sum score (2.95), followed by Africa (2.52). Half of the students experienced some kind of difficulty in adapting to the local culture. Most students felt accepted by the local

population (87%). A minority frequently suffered from homesickness (5%), which was associated with lack of a functioning mobile phone network (p=0.04) and with the destination (p=0.002). An association was found between the continent that was visited and feelings of disgust or shock (p=<0.001). Nearly all students traveling to Africa (91%) reported feelings of disgust or shock by something they encountered while abroad (Table 1). There was no significant difference between Dutch and Belgian students regarding the four culture shock items (see Supplementary Table S3).

Malaria prevention

Thirty-nine percent (185/479) traveled to a malaria endemic region and started chemoprophylaxis; mostly atovaquone/proguanil (70%) or mefloquine (24%). Nine students obtained the prophylaxis locally. The majority also used a bed net (83%). In addition, 61 students carried prophylaxis, but did not need to use it, as they remained in low or non-endemic regions (see Supplementary Table S4).

A quarter experienced side effects after starting malaria prophylaxis, 26% (33/129) on atovaquone/proguanil and 30% (13/44) on mefloquine. Atovaquone/proguanil mostly caused gastrointestinal complaints (19/129, 15%) and mefloquine psychological symptoms and sleep disorder (12/44, 27%). Weight loss during the elective was not associated with a higher incidence of mefloquine related side effects (p=0.13). Twenty-four students (13%) stopped using prophylaxis prematurely due to side effects or because they forgot to take the pills or came to know that they were staying in a low or non-endemic region. This led to three students being unprotected in a high endemic region (Kenia, Tanzania and Rwanda). Only two students discussed stopping their prophylaxis with a medical professional (see Supplementary Table S4). In this large student cohort, four cases of malaria were reported in students visiting Africa despite the use of malaria prophylaxis. Only one was reported to be confirmed by laboratory tests. All recovered without sequelae.

Table 1 Culture shock in 464 Dutch and Belgian medical students, stratified by continent*

	All students N=464	South America N=178 (38.4)	Africa N=176 (37.9)	Asia N=82 (17.7)	Central America N=21 (4.5)	Middle East N=7 (1.5)
Difficulty adapting						
Most of the time	35 (7.5)	15 (8.4)	17 (9.7)	2 (2.4)	1 (4.8)	0
Occasionally	235 (50.6)	87 (48.9)	89 (50.6)	42 (51.2)	14 (66.7)	3 (42.9)
Not at all	194 (41.8)	76 (41.7)	70 (39.8)	38 (46.3)	6 (28.6)	4 (57.1)
Homesick						
Most of the time	24 (5.2)	2 (1.1)	13 (7.4)	4 (4.9)	4 (19.0)	1 (14.3)
Occasionally	239 (51.5)	86 (48.3)	92 (52.3)	43 (52.4)	14 (66.7)	4 (57.1)
Not at all	201 (43.3)	90 (50.6)	71 (40.3)	35 (42.7)	3 (14.3)	2 (28.6)
Feeling accepted						
No	28 (6.0)	16 (9.0)	5 (2.8)	5 (6.1)	2 (9.5)	0
Not sure	32 (6.9)	11 (6.2)	10 (5.7)	9 (11.0)	2 (9.5)	0
Yes	404 (87.1)	151 (84.8)	161 (91.5)	68 (82.9)	17 (81.0)	7 (100)
Shocked or disgusted						
Many things	33 (7.1)	4 (2.2)	22 (12.5)	5 (6.1)	1 (4.8)	1 (14.3)
Afew things	324 (69.8)	107 (60.1)	139 (79.0)	59 (72.0)	16 (76.2)	3 (42.9)
None	107 (23.1)	67 (37.6)	15 (8.5)	18 (22.0)	4 (19.0)	3 (42.9)
Culture shock sum score***, *mean (SD)*	2.31 (1.40)	2.05 (1.46)	2.52 (1.30)	2.26 (1.42)	2.95 (1.02)	2.00 (1.73)

Data are presented as n (%).

* Data is missing of 15 Dutch students (3%) due to an earlier version of the questionnaire without culture shock questions. This includes the student visiting Eastern Europe and is therefore not reported in this table. Students answered the following questions regarding culture shock: Do you feel strain from the effort to adapt to a new culture? (difficulty adapting), Have you been missing your family and friends back home? (homesick), Do you feel generally accepted by the local people in the new culture? (feeling accepted), Have you found things in your new environment shocking or disgusting?

P-values for the relation between the culture shock variables and the continent were calculated using the Chi-Square test: difficulty adapting (p=0.309), homesickness (p=0.002), feeling accepted (p=0.181) and shocked or disgusted (p<0.001).

***Answer categories of culture shock questions were scored 2, 1 or 0 (according to decreasing severity) with a maximum score of 8 for each student.

Risk of blood-borne viral infection

One in three students (134/441, 30%) visited a country with a HIV prevalence of 5% or more. Students visiting these countries performed more invasive procedures than students visiting countries with a lower HIV prevalence (p=0.002). Most students (94%) had access to post-exposure prophylaxis (PEP) for HIV. Thirty-three students had a definite needle-stick or splash injury (Table 2). In almost all cases, either the source was tested for viral infection (70%) and/or PEP was started (24%). Almost all incidents were discussed with a local physician (91%). In addition, there were 24 possible incidents. Just under half of the students dealt with these incidents adequately in accordance with the national guidelines. After returning home, only a minority (28%) actively reported the (possible) injury to a health professional.

Overall, 22% (105/468) had sex during their time abroad. Eleven students (2%) opted not to answer this question. Forty students (38%) reported having had sex with their own partner and 63% with a new partner, whereof half with a local person (Dutch students: 19/81, 23%; Belgian students 15/24, 63%). Almost one in six sexual encounters (17%) with a new partner was unprotected (Table 3).

Fifteen students (3%) received an intramuscular injection and six (1%) were given intravenous treatment, mostly antibiotic therapy. Seven (2%) visited a local dentist and three students (1%) got a tattoo.

Travelers' diarrhea

Travelers' diarrhea (TD) occurred in 222 students (46%), more often in Belgian students than Dutch students (61% versus 43%, p=0.002) (Table 3). The incidence was highest for travelers to Africa (46%), followed by South America (25%) and Asia (23%). Accompanying symptoms were predominantly abdominal cramps (93%), watery stool (76%), fecal urgency (77%), nausea (57%), vomiting (26%) and fever (23%). Six students reported bloody diarrhea (3%). One in four students had symptoms for more than one week (24%). One hundred and thirteen students (51%) experienced more than one episode of diarrhea. Almost half (46%) used self-treatment: loperamide (79%), oral rehydration solution (49%), an antibiotic (30%) or activated carbon (3%). Twelve students (5%) consulted a local physician. Two students were admitted to hospital with fever and gastroenteritis. Many students experienced moderate inconvenience due to the gastro-intestinal complaints:

71 (32%) were confined to their accommodation and an additional 28 (13%) needed to change planned activities. One student was forced to interrupt the elective and return home. Students who stayed in an accommodation without running water or without a refrigerator had a significantly higher chance of developing TD (both $p<0.001$).

Other health-related events while abroad

In Surinam there was one case of cutaneous larva migrans and three students with fever were diagnosed with chikungunya, dengue fever and zika by a local doctor. Two of these students needed to change their activities for several days. Five students reported a bite from a dog (one in Surinam, two in Tanzania), monkey (Thailand) or cat (Cuba). Three of the five students had been vaccinated for rabies in the past. None received post-exposure prophylaxis. There were no cases of rabies.

Thirteen students (3%) were involved in a traffic accident. All injuries were minor. Eighty-five students (18%) suffered injuries during leisure activities: four fractures of the extremities, and 81 minor injuries. One student with a fibula fracture was repatriated from Bolivia. Twenty-five students (25/471, 5%) experienced threat or intimidation, whereof three also encountered physical violence. Most of these cases occurred in Africa (60%) and South America (24%). Twenty students (4%) suffered from altitude sickness; nine in South America, six in Asia and five in Africa (Table 3). Altitude sickness was reported more in Belgian than Dutch students (11% versus 3%, $p=0.002$).

Table 2 Invasive procedures among medical students during an elective abroad stratified by adult HIV prevalence rates at destination

			WHO rates (n=441)*							
	All students		**HIV <1%**		**HIV 1-5%**		**HIV 5-10%**		**HIV 10-20%**	
	N=479		**N=123**		**N=184**		**N=59**		**N=75**	
Invasive procedures**										
Surgical practice	262	(54.7)	68	(55.3)	100	(54.3)	33	(55.9)	57	(76.0)
Obstetric practice	195	(40.7)	54	(43.9)	66	(35.9)	42	(71.2)	30	(40.0)
Suturing	179	(37.4)	47	(38.2)	64	(34.8)	23	(39.0)	42	(56.0)
Placing an intravenous catheter	152	(31.7)	19	(15.4)	49	(26.6)	25	(42.4)	56	(74.7)
Performing phlebotomy	137	(28.6)	23	(18.7)	36	(19.6)	20	(33.9)	56	(74.7)
None of the above	98	(20.5)	19	(15.4)	39	(21.2)	2	(3.4)	8	(10.8)
Availability to PEP										
Locally available#	205	(42.8)	32	(26.0)	89	(48.4)	20	(33.9)	59	(78.7)
Unknown	103	(21.5)	39	(31.7)	47	(25.5)	4	(6.8)	0	
Pre-travel allocated	82	(17.1)	17	(13.8)	18	(9.8)	34	(57.6)	13	(17.6)
No invasive procedures performed	58	(12.1)	26	(21.1)	11	(6.0)	0		2	(2.7)
Not available	31	(6.5)	9	(7.3)	19	(10.3)	1	(1.7)	1	(1.4)
Needle stick or splash injury $										
Definite ◊	*33*	*(6.9)*	*6*		*12*		*1*		*14*	
Action taken										
Discussed injury with physician	30	(91.0)	5		11		1		13	
Source tested for HIV/HepB/HepC	23	(69.7)	4		9		1		9	
PEP used after injury	8	(24.2)	0		2		0		6	

	All students N=479		WHO rates (n=441)* HIV <1% N=123	HIV 1-5% N=184	HIV 5-10% N=59	HIV 10-20% N=75
Possible	*24*	*(5.0)*	*8*	*6*	*2*	*7*
Action taken						
Discussed injury with physician	9	(37.5)	2	1	2	4
Source tested for HIV/HepB/HepC	4	(16.7)	1	0	0	4
PEP used after injury	0		0	0	0	0

Data are presented as n (%); PEP=post-exposure prophylaxis for HIV.

* WHO rates were not available for several visited countries (38/479, 8%).

** Students could select >1 answer.

[#] Available in clinic or locally bought.

[$] Total number of students is 53, but two students experienced both a definite needle stick and splash injury (one in country with a HIV prevalence of 10-20% and one in a country with a HIV prevalence <1%), one other student experienced both a possible stick and splash injury (HIV prevalence 10-20%), and another student experienced a definite needle stick injury but also a possible splash injury (HIV prevalence 1-5%). For another student with a possible splash injury the HIV prevalence was unknown.

[◊] Incidents occurred during suturing, needle recapping, performing phlebotomy or assisting during surgery.

Table 3 Health risks and health related incidents during a foreign elective

	All students N=479	
Sexual contacts*	109/468	(23.3)
New partner involved	69/109	(63.3)
Protected	57	(82.6)
TD	222	(46.3)
Fever not related to TD complaints	36	(7.5)
Malaria**	4	(0.8)
Schistosomiasis	1	(0.2)
Altitude sickness	20/472	(4.2)
Bitten by an animal	5	(1.0)
Traffic accidents	13/474	(2.7)
Injuries during leisure activities	85/474	(17.9)
Victim of physical violence	4/473	(0.8)
Victim of threat or intimidation	25/471	(5.3)

Data are presented as n and %; TD=traveler's diarrhea.

* 11 students did not answered this question, two students had both a new local and non-local partner (condom used) and one student had sex with own partner, but also with a new local and non-local partner (no condom used); so total new sexual contacts add up to 109 instead of 105.

** Only one was reported to be confirmed by a laboratory test.

Antibiotic use

One third (30%) carried prescribed antibiotics to their destination, Belgian students more often so than Dutch student (80% versus 18%, p<0.001). Sixty-one students (13%) used an antibiotic: 22% of Belgian students and 10% of Dutch students (p=0.002). Ciprofloxacin, azithromycin, and amoxicillin were used most frequently. Almost half of the antibiotics (46%) had been prescribed in the home country. Antibiotics were mainly used for gastro-intestinal complaints (53%), skin- (15%), urinary-tract- (13%) or respiratory-tract infections (12%).

Post-travel gastro-intestinal complaints and other health problems

Students who experienced TD were more likely to report diarrhea for ≥ 3 days per month at three and six months after travel than before travel and this pattern was not seen in students without TD. The prevalence of abdominal discomfort was not different after travel than before (see Supplementary Table 5).

Almost one fifth (18%) experienced ongoing health problems in the first three months after returning home. Many (42%) attributed these complaints to their stay abroad (e.g. respiratory and urinary tract infections and gastrointestinal complaints) and 18 of these students were hereby limited in their activities. Four students had to interrupt their study for several days to weeks due to ulcerative keratitis, retinal detachment and fractures. The ocular problems were deemed unrelated to travel.

Post-travel health checks

Tuberculosis (TB)

Students who participated in an internship abroad were advised to be screened for TB after returning home. Nearly two-thirds (n=281) visited a highly endemic country (>50/100.000 cases of active TB per year). Only half (n=142) were screened after returning home. Screening was more common among Dutch than Belgian students (57% vs 27%). Six students had a positive test (6/142, 4%). Most were screened with a tuberculin skin test (TST), which yielded four positives. A minority (n=16) was screened with a QuantifFERON test (QFT) which yielded two positives. Five students were screened with QFT after the TST was positive. Two tested positive on the QFT, whereof one was treated for latent TB (Table 4).

Methicillin-resistant Staphylococcus Aureus (MRSA)

Post-travel screening for MRSA was done in 45%. Only 4% of the Belgian students were checked and 55% of the Dutch students ($p<0.001$), which reflects local policy (Table 4). Only one student was identified as an MRSA carrier which resulted in a two-week delay in starting a research internship. A confirmatory test was negative. MRSA screening was performed by the teaching hospitals or the university's occupational health service.

Schistosomiasis

Three hundred and ninety one students (82%) visited a schistosomiasis endemic country, whereof 199 (50%) were exposed to fresh (surface) water. Seventeen students (9%) were offered praziquantel in the endemic country and 14 used it. Five students started treatment within six weeks after the last freshwater contact, which is considered too early. Only 19 students (10%) consulted a physician upon return and mentioned the freshwater contact. Eleven students (6%) were screened and in one student returning from Malawi schistosomiasis was diagnosed and treated (Table 4).

Table 4 Post-travel screening for TB, MRSA and schistosomiasis in Dutch and Belgian medical students visiting endemic areas

	All students N=479		Dutch students N=385		Belgian students N=94	
TB						
Visited highly endemic country *	281	(58.6)	221	(57.4)	60	(63.9)
Post-travel screening for latent TB**						
None performed	139	(49.5)	95	(43.0)	44	(73.3)
TST	126	(44.8)	110	(49.8)	16	(26.7)
0 mm	117		101		16	
0-5 mm	5		5		0	
5-10 mm	4		4		0	
>10 mm	0		0		0	
QuantiFERON-TB blood test	21	(7.5)	21	(9.5)	0	
Positive	2		2			
Negative	15		15			
Unknown	4		4			
Referred to MHS for TB risk assessment post-travel	16/281	(5.7)	16/221	(7.2)	0	
MRSA						
MRSA screening	214	(44.7)	210	(54.5)	4	(4.3)
Schistosomiasis						
Visited schistosomiasis endemic country	391	(81.6)	338	(87.8)	53	(56.4)
Swum or waded in fresh surface water#	199/391	(50.9)	166/338	(49.1)	33/53	(62.3)
Offered local praziquantel for treatment of possible infection	17	(8.5)	14	(8.4)	3	(9.1)
Used praziquantel	14		11		3	
Reported surface water contact to physician in home country	19	(9.5)	14	(8.4)	5	(15.2)
Diagnostic test performed in home country	11	(5.5)	6	(3.6)	5	(15.2)
Infection with schistosoma	1		1		0	

Data are presented as n (%). TB=tuberculosis; MRSA=Methicillin-Resistant Staphylococcus Aureus; TST=Tuberculin Skin Test; MHS=Municipal Health Service.

*high=(mean) registered TB incidence >50/100.000, low=(mean) registered TB incidence <50/10.000.

**In five Dutch students a QuantiFERON-TB blood test was performed after the TST. These students had visited South Africa, Indonesia, Malawi and the Philippines. One of these students was already positive before having travelled. The others had not been tested at the time. Two of these students had a positive QuantiFERON, whereof one was treated for latent TB.

#Data is missing of 33 students with surface water contact (14%).

Discussion

In this multicenter study we assessed pre-travel advice, health risks and post-travel care in Dutch and Belgian medical students during an elective in low- and middle-income countries. We found that a large proportion of medical electives was performed in a limited number of clinics in specific countries, based on existing collaborations. This offers the opportunity to organize travel-care efficiently for a large group of students (recommendation 1). The quality of housing was fairly high, with the vast majority having access to running water, a refrigerator and an internet connection. The overall use of malaria chemoprophylaxis was good. Few students in endemic areas were unprotected, after they had stopped their prophylaxis due to side-effects. Pre-travel instructions on how and when to start an alternative chemoprophylaxis need to be stressed, accompanied by contact details of a professional back home, so students can confer in case of problems while abroad (recommendation 2). With approximately 7%, the incidence of needle stick and splash injuries was higher than in previous studies (both 2%) [14, 15]. This was in spite of the fact that at some of the universities, medical students were required to obtain a certificate of competency for invasive procedures, before leaving for an elective. Most incidents were dealt adequately in accordance with the national guidelines. However, an additional 5% reported a possible needle-stick or splash injury and in this group just under half dealt with it adequately. It needs to be stressed that when in doubt, students should discuss possible exposure to body fluids with an attending physician or a health professional back home as soon as possible (recommendation 3). In our study, 2.5% had unprotected sex with a new partner, which is less than in the study by Angelin et al (6.6%) [15]. Many medical schools provide PEP kits to students at substantial cost. Of interest, a recent study has shown that a redispensing process is feasible and can result in substantial cost saving [16].

One in five suffered injury, obtained during leisure activities. One in fifty sustained minor injury from a traffic accident. Furthermore, it is of concern that one in twenty felt threatened or intimidated, with 1% encountering physical violence. Nearly all incidents occurred outside the workplace and mainly in Africa and South America.

Infection with rabies is rare among travelers. Nevertheless, students should be counseled regarding the risk of this lethal infection (recommendation 4). In our study,

five students (1%) sustained an animal bite: three out of five had been vaccinated in the past, none received post-exposure prophylaxis.

As was to be expected, travelers' diarrhea was very common (46%). This may lead to post-infectious irritable bowel syndrome (IBS). The incidence of IBS has been estimated to be between 1.5 and 7.2% [17, 18]. For reasons of efficiency, we only included a subset of questions from the validated ROME questionnaire for IBS. However, we did correct the results for pre-existent bowel complaints. Six months after travel, among those who had suffered from TD, 3% had new complaints of diarrhea which they did not have before traveling, and 1% had new-onset abdominal complaints combined with diarrhea. No such pattern was seen in those without TD. Infection with *Giardia lamblia* may cause post-travel gastro-intestinal complaints. This was not investigated in our study [19].

The way in which post-travel care is organized is very much university dependent. Overall, we found post-travel screening for TB and schistosomiasis to be lacking. This is probably related to the fact that a post-travel consult is not part of routine care. It is left to the discretion of students or, in case of screening for TB, it is part of routine policy for health-care workers when starting a position in a new hospital. Only half of the students visiting a highly endemic country were screened for TB upon returning home. Six students tested positive and one of them was treated for latent TB. We recommend that all medical students who visit highly endemic areas for at least three months and are planning to work in a health care setting should either be offered a vaccination with BCG at least six weeks before travelling or should be screened for TB with a TST, eight weeks after returning home. In case of a positive TST, a QuantiFERON blood test can help to diagnose latent TB (recommendation 5) [20].

Regarding schistosomiasis, few of those who were at risk were screened and a number of students used praziquantel within six weeks after the last fresh water contact, at which time the parasite may not yet be fully susceptible to treatment [21]. Handing out information on screening and treatment for schistosomiasis may help increase the percentage that is screened and the correct use of treatment (recommendation 6).

Table 5 Recommendations for universities who offer medical students the opportunity to perform an international elective

Recommendation 1	Organize collective pre-travel health advice tailored to the contracted health care facilities abroad and according to the broad geographical zone that is to visited.
Recommendation 2	Counsel on how and when to start an alternative chemoprophylaxis while staying in malaria endemic areas and provide contact details of professional back home for medical advice.
Recommendation 3	Distributing guidelines on how and when to discuss (possible) exposure to body fluids because of needle-stick or splash incidents with a physician.
Recommendation 4	Counsel students on animal associated injuries and offer rabies pre-exposure vaccination and provide contact details of a professional back home for medical advice.
Recommendation 5	Offer a BCG vaccination pre-travel or organize mandatory post-travel follow-up test moments for students who visited highly endemic areas for at least three months to work in a health care setting.
Recommendation 6	Counsel on post-travel screening and treatment of schistosomiasis.

This study has a number of strengths. First, it is a multicenter study in which students were recruited before departure. This increases generalizability and limits selection bias. Second, questionnaires were taken before and at three time-points after travel, to limit recall bias and to correct for pre-travel items such as bowel complaints. Third, the follow up rate was high (84%), which limits information bias.

This study also has its limitations. First, generalizability is influenced by the fact that many students visited a limited number of foreign medical clinics, often based on past colonial ties and established collaborations between foreign hospitals and the universities in The Netherlands and Belgium. Second, as in any observational questionnaire study, recall bias can occur. Third, most students combined the elective with a holiday. We could not distinguish health complaints that occurred during the elective from those that occurred during the holiday. Lastly, due to the length of the study, guidelines such as for malaria prophylaxis may have changed over time.

In addition to our recommendations, we propose a number of further suggestions to improve pre- and post-travel care for medical students. Many students enroll in general meetings on global health and electives before travelling. By organizing these meetings according to the broad geographical zone that is to be visited (e.g.

Central America, Africa, and Asia), relevant information can be conveyed more efficiently. During such meetings students could meet predecessors who can share their valuable experiences. In line with this, we envision a mobile app, similar to TripAdvisor® for tourists, to guide students and share experiences. Furthermore, an obligatory refresher training on invasive procedures could be offered before departure [22, 23]. Compliance with post-travel screening could be improved upon by linking a post-travel consult to the granting of the study credits.

Conclusions

This study demonstrates the need for an update of the pre- and post-travel educational program for Dutch and Belgian medical students who are planning to perform a medical elective in a LOMIC country. In addition to the recommendations that are summarized in Table 5, we recommend a centrally organized post-travel check-up.

List of abbreviations

LOMIC (low- or middle-income countries), MRSA (Methicillin-Resistant Staphylococcus Aureus), TD (travelers' diarrhea), TB (tuberculosis), VU (Vrije Universiteit), LCR (National Travel Advice Coordination Center), HIV (Human Immunodeficiency Virus), WHO (World Health Organization), SPSS (Statistical Package for the Social Sciences), LUMC (Leiden University Medical Center), PEP (post-exposure prophylaxis for HIV), TST (Tuberculin Skin Test), QFT (QuantiFERON-TB blood test), IBS (irritable bowel syndrome), BCG (Bacillus Calmette-Guérin), KAP (Knowledge, Attitude and Practice).

Ethics approval and consent to participate

The study was endorsed by the Medical Ethical Committee (CME) of the Leiden University Medical Center (LUMC), Leiden, the Netherlands (registry number P11.046). They decided that the study does not fall under the scope of the Medical Research Involving Human Subjects Act (in Dutch: WMO). Participants provided their digital informed consent by completing the first questionnaire.

Conflict of interests

All authors declare that they have no conflict of interest.

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Authors' contributions

Designed the study: DS, NK, LV
Data collection: JV, AB, EJ, NK, EH
Statistical analysis: JV
Interpretation of results: JV, AB, DS, LV
Drafting of manuscript: JV, AB, DS, LV
Reviewed, commented and approved the final manuscript: all authors

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Supplementary data

Supplementary Table S1 Questionnaire items

Number of topics	T1 two weeks pre-travel	T2 two weeks post-travel	T3 three months post-travel	T4 six months post-travel
General information				
Demographics	5	2	-	-
Information on elective	3	13	-	-
Travel dates	2	2	-	-
Procedures	1	2	-	-
Holiday	-	2	-	-
Type of elective	-	7	-	-
Hygienic circumstances	-	7	-	-
Medical arrangements and usage				
HIV prophylaxis (including PEP)	2	3	-	-
Knowledge HIV-prevalence	1	1	-	-
PEP availability and usage	1	2	-	-
Malaria chemoprophylaxis	-	16	-	-
Antibiotics	-	3	-	-
Advice and vaccination	-	8	-	-
Hepatitis B	-	1	-	-
Pre-travel advice[#]	-	5	-	-
Other vaccinations	-	2	-	-
Exposure during elective				
Splash- and needle-stick injuries*	-	21	-	-
Fresh water contact	-	-	-	3
Sexual contacts	-	3	-	-
Culture shock[$]	-	5	-	-
Injuries	-	1	-	-
Traffic accidents	-	1	-	-
Violence	-	2	-	-
Animal attacks	-	4	-	-
Rabies	-	2	-	-

Number of topics	T1 two weeks pre-travel	T2 two weeks post-travel	T3 three months post-travel	T4 six months post-travel
Medical complaints and treatment				
Fever	-	8	10	-
Abdominal	5	22	5	5
Other	-	4	3	2
Post-exposure health check				
MRSA	-	-	4	4
TB	-	-	9	7
Schistosomiasis	-	-	-	4

Data are presented as number of items in the questionnaires. PEP: Post-Exposure Prophylaxis; HIV: Human immunodeficiency virus; MRSA: Methicillin-Resistant Staphylococcus Aureus. TB: tuberculosis

[#] Including questions about the course “International Health” or similar.

*Splash injury: accidental spraying of body fluids onto exposed mucocutaneous surfaces. Needle-stick injury: accidental skin puncture with a sharp medical instrument which has potentially been in contact with human body fluids.

[$]Including question about the most valuable experience during the internship.

Supplementary Table S2 Demographic and travel characteristics of 479 Dutch and Belgian medical students conducting an elective abroad.

	All students N=479		Dutch students N=385		Belgian students N=94	
Gender, female	363	(75.8)	297	(77.1)	66	(70.2)
Median age, *years (IQR)*	24.0	(23-25)	24	(22-25)	24	(23-24)
Academic year completed						
First	2	(0.4)	2	(0.5)	0	
Second	39	(8.1)	38	(9.9)	1	(1.1)
Third	58	(12.1)	58	(15.1)	0	
Fourth	113	(23.6)	113	(29.4)	0	
Fifth	210	(43.8)	145	(37.7)	65	(69.1)
Sixth	57	(11.9)	29	(7.5)	28	(29.8)
Pre-travel advice and source*	446	(93.1)	358	(93.0)	88	(93.6)
Travel Clinic	207		148		59	
Health department of university	155		153		2	
Municipal Health Service	80		78		2	
General Practitioner	65		42		23	
International office of university	65		60		5	
Internet	37		20		17	
Other	20		14		6	
Type of elective						
Clinical	375	(78.3)	285	(74.0)	90	(95.7)
Pre-clinical	60	(12.5)	57	(14.8)	3	(3.2)
Research	35	(7.3)	35	(9.1)	0	
Social	9	(1.9)	8	(2.1)	1	(1.1)
Department of elective*						
Gynaecology / obstetric	211	(44.1)	130	(33.8)	81	(86.2)
Pediatrics	183	(38.2)	112	(29.1)	71	(75.5)
Surgery	75	(15.7)	65	(16.9)	10	(10.6)
Internal medicine	63	(13.2)	49	(12.7)	14	(14.9)
Dermatology	24	(5.0)	22	(5.7)	2	(2.1)
Ear, nose and throat	21	(4.4)	20	(5.2)	1	(1.1)
Other◊	181	(37.8)	165	(42.9)	16	(17.0)
Type of institution*						
Hospital in a large city	341	(71.2)	266	(69.1)	75	(79.8)
Hospital in a village/small city	108	(22.5)	77	(20.0)	31	(33.0)

	All students N=479		Dutch students N=385		Belgian students N=94	
Primary health center in rural area	65	(13.6)	54	(14.0)	11	(11.7)
Other	55	(11.5)	52	(13.5)	3	(3.2)
Travel destination#						
South America	185	(38.6)	141	(36.6)	44	(46.8)
Africa	182	(38.0)	147	(38.2)	35	(37.2)
Asia	82	(17.1)	72	(18.7)	10	(10.6)
Central America	22	(4.6)	17	(4.4)	5	(5.3)
Middle-East	7	(1.5)	7	(1.8)	0	
Eastern Europe	1	(0.2)	1	(0.3)	0	
Median travel duration, *days (IQR)*	67	(48-85)	61	(43.5-72.5)	91	(87-92)
Elective combined with holiday	310	(64.7)	269	(69.9)	41	(43.6)
Holiday duration						
One week or less	84		59		25	
2 weeks	102		92		10	
3 weeks	68		63		5	
4 weeks	34		33		1	
5 weeks or more	22		22		0	
Facilities in accommodation						
Running water	409	(85.4)	337	(87.5)	72	(76.6)
Toilet/sanitation	473	(98.7)	380	(98.7)	93	(98.9)
Electricity 24 hours a day	382	(79.7)	309	(80.3)	73	(77.7)
Well-functioning refrigerator	403	(84.1)	316	(82.1)	87	(92.6)
Well-functioning air-conditioning	182	(38.0)	148	(38.4)	34	(36.2)
Internet connection within 30 minutes distance	450	(93.9)	361	(93.8)	89	(94.7)
Functioning mobile phone network	463	(96.7)	373	(96.9)	90	(95.7)

Data are presented as n (%), unless otherwise stated.

*Students could select >1 answer

◊E.g. traditional Chinese medicine, primary health, General Practitioner, infectious diseases, emergency department

#Travel destination visited were divided into 6 continents (n=no. of travelers per destination); South-America (n=185): Surinam (n=140), Chili (n=13), Ecuador (n=10), Argentina (n=6), Paraguay (n=5), Uruguay (n=4), Bolivia (n=3), Brazil (n=2), Guyana (n=1), Peru (n=1); Africa (n=182): South-Africa (n=68), Tanzania (n=30), Malawi (n=17), Rwanda (n=11), Ghana (n=11), Cameroon (n=8), Benin (n=7), Uganda (n=7), Kenya (n=5), Gabon (n=3), Zambia (n=3), Ethiopia (n=2), Morocco (n=2), Mozambique (n=2), Gambia (n=1), Lesotho (n=1), Mali (n=1), Senegal (n=1), Tunisia (n=1), Zimbabwe (n=1); Asia (n=82): China (n=28), Nepal (n=21), Indonesia (n=12), Cambodia (n=5), Philippines (n=5), Thailand (n=5), India (n=4), Vietnam (n=1), Taiwan (n=1); Central America (n=22): Cuba (n=11), Nicaragua (n=5), Guatemala (n=2), Dominican Republic (n=1), Guadeloupe (n=1), Martinique (n=1), Mexico (n=1); Middle-East (n=7): Israel (n=3), Turkey (n=3), Iraq (n=1); Eastern Europe (n=1): Bulgaria (n=1).

Supplementary Table S3 Culture shock in 464 Dutch and Belgian medical students during an elective abroad.

	All students* N=464		Dutch students N=370		Belgian students N=94		p-value**
Difficulty to adapt							0.657
Most of the time	35	(7.5)	30	(8.1)	5	(5.3)	
Occasionally	235	(50.6)	186	(50.3)	49	(52.1)	
Not at all	194	(41.8)	154	(41.6)	40	(42.6)	
Homesick							0.435
Most of the time	24	(5.2)	21	(5.7)	3	(3.2)	
Occasionally	239	(51.5)	186	(50.3)	53	(56.4)	
Not at all	201	(43.3)	163	(44.1)	38	(40.4)	
Feeling accepted							0.742
No	28	(6.0)	23	(6.2)	5	(5.3)	
Not sure	32	(6.9)	27	(7.3)	5	(5.3)	
Yes	404	(87.1)	320	(86.5)	84	(89.4)	
Shocked or disgusted							0.113
Many things	33	(7.1)	30	(8.1)	3	(3.2)	
Afew things	324	(69.8)	251	(67.8)	73	(77.7)	
None	107	(23.1)	89	(24.1)	18	(19.1)	
Culture shock sum score[#], *mean (SD)*	2.31	(1.40)	2.32	(1.45)	2.26	(1.18)	0.658

Data are presented as n (%), unless otherwise stated. Students answered the following questions regarding culture shock: Do you feel strain from the effort to adapt to a new culture? (difficulty to adapt), Have you been missing your family and friends back home? (homesick), Do you feel generally accepted by the local people in the new culture? (feeling accepted), Have you found things in your new environment shocking or disgusting?

*Data is missing for 15 Dutch students (3%) due to an earlier version of the questionnaire without the culture shock questions.

**Pearson Chi-square was used for the culture shock items and an unpaired t-test for the culture shock sum score.

[#]Answer categories of culture shock questions were scored 2, 1 or 0 (according to decreasing severity) with a maximum score of 8 for each student.

Supplementary Table S4 Malaria chemoprophylaxis among 185 Dutch and Belgian medical students traveling to an area that was endemic for malaria.

	All students N=185		Dutch students N=140		Belgian students N=45	
Type of chemoprophylaxis						
Atovaquone/proguanil	129	(69.7)	94	(67.1)	35	(77.8)
Mefloquine	44	(23.8)	36	(25.7)	8	(17.8)
Doxycycline	5	(2.7)	3	(2.1)	2	(4.4)
Proguanil	6	(3.2)	6	(4.3)	0	
Unknown	1	(0.5)	1	(0.7)	0	
Prescribed in home country	176	(95.1)	131	(93.6)	45	(100)
Purchased locally[#]	9	(4.9)	9	(6.4)	0	
Experienced side effects	48	(25.9)	34	(24.3)	14	(31.1)
Atovaquone/proguanil	33/129	(25.6)	24/94	(25.5)	9/35	(25.7)
Sleep disorder	9		7		2	
GI tract	19		13		6	
Other	5		4		1	
Mefloquine	13/44	(29.5)	9/36	(25.0)	4/8	(50.0)
Sleep disorder	12		8		4	
GI tract	1		1		0	
Other[$]	2/12	(16.7)	1/10	(10.0)	1/2	(50.0)
Stopped prematurely	24	(13.0)	20	(14.3)	4	(8.9)
Atovaquone/proguanil	15/129	(11.6)	13/94	(13.8)	2/35	(5.7)
Mefloquine	3/44	(6.8)	3/36	(8.3)	0	
Doxycycline	3/5	(60.0)	1/3	(33.3)	2/2	(100)
Proguanil	3/6	(50.0)	3/6	(50.0)	0	
Reason for stopping prematurely*						
No malaria in the area**	17	(70.8)	14	(70.0)	3	(75.0)
Forgotten	6	(25.0)	4	(20.0)	2	(50.0)
Side effects	4	(16.7)	4	(20.0)	0	
Other***	6	(25.0)	5	(25.0)	1	(25.0)
Discussed stopping with a professional	2	(8.3)	1	(5.0)	1	(25.0)
Used a bed net	154	(83.2)	114	(81.4)	40	(88.9)

Data are presented as n and %; GI=gastrointestinal.

[#]Atovaquone/proguanil n=7, doxycycline n=1, unknown n=1.

[$]Doxycycline n=1, proguanil n=1.

*nine students filled in >1 reason; 1 student stopped atovaquone/proguanil and 1 students stopped doxycycline while this was not brought from the home country.

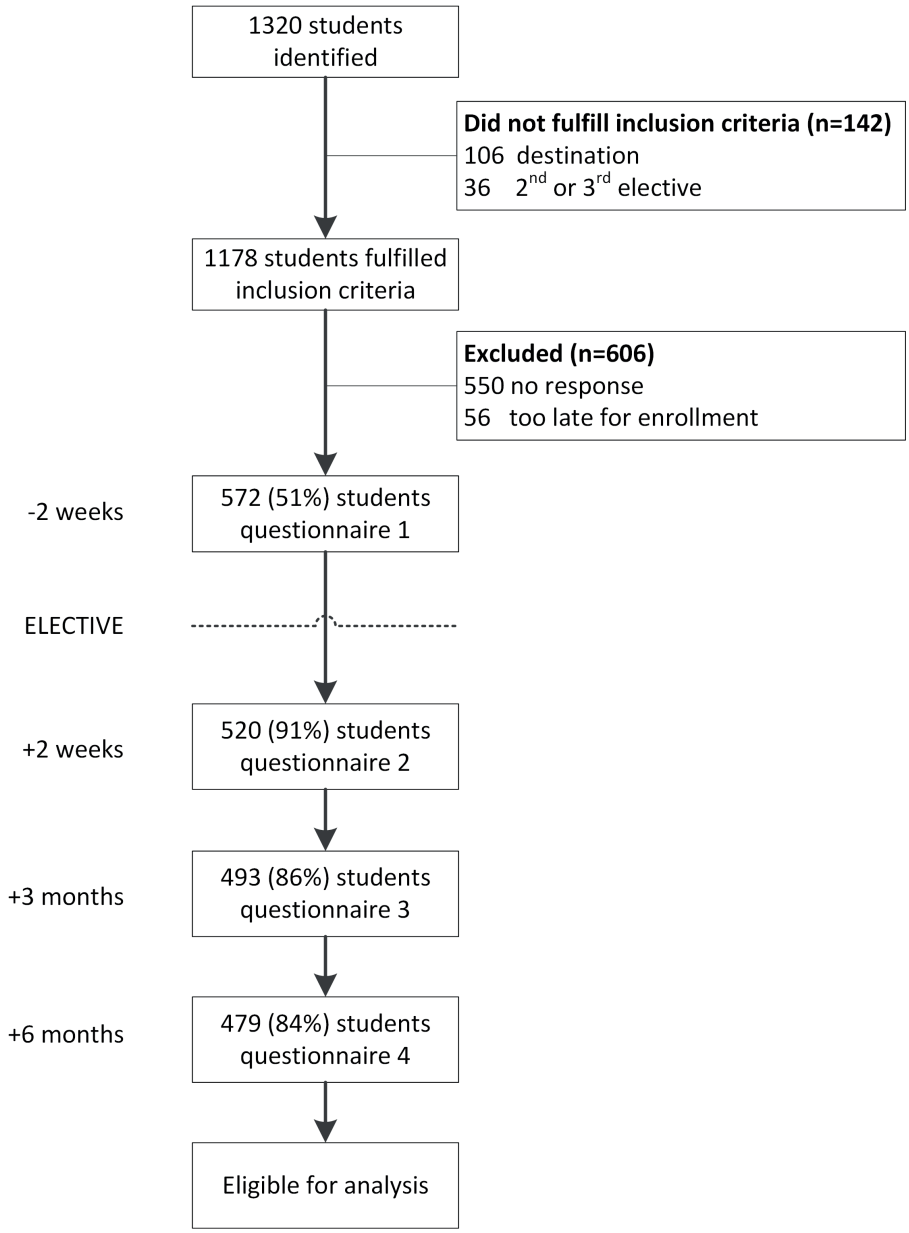
**Includes three students to a high endemic region in Kenia, Tanzania and Rwanda.

***Illness n=3, already experienced malaria despite prophylaxis n=1, only when visiting malaria-risk area n=2.

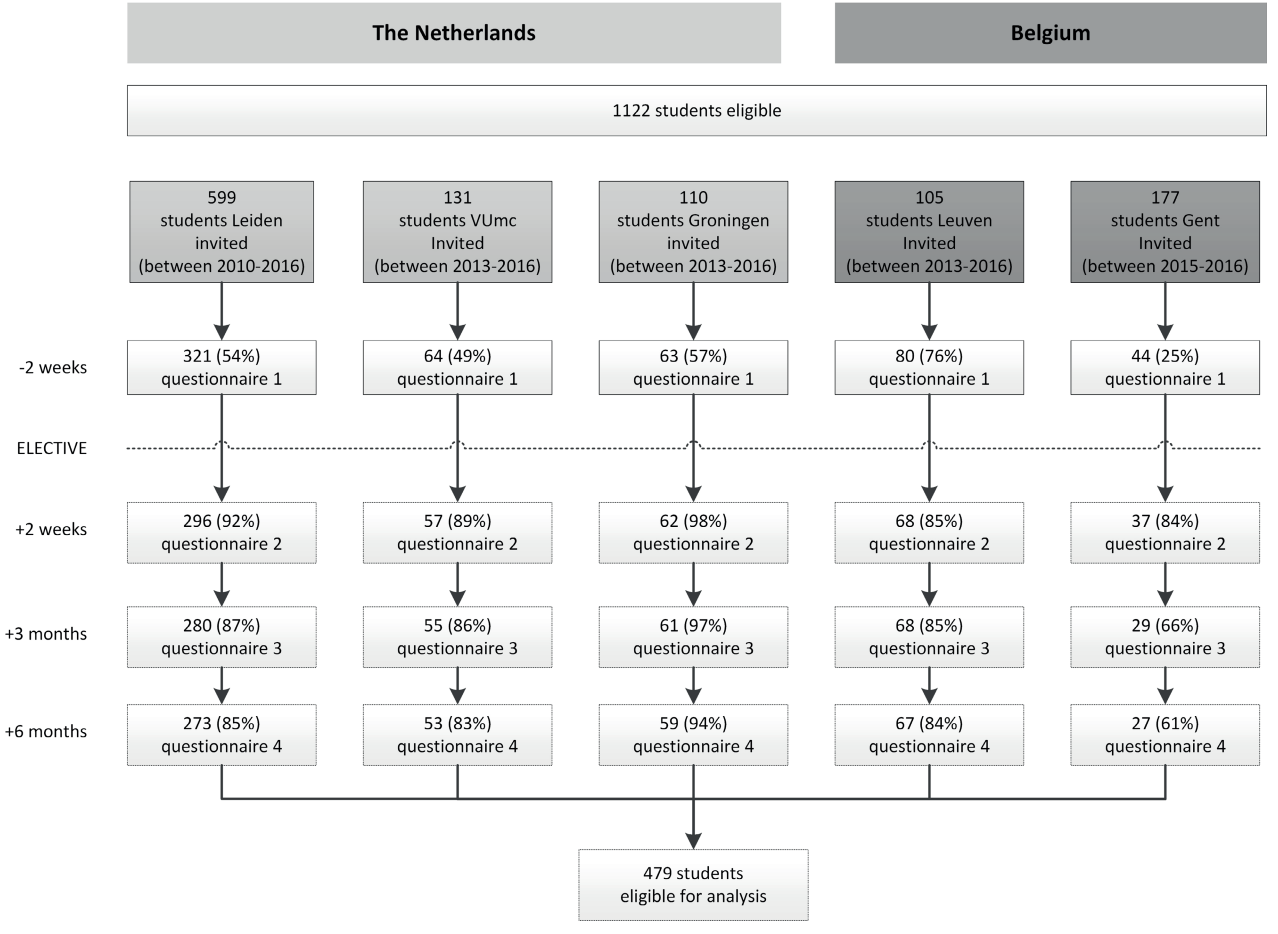
Supplementary Table S5 Abdominal complaints before and after a foreign elective, stratified by occurrence of TD during the elective.

	Students with TD (n=222)						Students without TD (n=257)					
	3 mo. pre-travel		3 mo. post-travel		6 mo. post-travel		3 mo. pre-travel		3 mo. post-travel		6 mo. post-travel	
Abdominal discomfort ≥ 3 days per mo. & onset > 6 mo. ago.	31	(14.0)	21	(9.5)	24	(10.8)	27	(10.5)	24	(9.3)	26	(10.1)
Diarrhea ≥ 3 days per mo.	5	(2.3)	16	(7.2)	12	(5.4)	4	(1.6)	1	(0.4)	5	(1.9)
Both symptoms	2	(0.9)	5	(2.3)	4	(1.8)	2	(0.8)	0		3	(1.2)

Data are presented as n (%). TD=travelers' diarrhea; mo=months. Abdominal discomfort that only occurred during the menstrual cycle was not classified as abdominal discomfort for the purpose of this analysis.



Supplementary Figure S1 Overall flowchart KAP2010 study



Supplementary Figure S2 Flowchart per center KAP2010 study

5

Predicting morbidity in older travelers during a short-term stay in the tropics: the ELDEST study

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Abstract

Background Older persons may suffer more from travel-related health problems because of ageing and underlying chronic disorders. Knowledge on who is more likely to have these health problems helps to tailor travel health advice more specifically. This study aimed to determine predictors of travel-related morbidity in older travelers by assessing their pre-travel characteristics and performance using physical and cognitive functioning tests.

Methods Multicentre prospective cohort study among older travelers (≥ 60 years) who consulted one of the participating Dutch travel clinics. Handgrip strength and cognitive performance were measured pre-travel. Participants completed questionnaires before departure and one and four weeks after return. A diary recorded health complaints during travel until two-week post-travel.

Results In total, 477 travelers completed the study (follow-up rate of 97%). Participants' median age was 66 years. The most visited regions were South-East Asia (34%) and South Asia (14%). Median travel duration was 19 days. Polypharmacy (≥5 medications per day) was not uncommon (16%). The median Charlson Comorbidity Index (CCI) score was 0. Self-reported travel-related infectious diseases concerned primarily respiratory tract infections (21%) and gastroenteritis (10%), whereas non-infectious complaints were injuries (13%), peripheral edema (12%), and dehydration (3%). Medical assistance was sought by 18%, mostly post-travel from their general practitioner (87%). Self-reported physical and mental health-related quality of life significantly improved during and after travel. Predictors for an increased risk of travel-related morbidity were higher CCI score, more travel experience, longer travel duration, higher number of daily medications, visiting northern Africa or South-East and East Asia, and phone and social media use.

Conclusion Older Dutch travelers are generally fit, well-prepared and suffer not only from common infectious health problems, but also from injuries. Travel improved their self-perceived health. The predictors could be used to identify the more at-risk older traveler and to decrease travel-related morbidity by optimizing pre-travel advice.

Introduction

Over the past decades, increase in life expectancy and vitality has led to a growing older population travelling internationally.[1] In previous studies 15-30% of all international travelers were older adults.[2-4] Between 1995 and 2017, the percentage of Dutch travelers to tropical destinations has almost doubled from 8% to 16%.[5] It is conceivable that this also holds true for older travelers.

The travel-related morbidity of older travelers is expected to differ from that of younger travelers due to physiological, medical and behavioural differences.[6-9] Due to their altered homeostasis older persons may suffer more from exposure to extreme climate and environmental conditions, potentially resulting in increased susceptibility to dehydration and hyper- or hypothermia.[10-13] In addition, older persons are more susceptible to infections due to impaired immune responses, waning immunity, and limited effectiveness of pre-travel vaccinations.[4, 14-17] Moreover, polypharmacy and underlying chronic disorders, including cardiovascular disease, diabetes mellitus (DM), and chronic respiratory diseases are more prevalent among older persons.[18-23] This poses a risk of decreased physical functioning, drug-related side effects and drug-drug interactions or exacerbations of pre-existing illnesses during travel.[10, 21, 24-26] Yet, older travelers choose different, possibly lower-risk destinations and travel modes and show less risky behaviour, which may diminish their travel-related health risks.[7, 27]

A case-control study by Gautret et al. revealed that the observed proportion of illnesses, such as lower respiratory tract infections (RTIs), trauma and injuries, urinary tract infections, and heart disease, was higher in the older travelers visiting a travel clinic post-travel compared with younger travelers.[6] Illnesses such as acute diarrhoea, upper RTIs, mild malaria, and dengue, were less frequently observed. However, the generalizability of these findings may be limited due to confounding by indication as only ill older travelers presenting themselves at the clinic post-travel were included.

Our aim was to identify predictors related to the occurrence of morbidity in older travelers during their tropical travel and shortly thereafter. To that end we evaluated their pre-travel performance using physical and cognitive functioning tests and

determined the incidence, duration and inconvenience of travel-related morbidity in a prospective cohort.

Methods

Design and participants

We conducted a multicentre prospective observational cohort study among older adults travelling to tropical destinations (ELDEST study, morbidity in ELDErly travelers during a Short-Term stay abroad). Travelers were informed and recruited during their regular visit at four Dutch travel clinics between July 2016 and November 2017 [LUMC in Leiden (coordinating centre), Harbor Hospital Rotterdam and Municipal Health Services (MHSs) Rotterdam-Rijnmond and Haaglanden]. Inclusion criteria were: age ≥ 60 years, a scheduled travel to a tropical destination, and a travel duration of ≤ 35 days. Exclusion criteria were inability to complete diary and questionnaires because of foreign language, or cognitive disability (i.e. suffering from memory disorders) or visiting the clinic less than two weeks prior to departure.

The study consisted of two parts. Part A collected pre-travel basic demographic information, and travelers completed physical and cognitive functioning tests. For logistical reasons, the cognitive test could not be performed at the MHSs sites. In part B, travelers completed pre- and post-travel questionnaires. In addition, a diary on travel-related health complaints was kept starting 1 week pre-travel, during travel until 2-week post-travel. Depending on their willingness to participate, travelers were included solely in part A or in both parts. This study was approved by the Medical Ethical Committee of the LUMC (registry number P16.056). All participants signed an informed consent. We followed the strengthening the reporting of observational studies in epidemiology (STROBE) reporting guideline.

Functional tests (part A)

Hand grip strength is correlated with physical functioning and several important health outcomes.[28] Grip strength was defined as the maximum strength from three attempts, measured with the Jamar Hydraulic hand dynamometer.[29, 30] The six item cognitive impairment test (6CIT) was conducted to assess the level of cognitive deficits.[31, 32] This test can be completed within 3-4 minutes and consists of six

weighted items including one memory, two attention and three orientation questions. The 6CIT is not influenced by education level.[32] A higher score is associated with more cognitive impairment (Supplementary Appendix 1).

Questionnaires (part B)

Questionnaires were pre-tested among older adults for clarity and comprehensibility before start of the study. Travelers completed questionnaires at different time points: one week pre-travel, one week post-travel and four week post-travel. If travelers reported health complaints in the third questionnaire, an additional questionnaire was filled out eight weeks post-travel.

Questionnaire 1 captured demographic data, medical history, medication and travel characteristics. In addition, three standardized tests were included to identify potential risk profiles based on health status, independence and (co)morbidity. Self-reported health status was assessed by the Short Form 36 health survey (SF-36) measuring eight health domains: physical functioning, social functioning, role limitations due to physical or emotional problems, mental health, vitality, bodily pain and general health perception.[33] A higher SF-36 score is associated with a better health status (range 0-100). The level of independence of performing daily activities (e.g. dressing) was measured using the Katz activities of daily living (Katz-ADL).[34, 35] A higher Katz-ADL score is associated with more dependence (range 0-26). The comorbidity burden was assessed with the Charlson Comorbidity Index (CCI), a tool to measure comorbidity and to estimate 10-year survival (Supplementary Appendix 2).[36, 37] Questionnaire 2 concerned travel preparation, risk behaviour, health complaints and treatment. Post-travel health complaints and (possible) medical treatment were evaluated in questionnaire 3 and 4. The SF-36 was repeated twice to measure changes in self-reported health.

Diary (part B)

Health complaints and experienced inconvenience were reported daily in a paper diary, starting one week pre-travel until two weeks post-travel. Every traveler received a digital thermometer for measuring body temperature in case of illness.

Definitions

Polypharmacy was defined as the use of five or more medications per day (not including malaria prophylaxis.[38] Diarrhoea was defined as the passage of three or more unformed stools during a 24-h period (WHO definition).[39] Fever was defined as body temperature ≥ 38°C. Travel destinations were categorized according to geographical regions of the United Nations Statistics Division.[40] Travel-related morbidity was categorized by evaluating the presence, duration, inconvenience, and treatment of predefined symptom clusters using the diaries (Supplementary Appendix 3). Symptom clusters were defined on the presence of health complaints, matching the Dutch General Practitioners guidelines as closely as possible.[41]

Sample size

We estimated that ~20% of older travelers would experience some kind of health problem during their foreign stay, but data for Dutch older travelers are lacking. Therefore, a formal power calculation was not performed. As many travelers as feasible were included within the timeframe of the project with the intention to collect complete data of at least 100 travelers aged between 70 and 79 years old, which would result in at least 20 travelers with health problems in this age group. Based on the age distribution of the participating centres in the past years and an attrition rate of 25%, a total of 625 inclusions were estimated to be required for this study to achieve this goal.

Statistical analysis

Statistical analyses were conducted using SPSS software, version 23 (IBM Corp). Firstly, descriptive analyses and univariable analysis were used for demographical, (physical) health status and travel characteristics of travelers participating in A and B. Travelers aged 60-69 years were compared with travelers 70 years or older in our cohort regarding the pre-travel health characteristics. Secondly, incidence, duration, experienced inconvenience and treatment of travel-related morbidity were determined. SF-36 scores were compared using Wilcoxon signed rank test. Thirdly, logistic regression analyses were performed to identify predictors for travel-related morbidity using univariable and multivariable analysis. Without preselection from the univariable analysis, variables were entered in a multivariable logistic regression

using backward elimination until the Akaike information criterion ($P < 0.157$) was minimized. In accordance with the guidelines for establishing prediction models, we selected the Akaike information criterion above the classic method of statistical significance with a *P*-value < 0.05 because otherwise important variables could be indicated as 'non predictive' due to the relatively small sample size.[42] The Nagelkerke R^2, Hosmer and Lemeshow test, Brier score and c-index of the model were assessed to determine the performance of the model. The 6CIT total score could not be included in the model, as it was unavailable for travelers which were included at the MHSs. Associations were reported as odds ratios, 95% confidence intervals (CI) and *P*-values.

Results

Study population and travel characteristics

In total, 1003 travelers were invited, of whom 649 were included in part A (35% non-participation). Of these, 477 travelers (73%) were available for case analysis (Part A and B, follow-up rate questionnaires 97%) (Figure 1). Demographic and travel characteristics are shown in Supplementary Table S1. The median age was 66 years (interquartily range [IQR] 63-70); 132 (28%) were aged 70 years and over.

Travelers were generally fit with an overall median 6CIT total score of 0 (IQR 0-2) and a median grip strength of 34 kg (IQR 28-45) (Table 1). The most visited regions were South-Eastern Asia (34%), and Southern Asia (14%) (Supplementary Figure S1). The median time spent abroad was 19 days (IQR 14-23). Almost all travelers owned a mobile phone (98%) and many used social media (60%) (Supplementary Table S1).

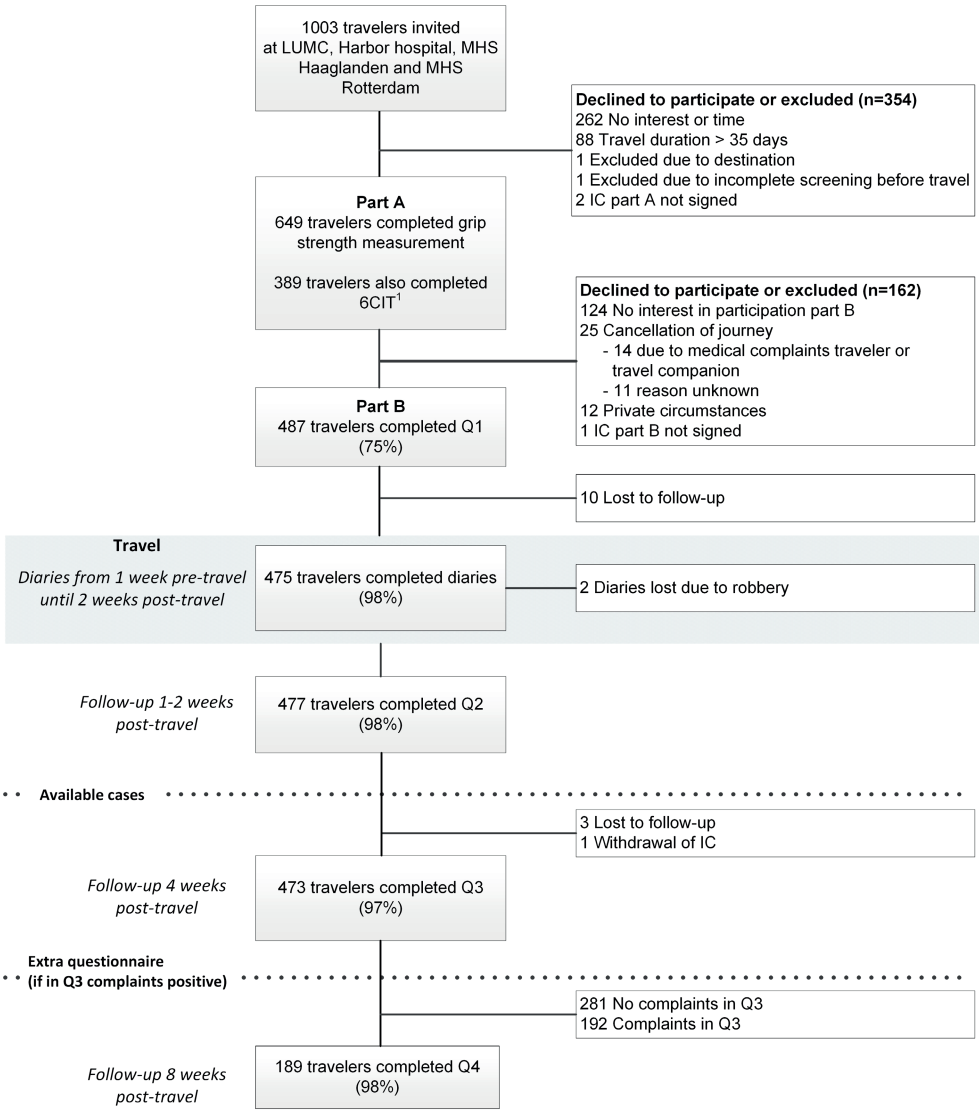

Figure 1. Flowchart of participants in the ELDEST study. [1] Only performed by participating travelers at two of the four clinics. 6CIT, Six Item Cognitive Impairment Test; IC, Informed Consent; LUMC, Leiden University Medical Centre; MHS, Municipal Health Service; Q, Questionnaire.

Pre-travel health characteristics

Polypharmacy was not uncommon among participants. One third of all travelers did not use any medication at all; 16% used five or more daily medications. In travelers aged 70 years and over polypharmacy occurred more frequently (P = 0.003). Katz-ADL revealed that 97% of travelers could be classified as independent. The median CCI was 0 (IQR 0-1), corresponding with an estimated 10-year survival of 92%.[36] Pre-travel performance scores, particularly grip strength, 6CIT, and CCI, were significantly worse in travelers aged ≥70 years. Overall, the three most observed pre-existing conditions were cardiovascular diseases (44%, mainly hypertension), malignancies (16%), and skin diseases (10%) (Table 1).

Travel preparation

The majority of travelers booked their travel online (60%). They frequently consulted sources for advice, such as the general practitioner (GP, 91%) and the internet (18%). Nearly all travelers had a travel insurance (97%). Travelers often carried self-medication for diarrhoea such as loperamide (73%), and oral rehydration solution (ORS, 60%) (Supplementary Table S2). Also hand-hygiene products, such as hand sanitizers (58%), were brought along of which 75% (207/275) used these regularly (Supplementary Table S3).

Risk behaviour

Travelers showed various kinds of risk behaviour such as consuming unpeeled fruit (76%), raw food products (27%, i.e. crustaceans or shellfish) or eating at street vendors (19%). Regular hand washing before a meal was practiced by 84% of travelers. About 20% reported contact with animals that mostly involved monkeys (91%) or dogs (48%) (Supplementary Table S3).

Malaria prophylaxis

If malaria prophylaxis was indicated (n=147), chemoprophylaxis and mosquito nets were used in 82% and 80% of travelers, respectively. Atovaquone/proguanil was mostly used (93%); only one traveler used mefloquine (1%). Most travelers were fully compliant (92%). Side effects are listed in Supplementary Table S4. No cases of malaria were reported.

Table 1. Pre-travel health characteristics of 477 older travelers to the tropics.

	Available cases All ages[a] N=477	Available cases 60-69y N=345	Available cases ≥70y N=132	Comparison p-value[h]
BMI, *kg/m², median (IQR)*	25.4 (23-28)	25.4 (23-28)	24.9 (23-28)	*P*=0.514[i]
Sensory function				
Wearing glasses or contact lenses[b]	366 (77)	261 (77)	105 (80)	*P*=0.395
Wearing hearing aid[b]	53 (11)	25 (7)	28 (21)	*P*<0.001
Influenza vaccination received in the past year[b]	265 (56)	167 (48)	98 (74)	*P*<0.001
Katz-ADL score, *median (IQR)*[bc]	0 (0-0)	0 (0-0)	0 (0-0)	*P*=0.138
0	461 (97)	336 (98)	125 (95)	
1	15 (3)	8 (2)	7 (5)	
Grip strength, *kg, median (IQR)*[d]	34 (28-45)	35 (28-46)	32 (25-42)	*P*<0.001[i]
6CIT total score, *median (IQR)*[e]	*N=303* 0 (0-2)	*N=225* 0 (0-2)	*N=78* 2 (0-4)	*P*=0.017
CCI score, *median (IQR)*	0 (0-1)	0 (0-1)	1 (0-2)	*P*<0.001
0	287 (60)	226 (66)	61 (46)	
1	79 (17)	58 (17)	21 (16)	
2	66 (14)	37 (11)	29 (22)	
3	23 (5)	13 (4)	10 (8)	
4	8 (2)	3 (1)	5 (4)	
≥5	14 (3)	8 (2)	6 (4)	
Number of medication per day, *median (IQR)*	1 (0-3)	1 (0-3)	1 (0-4)	*P*=0.011
None	159 (33)	125 (36)	34 (26)	
1-5	271 (57)	195 (57)	76 (58)	
6-10	42 (9)	23 (7)	19 (14)	
11-13	5 (1)	2 (1)	3 (2)	
Polypharmacy (≥5 medications per day)	77 (16)	45 (13)	32 (24)	*P*=0.003
Medical history				
Any cardiovascular disease[f]	212 (44)	131 (38)	81 (61)	-
Hypertension	134	88 (26)	46 (36)	*P*=0.039
Cardiac arrhythmia	32	16 (5)	16 (12)	*P*=0.003
Myocardial infarct	13	7	6	*P*=0.204
Angina pectoris	5	3	2	*P*=0.620
Cardiac failure	3	2	1	-

	Available cases All ages[a] N=477	Available cases 60-69y N=345	Available cases ≥70y N=132	Comparison p-value[h]
Malignancy	76 (16)	41 (12)	35 (27)	*P*<0.001
With metastases	8	5	3	
Skin disease	49 (10)	34	15	*P*=0.627
Urinary tract infection(s) <12 months pre-travel[b]	36 (8)	26	10	*P*=0.995
Pulmonary disease	39 (8)	29	10	*P*=0.767
Asthma	22	19	3	
COPD	14	9	5	
Auto-immune disorder[b]	32 (7)	18	14	*P*=0.036
Diabetes mellitus	30 (6)	19 (6)	11 (8)	*P*=0.259
With complications	7	5	2	
Gastric disease	22 (5)	17	5	*P*=0.808
Intestinal disease	16 (3)	10	6	*P*=0.397
Ulcerative colitis/Crohn's disease	3	2	1	
Renal disease	15 (3)	8	7	*P*=0.138
Kidney transplant	5	3	2	
Liver disease	6 (1)	4	2	*P*=0.671
HIV	1 (0)	0	1	-
Dementia[g]	1 (0)	0	1	-

Data represent absolute numbers (N) and percentages (%), unless otherwise specified. Abbreviations: BMI, body mass index; IQR, interquartile range; Katz-ADL, Katz activities of daily living; 6CIT, Six Item Cognitive Impairment Test; CCI, Charlson comorbidity index; COPD, Chronic obstructive pulmonary disease; HIV, human immunodeficiency virus.

[a] Available cases are eligible travelers that participated in part A and B.

[b] Percentages were calculated over the total number of travelers that answered the concerning question. Some travelers did not fill in the questions concerning these items, resulting in a maximum of three missing values.

[c] Katz-ADL: range 0-26.

[d] Grip strength: range 0-90 kg. For procedure, see Supplementary Appendix 1.

[e] 6CIT: range 0-28 . For procedure, see Supplementary Appendix 1. Measurements were unavailable for travelers included at the Municipal Health Services.

[f] This group variable represents the number of cardiovascular events including hypertension (n=134), cardiac arrhythmia (n=32), myocardial infarct (n=13), angina pectoris (n=5), cardiac failure (n=3), transient ischemic attack (n=8), cerebral infarction (n=3) peripheral vascular disease (n=14). Some travelers had multiple cardiovascular events therefore no comparison could be calculated between both age groups.

[g] Early vascular dementia; researchers decided that participating partner was allowed to help filling in the questionnaires and diary.

[h] Pearson's Chi-Square test or Fisher Exact test was used, unless otherwise specified.

[i] Unpaired t-test was used.

Morbidity during and shortly after travel

One out of five travelers (21%) suffered from a RTI, of which one in ten travelers had a pre-existent pulmonary disease [e.g. asthma or chronic obstructive pulmonary disease (COPD)]. Almost one third of the RTIs (27%) were complicated (Table 2). One in six travelers with an uncomplicated RTI also reported these complaints pre-travel. Among all 98 travelers with an RTI, 30% experienced inconvenience, 16% used an antibiotic and 12% consulted a doctor.

Gastroenteritis (GE) was observed in 47 travelers (10%), of which six (13%) were complicated (Table 2). One in five travelers had a gastrointestinal disease in their medical history, mostly gastroesophageal reflux or irritable bowel syndrome. Almost half of the travelers (46%) with uncomplicated and all complicated GE experienced inconvenience and altered their program or stayed in their accommodation. Eight travelers (20%) consulted a doctor and many used self-medication. The relative risk (RR) of contracting GE appeared to be higher for travelers using a proton-pump inhibitor, but was not significant (RR = 1.75, 95% CI 0.97 to 3.18, P = 0.07). Dehydration occurred in 18 travelers (4%), of whom six had GE, and four were taking diuretics. Two dehydrated travelers (11%) used ORS.

Despite the presence of comorbidities in 40% of travelers, exacerbations of pre-existent conditions were reported in only 5% of the travelers (Supplementary Table S5). Eight travelers (2%) experienced cardiovascular complaints; 88% had a pre-existing cardiovascular disease such as hypertension or cardiac arrhythmias (Table 2). One traveler with cardiac arrhythmia consulted a doctor. In 59 travelers (12%) with peripheral edema, 47% had a medical history of cardiovascular disease (mostly hypertension). A higher comorbidity burden (CCI) and the use of more daily medication was associated with a higher travel-related morbidity (P = 0.04 and P = 0.14 respectively, data not shown).

A total of 61 travelers (13%) suffered mostly minor injuries, such as cuts, abrasions or spraining (Supplementary Table S5) often caused by accidental falling (30%). No fractures were reported. One traveler reported a dog bite (WHO category II) in Malawi.

Medical assistance

Medical assistance for health complaints possibly related to their travel was primarily sought between the first week to two months after return (81%), mostly at the GP (87%). Respiratory (27%) and gastrointestinal complaints (21%) were the main reasons of consultation. Only seven travelers consulted a GP (57%) or an emergency room (43%) during travel, mostly for gastrointestinal complaints, wounds or altitude sickness. Five travelers were hospitalized post-travel, none during travel. No mortality was observed (Table 3).

Self-reported health

There was a significant improvement in mental health sum score and associated domains during travel (all $P < 0.001$). Improvement in self-perceived physical health was observed within the bodily pain domain ($P < 0.001$, data not shown). After travel, there were still significant improvements noticeable in the mental health sum score, vitality and general mental health (all $P < 0.001$) in comparison with pre-travel. In addition, a significant improvement in the physical health sum score ($P = 0.01$) and bodily pain ($P < 0.001$) were observed (Supplementary Table S6).

Predictors for travel-related morbidity

Multivariable analysis demonstrated that travelling to Northern Africa or South-East and East Asia, phone and social media use, higher CCI score, higher number of medications per day, more tropical travel experience and longer travel duration seemed to be associated with increasing odds for travel-related morbidity. Travelers with a better SF-36 mental health sum score pre-travel, travelling with family and travelers with higher education appeared to have reduced odds for travel-related morbidity. Grip strength and Katz-ADL were not identified as predictors (Table 4).

Table 2. Self-reported morbidity in 475 older travelers travelling during and up to 2 weeks after travel to the tropics[a]

	Cumulative incidence	Incidence density (cases/100 travel months)	Mean duration of complaints in days (range)[f]		Number of travelers with symptoms in the week before travel	Number of travelers forced to alter program or confined to accommodation	Medication used				Medical assistance[g]
							Antibiotic	Loperamide	Activated carbon	ORS	
Symptom clusters[b]	N (%)	Travel months: 512	Mean	Range	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Infections (general)[c]	21 (4)	4.1	2.4	(1-7)	0	12 (57)	3 (14)	0	0	0	4 (19)
Gastroenteritis											
Uncomplicated	41 (9)	8.0	1.8	(1-5)	3 (7)	19 (46)	3 (7)	16 (39)	3 (7)	13 (32)	8 (20)
Complicated	6 (1)	1.2	3.5	(1-7)	1 (17)	6 (100)	2 (33)	3 (50)	2 (33)	2 (33)	
Dehydration[d]	18 (4)	3.5	4.9	(1-18)	1 (6)	8 (44)	0	0	0	2 (11)	1 (6)
Respiratory tract infection											
Uncomplicated	72 (15)	14.1	3.1	(1-7)	12 (17)	23 (32)	10 (14)	0	0	0	12 (17)
Complicated	26 (6)	5.1	12.2	(4-21)	0	6 (23)	6 (23)	0	0	0	
Urinary tract infection											
Uncomplicated	2 (1)	0.4	1.0	(1-1)	0	0	1 (50)	0	0	0	0
Complicated	2 (1)	0.4	28.0	(20-36)	1 (5)	0	1 (50)	0	0	0	0
Cardiovascular complaint											
Angina pectoris	5 (1)	1.0	5.4	(1-21)	2 (40)	1 (20)	0	0	0	0	1 (20)
Cardiac failure	3 (1)	0.6	4.0	(2-6)	1 (33)	1 (33)	0	0	0	0	
Peripheral edema	59 (12)	11.5	9.8	(3-25)	2 (3)	9 (15)	0	0	0	0	2 (3)
Musculoskeletal complaints[e]	11 (2)	2.1	6.6	(1-14)	0	5 (45)	0	0	0	0	2 (18)
Total	**266 (56)**	**52.0**			**23 (9)**	**90 (34)**	**26 (10)**	**19 (7)**	**5 (2)**	**17 (6)**	**30 (11)**

Data represent absolute numbers (N) and percentages (%), unless otherwise specified. Abbreviation: ORS oral rehydration solution

[a] Two diaries were robbed, resulting in 475 diaries.

[b] Data represent the number of cases fulfilling criteria of defined symptom clusters, see Supplementary Appendix 3. Some travelers fulfilled the criteria for multiple symptom clusters.

[c] Infections that did not fulfil criteria of another symptom cluster.

[d] Dehydration was observed in 18 travelers, of whom six travelers also experienced gastroenteritis.

[e] Three travelers reported pre-travel 'stiffness' and one was known with rheumatoid arthritis.

[f] Duration of complaints meeting symptom cluster criteria.

[g] Represents medical assistance needed for same symptom cluster, as indicated in questionnaire or diary.

Table 3. Medical consultations due to possible travel-related illnesses during the travel and post-travel period.

	During travel N=7	1-2 weeks post-travel N=33	2-4 weeks post-travel N=34 [a]	4-8 weeks post-travel N=22[a]	Subtotal post-travel N=79	Total study period N=84
Type of medical assistance [b]						
General practitioner	4 (57)	28 (85)[d]	27 (79)	14 (61)	69 (87)	73 (87)
Medical specialist	0	2 (6)	6 (18)[e]	7 (30)	15 (19)	15 (18)
Emergency room	3 (43)	0	0	0	0	3 (4)
Hospital admission	0	3 (9)[f]	1 (3)[g]	1 (4)[h]	5 (6)	5 (6)
Reason for seeking medical assistance						
Infections (general)	0	2 (6)	2 (6)	0	4 (5)	4 (5)
Gastrointestinal complaints	3 (43)	6 (18)	4 (12)	5 (22)	15 (19)	18 (21)
Dehydration	0	1 (3)	0	0	1 (1)	1 (1)
Respiratory complaints	0	7 (21)	10 (29)	6 (26)	23 (29)	23 (27)
Urinary tract complaints	0	1 (3)	2 (6)	3 (13)	6 (8)	6 (7)
Cardiovascular complaints	0	1 (3)	3 (9)	0	4 (5)	4 (5)
Peripheral edema	0	3 (9)	0	0	3 (4)	3 (4)
Musculoskeletal complaints	0	3 (9)	6 (18)	3 (13)	12 (15)	12 (14)
Ear nose throat complaints	1 (14)	6 (18)	2 (6)	3 (13)	11 (14)	12 (14)
Other	3 (43)	3 (9)	5 (15)	2 (9)	10 (13)	13 (15)
Total medical consultations [c]	7 (100)	33 (100)	34 (100)	22 (96)	89 (113)	97 (115)

Data represent absolute numbers (N) and percentages (%). Medical support for complaints that were (possibly) travel-related, as was judged by a clinician. Regular medical appointments such as annual influenza vaccination of measuring blood pressure were excluded.

[a] In the period of 2-4 weeks post-travel, three travelers were lost to follow-up. In the period 4-8 weeks post-travel, an additional three travelers who did reported medical complaints in questionnaire 3 did not fill in questionnaire 4.

[b] Travelers that received multiple types of medical assistance were only indicated once in the table at the highest level of care that was received.

[c] Totals may exceed 100% since some travelers sought medical support multiple times (10 travelers twice, one traveler thrice).

[d] Among which one traveler with African tick bite fever.

[e] Among which one traveler with scabies.

[f] Dehydration due to gastroenteritis, acute cardiac failure and arthritis.

[g] Sepsis.

[h] Acute cholecystitis.

Table 4. Best predicting characteristics for developing travel-related morbidity in 475 older travellers to the tropics.

	No morbidity	Morbidity	Univariable analysis		Multivariable analysis	
	N=281	N=194	OR [95% CI]	*P* value	OR [95% CI]	*P* value
Gender, female	131 (47)	100 (52)	1.22 [0.84 - 1.78]	0.29		
Age, *years, median (IQR)*	66 (62-70)	66 (63-71)	1.02 [0.98 - 1.05]	0.30		
Educational level						
Primary education (=ref)	19 (7)	19 (10)	1.00	0.04	1.00	0.03
Secondary education	85 (30)	75 (39)	0.88 [0.44-1.79]		0.80 [0.37 - 1.74]	
Higher education	177 (63)	100 (52)	0.57 [0.27 - 1.12]		0.48 [0.23 - 1.02]	
Immigrant	23 (8)	15 (8%)	0.94 [0.48 - 1.85]	0.86		
Travel advice obtained at MHS	101 (36)	71 (37)	1.03 [0.70 - 1.50]	0.88		
Travel experience to tropics: number of journeys in preceding 5 years, *median (IQR)*	2 (1-5)	2 (1-5)	1.00 [0.98 - 1.02]	0.95	1.05 [0.985 – 1.13]	0.13
Tropical travel destination						
Caribbean, Central and South America (=ref)	44 (16)	36 (19)	1.00	0.03	1.00	0.02
Northern Africa	4 (1)	7 (4)	2.14 [0.58 - 7.88]		3.8 [0.91 - 15.82]	
Sub Saharan Africa	88 (31)	37 (19)	0.51 [0.29 - 0.92]		0.63 [0.34 - 1.20]	
Central, South and Western Asia/Middle East	102 (36)	76 (39)	0.91 [0.54 - 1.55]		0.87 [0.49 - 1.56]	
South-East and East Asia	42 (15)	38 (20)	1.11 [0.59 - 2.06]		1.56 [0.78 - 3.11]	
Travel duration, *days, median (IQR)*	18 (14-23)	20 (15-24)	1.03 [1.01 – 1.06]	0.02	1.04 [1.004 - 1.070]	0.03
Duration between pre-travel consult and departure, *days, median (IQR)*	38 (21-52)	37 (22-50)	1.00 [0.99 – 1.00]	0.44		

	No morbidity	Morbidity	Univariable analysis		Multivariable analysis	
	N=281	N=194	OR [95% CI]	*P* value	OR [95% CI]	*P* value
Purpose of travel						
Business (=ref)	10 (4)	5 (3)	1.00	0.79		
Visiting friends or relatives	40 (14)	30 (15)	1.50 [0.46 - 4.85]			
All other	231 (82)	159 (82)	1.38 [0.46 - 4.10]			
Travel group composition						
With an organized group travel (=ref)	50 (18)	46 (24)	1.00	0.17	1.00	0.12
With family	191 (68)	116 (60)	0.66 [0.42 - 1.05]		0.63 [0.38-1.04]	
All other	40 (14)	32 (16)	0.87 [0.47 - 1.61]		0.94 [0.47-1.85]	
Type of accommodation during travel						
Accommodation owned by participant/family/friends (=ref)	26 (9)	20 (10)	1.00	0.43		
Luxurious rented accomodation	241 (86)	159 (82)	0.86 [0.47 - 1.60]			
Nonluxurious accomodation	13 (5)	15 (8)	1.39 [0.55 - 3.54]			
Phone use						
No phone (=ref)	7 (2)	4 (2)	1.00	0.16	1.00	0.11
Regular mobile phone	33 (12)	35 (18)	1.86 [0.50 - 6.93]		2.24 [0.53-9.44]	
Smartphone	241 (86)	155 (80)	1.13 [0.32 - 3.91]		1.21 [0.31-4.77]	
Social media use	166 (59)	119 (61)	1.08 [0.74 - 1.57]	0.69	1.55 [0.996-2.42]	0.05
BMI, *kg/m*^{2}, *median, (IQR)*	25 (23-27)	25 (23-28)	1.02 [0.97 - 1.07]	0.51		
Sensory function						
Wearing hearing aid	30 (11)	23 (12)	1.13 [0.63 - 2.01]	0.67		
Wearing glasses or contact lenses	220 (78)	144 (74)	0.82 [0.53 - 1.25]	0.35		

	No morbidity	Morbidity	Univariable analysis		Multivariable analysis	
	N=281	N=194	OR [95% CI]	*P* value	OR [95% CI]	*P* value
Katz-ADL score, *median (IQR)*	0 (0-0)	0 (0-0)	1.23 [0.46 - 3.60]	0.63		
6CIT total score, *median (IQR)*[a]	0 (0-2)	2 (2-2)	1.13 [1.01 - 1.27]	0.04		
Grip strength, *kg, median (IQR)*	36 (28-46)	32 (28-44)	0.99 [0.97 – 1.01]	0.15		
Influenza vaccination received <1 year	147 (53)	116 (60)	1.13 [0.91 - 1.92]	0.14		
Number of daily medications, *median (IQR)*	1 (0-3)	2 (0-4)	1.13 [1.05 - 1.22]	0.001	1.07 [0.977-1.17]	0.14
CCI score, *median (IQR)*	0 (0-1)	0 (0-2)	1.20 [1.06 - 1.35]	0.003	1.15 [1.006-1.31]	0.04
SF-36 sum scores pre-travel, *median (IQR)*						
Physical health	92 (85-95)	87 (77-93)	0.97 [0.95 - 0.98]	<0.001		
Mental health	90 (86-94)	87 (79-91)	0.96 [0.94 - 0.98]	<0.001	0.96 [0.944-0.981]	<0.001

Data represent absolute numbers (N) and percentages per category (%), unless otherwise specified. Variables were selected for the multivariable regression analysis using backward selection until the Akaike information criterion ($P \leq 0.157$) was satisfied. Abbreviations: OR, odds ratio; IQR, interquartile range; ref, reference; MHS, Municipal Health Service; BMI, body mass index; Katz-ADL, Katz activities of daily living; 6CIT, Six Item Cognitive Impairment Test; CCI, Charlson comorbidity index; SF-36, Short-Form 36 survey.

[a] Not included in the multivariable regression analyses since measurements were unavailable for travelers included at the Municipal Health Services. Model: constant = 9.02, Nagelkerke R^2=0.18, Hosmer and Lemeshow test $P = 0.53$, c-index=0.71, Brier score=0.2087.

Discussion

In this multicentre prospective study we assessed whether physical and cognitive performance tests could predict travel-related morbidity in Dutch older travelers during a short-term stay in the tropics. We found that a higher CCI score and higher number of daily medications, but also more tropical experience, longer travel duration, travelling to Northern Africa or South-East and East Asia, and phone and social media use were associated with higher odds for travel-related morbidity. The participants were generally experienced and well-educated, physically and mentally fit with little (co)morbidity or polypharmacy and well-connected to the digital world of internet, social media and smartphones. As expected, travelers in higher age groups scored worse on performance measurements although these groups were not identified as predictors.

Our cohort had considerable travel experience, was well-prepared for their tropical trip, and showed limited risk-seeking behaviour. This last aspect is in line with the retrospective study of Alon et al. who demonstrated that older travelers practiced less risky eating and drinking habits and were more compliant with anti-malarial chemoprophylaxis than younger travellers.[7] Most older travelers in our cohort were fully compliant (92%). It is noteworthy that a substantial number of our travelers used a smartphone and social media. This could imply that these methods of communication could be used for future (intervention) strategies as mobile technology will impact travel medicine more and more.[43-45]

In accordance with previous literature[6, 7], older travelers frequently experienced 'classic' travel-related morbidities, such as gastrointestinal and respiratory infections, but they also reported complaints which are more likely to occur in older people such as dehydration (4%), cardiovascular complaints (2%), peripheral edema (12%) and accidental falls (4%). Unexpectedly, exacerbations of pre-existing illness were only rarely reported. In the post-travel questionnaire 141 travelers (30%) reported to have experienced diarrhoea, of whom 12 travelers did not temporarily stop their diuretics. Since older persons are more prone to complications such as hypotension or renal failure following dehydration, it is important to discuss during the pre-travel consult in which situations diuretics should be discontinued (e.g. during periods of vomiting and/or diarrhoea).[46] Less anticipated complaints were injuries (13%), skin (12%) and musculoskeletal complaints (2%). Especially falling deserves further

investigation, as falls are a major determinant of morbidity and mortality in older adults.[47, 48]

Medical assistance was frequently sought, but mostly post-travel. Underlying reasons for late medical consultation were not studied. Possible explanations are previous experience with similar complaints that appear to be self-limiting, preference for own GP, or unexpected longer duration of complaints after travel.[49]

Our findings that older travelers experienced significant improvement in the self-reported mental- and physical health during and after travel extend earlier findings.[50-52] This kind of effects of travel appears to have a positive effect on the perceived health of the traveler and could therefore outweigh the impact of health problems. Although this positive effect decreased on return, travelers still experienced improved health as compared with before travel.[50] A survey study on the well-being and health among employees of German companies after a, mostly European, holiday revealed that enough leisure time, warmer destinations, being physically active, good sleep and making new social contacts facilitate improved health whereas dealing with a greater time-zone difference (i.e. jetlag) was associated with a decreased health.[52] Most of our study participants travelled to warmer tropical destinations, whereby they frequently cross different time-zones. Interestingly, in the employee study an older subgroup aged 50-62 (18%) was analysed, and they found that age was associated with differences in holiday organization (e.g. duration and travel time), but did not affect the positive health changes on its own.[52] The findings in our study cohort underline that travelling to the tropics does not only entail morbidity for the older traveler, but could positively affect both their mental and physical health. We did not address possible improvements on existing co-morbidities.

We hypothesized that pre-travel, validated physical and mental health performance measures might identify older travelers more at risk for travel-related morbidity. Grip strength was chosen as an objective measure of physical performance, but no association was found. The same holds for the level of independence measured with the Katz-ADL. A possible explanation for these findings could be that most included travelers are fit and living an active and independent life, what enables them to undertake tropical journeys.

Finally, we identified several demographic (phone and social media use), travel (duration, destination, experience) and health characteristics (CCI and medication)

as predictors of travel-related morbidity. We used the Akaike information criterion in order not to overlook any important associations. In line with our findings, previous research also identified travel duration and destination as predictors, but not specifically in the older traveller.[50, 53] Interestingly, age was not found to be an independent predictor for morbidity, even though pre-travel characteristics were found to be significantly different when comparing age groups (Table 1). The direction of some effect sizes seems counterintuitive (e.g. more travel experience seems to be associated with higher morbidity rates). It is therefore important to note that this model aimed to identify prognostic and not etiologic relationships between characteristics and travel-related morbidity. This relationship might be confounded by other characteristics, such as risk behaviour.[12, 53] Risk behaviour was not included in the multivariable regression model, since this cannot validly be measured pre-travel.[54] The identified predictors could be used to identify older travelers with a relatively high risk for travel-related morbidity. Most of them could be easily assessed since they are part of the current pre-travel consultation (destination, duration, and travel experience) or could easily be assessed at that moment (educational level, phone and social media use and CCI score). Future research should be conducted to confirm the association between the identified predictors and travel-related morbidity.

The strengths of this study are the multicentre approach, the large sample size of > 100 travelers aged 70 and over, the high follow-up rate of 97%, the limitation of recall bias using a diary during travel and questionnaire shortly after return, the use of validated measurement tools, the use of well-defined symptom clusters to quantify reported morbidity and the collection of baseline data before departure which limits selection bias and offers the opportunity to compare health status pre- and post-travel.

The study also has some limitations that need to be discussed. This study population might not be completely representative for the older population in general (‘healthy traveler bias’). Compared with travelers who participated only in part A or partly in B, travelers who participated in A and B were slightly younger, had a higher grip strength and were less cognitively impaired (Supplementary TableS7). Also, when other aspects are taken into account, our travelers appeared to be fitter than the average age-matched Dutch population. A pre-existing illness was reported by

40% of our travelers, which is lower than the anticipated 50% in the general non-travelling Dutch population of 65 years and older[55], but comparable with the 43% in Swiss travelers who also visited non-tropical destionations.[56] Also polypharmacy was somewhat lower in our study population (16%) than the 20% rate in the Dutch population aged 55 years and older.[57] Therefore, the true incidence of morbidity in the older traveller might be higher. For that reason, we also compared the data of our group travelers aged between 70 and 79 years (n=117) with the data from individuals of the same age group of the AT-AGE study (n=303) in which an identical measurement procedure had been used in different primary care practices. [58] Linear regression demonstrated no significant mean difference in the maximal grip strength between both cohorts, after correcting for age and gender (mean difference 1.3, 95% CI -0.2 to 2.8, $P = 0.096$). This implied that the older travelers visiting the clinic pre-travel physically did not differ (much) from the older adults visiting primary care practices. Of interest, a recent retrospective study among older travelers visiting an Irish travel health clinic pre-travel demonstrated similar health (e.g. about one third used no medication, majority had a medical condition) and travel characteristics (e.g. South Eastern Asia and South America as popular destinations, travel duration of 3 weeks, mostly travelling for leisure or visiting friends or family) as in this ELDEST cohort.[59]

In practice

This study demonstrates that older Dutch travelers to the tropics are generally fit, well-prepared and experienced relatively low rates of morbidity. Although several travelers encountered travel-related morbidity, these travelers did not solely entail illness, as the participants perceived both improved mental- and physical health after travel. Special attention should be given to travelers with the identified predictors (e.g. long travel duration, destinations in Northern Africa or South-East and East Asia, high CCI score, multiple daily medications, using a mobile phone and media use). Furthermore, extensive travel experience should not reassure the travel advisor.

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Abbreviations

DM (Diabetes Mellitus), ELDEST (morbidity in ELDErly travelers during a Short-Term stay abroad), LUMC (Leiden University Medical Centre), MHSs (Municipal Health Services), STROBE (Strengthening the Reporting of Observational studies in Epidemiology), 6CIT (Six item Cognitive Impairment Test), SF-36 (Short Form 36 health survey), Katz-ADL (Katz Activities of Daily Living), CCI (Charlson Comorbidity Index), WHO (World Health Organization), SPSS (Statistical Package for the Social

Sciences), IQR (interquartile range), GP (General Practitioner), RTI (Respiratory Tract Infection), COPD (Chronic Obstructive Pulmonary Disease), GE (Gastroenteritis), RR (Relative Risk), CI (confidence interval), ORS (Oral Rehydration Solution), AT-AGE (Age and Thrombosis: Acquired and Genetic risk factors in the Elderly).

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Supplementary data

Supplementary Table S1. Demographic and travel characteristics of a cohort of 477 older travelers to the tropics.

	Available cases[a] N=477
Age, *years, median (IQR)*	66 (63-70)
Age group	
60-69 y	345 (72)
70-79 y	117 (25)
≥80 y	15 (3)
Gender, *female*	232 (49)
60-69y	174/345 (50)
70-79y	53/117 (45)
≥80y	5/15 (33)
Education level[b]	
Primary education	38 (8)
Secondary education	162 (34)
Higher education	277 (58)
Immigrant	39 (8)
Travel experience to tropical destinations[c]	437 (92)
If travel experience, number of journeys in preceding 5 years	
0	99 (21)
1-5	280 (59)
6-10	28 (6)
>10	28 (6)
Most visited tropical destinations[de]	
South-Eastern Asia	163 (34)
Southern Asia	68 (14)
South America	58 (12)
Eastern Africa	51 (11)
Southern Africa	45 (9)
Western Africa	31 (6)
Central America	22 (5)
Travel duration, days, *median (IQR)*	19 (14-23)
<1 week	6 (1)
1-2 weeks	117 (25)
2-3 weeks	181 (38)

	Available cases[a] N=477
3-4 weeks	113 (24)
4-5 weeks	60 (13)
Purpose of travel	
Holiday	380 (80)
Visiting friends or relatives	70 (15)
Business	15 (3)
Volunteering	12 (3)
Most frequent travel group composition	
With partner	237 (50)
With an organized group travel	96 (20)
With friends	36 (8)
Solo	30 (6)
With children	23 (5)
Most frequent type of accommodation during travel[e]	
Hotel	346 (73)
Lodge	66 (14)
With friends/family	48 (10)
Guesthouse	29 (6)
Cruiseship	18 (4)
Used a mobile phone	466 (98)
Smartphone[c]	397 (85)
Social media use[ce]	285 (60)
Most frequently used	
Facebook	221 (47)
LinkedIn	136 (29)
YouTube	51 (11)

Data represent absolute numbers (no.) and percentages per category (%), unless otherwise specified.

[a] All eligible travelers that participated in part B and were not lost to follow-up before questionnaire 2 were designated available cases, while all other eligible travelers were designated unavailable cases.

[b] Education level: according to classification Central Bureau for Statistics, the Netherlands.

[c] Percentages were calculated over the total number of travelers that answered the concerning question. Some travelers did not fill in the questions concerning these items, resulting in a maximum of 3 missing values.

[d] Travel destination: categorized according to geographical regions described by the United Nations Statistics Division.

[e] Totals may exceed 100% since multiple options per participant can apply

Supplementary Table S2. Travel preparation of a cohort of 477 older travelers to the tropics.

	Available cases N=477
Method of booking	
Online	287 (60)
Travel agency	165 (35)
Telephone	17 (4)
Duration between pre-travel consult and departure, *days, median (IQR)*	37 (21-51)
Most frequent additional pre-travel advice sought [a]	
General practitioner	432 (91)
Internet	84 (18)
Travel bureau	38 (8)
Pharmacy	36 (8)
Medical specialist	17 (4)
Insurance status	
Travel insurance	464 (97)
Including medical costs	413 (87)
Including repatriation	417 (89)
Health insurance covers medical costs abroad	416 (89)
Medicines and travel (n=318)[b]	
Took extra supply of regular medication	257 (81)
Travelled with personal prescription information sheet	248 (78)
Medication against GI complaints in carry-on bag[a]	
Loperamide	347 (73)
ORS	284 (60)
Activated carbon	89 (19)
Antibiotics	62 (13)
Hand hygiene products in carry-on bag[a]	
Hand sanitizer	275 (58)
Wet wipes	187 (39)
Soap	127 (27)

Data represent absolute numbers (no.) and percentages (%), unless otherwise specified. GI, gastrointestinal complaints. Percentages were calculated over the total number of travelers that answered the concerning question. Some travelers did not fill in the questions concerning these items, resulting in a maximum of 10 missing values. Abbreviations: ORS, Oral Rehydration Solution.

[a] Total may exceed 100% since multiple options per participant can apply.

[b] Within group of travelers that used medication.

Supplementary Table S3. Risk behavior in a cohort of 477 older travelers to the tropics.

	Available cases N=477	
Washing hands regularly[a]		
After using the toilet	459	(96)
Before meal	400	(84)
Using hand sanitizer regularly[◊]	207	(43)
Using tap water for toothbrushing	251	(53)
Using bottled water from sealed bottle for toothbrushing	254	(53)
Hand contact with animals (e.g. stroking or holding)[a]	97	(20)
Monkey	88	(91)
Dog	47	(48)
Cat	28	(29)
Elephant	14	(14)
Snake	6	(6)
Camel/dromedary	5	(5)
Drinking/eating[a]		
Food from hotel buffay	381	(80)
Fruit that was not cleaned by participant	362	(76)
Freshly squeezed juices	311	(65)
Salad prepared by others	302	(63)
Drinks with icecubes	216	(45)
Soft ice	126	(26)
Food from food stands	92	(19)
Raw crustaceans	43	(9)
Products containing raw eggs	37	(8)
Leftovers from previous meal	32	(7)
Raw shellfish	27	(6)
Non pasteurized cheese	21	(4)
Raw or medium rare meat	18	(4)
Pasteurized milk	7	(1)
Barefoot walking[a]		
Only at the beach	204	(43)
On the street	34	(7)
Swimming in the sea	146	(31)
Had contact with mud or soil	165	(35)
Visited a local market	369	(78)

Data represent absolute numbers (no.) and percentages (%). Percentages were calculated over the total number of travelers that answered the concerning question. Some travelers did not fill in the questions concerning these items, resulting in a maximum of four missing values. Percentages were calculated over the total number of travelers that answered the question.

[a] Total may exceed 100% since multiple options per participant can apply.

[◊] 20 travelers used a hand sanitizer they did not brought themselves.

Supplementary Table S4. Malaria prophylaxis in a cohort of 477 older travelers to the tropics.

	Available cases N=477
Malaria chemoprophylaxis started	
No, it was not recommended by the clinic	330 (69)
No, but it was recommended by the clinic*	27 (6)
Yes	120 (25)
Type of chemoprophylaxis	
Atovaquone/proguanil	112 (93)
Mefloquine	1 (1)
Proguanil	7 (6)
Side effects	
Atovaquone/proguanil	18 (15)
Mefloquine	0
Proguanil	0
Type of side effects from atovaquone/proguanil[a]	
Gastrointestinal complaints	9 (50)
Abdominal pain	3
Nausea	3
Diarrhoea	3
Sleeping complaints	7 (39)
Sleeplessness	3
Strange/vivid dreams	4
Dizziness	6 (33)
Headache	1 (6)
Compliance malaria chemoprophylaxis	
Full compliance	110 (92)
Reasons for non compliance	
Side effects	4 (30)
Too few tablets brought	2 (20)
Other**	4 (40)
Bed net used[b] ***	
No, it was not recommended by the clinic	329 (69)
No, but it was recommended by the clinic	29 (6)
Yes	117 (25)

Data represent absolute numbers (no.) and percentages (%).

[a] Total may exceed 100% since patients could report multiple side effects.

[b] Percentages were calculated over the total number of travelers that answered the concerning question. Some travelers did not fill in the questions concerning these items, resulting in a maximum of two missing values.

*One traveler got robbed of personal belongings, including the chemoprophylaxis. One traveler brought the chemoprophylaxis as standby emergency treatment. Another traveler did so due to low temperatures and no mosquitos were noticed.

**Only in specific areas (n=2), staying on altitude (n=1), unknown reason (n=1).

***Main reason for not using a bed net was the presence of a functioning air-conditioning.

Supplementary Table S5. Morbidity documented in questionnaires during and up to two weeks after returning home in 477 older travelers to the tropics.

	Available cases N=477
Injury	61 (13)
Fallen	18
Cut	10
Bitten, licked or scratched by animal	1
Other minor injuries	32
Exacerbation of chronic health complaints	22 (5)
Travelers' diarrhea (subjective)[a]	141 (30)
Medication temporariliy discontinued	10 (2)
Diuretics (n=19)	3
Antihypertensives (n=49)	2
Statins (n=40)	5
Obstipation[b]	34 (7)
Skin complaints[b]	59 (12)
Exacerbation of chronic skin disease	10 (17)

Data represent absolute numbers (no.) and percentages (%).

[a] Travelers' diarrhea was defined as the passage of three or more unformed stools during a 24-hour period.

[b] Percentages were calculated over the total number of travelers that answered the concerning question. Some travelers did not fill in the questions concerning these items, resulting in a maximum of two missing values.

Supplementary Table S6. Changes in self-perceived health after vs pre-travel versus using SF-36 in 477 older travelers to the tropics.

	Post-travel (median, IQR)	**Pre-travel** (median, IQR)	**p value**[b]	**Individual difference**[c] (median, IQR)	**Interpretation** Change in self-perceived health (S/NS)
Mental health sum score	**91 (86; 95)**	**89 (83; 93)**	**0.00**	**+3 (-2; 6)**	**Improved mental health** (S)
Vitality (energy/fatigue)	85 (75; 90)	80 (70; 90)	0.00	+5 (-5; 10)	Improved vitality (S)
Social functioning	100 (100; 100)	100 (100; 100)	0.15	+13 (-13; 13)	Improved social functioning (NS)
Role emotional	100 (100; 100)	100 (100; 100)	0.86	-33 (-33; 33)	More impairment due to emotional problems (NS)
General mental health[a]	92 (84; 96)	88 (80; 92)	0.00	+4 (-4;8)	Improved mental health (S)
Physical health sum score	**91 (82; 95)**	**89 (82; 94)**	**0.01**	**+1 (-4; 5)**	**Improved physical health** (S)
Physical functioning	95 (85; 100)	95 (85; 100)	0.23	+5 (-5; 5)	Improved physical functioning (NS)
Role physical	100 (100; 100)	100 (100; 100)	0.83	+25 (-50; 50)	Less impairment due to physical problems (NS)
Bodily pain	100 (87; 100)	88 (75; 100)	0.00	+13 (13; 25)	Less bodily pain (S)
General health perceptions	75 (65; 85)	75 (65; 85)	0.58	+5 (-10; 10)	Improved general health (NS)

Data represent median SF-36 scores (range 0-100). Abbreviations: SF-36, Short-Form 36 survey; S, significant; NS, not significant.

[a] One participant did not answer the question concerning this item, resulting in one missing value.

[b] Analysis of differences between post and pre-travel SF-36 scores was performed by Wilcoxon signed rank test.

[c] Positive values correspond with an health improvement within travelers, while negative values correspond with a decrease in health.

Supplementary Table S7. Comparison of available and partly available cases of 649 older travelers to the tropics.

	Available cases[a]		Partly available cases[a]		Comparison[b]
	N = 477		N = 172		p value
Gender, female	232	(49)	87	(51)	0.72
Age, median, *years (IQR)*	66	(63-70)	67	(63-71)	0.06
Age groups					
60-69 y	345	(72)	112	(65)	
70-79 y	117	(25)	52	(30)	
≥80 y	15	(3)	8	(5)	
Grip strength, *kg, median (IQR)*[c]	34	(28-45)	33	(26-42)	0.046
6CIT total score, *median (IQR)*[d]	0	(0-2)	2	(0-4)	0.001
Most visited tropical destinations[ef]					
South-Eastern Asia	163	(34)	40	(23)	
South America	58	(12)	36	(21)	
Southern Asia	68	(14)	22	(13)	
Eastern Africa	51	(11)	15	(9)	
Southern Africa	45	(9)	20	(12)	
Western Africa	31	(6)	7	(4)	
Central America	22	(5)	3	(2)	
Western Asia and Middle East	14	(3)	7	(4)	
Northern Africa	13	(3)	7	(4)	
Eastern Asia	14	(3)	4	(2)	
Carribean	12	(3)	6	(3)	
Central and Middle Africa	10	(2)	1	(1)	
Central Asia	5	(1)	0	(0)	
Eastern Europe	1	(0)	1	(1)	

Data represent absolute numbers (n) and percentages per category (%), unless otherwise specified.

Abbreviations: 6CIT, Six Item Cognitive Impairment Test.

[a] All eligible travelers that participated in part A only or were lost to follow-up before questionnaire 2 were designated partly available cases, while all other eligible travelers were designated available cases.

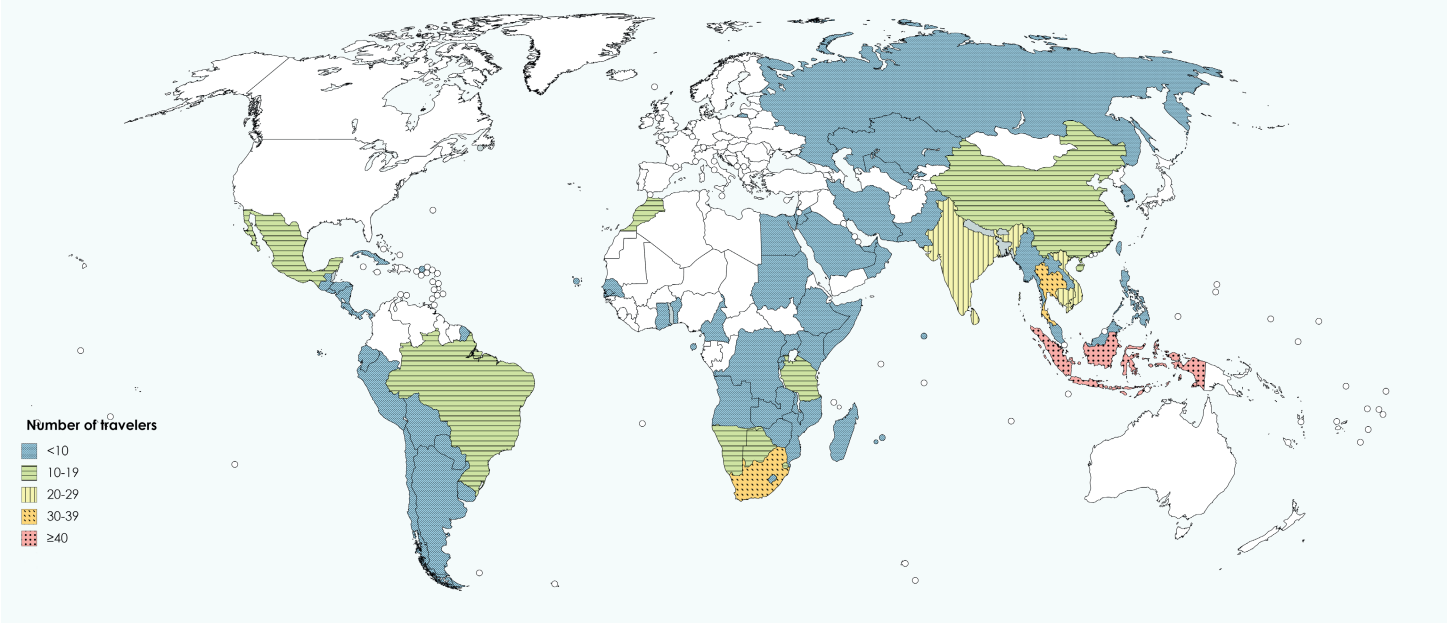
[b] Mann Whitney U test was used for analysis of continuous variables. Pearson's Chi-square test was used for analysis of categorical variables.

[c] Grip strength: Range 0-90 kg, see eAppendix 1.

[d] 6CIT: Range 0-28, see eAppendix 1.

[e] Travel destination: categorized according to geographical regions described by the United Nations Statistics Division.

[f] Totals may exceed 100% since some travelers visited multiple destinations.



Supplementary Figure S1. Most visited destinations of 477 older Dutch travelers (≥60 years) traveling to the tropics for a short-term stay.

Supplementary Appendix 1. Protocol functional tests measurements

Hand grip strength measurement protocol

1. Participant sit in a chair with back support and without arm rests.
2. The arm/elbow of the participant should be at 90˚, thumbs facing upwards (Figure 1)
3. Measurement is taken by the dominant hand (participant is asked 'which hand do you use to write'). If the participant is not able to use the dominant hand, the non-dominant hand is used. The reason for not using the dominant hand is noted. For all measurements, the dynamometer was set to the second handle position from the inside, as most people squeeze on their maximum power in this position.[1]
4. The participant is encouraged to squeeze the Jamar hand dynamometer (Figure 2) as tightly as possible for 2-3 seconds.
5. Grip strength in kilograms is read from the outside dial and recorded on the data entry form (range of 0-90 kg).
6. In total four measurements are performed of which the first one is a test measurement and is not noted on the form.
7. In order to interfere as little as possible with regular practice in the travel clinics, hand grip strength was measured after travel consultation and administration of vaccinations.

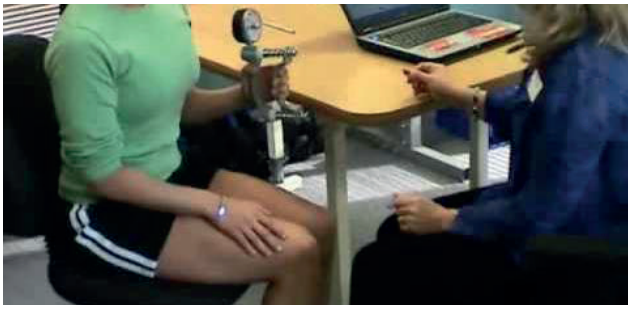


Figure 1

Figure 2

Six Item Cognitive Impairment Test (6CIT, range 0-28 points)

Question	Score range	Score
1. What year is it?	Correct – 0 points Incorrect – 4 points	
2. What month is it?	Correct – 0 points Incorrect – 3 points	
Give the patient an address phrase to remember *e.g. Jan, de Vries, Molenstraat 12, Groningen*		
3. What time is it (without looking at the clock) *4. A margin of 1 hour*	Correct – 0 points Incorrect – 3 points	
4. Count backwards from 20 to 1	Correct – 0 points 1 error – 2 points >1 error – 4 points	
5. Say the months of the year in reverse *6. Dec, Nov, Oct, Sep, Aug, Jul, Jun, May, Apr, Mar, Feb, Jan*	Correct – 0 points 1 error – 2 points >1 error – 4 points	
6. Repeat address phrase *7. Score: [Jan] [de Vries] [Molenstraat] [12] [Groningen]*	Correct – 0 points 1 error – 2 points 2 errors – 4 points 3 errors – 6 points 4 errors – 8 points All wrong – 10 points	
Total score	**0 - 28**	**___ / 28**

Supplementary Appendix 2. Standardized tests to identify potential risk profiles

SF-36 health survey including eight health concepts[2]:

Physical health sum score

- Physical functioning;
- Role limitations because of physical health problems;
- Bodily pain; and
- General health perceptions.

Mental health sum score

- Vitality (energy/fatigue);
- Social functioning;
- Role limitations because of emotional problems
- General mental health;

Katz-ADL[3,4]

Question	Answers (score)
Receiving assistance in bathing?	yes (1) / no (0)
Receiving assistance getting dressed?	yes (1) / no (0)
Receiving assistance in going to the toilet?	yes (1) / no (0)
Using incontinence pads?	yes (1) / no (0)
Receiving assistance moving from bed to chair?	yes (1) / no (0)
Receiving assistance in feeding?	yes (1) / no (0)

Charlson Comorbidity Index (CCI), a tool to measure comorbidity which has been used previously to estimate 10-year survival.[5,6]

Item	CCI Score
Myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Connective tissue disease	1
Ulcer disease	1
Mild liver disease	1
Diabetes mellitus	1
Hemiplegia	2
Moderate or severe renal disease	2
Diabetes mellitus with end organ damage	2
Any tumor	2
Leukemia	2
Lymphoma	2
Moderate or severe liver disease	3
Metastatic solid tumor	6
Acquired immunodeficiency syndrome	6

Supplementary Appendix 3. Symptom clusters for health complaints in diaries.[7]

Symptom cluster	Criteria	Restriction	Duration
General infections	Fever (temperature ≥ 38.0°C).	Not fulfilling criteria of another symptom cluster	
Uncomplicated gastroenteritis	Watery or unformed stools more than three times per 24 hours and one or more of the following complaints; nausea, vomiting, abdominal cramps and fecal incontinence.	No fever or bloody stools.	Maximum: 14 days
Complicated gastroenteritis	Watery or unformed stools more than three times per 24 hours and one or more of the following complaints; fever and bloody stools. Or Uncomplicated gastroenteritis that lasted longer than 14 days.		
Dehydration	Two or more of the following; urination less than four times per 24 hours, dark urine, thirst, dry mucosae and orthostatic dizziness.		
Uncomplicated respiratory tract infection	Cough and one or more of the following complaints: nasal constipation, sore throat and coughing up sputum.	No dyspnea, pain on the chest or heart palpitations	Maximum: 7 days
Complicated respiratory tract infection	Cough and fever and one or more of the following complaints; dyspnea at rest or pain on the chest related to respiration Or Uncomplicated respiratory tract infection that lasted longer than 7 days	No heart palpitations and the pain on the chest was not elicited by exercise	
Uncomplicated urinary tract infection	Painful urination	No fever	Maximum: 7 days
Complicated urinary tract infection	Two or more of the following; painful urination, fever and flank pain Or Uncomplicated urinary tract infection that lasted longer than 7 days		

Symptom cluster	Criteria	Restriction	Duration
Angina pectoris	Pain on the chest elicited by exercise	No fever or pain on the chest related to respiration	
Cardiac failure	Swollen ankles or lower legs and dyspnea at rest		
Peripheral edema	Swollen ankles or lower legs	No dyspnea	Minimum: 3 days
Musculoskeletal complaints	Knee-, neck/shoulder- or back pain		

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PART II

Travel and antimicrobial resistance

6

Extended-spectrum β-lactamase-producing *Enterobacteriaceae* among travelers from the Netherlands

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Abstract

Background A prospective cohort study was performed among travelers from the Netherlands to investigate the acquisition of carbapenemase-producing *Enterobacteriaceae* (CP-E) and extended-spectrum ß-lactamase producing *Enterobacteriaceae* (ESBL-E) and associated risk factors.

Methods Questionnaires were administered and rectal swabs were collected and tested before and after return.

Results Of 370 travelers, 32 (8.6%) were colonized with ESBL-E before travel, 113 (31%) acquired an ESBL-E during travel and 26 were still colonized six months after return. No CPE were found. Independent risk factors for ESBL-E acquisition were travel to South and East Asia. Multilocus sequence typing showed extensive genetic diversity among *Escherichia coli*. Predominant ESBLs were CTX-M enzymes.

Conclusion The acquisition rate, 30.5%, of ESBL-E in travelers from the Netherlands to all destinations studied was high. Active surveillance for ESBL-E and CP-E and contact isolation precautions may be recommended at admission to medical facilities for patients who traveled to Asia during the previous six months.

Introduction

The effect of international travel on the spread of multidrug resistant *Enterobacteriaceae* (MDR-E) became more evident during 2007-2010. Data obtained during that time from prospective studies among returning travelers from Australia, Canada, Sweden and the United States (New York, New York) revealed high rates of extended-spectrum ß-lactamase producing *Enterobacteriaceae* (ESBL-E) carriage, varying from 18 to 25% after foreign travel (1-4). Two of these studies also reported a pre-travel ESBL-E carriage rate of 7.8%.

The identification of carbapenemase-producing *Enterobacteriaceae* (CP-E) produced another set of challenges. Carbapenemases, such as *Klebsiella pneumoniae* carbapenemases (KPC), New Delhi metallo-β-lactamase (NDM), OXA-48, VIM and IMP, are plasmid-encoded enzymes, which have emerged worldwide. The rate of acquisition of CP-E during foreign travel is unknown; no surveillance system to date tracks these rates, and such as the situation recently reviewed by Van der Bij and Pitout (5). In the Netherlands, CP-E were found for the first time in 2010 (6).

No data were available on the pre-and post travel carriage rates among travelers from the Netherlands. Our objective was to investigate whether these travelers are at risk of MDR-E (ESBL-E and/or CP-E) by use of a prospective cohort study design. Because detailed microbiological data of the isolates and epidemiological data are crucial for assessing the real public health impacts of these organisms, we also investigated the persistence of intestinal colonization and possible spread to household contacts six months after the travelers returned.

Materials and Methods

Study design

A prospective cohort study was conducted at the travel clinic at the Leiden University Medical Center (LUMC) and at the Hollands Midden Municipal Health Services (MHS) in Leiden, the Netherlands. During March - September 2011, all adults who made an appointment for travel advice and had the intention to travel to areas outside Europe, North America, and Australia were invited to participate in the study.

Travelers < 18 years of age and those who traveled >3 months were excluded. Only one person in a couple or travel group was included.

Participants were asked to complete an electronic questionnaire and to deliver a rectal swab sample immediately before and immediately after travel. Questionnaires were used to collect demographic data, previous medical history, and travel information. Travelers who acquired MDR-E after foreign travel were asked to fill out a third questionnaire and deliver a third rectal swab 6 months after return.

If travelers were positive for MDR-E 6 months after return, their household contacts were also requested to submit a rectal swab and questionnaire. Household contacts were defined as persons who shared the same household with a participant on a regular basis. MDR-E–positive participants were asked to deliver a fourth rectal swab at the same time. The study was approved by the Leiden University Medical Center medical ethics committee.

Bacterial isolates

Rectal swab samples were collected with Stuart Agar Gel Medium Transport Swabs (Copan Diagnostics, Corona, CA). The swabs were inoculated in trypticase soy broth supplemented with cefotaxime 0.25 mg/L and vancomycin 8 mg/L (MP products, Groningen, the Netherlands) and incubated for 24 hours at 37°C. After overnight incubation, the trypticase soy broth samples were subcultured on chromogenic ESBL screening agar (ESBL-ID; bioMérieux, Marcy-l'Étoile, France) and sheep blood agar as a growth control. All gram-negative rods growing on the ESBL-ID were identified by using MaldiTof-MS with BioTyper software version 3.0 (Bruker Daltonics, Breman, Germany), and antimicrobial drug susceptibility testing was performed by using the VITEK2 system (BioMérieux). All isolates underwent ESBL confirmatory disk testing by disk diffusion for ceftazidime and cefotaxime or cefepime (in cefoxitin resistant isolates), with and without clavulanic acid, as recommended by Clinical and Laboratory Standards Institute guidelines (www.clsi.org).

MICs for meropenem and ertapenem were determined using Etests (AB Biodisk, Solna, Sweden) according to the manufacturer's instructions. MICs were interpreted using EUCAST criteria (http://www.eucast.org/clinical_breakpoints/).

Molecular characterization of β-lactamases

Molecular characterization of the β-lactamase genes in ESBL-E was performed by using Check-MDR CT103 microarray, version 1.1 (Checkpoints B.V., Wageningen, The Netherlands) to test microarrays. The principals of the microarray system and interpretation software have been described (7). Concisely, the system combines ligation-mediated amplification with the detection of amplified products on a microarray to detect the various carbapenemase genes: OXA-48, NDM-1, IMP, VIM and KPC; CTX-M groups: CTX-M group 1, 2, 9 or combined 8/25; and the most prevalent ESBL-associated single-nucleotide polymorphisms (SNPs) in TEM and SHV-variants. Furthermore, the six plasmid-mediated AmpC β-lactamases can be identified (www.lahey.org/studies).

Molecular typing of *Escherichia coli* isolates

Multilocus sequence typing (MLST) was performed on all *E. coli* isolates by using seven housekeeping genes (*adk, fumC, gyrB, icd, mdh, purA* and *recA*) to determine the corresponding sequence type (ST) and to designate sequence type complex (STC) using the MLST Databases at the Environmental Research Institute, University College Cork website (http://mlst.ucc.ie/mlst/dbs/Ecoli).

Data analysis

A logistic regression model was used to determine risk factors for the acquisition of ESBL-E/CP-E after foreign travel in a total of 338 participants. Associations between acquiring an ESBL-E/CP-E after travel and different variables are calculated as odds ratios and p-values. Participants who were positive for ESBL-E/CP-E before travel were analyzed separately. Database processing and statistical analyses (univariate and multivariate analysis) were performed using the SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA). MLST analysis was performed using BioNumerics software v.6.6 (Applied Maths, St-Martens-Lathem, Belgium).

Results

Study population and travel characteristics

In total, 521 participants were invited to participate in the study; 370 travelers completed two questionnaires and sent in two rectal swabs and were included in the analysis (Figure 1). The median age of the study population was 33 years (range 19-82), and 234 (63.2%) were women. The median length of stay abroad was 21 days (range 6-90 days). The most common reason for travel was vacation (n=277). Of the 370 participants, 113 (30.5%) whose pre-travel swab samples were negative, acquired MDR-E during foreign travel. Of these 113 participants, 19 (16.8%) still carried MDR-E six months after return. In 32 of the 370 travelers (8.6%), MDR-E was identified before travel. Twenty of these 32 participants (62.5%) returned with MDR-E, seven of whom were still colonized after six months (35%). No MDR-E was found before or after travel in 225 participants (60.8%).

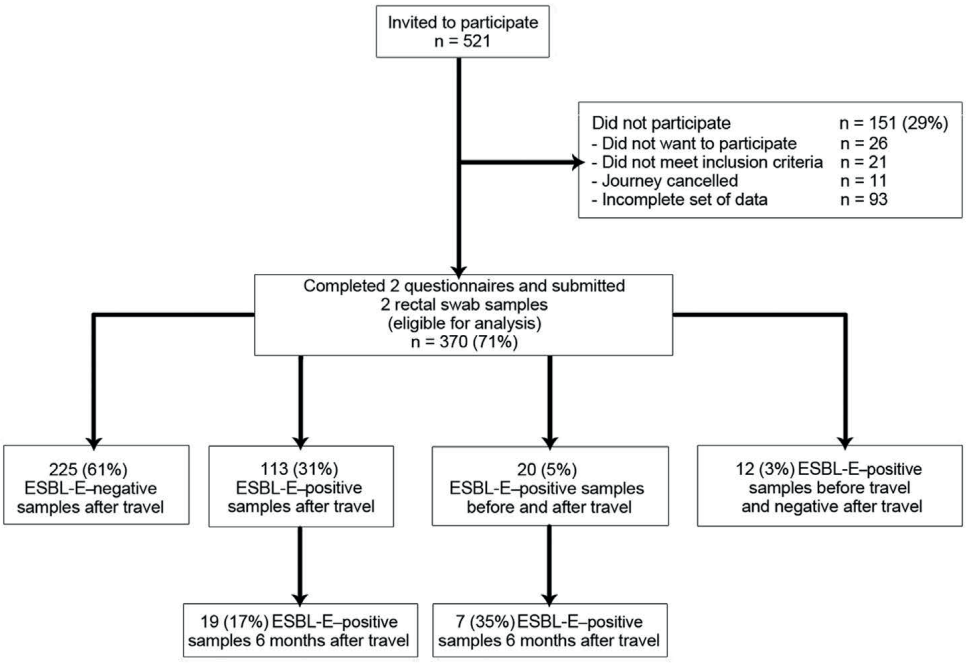

Figure 1. Flowchart of participants in the study.

Travel-associated risk factors for ESBL-acquisition in returning travelers

For the analysis of travel-associated risk factors, data for 338 participating returning travelers with negative pre-travel rectal swab sample test results were used (Technical Appendix Table 1, wwwnc.cdc.gov/EID/article/19/8/13-0257-Techapp1.pdf). In total, 65 countries were visited; these are subdivided in 10 subcontinents. The most common destinations were Indonesia (n=62), Thailand (n=30), Malaysia (n=27), Cambodia (n=21), People's Republic of China (n=39), Kenya (n=30), Tanzania (n=24), Surinam (n=20), and South Africa (n=19).

The highest ESBL-E acquisition rates were identified among participants who visited countries in Asia: 73% in South Asia and 67% in East Asia. Univariate and multivariate analysis showed that the travel destinations South and East Asia were significant risk factors for the acquisition of ESBL-E ($p<0.001$). Participants traveling to Asia (all subcontinents) were more likely to return with ESBL-E colonization after a self-arranged trip (odds ratio 1.7; $p=0.07$) or if they stayed in hostels/lodges (odds ratio 1.9; $p= 0.08$), although this finding was not statistically significant. There were no other risk factors for the acquisition of ESBL-E after foreign travel. The incidence proportions of ESBL-E after foreign travel are listed in Table 1.

Table 1. Incidence proportions and incidence rates for ESBL-E* colonization in 338 travelers from the Netherlands.

Destination	No. of travelers	No. (%) of travelers with ESBL-E after return	Incidence proportion, % (SE)	Person days, all travelers	Mean duration of travel, all travelers	ESBL incidence rate per 100 pdt* (SE†)
Southeast Asia	110	37 (34)	34 (4.5)	2,980	27	1.24 (0.20)
East Asia	33	22 (67)	67 (8.3)	776	24	2.83 (0.60)
South Asia	25	18 (72)	72 (9.2)	599	24	3.01 (0.70)
Central Asia	3	1 (30)	33 (33.3)	94	31	1.06 (1.06)
North Africa	10	4 (40)	40 (16.3)	112	11.2	3.57 (1.76) ‡
Middle Africa	56	17 (30)	30 (6.2)	1,637	29	1.04 (0.25)
Southern Africa	25	3 (12)	12 (6.6)	631	25	0.48 (0.27)
Middle East	15	2 (13)	13 (9.1)	222	14.8	0.90 (0.64)
Central America and the Caribbean	28	7 (25)	25 (8.3)	544	19	1.29 (0.48)
South America	32	2 (6)	6 (4.4)	922	29	0.22 (0.15)
Total	338	113 (33)	33 (2.6)	8,536	25	1.32 (0.12)

* ESBL-E: extended-spectrum β-lactamase *Enterobacteriaceae;* Pdt: person days of travel;

† SE standard error.

‡ The ESBL incidence rate per 100 person days of travel is represented by 4 ESBL-E carrying returning travelers from North Africa. Three of them had traveled for 7 days and one traveler had a 25-day stay abroad, which accounts for the high SE.

Microbiological results and molecular characterization

A total of 133 participants were colonized with MDR-E after travel. This group consisted of 113 travelers who had initially negative pre-travel swab samples. In addition, twenty participants who had positive pre-travel samples also returned colonized with MDR-E. The ESBL-E of these 133 post-travel swab samples consisted of 146 *E. coli*, 10 *K. pneumoniae,* and two *Enterobacter cloacae* isolates.

No carbapenemase-producing MDR-E were found among the pre-and post travel isolates. Molecular characterization of the post-travel isolates demonstrated that CTX-M group 1 ESBL (n=110) predominated (CTX-M-1 like, n=4; CTX-M-3 like, n=1; CTX-M-15 like, n=85; CTX-M-32 like, n=20), followed by CTX-M group 9 ESBL (n=42), CTX-M group 2 (n=2) and CTX-M group8/25 (n=1). One *E. coli* isolate carried an SHV-ESBL (238S+240K). In addition, some isolates coproduced plasmid-mediated AmpC β-lactamase, ACT/MIR (n=1) or CMY-2 (n=2).

Thirty-four ESBL-E were isolated from pre-travel rectal swab samples from 32 participants: 29 samples (85.3%) of them were positive for *E. coli,* four *Klebsiella pneumoniae* (11.8%), and one *Citrobacter freundii* (2.9%). The CTX-M group 1 ESBL (n=22) comprised (CTX-M-1 like, n=4; CTX-M-15 like, n=16; CTX-M-32 like, n=2); the remaining ESBL isolates belonged to CTX-M group 9 ESBL (n=8) and CTX-M group 2 (n=1). Two *E. coli* isolates carried an SHV-ESBL (238S+240K).

Co-resistance to other classes if antimicrobial drugs was common in pre- and post-travel isolates; 67% displayed resistance to trimethoprim/sulphamethoxazole, 36% to ciprofloxacin, 37% to tobramycin, 35% to gentamicin, and 29% to nitrofurantoin. All isolates were susceptible to colistin and carbapenems.

MLST of ESBL-producing *E. coli* isolates

MLST of 146 *E. coli* isolates from the post-travel samples identified 86 different sequence types (ST); 31 new STs were found. The most prevalent STs were: ST38 (12%; n=17), ST10 (7%; n=10), and ST131 (4%; n=9). The distribution of the CTX-M groups and types and STs is displayed in Figure 2. There was no association between ST and ESBL-type, nor were STs associated with specific travel destinations. Pre-travel isolates showed a similar diversity of STs, of which three were ST131.

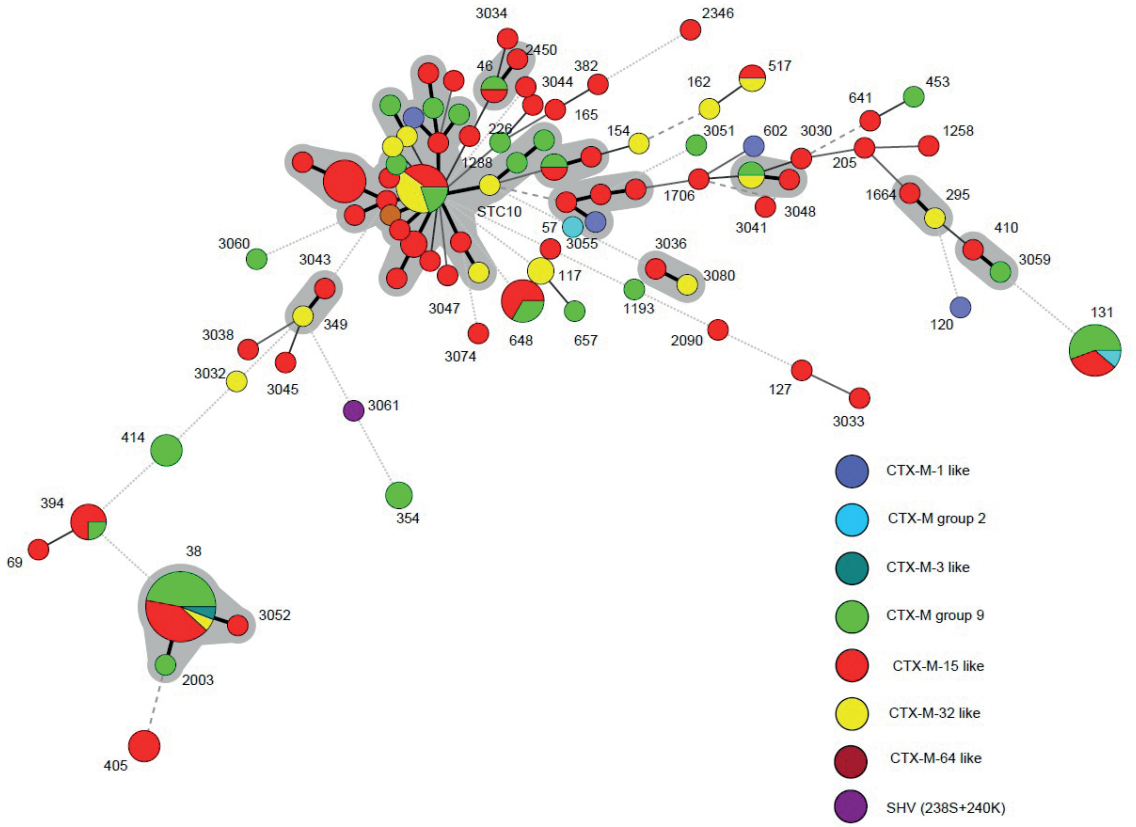

Figure 2. Multiocus sequence typing of *Escherichia coli* (n=146) from the post-travel isolates of 133 travelers from the Netherlands. The numbers indicate the most prevalent sequence types (STs). Grey shadow indicates that more than one ST belongs to the same complex. The following sequences belong to STC10: ST4,10, 34,43, 44,48, 167, 193, 215,218,227 and 617. Thick connecting lines indicate single locus variants; thin connecting lines indicate variants with two or three loci difference; dashed connecting lines indicate variants with four loci difference; dotted connecting lines indicate five to seven loci differences.

Prolonged carriage and household contacts

Of the 133 participants whose samples were positive for ESBL-E after return, 127 (95.4%) completed the follow-up survey and provided samples after six months.

ESBL-E was isolated from 26 samples (20.4%) (Table 2). None of these participants reported the use of antimicrobial drugs or were hospitalized during the previous six months; none were health care workers, and none reported contact with farm animals. Diarrhea was reported by seven participants.

Of 113 participants who had initially negative pre-travel samples and positive samples immediately after return, 19 (16.8%) were still colonized after six months. Of these, seven participants had samples that were positive for *E. coli* with the same ST six months after return. Nine participants were positive for *E. coli* and had a different ST six months after return; three were positive for a different species six months after return. Eleven household contacts of four MDR-E-positive participants agreed to cooperate and submitted a rectal swab sample. ESBL-producing *E. coli* was isolated from two household contacts (18.1%), each from different households. The first household contact carried a different ESBL-producing *E. coli* than the associated traveler before and after the trip. Both isolates carried a CTX-M group 9 enzyme. The second household contact was positive for SHV-ESBL producing *E. coli* ST2599. The associated traveler's samples were positive for *E. coli* ST617 and ST38 immediately after the trip, *K. pneumoniae* six months after return, and the fourth rectal swab sample was positive for a CTX-M-15 like *E. coli* ST3363.

Of 20 participants who samples were positive before and after return, seven participants (35.0%) were still colonized six months after return. Of these seven participants, five (20%) carried a similar strain: two carried a CTX-M- group 9-producing *E. coli* with an identical ST as before the trip, two carried a similar ST but with a different CTX-M group enzyme as before the trip, and one participant carried a CTX-M group 1 producing *K. pneumoniae* during the study period; two participants returned with an *E. coli* with a different ST. No household contacts were included in this subgroup of travelers.

Table 2. Microbiological and molecular characteristics of rectal swab samples collected from travelers from the Netherlands immediately pre-and post-travel and six months after return.

				Immediate post-travel samples						Post-travel sample six mo. after return†		
	Pre-travel samples			Isolate 1			Isolate 2					
ID	Species	CTX-M group	ST	Species	CTX-M group	ST	Species	CTX-M group	ST	Species	CTX-M group	ST
25	Neg	NA	NA	*E. coli*	9	131	Neg	NA	Na	*E. coli*	9	131
45	Neg	NA	NA	*E. coli*	1	405	*E. coli*	9	338	*E. coli*	1	405
56	Neg	NA	NA	*E. coli*	1	3036	*E. coli*	1	517	*E. coli*	1	3267
60	Neg	NA	NA	*E. coli*	1	648	*K. p.*	1	Nd	*E. coli*	1	648
61	Neg	NA	NA	*E. coli*	1	648	*E. coli*	9	227	*E. coli*	1	131
62	Neg	NA	NA	*E. coli*	9	3037	Neg	NA	NA	*E. coli*	9	501
80	Neg	NA	NA	*E. coli*	1	131	Neg	NA	NA	*E. coli*	9	1177
86	Neg	NA	NA	*E. coli*	1	93	*E. coli*	1	2090	*E. cloacae*	9	ND
137	Neg	NA	NA	*E. coli*	1	155	*E. coli*	1	617	*E. coli*	9	131
204	Neg	NA	NA	*E. coli*	1	38	Neg	NA	NA	*K. p.*	1	ND
211	Neg	NA	NA	*E. coli*	1	3044	Neg	NA	NA	*K. p.*	1	ND
222	Neg	NA	NA	*E. coli*	9	2003	Neg	NA	NA	*E. coli*	9	2003
238	Neg	NA	NA	*E. coli*	9	414	Neg	NA	NA	*E. coli*	9	10
251	Neg	NA	NA	*E. coli*	1	34	Neg	NA	NA	*E. coli*	1	450
309	Neg	NA	NA	*E. coli*	1	3045	Neg	NA	NA	*E. coli*	1	3045
373	Neg	NA	NA	*E. coli*	1	38	Neg	NA	NA	*E. coli*	1	3266
387	Neg	NA	NA	*E. coli*	1	131	Neg	NA	NA	*E. coli*	1	131
454	Neg	NA	NA	*E. coli*	9	10	Neg	NA	NA	*E. coli*	9	10
474	Neg	NA	NA	*E. coli*	1	154	Neg	NA	NA	*E. coli*	1	131

	Pre-travel samples			Immediate post-travel samples						Post-travel sample six mo. after return†		
				Isolate 1			Isolate 2					
ID	Species	CTX-M group	ST	Species	CTX-M group	ST	Species	CTX-M group	ST	Species	CTX-M group	ST
12	*E. coli*	9	38	*E. coli*	1	3074	Neg	NA	NA	*E. coli*	1	38
105	*E. coli*	1	191	*E. coli*	1	120	*E. coli*	1	38	*E. coli*	1	120
255	*E. coli*	9	131	*E. coli*	1	617	Neg	NA	NA	*E. coli*	9	131
269	*K. p.*	1	ND	*K. p.*	1	ND	Neg	NA	NA	*K. p.*	1	ND
283	*E. coli*	9	131	*E. coli*	1	46	Neg	NA	NA	*E. coli*	9	131
505	*E. coli*	1	1163	*E. coli*	1	69	Neg	NA	NA	*E. coli*	9	3268
512	*E. coli*	9	657	*E. coli*	9	657	Neg	NA	NA	*E. coli*	1	657

*ID, participant identification number; CTX-M, extended-spectrum β-lactamase enzyme; ST, sequence type; Neg, no species were isolated from sample; *E. coli*, *Escherichia coli*; *K.P.*, *Klebsiella pneumoniae*; NA, not applicable; ND, no sequence type data available; Neg, negative pre-travel swab sample.

† None of the participants with a positive rectal swab sample after six months reported antimicrobial drug use during the six months after return.

Discussion

The results of this study show a high ESBL-E carriage rate of 30.5% among healthy participating travelers from the Netherlands after return. This finding is worrisome, because this ESBL-E carriage rate is higher compared with those in recent studies that identified international travel as an independent risk factor for ESBL-E colonization (1-4). It is striking that none of the potential travel-associated risk factors investigated in the present study, other than traveling to South and East Asia, were found to contribute to this high ESBL-E carriage rate. Additional risk factors were not revealed by including in the univariate analysis the 13 participants who had a positive pre-travel sample and acquired an ESBL-producing *E. coli* during travel with a different ST than before the trip.

Tangden *et al*. associated gastroenteritis during travel with the risk for ESBL-E acquisition among travelers from Sweden (3). That association was not found in this study, which may reflect less fecal-oral contamination while traveling. Baaten *et. al*. reported that diseases transmitted by the fecal-oral route among travelers to non-industrialized countries have declined because of improved hygiene standards at the destination as measured by the human developmental index, sanitation index, and the water source index (8). The sanitation index (SI) levels, which represent the proportion of the population that has access to sanitation, were the lowest for Sub-Saharan Africa and the Indian subcontinent. On the basis of these indices, we would expect the incidence of ESBL-E acquisition to be similar among travelers in countries in Asia and Africa. Nonetheless, participating travelers to Asia had the highest post-travel colonization rates. Travelers to Asia most likely differ in their eating habits compared with travelers to African countries, since the former are more likely to eat in individual establishments outside of hotels or from street vendors. Thus, the high incidence rate found for returning travelers from Asia in this study may result from the increased risk of food-borne exposure.

No CP-E were found despite the fact that countries were visited where CP-E are prevalent in hospitals and in the environment (5). Other known risk areas besides India for the acquisition of CP-E, such as the United States, Greece, Italy, and the Balkan region were not included in this study, because these travelers do not visit the Travel Clinic of the LUMC. Many citizens from the Netherlands have relatives in

North African countries or Turkey whom they visit frequently. OXA-48 producing bacteria are endemic in these countries (9). These travelers do not consult travel clinics and may well return carrying OXA-48 producing isolates unnoticed.

Peirano *et. al.* (2) reported that the prevalence of ST131, an uropathogenic *E. coli* notorious for its worldwide expansion and spread of CTX-M-15, was similar among travelers and non-travelers from the Calgary region. The most prevalent ESBL among the travelers participating in this study was the CTX-M-15-like enzyme. However, this enzyme was found in a plethora of different sequences types of *E. coli*. Participants in the Leiden area not only showed a great heterogeneity of STs, but also harbored different CTX-M-types after travel and six months after return. The majority of the *E. coli* strains identified in the participants in this study were of STs that clustered around ST10 and belonged to sequence type complex 10 (STC10). STC10 strains essentially belong to the non-virulent, commensal phylogenetic group A (10). In a recent study based in French, isolates belonging to STC10 were found to be the most prevalent among fecal samples from healthy carriers of nalidixic acid resistant (but ESBL-negative) *E. coli* (11). It is also the most prevalent STC in the MLST database. Data from this study show transmissible genetic elements containing resistance genes are exchanged with naïve *E. coli* strains of the human intestinal microbiota during foreign travel combined with foodborne exposure.

Although 26 participants had positive results for ESBL-E six months after travel, they were not all positive for the same strain enterobacterial strain that was identified immediately after travel. In eight travelers colonized with *E. coli,* an ESBL of the same CTX-M group was identified in the immediate post-travel sample as after six months, but *E. coli* with a different ST was detected. In 11 travelers, the strain persisted during the study period. It is possible that more strain types were present in the rectal samples where colony morphology of different strains was not discriminative. However, it is also possible that the transfer of ESBL genes between strains within a host is a frequent occurrence. Or, the acquisition of a new ESBL-E occurs at the expense of the resident strain.

Inter-household transmission of ESBL-E has been demonstrated in the community setting (12,13). Clonally related strains could be found for 66% of the isolates from infected community patients and their corresponding household contacts (13). Because of the limited data on household contacts in the present

study, the transmission dynamics of ESBL-E in households after foreign travel remains to be discovered.

The high pre-travel ESBL-E carriage rate among our study participants (8.6%) was an unexpected finding. Two recent studies on the ESBL-E carriage rate in the community have been conducted in the Amsterdam area. In the first study, 10.1% of the fecal samples from outpatients with gastrointestinal discomfort being assessed by their general practitioners yielded ESBL-E, predominantly CTX-M-15 producing *E. coli* (14). In a second study, investigating the prevalence of ESBL-E carriage in the general community, a carriage rate of 8.5% was found (15). Although no data on travel history were given, the investigators pointed out that foreign travel might be responsible for at least part of ESBL-E carriage rate among outpatients from the Netherlands. This finding is supported by data from our study: 50% of participants who had a positive pre-travel sample had traveled during the previous 12 months. This high percentage of carriers identified in this study before travel points toward ongoing importation of ESBL-E. Other potential reservoirs for ESBL-E are poultry and retail meats, which have been found to be contaminated with ESBL-producing *E. coli* strains harboring the genes on identical plasmids as found in human isolates (16,17).

International travel is growing and the number of intercontinental flights has increased during the past decade. The findings in this study support the role of international travel on the ESBL-E acquisition and carriage rate in travelers from the Netherlands, especially to South and East Asia. The high pre- and post travel carriage rates among persons traveling from the Netherlands indicate that the consequences of increased foreign travel are already manifest in this country. The lack of apparent travel-associated risk factors, the spread of CTX-M enzymes through a highly diverse population of *E. coli,* the association of ESBL-production with multidrug resistance and the possible role of other sources make containing the spread difficult. These factors also complicate the implementation of other strategies, such as pre-travel advice, and imply that all travelers to Asia should be considered for carriage of ESBL-E. Although CP-E were not found in this study, CP-E have been introduced into the Netherlands by returning travelers (6,18-20), and introduction by asymptomatic travelers to the Netherlands from countries where CP-E are endemic may largely go unnoticed. There is no reason to assume that, after CP-E are introduced, their spread will be less dynamic than that of ESBL-E. This interference

has serious implications for the implementation of screening methods and effective infection control strategies. On the basis of the results of this study, we recommend active surveillance of CP-E and ESBL-E and at least temporary contact isolation precautions for patients being admitted to hospitals after travel to Asia during the previous six months.

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Technical Appendix Table. Person and travel characteristics and risk factors for ESBL-E acquisition in a cohort of 338 travelers from the Netherlands*

Variable	No. (%) negative pre- and post-travel N=225	No. (%) positive post-travel only N=113	Univariate analysis OR (95% CI)	p-value †	Multivariate analysis OR (95% CI)	p-value
Gender, female	144 (64.0)	69 (61.1)	0.88 (0.55-1.41)	0.60		
Age						
18-25 y	54 (24.0)	28 (24.8)	1.0			
26-33 y	66 (29.3)	24 (21.2)	0.39 (0.17-0.92)	0.03		
34-51 y	56 (24.9)	29 (24.8)	064 (0.28-1.61)	0.37		
≥52y	43 (21.8)	33 (29.2)	1.46 (0.60-3.54)	0.41		
Vegetarian	13 (5.8)	6 (5.3)	0.91 (0.34-2.47)	0.86		
Health care worker	59 (26.2)	27 (23.9)	0.88 (0.52-1.49)	0.64		
Daily contact with farm animals	8 (3.6)	4 (3.5)	1.0 (0.29-3.38)	0.99		
Visit to identified risk areas during previous 12 mo.			1.01 (0.64-1.61)	0.96		
None	138 (61.3)	69 (61.1)				
Africa	26 (11.6)	15 (13.3)				
Asia	21 (9.3)	12 (10.6)				
India	5 (2.2)	4 (3.5)				
Middle East	26 (11.6)	13 (11.5)				
Central America and Caribbean Region	17 (7.6)	7 (6.2)				
South America	6 (2.7)	5 (4.4)				
Medical problem‡						
None	161 (71.6)	84 (74.3)				
Inflammatory Bowel Disease	2 (0.9)	1 (0.9)				
Chronic diarrhea	3 (1.3)	0				

Variable	No. (%) negative pre- and post-travel N=225	No. (%) positive post-travel only N=113	Univariate analysis OR (95% CI)	p-value †	Multivariate analysis OR (95% CI)	p-value
Chronic constipation	3 (1.3)	1 (0.9)				
Irritable bowel syndrome	17 (3.1)	7 (6.2)				
Diabetes mellitus	3 (1.3)	1 (0.9)				
Gastro esophageal reflux	12 (5.3)	4 (3.5)				
Recurrent urinary tract infections	4 (1.8)	1 (0.9)				
Autoimmune disease	7 (3.1)	2 (1.8)				
Abdominal pain with unknown origin	5 (2.2)	2 (1.8)				
Gallbladder problems	4 (1.7)	1 (0.9)				
Transplantation	1 (0.4)	0				
Coeliac disease	0	2 (1.8)				
Other	30 (13.3)	18 (15.9)				
Antibiotic use during 12 mo. before travel	47 (20.9)	17 (15.1)	0.85 (0.56-1.29)	0.45		
Hospitalization during 12 mo. before travel						
<3 mo prior	5 (2.2)	3 (2.7)				
3-6 mo prior	2 (0.9)	1 (0.9)				
6-9 mo prior	1 (0.4)	1 (0.9)				
9-12 mo prio	2 (0.9)	2 (1.8)				
Travel destination, by subcontinents§						
Southeast Asia	73 (32.4)	37 (32.7)	1.01 (0.63-1.64)	0.96		
East Asia	11 (4.9)	22 (19.5)	4.70 (2.19-10.1)	<0.001	3.95 (1.78-8.73)	0.001
South Asia	7 (3.1)	18 (15.9)	5.90 (2.39-14.60)	<0.001	5.09 (2-12.92)	0.001
Central Asia	2 (0.9)	1 (0.9)	1.0 (0.089-1.11)	0.99		

Variable	No. (%) negative pre- and post-travel N=225	No. (%) positive post-travel only N=113	Univariate analysis OR (95% CI)	p-value †	Multivariate analysis OR (95% CI)	p-value
Middle East	13 (5.8)	2 (1.8)	0.29 (0.07-1.33)	0.11	0.28 (0.06-1.30)	0.103
North Africa	6 (2.7)	4 (3.5)				
Central Africa	39 (17.3)	17 (15)				
Southern Africa	23 (10.2)	3 (2.7)	0.24 (0.07-0.82)	0.02	0.24 (0.07-0.85)	0.027
Central America and the Caribbean	21 (9.3)	7 (6.2)	0.64 (0.26-1.56)	0.33		
South America	30 (13.3)	2 (1.8)	0.12 (0.027-0.50)	0.004	0.14 (0.03-0.59)	0.008
Median duration of stay in days (range)	21 (6-90)	22 (6-89)	0.99 (0.976-1.004)	0.17	1.0 (0.97-1.0)	0.22
Type of travel						
Self-arranged travel	95 (42.2)	52 (46)	1.17 (0.74-1.84)	0.51		
Backpacking	51 (22.7)	25 (22.1)	0.97 (0.56-1.67)	0.91		
Organized group travel	62 (27.6)	27 (23.9)	0.83 (0.49-1.39)	0.47		
Cruise	1 (0.4)	0				
Other	16 (7.1)	9 (8)				
Reason for travel						
Vacation	166 (73.8)	83 (73.5)				
Visiting family/friends	8 (3.6)	8 (7.1)				
Business	15 (6.7)	9 (8.0)				
Study	18 (8)	7 (6.2)				
Volunteer work	10 (4.4)	5 (4.4)				
Travel group composition						
Alone	25 (11.1)	14 (12.4)	1.13 (0.56-2.27)	0.73		
With one partner	102 (45.3)	44 (38.9)	0.77 (0.49-1.22)	0.26		

Variable	No. (%) negative pre- and post-travel N=225	No. (%) positive post-travel only N=113	Univariate analysis OR (95% CI)	p-value †	Multivariate analysis OR (95% CI)	p-value
More partners	44 (19.6)	30 (26.5)				
Group travel	54 (24)	25 (22.1)	1.23 (0.78-1.93)	0.37		
Accommodation during travel						
Luxury hotels	78 (34.7)	34 (30.1)	0.81 (0.50-1.32)	0.40		
Hostels	50 (22.2)	30 (26.5)	1.27 (0.75-2.13)	0.38		
Budget hotels	49 (21.8)	27 (23.9)	1.13 (0.66-1.93)	0.66		
Own holiday home	16 (7.1)	3 (2.7)				
Camping	10 (4.4)	6 (5.3)				
With family/friends	8 (3.6)	5 (4.4)				
Locals	7 (3.1)	3 (2.7)				
Boat	4 (1.8)	2 (1.8)				
Other	3 (1.3)	3 (2.7)				
Diarrhea during travel	83 (36.9)	45 (39.8)	1.13 (0.71-1.80)	0.60		
Companion travelers with diarrhea	115 (51.1)	61 (54.0)	1.1 (0.71-1.77)	0.62		
Antibiotic use during travel	10 (4.4)	9 (8.0)	1.86 (0.73-4.72)	0.19	1.98 (0.72-5.47)	0.16

* Data are presented as no. (%), unless stated otherwise. Blank cells indicate no data available for value. Or, odds ratio; UTI, urinary tract infection.

†Variables with $p < 0.2$ in the univariate analysis were included in the multivariate logistic regression model.

‡Participants could report more than one medical problem

§Travel destinations visited by the travelers who completed the study were divided in 10 subcontinents (n= no. of travelers per destination. One participant could have visited more than one country):

Southeast Asia: Cambodia (n=21), Philippines (n=1), Indonesia (n=62), Laos (n=9), Malaysia, (n=27), Singapore (n=9), Thailand (n=30) and Vietnam (n=17)

East Asia: China (n=39), Japan (n=1), Mongolia (n=4) and Taiwan (n=1)

South Asia: Bangladesh (n=1), India, (n=20) Maldives (n=2), Nepal (n=8) and Sri Lanka (n=5)

Central Asia: Kazakhstan,(n=2), Kyrgyzstan (n=2) Uzbekistan (n=2) and Turkmenistan (n=1)

Middle East: Iran (n=1), Jordan (n=1), Turkey (n=14) Emirates(n=3)

North Africa: Egypt (n=10) and Morocco (n=5)

Middle Africa: Benin (n=1), Cameroon (n=1), Congo (n=7), Gambia (n=2), Ghana (n=1), Kenya (n=30), Liberia (n=1) , Rwanda (n=1) , Sierra Leone (n=1), Tanzania (n=24) and Uganda (n=9)

Southern Africa: Angola (n=1), Botswana (n=5), Lesotho (n=2), Madagascar (n=3), Malawi (n=5), Mauritius (n=1), Mozambique (n=2), Namibia (n=7) South Africa (n=19), Swaziland (n=6) , Zambia (n=6)and Zimbabwe. (n=1)

Central America and the Caribbean: Belize (n=2), Bonaire (n=1), Costa Rica (n=9), Cuba (n=5), Curacao (n=1), Dominican Republic (n=4), Grenada (n=1) Guatemala (n=4), Honduras (n=2), Mexico (n=9), Nicaragua (n=5) and Panama (n=3)

South-America: Argentina (n=3), Bolivia (n=2), Brazil (n=5), Chile (n=2), Ecuador (n=3), Guyana (n=3, Peru (n=3), Surinam (n=20), Trinidad and Tobago (n=2) and Venezuela (n=1)

7

Extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBL-PE) among travelers to Africa: destination-specific data pooled from three European prospective studies

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Abstract

Background One third of travelers to low- and middle-income regions of the tropics and subtropics become colonized by extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL-PE). The risk varies by destination and, for each traveler, may be substantially further increased by travelers' diarrhoea (TD) and antibiotic use. Despite the risk of TD in Africa, ESBL-PE acquisition rates in all studies are lower there than in Asia. Africa has become increasingly popular as a destination for international travelers, yet minimal data are available from the continent's subregions and countries.

Methods We analysed subregion- and country-specific data on carriage and risk factors for ESBL-PE colonization pooled from three prospective studies conducted between 2009 and 2013 among Finnish and Dutch travelers. The data were subjected to multivariable analysis of risk factors. In addition, we compared our data to two recent large investigations reporting data by subregion and country.

Results Our joint analysis comprised data on 396 travelers. The ESBL-PE colonization rate was highest in Northern Africa, followed by Middle and Eastern Africa, and lowest in Southern and Western Africa. Of individual countries with more than 15 visitors, the highest rates were seen for Egypt (12/17; 70.6%), Ghana (6/23; 26.1%), and Tanzania (14/81; 17.3%); the rates among travelers to Egypt were comparable to those reported in South and Southeast Asia. In a pooled multivariable analysis, travel destination, age, overnight hospitalisation abroad, TD, and use of fluoroquinolones were independently associated with increased ESBL-PE colonization rates.

Conclusions Even in areas with relatively low risk of colonization, antimicrobials clearly predispose to colonization with ESBL-PE. Travelers to Africa should be cautioned against unnecessary use of antibiotics.

Introduction

Every third traveler from industrialised countries that visits developing regions becomes colonized by extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL-PE) [1-11]. While rates as high as 88% have been reported for travelers to South Asia [4-8,10,11] and 69% to Southeast Asia [4,6-8,10,11], considerably lower risks have been detected among travelers to the African continent, varying between 12% and 45% [3,4,6-8,10,11].

Data on colonization among visitors to various African countries or subregions remain scarce, as the vast majority of prospective studies report acquisition rates either for the whole continent [1,9] or only part of the subregions [3,4,6,8-10,12,13]; a few investigations provide data on a number of individual countries [7,11]. Travel destination, antibiotic use, age, and travelers' diarrhoea (TD) have been identified as major risk factors. Several other additional factors have been shown in single studies: type of travel, meal location and consumption of certain food products, such as ice cream and pastries [1,3-7,9-11,14]. While these factors all predispose to ESBL-PE colonization in general, studies presenting colonization risk factors by individual geographic areas are few [5,11], and none have focused exclusively on Africa. As the continent attracts increasing numbers of travelers [15], we decided to review the data published and pool subregion-derived findings of our three earlier investigations [4,6,10]. Combining these data with subregional carriage rates from two recent studies [7,11], our paper offers an insight into the subregion-related colonization risk of travelers to Africa.

Methods

Study design, volunteers and samples

To assess the colonization rates of ESBL-PE in Africa, we combined the data of travelers to Africa from three large studies:

(1) Finnish study by Kantele et al [6]. The volunteers travelled in 2009-2010; 196 of the 430 (45.6%) travelled in Africa. Faecal samples were used for analyses.

(2) Dutch study I by Paltansing et al [4]. The volunteers travelled in 2011; 103 of 338 (30.5%) travelled in Africa. Rectal swabs were used for analyses.

(3) Dutch study II by Reuland et al [10]. The volunteers travelled in 2012-2013 (of the travelers reviewed here, all but one travelled in 2012); 97 of 418 (23.2%) travelled in Africa; 63 (64.9%) faecal samples and 34 (35.1%) rectal swabs were analysed. In the original article, the authors report that the colonization rates were similar regardless of sample technique.

For all three prospective studies, the volunteers provided both pre- and post-travel stool samples / rectal swabs. Of the 14 (3.5%) travelers with pre-travel samples positive for ESBL-PE, three had the same strain detected in post-travel samples. In six volunteers, the post-travel sample was negative; these were included in the ESBL-PE(-) group. The five that contracted a different type of ESBL-PE during travel were included in the ESBL-PE(+) group. Travelers who contracted a new ESBL-PE strain during travel constituted the ESBL-PE(+) group, while all others belonged to the ESBL-PE(-) group. The following information was available from all three studies in comparable format: travel itinerary, travel duration, travel dates, age, sex, antimicrobial usage, occurrence of TD, and possible hospitalisation abroad (overnight stay or more).

In all studies, written informed consent was obtained from all participants and the Ethics Committees in the respective organisations approved the study protocols.

Collection of stool samples and identification of ESBL-PE strains

We have described earlier in detail the approaches to collection of samples (stools or swabs) and methods used for identification of ESBL-PE and carbapenemase-producing *Enterobacteriaceae* (CPE) [4,6,10].

Definition of TD and geographical subregions

For the purpose of the present study, TD was defined as three or more loose or liquid stools per day. Geographical subregions in Africa were defined according to the United Nations [16]: Southern Africa, Western Africa, Middle Africa, Eastern Africa, and Northern Africa. Travelers visiting more than one subregion in Africa were categorised on the basis of longest stay.

Statistical analyses

Statistical analyses were carried out with SPSS software version 24 (IBM Corp, Armonk, NY) and Stata version 15.1 (StataCorp. College Station, TX). Binomial regression model was used to obtain profile likelihood confidence intervals for the proportions of travelers with given risk factors and positive for ESBL-PE. The chi-square test, Fisher's exact test or binary logistic regression analysis were used to compare categorical variables when applicable. Binary logistic regression was used with continuous variables. Variables with a p-value <0.2 in the univariate analysis for ESBL-PE colonization were subjected to multivariable analysis together with doxycycline as antimalarial, gender and duration of travel in days. The shape of the form for travel duration and age were assessed by cubic splines and appeared log-linear. The interaction between variables of interest and studies was assessed. The final model was built using binary logistic regression analysis with a stepwise backward selection of variables by Akaike Information Criteria (AIC). Factors with 95% confidence intervals ranging only either above or below 1 were considered significant. The three studies pooled in the present paper [4,6,10] and the two others [7,11] used for comparisons were all brought together to produce a forest plot analysis. Heterogeneity between studies in forest plot was measured with I^2; values above 75% were considered high, 25%–75% moderate, and below 25%. For our pooled data, the interaction between studies and geographical subregions was analysed in the multivariable model.

Results

Demographic data, background characteristics, and occurrence of TD

Demographic data on travelers are presented in Table 1. Of the 396 travelers included in this study, 237 (59.8%) were women. The median age was 36 years (IQR 27-53) and the median duration of travel 19 days (IQR 14-25). One fourth of the travelers (n=105; 26.5%) had visited more than one country in Africa. The majority of the travelers visited either Western (27.8%) or Eastern (46.7%) Africa. Twenty-three (5.8%) had visited more than one subregion in Africa. In addition to Africa (or Europe *en route* to Africa), two volunteers (0.5%) had visited Jordania and two (0.5%) United Arab Emirates.

TD rates were lowest in Southern Africa (15/58; 25.9%); in other areas 37.8-46.7% of travelers contracted TD (Table 2). Of the 44 (11.1% of all travelers) courses of antibiotics, 30 (68.2%) were taken for TD. Eight (2.0% of all travelers) used beta-lactam antibiotics and 25 (6.3%) used fluoroquinolone antibiotics during travel.

ESBL-PE acquisition rates by subregion in the pooled data

In the pooled data (Table 2, Figure 1), 61 (15.4%) travelers became colonized by ESBL-PE; one Dutch traveler to Egypt became colonized by CPE. The highest ESBL-PE colonization rates were seen among travelers to Northern Africa (12/28; 42.9%), followed by Middle Africa (4/15; 26.7%) and Eastern Africa (30/185; 16.2%). Of travelers to Western and Southern Africa, 10.0% (11/110) and 6.9% (4/58), respectively, acquired ESBL-PE (Tables 1 and 2).

Of the nine countries with more than 15 visitors (Table 3), the highest ESBL-PE acquisition rates were seen among travelers to Egypt (12/17; 70.6%), Ghana (6/23; 26.1%), Tanzania (14/81; 17.3%), Uganda (4/26; 15.4%) and Kenya (12/82; 14.6%). As for the lowest colonization rates, of the 26 travelers to Senegal, three (11.5%) became colonized by ESBL-PE, in South Africa, 5/49 (10.2%) became colonized and in the Gambia the rate was only 3.4% (2/58); none of the 21 visitors to Namibia acquired ESBL-PE.

Results of the multivariable analysis for risk factors of ESBL-PE colonization in Africa

The initial univariate analysis (Table 1) detected the following factors with $p < 0.2$: age, original study, sampling technique, subregion in Africa, use of fluoroquinolones, beta-lactams or other AB / regimen not known, TD, and overnight hospitalisation abroad. When all of these factors, together with gender, duration of travel, and use of doxycycline as antimalarial were subjected to multivariable analysis, the following were found to be independently associated with increased risk: travel to Northern Africa, overnight hospitalisation abroad, age, TD and use of fluoroquinolones (Table 1).

Table 1 Demographics and risk factors of ESBL-PE acquisition in pooled data on 396 travelers from Finland and the Netherlands

				Univariate analysis			Multivariable analysis		
Characteristic	**total n (% of all)**	**ESBL-PE(+) n (%)**	**95% CI (%)[a]**	**P**	**OR**	**95% CI**	**P**	**AOR**	**95% CI**
Total	396 (100.0)	61 (15.4)							
Gender									
Male	159 (40.2)	24 (15.1)	10.1-21.2		1.0				
Female	237 (59.8)	37 (15.6)	11.4-20.6	0.889	1.0	0.6-1.8			
Age[b]									
Age, *median, years*	36 (IQR 27-53)	38.5 (IQR 25.5-55.5)		0.071	1.0	1.0-1-0	0.002	1.0	1.0-1.1
Study									
Kantele et al [6]	196 (49.5)	25 (12.8)	8.6-17.9		1.0			1.0	
Paltansing et al [4]	103 (26.0)	29 (28.2)	20.1-37.3	0.001	2.7	1.5-4.9	0.303	3.7	0.3-50.0
Reuland et al [10]	97 (24.5)	7 (7.2)	3.2-13.5	0.158	0.5	0.2-1.3	0.962	1.1	0.1-25.1
Sampling method									
Rectal swab	137 (34.6)	32 (23.4)	16.8-30.9	0.001	2.4	1.4-4.2	0.648	1.5	0.3-7.8
Stool sample	259 (65.4)	29 (11.2)	7.7-15.4		1.0				
Year of travel[b]									
(year of travel as a continuous variable)				0.909	1.0	0.8-1.2	0.609	0.8	0.3-2.1
2009	122 (30.8)	17 (13.9)	8.6-20.8						
2010	74 (18.7)	8 (10.8)	5.1-19.2						
2011	103 (26.0)	29 (28.2)	20.1-37.3						
2012-2013	97 (24.5)	7 (7.2)	3.2-13.5						
Destination subregion									
Southern Africa	58 (14.6)	4 (6.9)	2.2-15.3		1.0			1.0	
Northern Africa	28 (7.1)	12 (42.9)	25.8-61.2	<0.001	10.1	2.9-35.8	0.001	12.4	3.1-57.3
Middle Africa	15 (3.8)	4 (26.7)	9.2-51.5	0.042	4.9	1.1-22.7	0.056	5.6	0.9-33.6
Eastern Africa	185 (46.7)	30 (16.2)	11.4-22.0	0.084	2.6	0.9-7.8	0.058	3.1	1.1-11.2
Western Africa	110 (27.8)	11 (10.0)	5.3-16.5	0.505	1.5	0.5-4.9	0.528	1.5	0.4-6.2

				Univariate analysis			Multivariable analysis		
Characteristic	**total n (% of all)**	**ESBL-PE(+) n (%)**	**95% CI (%)[a]**	**P**	**OR**	**95% CI**	**P**	**AOR**	**95% CI**
Antibiotics									
no AB	352 (88.9)	44 (12.5)	9.3-16.2		1.0				
AB	44 (11.1)	17 (38.6)	25.2-53.4	<0.001	4.4	2.2-8.7			
AB: beta-lactams									
No	388 (98.0)	57 (14.7)	11.4-18.4		1.0			1.0	
Yes	8 (2.0)	4 (50.0)	19.1-80.9	0.022	5.8	1.4-23.9	0.118	3.4	0.5-21.9
AB: fluoroquinolones									
No	371 (93.7)	51 (13.7)	10.5-17.5		1.0			1.0	
Yes	25 (6.3)	10 (40.0)	22-5-59.5	0.002	4.2	1.8-9.8	0.005	4.7	1.5-13.9
AB others (other than beta-lactams or FQ) / unknown									
No	382 (96.5)	56 (14.7)	11.4-18.4		1.0			1.0	
Yes	14 (3.5)	5 (35.7)	14.6-61.7	0.048	3.2	1.0-10.0	0.059	3.8	0.9-14.6
Doxycycline as antimalarial									
No	362 (91.4)	56 (15.5)	12.0-19.4		1.0				
Yes	34 (8.6)	5 (14.7)	5.5-29.0	0.906	0.9	0.4-2.5			
Travelers' diarrhoea (TD)									
no TD	243 (61.4)	30 (12.3)	8.6-16.9		1.0				
TD	153 (38.6)	31 (20.3)	14.4-27.1	0.034	1.8	1.0-3.1	0.033	2.1	1.1-4.1
Overnight hospitalisation abroad (information missing n=1)									
No	389 (98.5)	57 (14.7)	11.4-18.4		1.0				
Yes	6 (1.5)	4 (66.7)	28.1-100	0.006	11.6	2.1-65.1	0.004	16.5	2.5-140.5
Duration of travel, (information missing n=1)[b]									
Median, days	19 (IQR 14-25)	18 (IQR 15-23)		0.828	1.0	1.0-1.0	0.276	1.0	1.0-1.0

[a] 95% confidence intervals are profile likelihood confidence intervals for proportion of ESBL(+) with given risk factor

[b] studied as a continuous variable in statistical analysis

Table 2 ESBL-PE colonization rates, occurrence of TD and antibiotic use in the pooled data on 396 travelers from Finland and the Netherlands in relation to geographical subregion visited

	All	Northern Africa	Middle Africa	Eastern Africa	Western Africa	Southern Africa
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Kantele et al (Finnish study) [6]						
total no. of travelers to subregion (% of all)	196	3 (1.5)	4 (2.0)	86 (43.9)	78 (39.8)	25 (12.8)
ESBL-PE (+)	25 (12.8)	2 (66.7)	1 (25.0)	14 (16.3)	5 (6.4)	3 (12.0)
AB	34 (17.3)	1 (33.3)	1 (25.0)	13 (15.1)	15 (19.2)	4 (16.2)
TD	71 (36.2)	1 (33.3)	1 (25.0)	34 (39.5)	29 (37.2)	6 (24.0)
Paltansing et al (Dutch study I) [4]						
total no. of travelers to subregion (% of all)	103	13 (12.6)	7 (6.8)	54 (52.4)	12 (11.7)	17 (16.5)
ESBL-PE (+)	29 (28.2)	7 (53.8)	3 (42.9)	14 (25.9)	4 (33.3)	1 (5.9)
AB	8 (7.8)	2 (15.4)	1 (14.3)	3 (5.6)	2 (16.7)	0 (0.0)
TD	39 (37.9)	7 (53.8)	4 (57.1)	19 (35.2)	5 (41.7)	4 (23.5)
Reuland et al (Dutch study II) [10]						
total no. of travelers to subregion (% of all)	97	12 (12.4)	4 (4.1)	45 (46.4)	20 (20.6)	16 (16.5)
ESBL-PE (+)	7 (7.2)	3 (25.0)	0 (0.0)	2 (4.4)	2 (10.0)	0 (0.0)
AB	2 (2.1)	0 (0.0)	0 (0.0)	2(4.4)	1 (16.7)	0 (0.0)
TD	43 (44.3)	5 (41.7)	2 (50.0)	17 (37.8)	14 (70.0)	5 (31.3)
Combined total of the three studies						
total no. of travelers to subregion (% of all)	396	28 (7.1)	15 (3.8)	185 (46.7)	110 (27.8)	58 (14.6)
ESBL-PE (+)	61 (15.4)	12 (42.9)	4 (26.7)	30 (16.2)	11 (10.0)	4 (6.9)
AB	45 (11.4)	3 (10.7)	2 (13.3)	18 (9.7)	18 (16.4)	4 (6.9)
TD	153 (38.6)	13 (46.4)	7 (46.7)	70 (37.8)	48 (43.6)	15 (25.9)

AB antibiotic use, *TD* travelers' diarrhoea

Table 3 ESBL-PE colonization rates from our pooled data of 396 travelers by country visited presented with the respective figures from studies by Ruppé et al [7] and Arcilla et al [11].

Country	Data pooled from three studies[a]: Total number of travelers (% of all visitors to Africa)	Data pooled from three studies[a]: ESBL-PE (+) cases / all visitors to country (%)	Data published by Ruppé et al[b] ESBL-PE (+) cases / all visitors to country (%)	Data published by Arcilla et al[c] ESBL-PE (+) cases / all visitors to country (%)
Northern Africa				
Egypt	17 (4.3)	12/17 (70.6)	-	24/30 (80.0)
Morocco	10 (2.5)	1/10 (10.0)	-	8/36 (22.2)
Tunisia	3 (0.8)	0/3 (0)	-	-
Middle Africa				
Cameroon	7 (1.8)	1/7 (14.3)	13/24 (54.2)	-
Central African Republic	-	-	0/1 (0.0)	-
Democratic Republic of Congo	8 (2.0)	3/8 (37.5)	-	-
Republic of Congo	6 (1.5)	2/6 (33.3)	8/13 (61.5)	-
Gabon	1 (0.3)	0/1 (0)	2/3 (66.7)	-
Sao Tome and Principe	-	-	0/1 (0.0)	-
Eastern Africa				
Djibouti	1 (0.3)	1/1 (100.0)	-	-
Ethiopia	14 (3.5)	2/14 (14.3)	2/4 (50.0)	-
Kenya	82 (20.7)	12/82 (14.6)	4/6 (66.7)	10/30 (33.3)
Madagascar	3 (0.8)	1/3 (33.3)	4/7 (57.1)	-
Malawi	14 (3.5)	2/14 (14.3)	-	-
Mauritius	1 (0.3)	1/1 (100.0)	-	-

Country	Data pooled from three studies[a]: Total number of travelers (% of all visitors to Africa)	Data pooled from three studies[a]: ESBL-PE (+) cases / all visitors to country (%)	Data published by Ruppé et al[b] ESBL-PE (+) cases / all visitors to country (%)	Data published by Arcilla et al[c] ESBL-PE (+) cases / all visitors to country (%)
Mozambique	8 (2.0)	1/8 (12.5)	0/1 (0.0)	-
Rwanda	5 (1.3)	0/5 (0)	-	-
Tanzania	81 (20.5)	14/81 (17.3)	7/11 (63.6)	14/57 (24.6)
Uganda	26 (6.6)	4/26 (15.4)	-	12/27 (44.4)
Western Africa				
Benin	13 (3.3)	1/13 (7.7)	4/11 (36.4)	-
Burkina Faso	2 (0.5)	0/2 (0)	4/8 (50.0)	-
Côte d'Ivoire	1 (0.3)	0/1 (0)	8/17 (47.1)	-
Gambia	58 (14.6)	2/58 (3.4)	-	8/49 (16.3)
Ghana	23 (5.8)	6/23 (26.1)	1/1 (100.0)	8/20 (40.0)
Guinea Bissau	1 (0.3)	0/1 (0)	0/3 (0.0)	-
Liberia	3 (0.8)	0/3 (0)	-	-
Mali	4 (1.0)	1/4 (25.0)	1/5 (20.0)	-
Nigeria	7 (1.8)	1/7 (14.3)	1/1 (100.0)	-
Senegal	26 (6.6)	3/26 (11.5)	17/45 (37.8)	-
Sierra Leone	3 (0.8)	1/3 (33.3)	-	-
Togo	6 (1.5)	2/6 (33.3)	9/12 (75.0)	-
Southern Africa				
Angola	1 (0.3)	0/1 (0)	1/3 (33.3)	-
Botswana	10 (2.5)	1/10 (10.0)	-	-
Lesotho	2 (0.5)	1/2 (50.0)	-	-
Namibia	21 (5.3)	0/21 (0)	-	-

Country	Data pooled from three studies[a]: Total number of travelers (% of all visitors to Africa)	Data pooled from three studies[a]: ESBL-PE (+) cases / all visitors to country (%)	Data published by Ruppé et al[b] ESBL-PE (+) cases / all visitors to country (%)	Data published by Arcilla et al[c] ESBL-PE (+) cases / all visitors to country (%)
South Africa	49 (12.4)	5/49 (10.2)	0/1 (0.0)	3/66 (4.5)
Swaziland	8 (2.0)	2/8 (25.0)	-	-
Zambia	13 (3.3)	1/13 (7.7)	-	-
Zimbabwe	7 (1.8)	1/7 (14.3)	-	-

There were no travelers to Burundi, Cape Verde, Chad, Equatorial Guinea, Eritrea, Guinea, Libya, Mauritania, Niger, Reunion, Seychelles, Somalia, South Sudan, and Sudan.

[a] The same traveler may have visited several countries.

[b] Only travelers that had visited only one country.

[c] The colonization rates of all individual countries visited were not published.

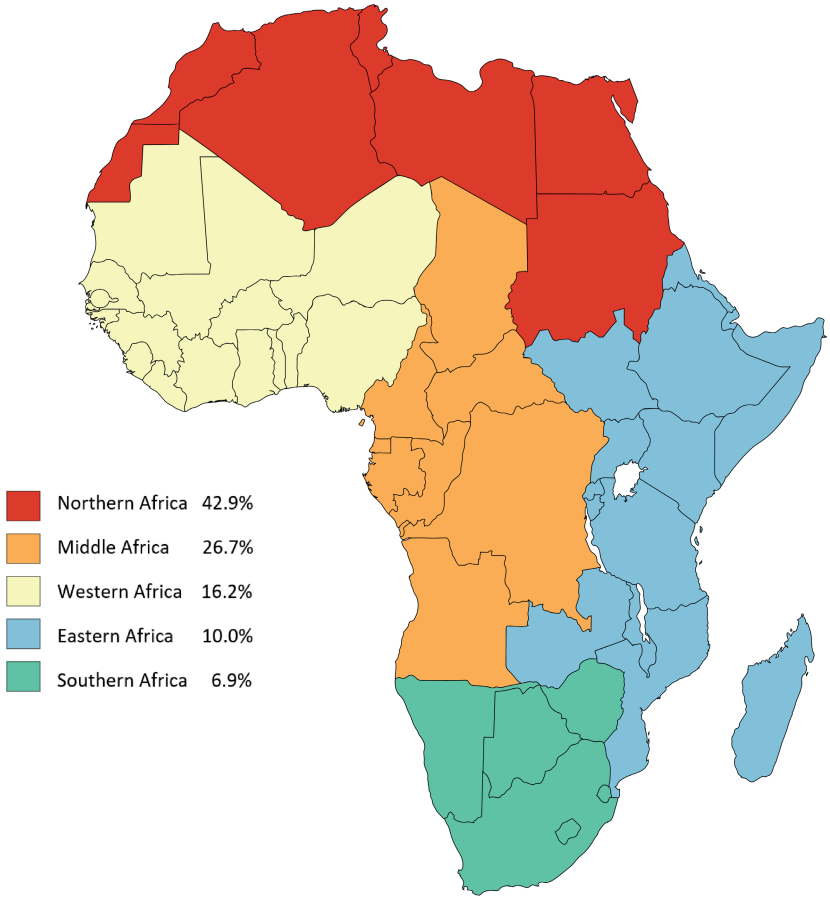


Figure 1 ESBL-PE acquisition rates in five African subregions; joint data on 396 travelers from Finland and the Netherlands (Created with Mapchart.net)

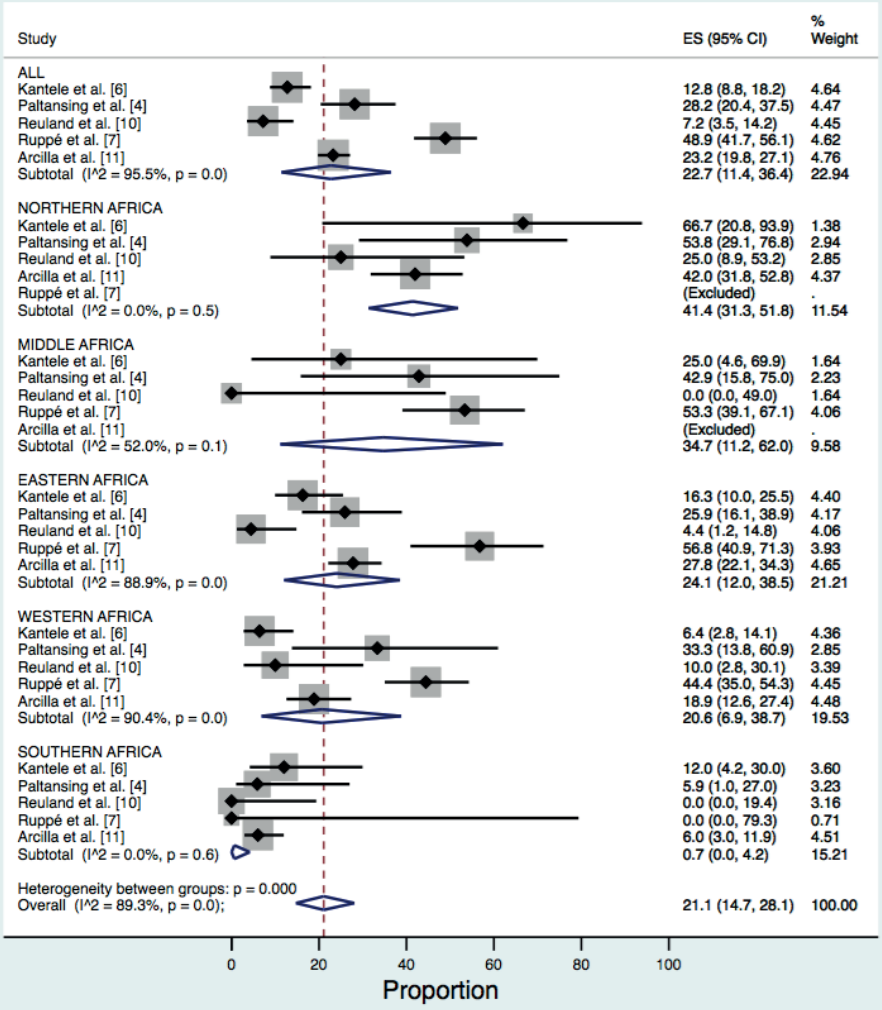
Results of meta-analysis of five studies

Table 4 and forest plot analysis (Figure 2) show the ESBL-PE colonization rates from the three studies pooled [4,6,10], together with investigations by Ruppé et al and Arcilla et al. [7,11] in relation to geographical subregion visited. For Southern and Northern Africa, heterogeneity between the five studies appeared low (I^2=0.0% and 0.0%, respectively), for Middle Africa moderate (I^2 52.0%), and Eastern and Western Africa high (I^2 88.9% and 90.4%, respectively). In the multivariable regression model of our pooled data, the interaction between subregions and the three studies was not found significant at 5% significance level.

Table 4 ESBL-PE colonization rates from the five studies [4,6,7,10,11] in relation to geographical subregion visited

	All	Northern Africa	Middle Africa	Eastern Africa	Western Africa	Southern Africa
Kantele et al [6] **(Finnish study) 2009-2010**						
ESBL-PE (+) among travelers n (% of all visitors to subregion)	25/196 (12.8)	2/3 (66.7)	1/4 (25.0)	14/86 (16.3)	5/78 (6.4)	3/25 (12.0)
Paltansing et al [4] **(Dutch study I) 2011**						
ESBL-PE (+) among travelers n (% of all visitors to subregion)	29/103 (28.2)	7/13 (53.8)	3/7 (42.9)	14/54 (25.9)	4/12 (33.3)	1/17 (5.9)
Reuland et al [10] **(Dutch study II) 2012-2013**						
ESBL-PE (+) among travelers n (% of all visitors to subregion)	7/97 (7.2)	3/12 (25.0)	0/4 (0.0)	2/45 (4.4)	2/20 (10.0)	0/16 (0.0)
Ruppé et al [7]**2012-2013 (**data on travelers visiting only one country)						
ESBL-PE (+) among travelers n (% of all v visitors to subregion)	89/182 (48.9)	N/A	24/45 (53.3)	21/37 (56.8)	44/99 (44.4)	0/1 (0)
Arcilla et al [11]**2012-2013**						
ESBL-PE (+) among travelers n (% of all visitors to subregion)	118/508 (23.2)	34/81 (42.0)	N/A	57/205 (27.8)	20/106 (18.9)	7/116 (6.0)
Combined total: ESBL-PE colonization rates	268/1086 (24.7)	46/109 (42.2)	28/60 (46.7)	108/427 (25.3)	75/315 (23.8)	11/175 (6.3)

Figure 2 Forest plots of ESBL-PE acquisition rates from five studies in relation to geographical subregions. Excluded = no travelers to subregion in study



Discussion

Africa is a continent with increasing numbers of travelers [15]. When pooling subregion- /country-specific data from three traveler studies [4,6,10], we found the risk of contracting ESBL-PE to vary significantly between the various parts of Africa. In addition, comparing our joint data with two recent large reports [7,11] providing subregion- and country-specific data enabled us to investigate the current subregion- and country-specific knowledge about ESBL-PE acquisition by travelers to Africa.

ESBL-PE colonization rates in Northern Africa

Our pooled data showed the highest acquisition rates (12/28; 42.9%) among visitors to Northern Africa, which accords with the results from the study by Arcilla et al (42.0%) [11]; Ruppé et al [7] did not report visitors to this subregion. Similar (43-44%) rates have been reported among Swedish travelers [3,12]. Visitors to Egypt appear to be at particularly high risk; 70.6% (12/17) of our subjects, 80.0% (23/40) of those in a study by Arcilla et al, and 50% (19/38) of those in another by Tham et al became colonized [11,14]. Moreover, all 12 travelers colonized by ESBL-PE in Northern Africa had visited Egypt. It is noteworthy that these proportions are as high as those among travelers to India/South Asia in various investigations [4-8,11]. Bassyouni et al reported carriage rates as low as 21% among healthcare workers in Egypt [17].

ESBL-PE colonization rates in Middle Africa

To our knowledge, only one previous study has reported ESBL-PE acquisition rates among visitors to Middle Africa; Ruppé et al [7] found 53.3% (24/45) of travelers to be colonized. In our pooled data, colonization rates in Middle Africa ranked second (4/15; 26.7%) among the subregions. In nonclinical samples obtained from local populations, carriage rates as high as 59% have been shown among healthy children in the Central African Republic [18], and 44-57% among inpatient carriers, hospital workers and their household members in Cameroon [19].

ESBL-PE rates in Eastern Africa

Colonization rates among travelers to Eastern Africa (30/185; 16.2%) were lower than those reported by Arcilla et al (57/205; 27.8%) [11], Lubbert et al (12/47; 25.5%)

[8], and Ruppé et al (17/29; 56.8%,) [7]. Our moderate colonization rates are supported by findings among local populations: ESBL-PE carriage rates between 11.6% and 16.5% have been reported for healthy community children in Tanzania, [20,21] and 5.3% for locals in Uganda, [22].

ESBL-PE colonization rates in Western Africa

ESBL-PE acquisition rates in Western Africa appear moderately low, but the results differ between studies: our pooled data showed proportions (11/110; 10.0%) close to those presented by Arcilla et al (20/106; 18.9%) [11], while higher rates have been found by Ruppé et al (44/99; 44.4%) [7] and Lubbert et al (5/12; 38.5%) [8] among German travelers to Western and Middle Africa. Moreover, in the research by Frickmann et al, 27.1% (13/48) of European military personnel with diarrhoea in Mali became colonized by ESBL-PE [23]. As for local populations, colonization rates of 22% have been reported for healthy volunteers in Burkina Faso [24] and 33% for healthy community children in Guinea-Bissau [25].

ESBL-PE colonization rates in southern Africa

Our low rates in Southern Africa (4/58; 6.8%) accord with those found by Arcilla et al (7/116; 6.0%)[11] and Lubbert et al (2/18; 11%) [8]. In our pooled data, the vast majority had visited South Africa or Namibia. Consistent with the low ESBL-PE acquisition rates, one study exploring local populations in South Africa reported maternal faecal carriage rates of 4.4% in South Africa [26].

Findings from multivariable analysis

Travelers' diarrhoea

ESBL-PE acquisition rates among those who contracted TD during travel (31/153; 20.3%) were higher than among those without TD (30/243; 12.3%) (AOR 2.1; 95% CI 1.1-4.1). This was expected, since TD was identified as a risk factor in two of the three original studies [6,10] and numerous others [1,3,7,8,11,12].

Antimicrobial medications

Forty-four (11.1%) travelers had taken antimicrobial medications during travel. Of the Finns, 17.3% (34/196) took antibiotics while this proportion was 5.0% (10/200) among the Dutch. In multivariable analyses, fluoroquinolone antibiotics were an

independent risk factor for ESBL-PE colonization (ESBL-PE(+) 40.0%; AOR 4.7; 95% CI 1.5-13.9). Other antibiotic groups did not reach statistical significance in the risk factor analysis, yet the numbers of travelers using each individual antibiotic type were small; eight had taken beta-lactams (ESBL-PE(+) 50.0%; AOR 3.4, CI 0.5-21.9) and 14 other antimicrobials (ESBL-PE(+) 35.7%; AOR 3.8 CI 0.9-14.6). Ruppé et al found beta-lactam usage to predispose to colonization by ESBL-PE (20/25; 80%)[7].

Even though taken by 34 (8.6%) travelers as an antimalarial, doxycycline was not associated with increased ESBL-PE rates (ESBL-PE(+) 5/34; 14.7%; AOR 0.9, 95% CI 0.4-2.5). This finding accords with other studies [7,11]. However, these data do not allow conclusions on the total impact of doxycycline on antimicrobial resistance, as these investigations only analysed the ESBL or CPE feature of the *Enterobacteriaceae*; the potential to select doxycycline-resistant strains in general or other types of multidrug-resistant bacteria was not explored. Indeed, we recently showed that fluoroquinolone intake predisposes selectively to colonization by fluoroquinolone-resistant bacteria [27]. Thus, the effect of doxycycline on other bacteria and travelers' microbiota deserves further research.

Increasing age as risk factor

Increasing age proved an independent risk factor for ESBL-PE colonization in Africa. Only two earlier reports [3,6] have described similar results, as opposed to several others [7,8,11]. Moreover, in one study conducted among returning travelers with diarrhoea, increasing age even appeared protective [28]. The role of age remains unclear. There may be other factors associated with increasing age, such as co-medications / comorbidities or altered immune response not covered in these studies that interfere with the analyses in either direction. As the risk of bacteraemic infections caused by resistant *Enterobacteriaceae* increases with age [29], the risk factors in the older age groups warrant further studies.

Overnight hospitalisation

In our joint data, overnight hospitalisation predisposed to colonization with ESBL-PE. Although numerous retrospective studies have shown high colonization rates by multiresistant bacteria among travelers hospitalized in high-prevalence countries [30-32], to our knowledge, this is the first study to actually show in a prospective setting hospitalisation abroad as a risk factor for ESBL-PE acquisition. In previous

prospective traveller studies, overnight hospitalisations has either not been analysed separately from other health care contacts in the risk factor analyses [7,11] or the proportion of travelers requiring a stay in hospital for treatment has been small or negligible (0-0.5%) [3,8]. In our data, six (1.5% of all subjects) needed overnight hospitalisation.

Travel destination

In multivariable analysis, when compared to Southern Africa, travel to Northern Africa was associated with higher colonization rates. The rates presumably vary between subregions and countries according to the background prevalence of the local populations [33]. They may also depend on several other factors, such as local culture-related food production and preparation habits and hygienic conditions and, of course, whether the traveler contracts TD and takes antibiotics (see above).

Other risk factors

Even though multiresistant *Enterobacteriaceae* have become increasingly prevalent globally [33], colonization rates were not found to increase during the study period (2009-2013). Neither individual studies nor sampling techniques were found statistically significant factors in the multivariable analysis. Travel duration was not seen to be associated with increased risk in univariate or multivariable analysis. This may be explained by a proportion of travelers becoming colonized already on arrival and the carriage resolving while abroad (Professor Kantele, unpublished observation).

Limitations of the study

As the data for the joint risk factor analysis were derived from three separate studies, some data had been collected in differing formats rendering the results incomparable. Moreover, although pooling served to increase the validity and precision of study results, the data remained insufficient in some occasions for analysis in any great detail: In Additional file 1: Table S1, we present the factors available from two out of three studies [4,6]: purpose of travel, diet (omnivore or vegetarian), type of accommodation, use of medications (antidiarrhoeals, proton-pump inhibitors, and antiemetics) and contact with local health care (other than hospitalisation). The five investigations appeared heterogeneous in the forest plot analysis, however, in the

multivariable analysis of the pooled data, the interaction between subregions and studies was not found statistically significant.

Information concerning mild gastrointestinal symptoms in the 'no TD' group was only available for the Finnish volunteers (48.8% of all 'no TD' cases). To pool the three studies, we had to define TD as three or more stools per 24 hours; milder diarrhoea cases were categorised as 'no TD', although even mild TD also may predispose to ESBL-PE acquisition.

Conclusion

ESBL-PE colonization rates in African subregions appear moderate, with the exception of Northern Africa, especially Egypt. Also on this continent, however, TD and antibiotic use increase the risk of individual travelers acquiring ESBL-PE.

Abbreviations

AB: antibiotic; ESBL: Extended-spectrum beta-lactamase; ESBL-PE: Extended-spectrum beta-lactamase-producing *Enterobacteriaceae;* TD: Travelers' diarrhoea

Ethics approval and consent to participate

In all studies, written informed consent was obtained from all participants and the Ethics Committees in the respective organisations approved the study protocols. (METc, NL29769.029.09) of the VU University Medical Centre (NTR Trial ID NTR2453); Ethics Committee of the Department of Medicine in Helsinki University Hospital (406/13/03/01/08); Medical Ethics Committee of the Leiden University Medical Center. (P11.036).

Consent for publication

Not applicable

Availability of data and material

The datasets generated and/or analysed during the current study are not publicly available due to ongoing further analyses on the data but are available from the corresponding author on reasonable request.

Competing interests

TL, JV, APvD, HH, GS, LV, declare no competing interests. AK has received honorary for lectures (Pfizer, MSD, Valneva, Immuron) and membership in advisory board (Valneva), and an investigator-initiated grant (Pfizer), none of these relevant to the current manuscript.

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Authors' contributions

Study concept and design TL, JV, GS, LV, AK; acquisition of data TL, JV, APvD, HH, GS, LV, AK; analysis and interpretation of results TL, JV, AK; drafting of manuscript TL, AK; statistical analysis TL; Critical comments of the manuscript JV, APvD, HH, GS, LV; final approval of version published TL, JV, APvD, HH, GS, LV, AK. All authors have read and approved the manuscript.

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Supplementary data

Additional Table S1 Factors available in same format only from the studies of Kantele et al [6] and Paltansing et al [4] and not included in the pooled data of this report.

	Total n (% of all)	ESBL-PE (+) n (%)	ESBL-PE (-) n (%)	P-value	Univariate OR	95% CI
Antidiarrhoeal medication (information missing: 97; 24.5%)						
None	244 (81.6)	41 (16.8)	203 (83.2)		1.0	
Loperamide	52 (17.4)	12 (23.1)	40 (76.9)	0.286	1.5	0.7-3.1
Other	3 (1.0)	1 (33.3)	2 (66.7)	0.464	2.5	0.2-27.9
PPI/antacid (information missing: 98; 24.7%)						
No	277 (93.0)	50 (18.1)	227 (81.9)		1.0	
PPI	18 (6.0)	4 (22.2)	14 (77.8)	0.658	1.3	0.4-4.1
Other antacid	3 (1.0)	0 (0)	3 (100.0)	0.999	n/a	n/a
Purpose of travel (information missing: 99; 25.0%)						
Holiday	216 (72.7)	38 (17.6)	178 (82.4)		1.0	
Work/business	37 (12.5)	5 (13.5)	32 (86.5)	0.679	0.8	0.3-2.2
Living abroad	14 (4.7)	3 (21.4)	11 (78.6)	0.612	1.4	0.4-5.3
Studying/ volunteering	21 (7.1)	7 (33.3)	14 (66.6)	0.057	2.6	1.0-6.7
VFR	9 (3.0)	4 (44.4)	5 (55.6)	0.041	4.1	1.1-16.2
Antiemetics (information missing: 98; 24.7%)						
No	293 (98.3)	55 (18.8)	238 (81.2)		1.0	
Yes	5 (1.7)	2 (40.0)	3 (60.0)	0.244	2.9	0.5-17.7
Diet (information missing: 164; 41.4%)						
Omnivore	214 (92.2)	49 (22.9)	165 (77.1)		1.0	
Vegetarian	18 (7.8)	2 (11.1)	16 (88.9)	0.247	0.4	0.1-1.9
Health care contact (information missing: 97; 24.5%)						
No	274 (91.6)	50 (18.2)	224 (81.8)		1.0	
Yes	25 (8.4)	7 (28.0)	18 (72.0)	0.235	1.7	0.7-4.4
Accommodation (information missing: 105; 26.5%)						
Hotel	152 (52.2)	23 (15.1)	129 (84.9)		1.0	
Guesthouse / lodge	62 (21.3)	13 (21.0)	49 (79.0)	0.302	1.5	0.7-3.2
With locals / own home	56 (19.2)	10 (17.9)	46 (82.1)	0.634	1.2	0.5-2.8
Other	21 (7.2)	7 (33.3)	14 (66.7)	0.045	2.8	1.0-7.7

PART III

Discussion and summary

8

Summary and general discussion

In order to provide travelers with an adequate pre-travel consultation, it is important that the traveler is well-informed with tailored information about their travel plans and associated (health) risks.[1] However, these risks are often not well known. Therefore, the overall aim of the research described in this thesis was to obtain more insight in the occurrence of health problems during and post-travel and associated inconvenience in specific groups of Dutch travelers. In this chapter the main findings of the included studies are summarized, and the study findings and future perspectives are discussed.

Part I: health problems and (risk) behavior

In **chapter 2 to 5** of this thesis, health risks and (risk) behavior in specific groups of Dutch travelers were evaluated.

Chapter 2 of this thesis describes a large retrospective study that explored the disease burden in over 77,000 Dutch travelers who received hospital-based care abroad or who died before reaching the hospital, over a 5-year period. Data were collected from three medical assistance centers (MACs) based in the Netherlands and the Dutch Ministry of Foreign Affairs. Diagnoses were classified according to the Global Burden of Disease (GBD) tool based on the International Classification of Diseases (ICD).

The MACs registered 75,385 medical consultations. The median age of travelers was 56 years. Most consultations occurred in Europe (e.g. France and Spain) and Asia (e.g. Thailand and Turkey). Four in five travelers received inpatient care, of which 36% concerned older travelers (65+) who had significantly longer hospital stays. For inpatient care the top five were injuries, cardiovascular diseases, digestive system diseases, enteric, and respiratory infections. This was slightly different in outpatients resulting in the following top five: injuries, enteric infections, cardiovascular diseases, digestive system diseases and other non-communicable diseases (e.g. such as urinary tract infections). One out of five travelers who received medical assistance was repatriated back home, mostly on a scheduled flight with or without medical escort. In cases of death, cardiovascular diseases (e.g. cardiac arrest, myocardial infarction) and injuries (mostly following road traffic accidents or accidental falls) were the leading causes.

To conclude, the data in this study provide an estimate of the incidence proportion of a variety of more serious health problems experienced by Dutch travelers abroad for which hospital-based care is required. This study showed that injuries and non-communicable diseases (e.g. cardiovascular disease) accounts for half of the inpatient cases and have a large influence on travelers health and travel plans, whilst this is less often the case for 'classical' infectious diseases such as respiratory tract - and enteric infections (16%).

Chapter 3 comprehends a prospective cohort study evaluating the degree of inconvenience of travelers' diarrhea (TD) in 390 adult travelers who stayed in the (sub)tropics for a short-term stay. The median duration of travel was 23 days. Two out of five travelers reported TD; it was often self-limiting (median duration 2.5 days). The majority could conduct their program as planned despite the diarrhea. Major inconvenience was reported in travelers with more severe additional symptoms (e.g. fever, vomiting), who required some kind of treatment and had the necessity to alter their activity program. Few travelers (5%) consulted a local physician for the diarrheal complaints, of which two travelers in Africa were hospitalized. An antibiotic was used by a small proportion of our Dutch travelers (9%). Despite the low number, this was still almost twice as many as the study of Belderok et al. reported. [2] Staying in luxury hotels increased the odds for contracting TD, while business travelers or visiting friends and relatives had reduced odds. By taking the degree of inconvenience caused by TD into account, researchers and policy makers may be able to better distinguish 'significant TD' from mild TD. This allows for a more precise sample size estimate of the target population for future studies on vaccination or stand-by antibiotic treatment and of the benefit of these interventions.

Chapter 4 describes a prospective cohort study in which we assessed pre-travel advice, health risks and post-travel care in 479 Dutch and Belgian medical students during an elective in low- and middle-income countries. Students were recruited from three Dutch and two Belgian universities. The majority (93%) obtained pre-travel health and safety advice. Belgian students stayed abroad longer than Dutch, and both groups lived mostly in good quality accommodations with access to running water, a refrigerator and internet connection. Especially students in Central America and Africa experienced culture shock. Half of all students encountered difficulties in adapting to local culture, although most felt accepted by the local population.

Almost 40% visited malaria endemic countries; nearly all (87%) used chemoprophylaxis as prescribed. Needle-stick or splash injuries were reported by 7% of all students. All were adequately dealt with in accordance with national guidelines (i.e. source testing and/or starting PEP). However, an additional 5% reported a possible needle-stick or splash injury and in this group just under half dealt with it adequately. A small part of the students had unprotected sex with a new partner (2.5%). A few students (3%) sustained minor injury from a traffic accident. However, one in five students suffered from an injury obtained during leisure activities. Some students (5%) experienced intimidation, were threatened or experienced physical violence, mostly outside the workplace and mainly in Africa and South America.

TD was the most common health problem reported (46%), with highest incidences in Africa, South America and Asia. A local physician was rarely consulted; two students were hospitalized. Many students experienced moderate inconvenience due to the TD complaints (e.g. confined to the accommodation, changing planned activities). One third of all students carried prescribed antibiotics; especially by Belgian students (80% versus 18%). One in five Belgian travelers used it, compared to one in ten Dutch students. Half of the antibiotics were used for gastrointestinal complaints.

In most universities post-travel screening for tuberculosis and schistosomiasis was lacking, probably because a post-travel consult is not part in routine care. Only half of the students visiting a highly endemic country were screened for tuberculosis and this was more commonly done in Dutch than Belgian students. In both groups, student willingness for methicillin-resistant Staphylococcus aureus (MRSA) and schistosomiasis screening was lower than in tuberculosis screening (45% and 6% respectively). Unfortunately, the post-travel screening appeared to be still on a similar, limited, level as reported in the earlier study among Dutch medical students. [3] Based on our results, we concluded that the Dutch and Belgian pre- and post-travel educational program thus require an update including a centrally organized post-travel health check. Several recommendations were therefore provided.

In **chapter 5**, we aimed to identify predictors related to the occurrence of travel-related morbidity in 477 older travelers (≥60 years) during their tropical travel

and shortly after. Pre-travel performance was evaluated using physical and cognitive functioning tests and the incidence, duration and inconvenience of travel-related morbidity was determined through questionnaires. For this prospective multicenter study, travelers were recruited during regular pre-travel visits at four travel clinics in the Netherlands. Hand grip strength, cognitive performance and the comorbidity burden appeared to be worse in travelers aged ≥70 years.

Cardiovascular diseases (mainly hypertension), malignancies and skin diseases where the most reported pre-existing conditions. Polypharmacy (≥ 5 medications per day) was uncommon (16%), with higher numbers (24%) in travelers aged ≥70 years. Self-reported travel-related infectious diseases concerned primarily respiratory tract infections (RTI) and gastroenteritis (GE); a similar pattern was seen in the study described in **chapter 2**. Non-infectious complaints were injuries, peripheral edema and dehydration. Antibiotics were not often used (6%) and were mainly used in travelers with a RTI or GE. Inconvenience was experienced by half of the travelers with GE and one third of the travelers with a RTI. Medical assistance was sought by 18%, mostly post-travel from their general practitioner. Five travelers were hospitalized post-travel, none during travel. Despite the presence of comorbidities in 40% of travelers, exacerbations of pre-existent conditions were reported in only 5%. A higher comorbidity burden (using the Charlson Comorbidity Index) and the use of more daily medication were associated with a higher travel-related morbidity.

We concluded that older Dutch travelers were generally experienced and well-educated, physically and mentally fit with little (co)morbidity or polypharmacy and well-connected to the digital world of internet and social media. They suffered not only from common infectious health problems, but also from injuries. However, traveling to tropical destinations did not only entail morbidity for the older traveler, but can positively affect both their mental and physical well-being. The following predictors could be used to identify the more at-risk older traveler and to decrease travel-related morbidity by optimizing pre-travel advice. Most of these will be easy to assess since they are part of the current pre-travel consultation (destination, duration, and travel experience) or could easily be assessed at that specific moment (educational level, phone and social media use and CCI score). Age was not identified as an independent predictor.

Part II: travel and antimicrobial resistance

In **chapter 6 and 7** of this thesis, antimicrobial resistance in international travelers were evaluated.

Over the years, studies described the prominent role of international travel in the spread of antimicrobial-resistant bacteria around the globe. In our prospective cohort study described in **chapter 6**, we included 370 adult Dutch travelers at the travel clinic of the LUMC and the Hollands Midden Municipal Health Services to investigate the acquisition of carbapenemase-producing *Enterobacteriaceae* (CP-E) and extended-spectrum ß-lactamase producing *Enterobacteriaceae* (ESBL-E) and associated risk factors. The median duration of travel was 21 days, mostly for leisure purposes. A small proportion (9%) was already positive before travel. A third of the travelers had a newly-acquired ESBL-E. This finding was subsequently confirmed in a later and larger Dutch study. [4] No CP-E were found. One in six travelers (17%) was still colonized six months after return. The highest acquisition rates were in travelers visiting South Asia (73%) and East Asia (67%). These are also the only identified risk factors for the acquisition of ESBL-E after foreign travel in our study. This was surprising as several other studies identified additional risk factors such as TD [5] and antibiotic use. [4-12] This can probably be explained by the relatively limited sample size in our study and the very strict policy regarding the prescription of antibiotics in the Netherlands for many years resulting in the lowest rate of antibiotic use within Europe. Correct use of antibiotics and only when it is really necessary is important to prevent antibiotic resistance. [13] This is also reflected in our study as antibiotic use during travel was low (6%).

Some studies indicated foreign hospitalization as a risk factor for the carriage of resistant organisms to the home country. [14-16] Luckily, none of our travelers were admitted to a hospital abroad. Following the results of our study, we recommended active surveillance for ESBL-E and CP-E when patients are admitted to a hospital and if they traveled to Asia in the past six months.

In **chapter 7**, part of our data (n=103) described in **chapter 6** were pooled with two other prospective studies of Finnish travelers (n=196) and another group of Dutch travelers (n=97). Our aim was to assess the colonization rates of ESBL-E and associated risk factors in travelers to Africa as the travelers number to these

destinations were increasing. Eastern (47%) and Western Africa (28%) were the most popular regions; 23 travelers (6%) visited more than one subregion in Africa. The median duration of travel was 19 days. The 396 included travelers provided pre- and post-travel stool samples/rectal swabs: 15% became colonized by ESBL-E; one traveler to Egypt became colonized by CP-E. The top three highest acquisition rates were in travelers visiting Northern Africa, followed by Middle Africa and Eastern Africa. The rates of Egypt were comparable to those reported in South and Southeast Asia. Of the total study population, 44 travelers (11%) used an antibiotic, of which 17 acquired an ESBL-E. This is three times higher than the colonization rate among travelers who did not use an antibiotic (13%). More Finnish than Dutch used an antibiotic (34/196, 17% versus 10/200, 5%). ESBL-E colonization rates among travelers experiencing TD during travel (20%) were higher than among those who did not (12%). Although only six travelers required admission to a hospital, 67% of them acquired an ESBL-E. Multivariable analysis demonstrated travel to Northern Africa, overnight hospitalization abroad, age, TD, and use of fluoroquinolones as risk factors for acquiring and ESBL-E. We concluded that ESBL-E colonization rates in travelers to Africa appeared to be moderate, except for travelers to Egypt who were at a high risk of becoming colonized.

Part III: discussion and summary

In the pre-covid era foreign travel to (sub)tropical areas was very popular among international travelers, including Dutch travelers. However, international travel almost completely came to a halt due to the COVID-19 pandemic starting in Wuhan, China in December 2019. This disease of the respiratory tract is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is easily transmitted by inhalation of air with contaminated droplets and droplet nuclei. International tourism was one of the most affected sectors: tourist arrivals declined with 71-73% throughout 2020 and 2021. [17] Worldwide millions of people became infected with COVID-19. According to the COVID-19 dashboard by the Center for Systems Science and Engineering (CSSE) at John Hopkins University there were over 531 million cases reported globally of which around 6.3 million deaths until the beginning of June 2022. The top five countries with the highest numbers of deaths per 100,000

inhabitants (i.e. country's general population including confirmed COVID-19 cases and healthy people) were Brazil, United States of America, Greece, Italy and the United Kingdom.[18] This pandemic not only showed that travel was one of the main drivers of the global spread, but also that travel is associated with an increased risk of acquiring (infectious) diseases.

Pre-travel consult assessment and risk perception

General travel advice

The starting point of traveling to (sub)tropical areas is a proper preparation: checking health- and travel insurance, scheduling a pre-travel consultation at a travel clinic or municipal health service for a travel health advice and, if needed, vaccinations. To enhance the effectiveness of a travel health consult it is important to know how travelers perceive risks. [19] Zimmermann et al. compared the risk perception of Swiss travelers with that of travel health experts before the pre-travel consultation and within 2-4 weeks after returning home. Topics included were rabies, mosquitoes, malaria, sexually transmitted infections (STIs), terrorist attacks, accidents, epidemic outbreaks and side effects after vaccination. The overall risk perception in both groups was quite similar, except for STIs and accidents which were rated less risky by travelers. Accidents was the only risk category that travelers ranked higher after return, whilst mosquito-borne diseases (e.g. malaria) were perceived as lower after return. Therefore, travel health providers should be aware of the differences in risk perception between the traveler and health care professional during the pre-travel consult. [20] Tardivo et al. advised that training of the travel health provider to assess risk perceptions of the traveler may lead to better adherence to preventive health measures and adaptation of risk-taking behavior through better tailored advice. [21] Flaherty underlines that travel medicine is not a "one size fits all" business as most travel risks depends on risky behavior of the traveler and are not vaccine-preventable. [22]

Travel advice for (medical) students

A specific group of Dutch travelers are the students traveling internationally for a medical elective for whom a tailored pre-travel preparation is needed. Besides discussing elective-specific risks during a pre-travel consult, students should also be

aware of other potential health risks associated with the psychological wellbeing, local road safety, performing risky behavior (e.g. diving, swimming alone, exposure to blood-borne viruses, sexual contacts), criminal injury (e.g. robbery, physical- or sexual violence). The numbers of (physical) violence in our study in **chapter 4** are lower than reported by Pedersen et al. [23, 24]: one in five American college students studying abroad reported any form of sexual violence by a local resident, mostly unwanted contacts by a male. Remarkably, alcohol was involved in about 80% of the sexual violence situations. It is also worrisome that two-thirds of the incidents in the American students occurred after the first four weeks abroad.

In addition, cultural awareness is important; speaking a little bit of the local language, and knowing the local social norms (e.g. appropriate dressing). [25, 26]

In order to facilitate the suggested tailored pre-travel advice for students, the international office of the LUMC in Leiden, the Netherlands has developed in 2018 a brochure for all electives abroad, not only for medical students but also for biomedical, pharmaceutical and vitality & ageing students in Leiden, the Netherlands. This brochure was handed out to students, after the inclusion period of the study described in **chapter 4.** This brochure includes tips and tricks for finding an internship, for which part of the curriculum it will be (e.g. bachelor or master), if the facilities of the selected internship meet the academic requirements and what steps have to be taken to arrange the internship itself, and general preparation tips (e.g. arranging local accommodation, contact predecessors, schedule a pre-travel advice, monitoring safety level at the destination via the Ministry of Foreign Affairs of the Netherlands, financial tips and tricks such as applying for a scholarship). Also contact details and instructions what to do in case of a needle-stick injury or other health or supervision problems during the internships are summarized. Also e-learnings are offered: the “Buitenland oriëntatie en onderwijs momenten (BOOM), e-learning “health risks while abroad” and the online Coursera course “Essentials of Global Health”. In addition to the current pre-travel Global Health courses for medical students who are planning an elective abroad, Storz et al. advises that students should also be provided with support for possible conflict situations, for example when a medical student is ‘asked’ to execute the role of qualified physician when there are insufficient trained staff members in the local clinic. It must keep in mind that the elective is a teaching opportunity and appropriate supervision and support

should be present. [27] For the university of the medical student it is therefore important to have not only close contact with the local clinic, but also to actually visit the facilities. Especially if it concerns a new clinic in the collaboration network of the specific university (personal communication, Evelien Hack, international office of the LUMC). It is advisable to have more empathy for the 'world' in which students live and work, to better understand their choices and their vision on conducting a medical elective abroad. More research is therefore needed in this specific group of young travelers.

Travel-related health problems

Travelers' diarrhea

Gastrointestinal health problems often emerge in studies investigating travel-related morbidity in travelers. It can occur anywhere, but most often when visiting low- or middle-income (LOMIC) countries in Asia and Africa. Experiencing TD in a high-risk area within the past year seems to have a protective effect for TD during a new trip. [28] Not routinely washing hands after toilet use, eating street food, young age, and trip duration were other risk factors identified. [29, 30]

The difficulty of labelling TD lies in the definition that is used. Traditional TD is defined as the passage of three or more unformed stools during a 24-h period with at least one additional symptom such as nausea, abdominal cramps, vomiting, fever or fecal urgency. [31] In **chapter 3**, **4** and **6** we used a broader definition: the passage of three or more unformed stools per 24 hours with or without additional symptoms (e.g. abdominal cramps, nausea, vomiting or fever). When analyzing the pooled data of three studies in **chapter 7** we noticed that even then different definitions were used. Thus, for analyzing purposes TD was broader defined: three or more loose or liquid stools per day. Lääveri et al. dealt with the same problem and explored their data of almost 400 travelers using the classical TD definition (i.e. ≥3 loose or liquid stools/day with or without additional symptoms) and the WHO definition (i.e. any number of diarrheal stools that is more frequent than normal for the individual). They reported that the difference mostly occurs in travelers with mild symptoms labeling them only as TD case when the WHO definition is used. As a result: 37% of the cases match the classical TD definition, whilst this is 65% for the WHO definition. [32] As mentioned in **chapter 3** it is therefore advisable to also taken into account the degree of inconvenience (i.e. mild, moderate, sever) in addition to the occurrence

of TD and associated symptoms when investigation TD in travelers and considering prescribing stand-by antibiotic treatment in view of the worldwide problem considering antimicrobial resistance. In this way, researchers and policy makers will be able to better distinguish 'significant TD' from mild TD, thus allowing for a more precise estimation of the number of travelers who are eligible for stand-by antibiotic prescriptions or vaccination and of the benefit of such preventive measures. This statement is supported by Belderok et al. [2] According to the Centers for Disease Control and Prevention (CDC), antibiotics can be used in persons with moderate TD, while it should be used in severe TD cases. For mild TD loperamide or bismuth subsalicylate (BSS) can be considered. [33] For some type of travelers, such as those using immunosuppressive medication or with inflammatory bowel disease, a prescribed stand-by antibiotic for self-treatment in case of TD is advisable. [34]

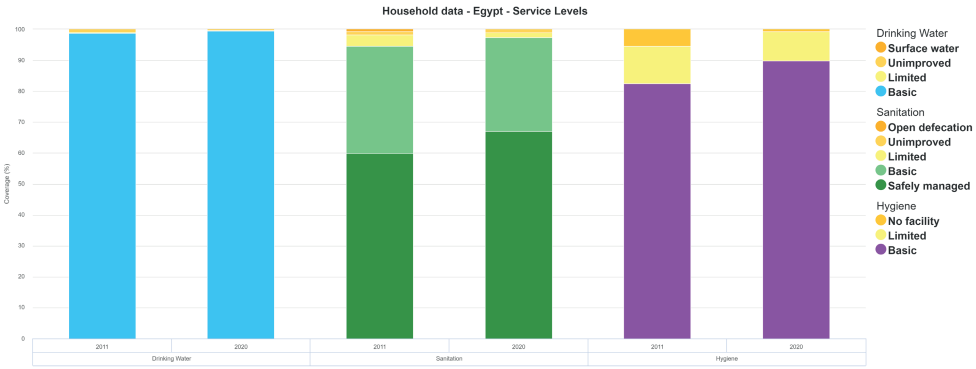
Extended-spectrum ß-lactamase producing Enterobacteriaceae (ESBL-E)

Since the study described in **chapter 6**, more research has been done concerning the global public health concern of antimicrobial resistance. Pre-travel ESBL-E carriage rates in travelers differ between 1-11% in a ten-year period between 2009-2019 [4, 8, 9, 11, 35-38]. Comparable colonization rates post-travel (20-58%) were found [8, 9, 11, 37, 39], as well as the risk factors travel destination [8, 9, 40] (especially India and Vietnam in the South East Asia region), antibiotic use [7, 8, 10, 40] and suffering from TD [4, 5, 7, 8, 10, 11, 37, 40-42]. Similar ESBL-E rates (29%) were found among almost 400 French medical students, who are traveling mostly for humanitarian missions (acquisition rate 34%) or for a clinical internship in a local hospital (acquisition rate 12%). South Asia (41%), South-East Asia (40%), and Africa (25%) were the continents with the highest acquisition rates. [36] No association was found between patient-related work and acquisition of an ESBL-E. [8] A study in second year medical students in Indonesia revealed a high EBSL-E carriage rate of 56%, in which colonization could have occurred during their contact with medical personnel when practicing medical skills in the hospital or from the community (such as contaminated river water) [43]. So far newly-acquired CP-E have rarely been reported in travelers, and if so mainly in travelers returning from Asia (e.g. India). [10, 36, 44-47]. A global challenge are over-the-counter antibiotics wherefore no prescription is needed, also in European countries (e.g. Cyprus, Greece, Romania). [48] According to Auta et al. this group of antibiotics are mostly purchased for acute

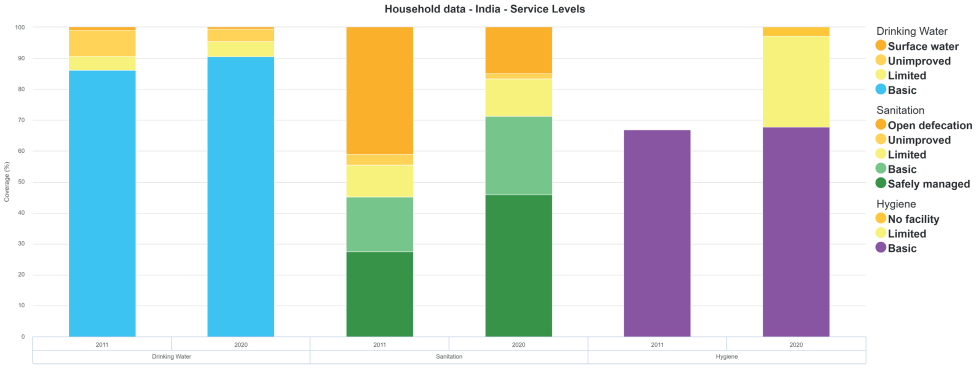
and self-limiting illness (e.g. upper respiratory tract infection, urinary tract infection or gastrointestinal complaints) in South America and Asia. Interestingly, pharmacists in Thailand are legally allowed to provide some type of antibiotics without the need of a prescription. [49]

Transmission between an ESBL-E positive traveler and their household contact(s) could not be properly examined in **chapter 6** due to limited number of participants. Arcilla et al. estimated a transmission probability of 12% within households of colonized travelers. [4] This transmission probability appeared to be more frequent (67%) in recently discharged ESBL-E positive hospitalized patients and their household members. [50] Riccio et al. identified providing assistance for fecal and urinary excretion as a risk factor for ESBL-E transmission between discharged patients and household contacts [51]. Proper hand hygiene in 'risky' situations (e.g. after using toilet, before meals) and restricting of antibiotics could be effective measures to reduce transmission within a household. [52] However, the evidence regarding the protective effect of hand hygiene during travel is scare and ambivalent. [4, 9]

Since 1990, the World Health Organization (WHO) and UNICEF have a shared monitoring program that reports global estimates of progress on drinking water (i.e. accessibility, availability and quality of the water for cooking, personal hygiene, drinking in households), sanitation (i.e. management of produced excreta) and hygiene (i.e. food hygiene, hand washing and menstrual hygiene management) [WASH]. [53] These three pillars play an important role in the infectious diseases burden and therefore also in the spread of multiresistant bacteria through the fecal-oral route. The antibiotics that are used by people can contaminate the environment- and subsequently food and drinking water. [54] The ESBL-E data described in **Chapter 6** and **7** were collected in 2011 and India and Egypt were one of the countries with high acquisition rates. Figure 1 gives an overview of the improvements that occurred in both countries during the past decade, especially concerning sanitation and hygiene. It is sobering to see that in 2011 in India almost half (40%) of the sanitation pillar belonged to open defecation; in 2020 this was reduced to 15%.



A.



B.

Figure 1. Progress on household drinking, sanitation and hygiene between 2011 and 2020 in India (A) and Egypt (B). Data were adopted from https://washdata.org/data/household#!/

Drinking water: surface water = drinking water directly from a lake, river dam, pond, stream, (irrigation) canal; unimproved = drinking water from an unprotected spring or dug well; basic = drinking water from an improved source and provided collection time ≤30 minutes for a roundtrip including queuing.

Sanitation: basic = availability of a handwashing facility with soap and water at home; limited = availability of handwashing facility lacking soap and/or water at home; no facility = no handwashing facility on premises.

Hygiene: safely managed = use of improved facilities that are not shared with other households and where excreta are safely disposed of in situ or removed and treated offsite; basic = the use of improved facilities which are not shared with other households; limited = use of improved facilities shared between ≥2 households; unimproved = use of pit latrines without a platform or slab, hanging latrines or bucket latrines; open defecation = disposal of human feces in forests, fields, open water, bushes, beaches or other open space or with solid waste.

Strengths and limitations

Strengths

A wide range of studies among Dutch travelers are investigated in this thesis and several strengths are worth mentioning. First, a major strength for all cohort studies is that we were able to include large numbers of travelers leading to large datasets; for some studies this was achieved through an intensive cooperation with participating centers. Therefore, it was possible to perform subgroup-analysis e.g. based on age (**chapter 5**) or university (Dutch and Belgian, **chapter 4**). Second, we had high follow-up rates lying between 84% - 97%. Third, we did not only investigate Dutch travelers in general, but also tailored studies on specific groups such as medical students and older travelers. This allowed us to provide a good overview and make practical recommendations in these specific patient groups. For example, in **chapter 5** 'young' older travelers were included so they can be compared with travelers aged 70 and above. We believe that this is a more real comparison than with younger travelers around 30-40 years of age as done in previous studies. [55-58] Lastly, except for the study described in **chapter 2**, we were able to include travelers before departure which increases the generalizability and minimalizing selection and recall bias. As a result, the traveler's perception could be measured both before- and after travel for several topics, such as risk behavior.

Limitations

There are also some limitations that should be discussed. First, several studies in this thesis are cohort studies. Disadvantages of such study design in general are recruitment bias, drop-outs ("lost to follow up") of participants leading to over- or underestimations, and difficulties confirming diagnoses for illness that occur during travel. [59] However, we were fortunate to realize high follow-up rates in our studies. Second, due to the retrospective design of the study in **chapter 2**, the findings will be skewed towards more serious health conditions for which hospital-based care is required and are therefore not representative of the most common health problems in travelers abroad as most illnesses are self-limiting and medical help is not necessary. We were unable to demonstrate possible causality, which is a known effect of using a retrospective study design. Third, especially in the studies from **chapters 4** and **5** we investigated a large variety of (health) topics, but some topics could have been questioned more in depth (e.g. [exacerbation of] musculoskeletal

complaints in older adults or sexual contacts by medical students while abroad) in order to have a more complete overview. However, this was not done due to feasibility aspects as the questionnaires were already quite extensive and we wanted to minimalize the risk of dropout. Fourth, the results in **chapter 5** can be subject to 'healthy traveler bias', meaning that the older travelers might not be completely representative for the general older Dutch population. In addition, only travelers to (sub)tropical destinations were included, whilst many older travelers also frequently travel to European countries. Lastly, although more than 300 travelers were included in the study described in **chapter 6**, the number of colonized travelers with ESBL-E, and travelers using an antibiotic during travel were limited, whereby frequently reported risk factors in literature could not be identified by us (e.g. antibiotic use and occurrence of TD). Also the percentage of TD was comparable between colonized and non-colonized travelers. In addition, differences in colonization rates among travelers described in **chapter 6** may be influenced by the method of sampling: rectal swab versus stool sample. However, according to Kotar et al. rectal swabs can indeed be used when rapid diagnostic results are needed or when the a stool sample ('golden standard') is unavailable. [60] In several other studies investigating ESBL-E acquisition rates in travelers it is however not always clear which method is used. Schaumburg et al. for example report that stool samples were collected using a faecal transwab® that is directly usable as rectal swab. [38] The most important aspect when using self-collected rectal swabs is providing proper instructions (i.e. presence of visible fecal material on the swab). [61] For the study in **chapter 6** travelers were instructed to rub a cotton swab between the buttocks through the stool that is present after defecation, before using toilet paper to clean it. The swab was then placed in the provided Stuart transport medium.

Recommendations for future research

Chapter 2 and **5** demonstrated that more and more older people are traveling around the globe, also to European countries close to their home country the Netherlands. In most studies older travelers are defined as persons aged 65 years and above. Based on the study described in **chapter 5** we believe that the definition of an older traveler should be revised and can be shifted to 70 years and over based on the findings in **chapter 2** and **5**. In **chapter 2** we found that 65% of the 25,646

travelers aged 65 and above who required medical assistance by a medical assistance center, concerned travelers ≥70 years. In **chapter 5**, almost one third of the study population were travelers aged 70 and over, and this age group used more medications per day, scored worse on the Charlson Comorbidity Index, and had a lower grip strength than travelers aged between 60-69 years.

Data collection in the studies described in this thesis are primarily executed using an existing database system (**chapter 2**), via web-based surveys (**chapter 3, 4 and 6**) or on paper (**chapter 5**). For future research it is of interest to investigate the use of mobile applications on smartphones through which health problems and risk behavior abroad can be evaluated. During the years several researchers developed mobile applications for smartphones to investigate real-time incidences of health problems and risk behavior (e.g. conducting adventurous sports, using alcohol/ drugs, road traffic safety) when people are traveling abroad. For instance, Swiss researchers investigating the use and efficacy of so-called 'mobile health' (mHealth) in their TOURIST 1 and TOURIST2 studies in order to profile destination-specific risks, give more tailored pre-travel information for future (Swiss) travelers and minimize the risk of recall bias in studies collecting only pre- and post-travel data. Their focus was not only on infectious diseases, but also the influence of travelling on mental health of the traveler, accidents or injuries and risky behavior (e.g. contact with animals). Data of travelers were collected by a) a short daily health questionnaire for which a pop-up was included in the app as a reminder; and b) environmental data via the application using GPS every 15 minutes, including data concerning the local weather conditions. All participants were also provided with a SIM card for local internet access ensuring accurate collection of requested data. [62-65] A remarkable finding in their first study was that travelers do perform risk behavior during travel, suggesting that their received pre-travel advice is commonly ignored. [66] Rodriguez et al. developed another app monitoring the daily health status of travelers at a predetermined time. They also offered the opportunity to have remote contact with the study physician when reporting health problems and the app was used as a reminder for malaria prophylaxis when indicated pre-travel by the study physician. [67] Using mHealth in travel medicine also brings numerous challenges: ethical, confidentiality and connectivity issues, but also the huge amount of data that is generated per traveler. [63]

In addition, telemedicine (i.e. practice of medicine using technology such as computers, phones, videos, to provide care to patients in a remote location) in health care settings in the Netherlands has increased exponentially during the COVID-19 pandemic. Using telemedicine for individual travelers in remote areas appears to be a useful tool. Rochat et al. investigated the interest for this method among Swiss travelers. Most travelers rated communication by e-mail as most prominent method for having contact with a specialized center when facing a health problem, followed by a phone and video call. Travelers were also willing to pay for it. [68] It is worth investigating if these possibilities can be of added value for the current pre-travel advices at travel clinics and MHSs in the Netherlands and also how this could be possibly implemented in Dutch travel health care.

Conclusions

Taken together, the results described in this thesis expand and deepen the knowledge of the disease burden that several groups of Dutch travelers can face while traveling abroad, varying from young medical students to the older traveler. The different studies provide more insights and practical advices regarding pre-travel information, which attributes both to practical tailored travel advice for Dutch travelers and will also be of interest for future research in the evolving world of travel medicine.

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9

Nederlandse samenvatting

Veel mensen reizen over de wereld, ongeacht hun leeftijd, gezondheid of reisdoel. In Nederland zijn in 2016 maar liefst 35 miljoen vakanties geregistreerd, waarvan 51% met een buitenlandse bestemming. In 2019 liep dit aantal op naar 41 miljoen, met bijna 23 miljoen reizen naar het buitenland.

Tijdens hun verblijf in het buitenland kunnen reizigers te maken krijgen met uiteenlopende, reisgerelateerde gezondheidsproblemen. Deze variëren van verwondingen tot infecties, psychische klachten of verergering van een reeds bestaande aandoening. In een retrospectief onderzoek (2013) lieten Nederlandse huisartsen zien dat één op de vijf Nederlandse reizigers tijdens de reis te maken kreeg met klachten over hun gezondheid.

In Nederland kunnen reizigers een afspraak maken voor een persoonlijk advies over preventieve maatregelen en vaccinaties bij een reizigersconsulent van een vaccinatiebureau of huisarts in verband met hun geplande reis naar (sub)tropische gebieden. Dit wordt bij voorkeur 4-6 weken voor vertrek geregeld. De gebruikte adviezen worden opgesteld aan de hand van de richtlijnen van het Landelijk Coördinatiecentrum Reizigersadvisering (LCR). De reizigersconsulent streeft ernaar om reizigers voor te lichten aan de hand van gepersonaliseerde en gemakkelijk te begrijpen informatie over mogelijke gezondheidsrisico's. Op die manier kunnen reizigers een weloverwogen beslissing nemen om de gegeven adviezen op te volgen. De mate waarin dit gebeurt is afhankelijk van de manier van communiceren tijdens het reizigersconsult en de inschatting van de reiziger zelf of het advies op hem/haar van toepassing is. Om de informatieoverdracht zo helder mogelijk te maken, wordt vaak gebruik gemaakt van (visuele) hulpmiddelen zoals wereldkaarten waarop malaria-gebieden zijn aangegeven en het meegeven van schriftelijke informatie over een specifiek onderwerp. Om het meest optimale, gepersonaliseerde reisadvies mogelijk te maken is het van belang dat de reiziger hiervoor een aantal documenten meeneemt: de reisroute, een medicijnoverzicht (indien van toepassing) en het vaccinatiepaspoort ('het gele boekje').

Zoals eerder aangegeven, is het van belang dat de reiziger goed geïnformeerd wordt over (mogelijke) gezondheidsrisico's tijdens de reis. Hoe groot die risico's precies zijn is echter vaak niet goed bekend. Het doel van dit proefschrift is daarom om meer inzicht te krijgen in hoe vaak gezondheidsklachten in specifieke groepen van Nederlandse reizigers optreden tijdens en na een reis en wat het mogelijk

ongemak daarvan is. Om deze vragen te beantwoorden en aanbevelingen te kunnen doen voor verbeteringen van het reisadvies, zijn diverse studies opgezet waarin reizigers rondom hun reis zijn gevolgd. De resultaten daarvan vormen dit proefschrift en de hoofdbevindingen van iedere studie worden hieronder verder besproken.

Hoofdbevindingen

In **hoofdstuk 2** tot en met **hoofdstuk 5** wordt het verschil tussen gezondheidsrisico's, (risico)gedrag en gezondheidsproblemen bij bepaalde groepen Nederlandse reizigers beschreven.

Hoofdstuk 2 beschrijft een studie waarvoor een omvangrijke database werd opgezet met de gecodeerde gegevens van drie alarmcentrales die een kantoor in Nederland hebben: Eurocross Assistance, ANWB Alarmcentrale en SOS International. Gegevens van ruim 77.000 Nederlanders die tussen 2010 en 2014 medische hulp hadden ontvangen in een buitenlands ziekenhuis, zowel binnen als buiten Europa, zijn verkregen. De medische hulp had zowel betrekking op spoedeisende hulp ("outpatient care") als een ziekenhuisopname ("inpatient care"). Tevens is informatie verzameld over Nederlanders die in het buitenland waren overleden, zonder dat zij medische hulp hadden gekregen. Om een zo compleet mogelijk beeld te krijgen, zijn ook gegevens van 2013-2014 van het Ministerie van Buitenlandse Zaken gebruikt. Het zijn gegevens van Nederlandse reizigers die onder bijzondere omstandigheden waren overleden in het buitenland. Dit alles had tot doel om de ziektelast onder reizigers in kaart te brengen. De studie liet zien dat vier van de vijf reizigers die medische hulp nodig hadden, werden opgenomen in een ziekenhuis, bijna 40% hiervan waren oudere reizigers (65+). De opnameduur van deze groep reizigers was aanmerkelijk langer dan bij jongere reizigers. De meeste medische hulpvragen vonden plaats in Europa en Azië en meer specifiek in Frankrijk, Spanje, Turkije en Thailand. Bij opgenomen reizigers waren de top vijf diagnoses als volgt: verwondingen, hart- en vaatziekten, aandoeningen van het spijsverteringsstelsel, darminfecties en luchtweginfecties. Voor reizigers die poliklinisch behandeld konden worden zag dit er iets anders uit: verwondingen, darminfecties, hart- en vaatziekten, aandoeningen van het spijsverteringsstelsel en andere niet-overdraagbare ziekten (bijv. urineweginfecties). Reizigers die overleden

waren nog voordat zij medische hulp kregen, waren veelal overleden ten gevolge van hart- en vaatziekten zoals aan een hartstilstand of aan verwondingen door bijvoorbeeld verkeersongevallen. Het merendeel van de reizigers hoefde na medische hulp niet gerepatrieerd te worden naar Nederland, maar voor 20% van de reizigers was dat wel nodig. De repatriëring vond meestal plaats met een reguliere lijnvlucht, met of zonder begeleiding van een medisch hulpverlener.

In **hoofdstuk 3** hebben wij onderzocht hoeveel ongemak Nederlandse reizigers ervaren wanneer zij tijdens hun reis te maken krijgen met diarreeklachten. Van de 390 geïncludeerde reizigers, rapporteerde 41% dat zij reizigersdiarree hebben gehad. De gemiddelde duur van de diarree was 2.5 dag, verliep in de meeste gevallen zonder complicaties en er was geen aanpassing in het geplande reisschema nodig. Ongemak werd vooral beschreven bij reizigers die last hadden van bijbehorende symptomen zoals koorts en overgeven, die medicijnen nodig hadden en bij degenen die juist wel hun reisprogramma moesten aanpassen. Een enkele reiziger had lokaal medische hulp nodig; twee reizigers in Afrika werden opgenomen. Het gebruik van een antibioticum in de groep met darmklachten was laag (9%). Een verblijf in luxe hotels vergrootte het risico op reizigersdiarree, terwijl zakenreizigers of reizigers die familie en/of vrienden bezochten juist minder risico liepen. Dit onderzoek heeft laten zien dat het verstandig is om bij toekomstige onderzoeken naar de behandelmogelijkheden van diarree, ook rekening te houden met de mate van ongemak die de reizigersdiarree veroorzaakt. Hierdoor kunnen beleidsmakers een betere inschatting maken van welke groep reizigers wel baat zou kunnen hebben bij preventieve maatregelen zoals vaccinatie of een antibioticumkuur die in geval van nood gebruikt kan worden.

In **hoofdstuk 4** hebben wij diverse aspecten onderzocht waarmee Nederlandse en Belgische medisch studenten te maken krijgen wanneer zij naar het buitenland gaan voor een stage. Deze aspecten hadden betrekking op de reizigersadvisering voor vertrek, gezondheidsrisico's en gezondheidsproblemen tijdens het buitenlandse verblijf en de medische nazorg na terugkomst in Nederland of België. Bijna alle studenten (97%) hadden een reizigersadvies ingewonnen. De leefomstandigheden in de lokale accommodatie waren voor de meeste studenten goed: aanwezigheid

van stromend water, een koelkast en een werkende internetverbinding. Maar liefst de helft van de 479 studenten ondervond moeilijkheden om zich aan te passen aan de lokale cultuur, terwijl ze zich meestal wel geaccepteerd voelden door de lokale bevolking. Dit fenomeen “cultuurshock” werd voornamelijk gerapporteerd door studenten in Centraal-Amerika en Afrika. Een klein aantal studenten rapporteerde dat zij procedures hadden uitgevoerd waarbij zij een prik- of spataccident hadden opgelopen. Het merendeel werd volgens de richtlijnen correct behandeld (d.w.z. testen van de bron en/of zelf starten met een “post-exposure profylaxis”-kuur). Echter, er was nog een kleine groep studenten die twijfelde of er wel sprake was van een echt prik- of spataccident, hiervan werd maar de helft correct afgehandeld. Er waren ook nog andere risico’s voor studenten. Sommigen hadden onbeschermd seksueel contact met een nieuwe partner, of waren veelal licht gewond geraakt bij een verkeersongeval. Voornamelijk studenten in Afrika en Zuid-Amerika rapporteerden geïntimideerd of bedreigd te zijn geweest of zelfs lichamelijk geweld meegemaakt te hebben. Dit gebeurde meestal buiten de locatie waar zij hun stage liepen. Bijna de helft van de studenten kreeg te maken met diarreeklachten zonder er al te veel ongemak van te hebben, dat was voornamelijk bij studenten in Afrika, Zuid-Amerika en Azië. Medische hulp was zelden nodig; slechts twee studenten werden opgenomen. Een derde van alle studenten had een antibioticumkuur uit hun thuisland meegekregen, waarbij dit hoofdzakelijk Belgische studenten betrof (80%). De screening op tuberculose, meticilline-resistente *Stafylococcus aureus* (MRSA) en schistosomiasis is bij de meeste universiteiten niet goed in orde, vermoedelijk omdat een medische “check-up” na terugkomst geen onderdeel is van de buitenlandse stage. Het is dus wenselijk dat de post-travel gezondheidscheck centraal per universiteit wordt geregeld. Het is ook belangrijk dat de informatievoorziening voor vertrek wordt verbeterd bijvoorbeeld over het juiste gebruik van malaria chemoprofylaxe, aanbieden van een BCG-vaccinatie voor studenten in hoog-risico gebieden voor tuberculose en een correcte omgang en afhandeling in situaties waarbij twijfel bestaat of een risicovolle handeling is misgegaan.

Hoofdstuk 5 beschrijft een prospectieve studie waarin 477 oudere reizigers (60+) werden geïncludeerd bij vier travel clinics. Ouderen kunnen vanwege hun leeftijd en

onderliggende aandoeningen meer last hebben van gezondheidsproblemen tijdens en na het maken van een verre reis. Om dit beter in kaart te brengen en hierdoor het reizigersconsult beter te laten aansluiten bij de specifieke behoeftes van deze doelgroep is de ELDEST studie opgezet. De gezondheidsstatus, reisvoorbereidingen, gezondheidsklachten tijdens en na de reis en eventueel benodigde medische hulp werden met vragenlijsten op verschillende tijdsmomenten en in een dagboekje verzameld. De reisduur was gemiddeld drie weken en vooral bestemmingen in Azië waren populair. De knijpkracht, het cognitief vermogen en de mate van last van onderliggende ziektes bleken slechter te zijn in 70+ reizigers. Hart- en vaatziekten (voornamelijk hoge bloeddruk), maligniteiten en huidziekten waren de meest gerapporteerde aandoeningen voor vertrek. Een vijfde van de deelnemers gebruikte vijf of meer medicijnen per dag (polyfarmacie). De meest gerapporteerde gezondheidsklachten waren luchtweg- en darminfecties, maar ook verwondingen zoals schaafwonden, botbreuken en kneuzingen. Verrassend genoeg werd een verergering van een onderliggende aandoening tijdens de reis nauwelijks gerapporteerd. Niemand werd opgenomen in een buitenlands ziekenhuis. Wel werd door één op de vijf reizigers medische hulp ingeschakeld, maar dit was voornamelijk bij de eigen huisarts na terugkomst in Nederland. Vijf reizigers werden na terugkomst in Nederland opgenomen in een ziekenhuis. De ELDEST studie laat zien dat er voor oudere reizigers een belangrijke rol voor de huisarts lijkt te zijn weggelegd. Tevens bleek het maken van een reis een gunstige invloed te hebben op de zelf gerapporteerde fysieke en mentale kwaliteit van leven. Om uit te zoeken of fysieke en cognitieve testen gezondheidsklachten tijdens een reis kunnen voorspellen, werd tijdens het reizigersconsult een knijpkrachtmeting en een cognitieve vragenlijst afgenomen. Zoals verwacht scoorden oudere reizigers hierop slechter, maar beide testen bleken geen voorspellende waarde te hebben voor het optreden van gezondheidsproblemen op reis. Mogelijk speelt bij deze groep reizigers fitheid en een actief en zelfstandig leven een rol waardoor zij in staat zijn om een verre reis te maken. Variabelen die wel een voorspellende functie leken te hebben voor het optreden van gezondheidsproblemen waren: meer reiservaring, een hoger aantal dagelijkse medicijnen, een hogere co-morbiditeit score, een langere reisduur, reizen naar Noord-Afrika of Zuidoost- en Oost-Azië en het gebruik van een smartphone en social media.

In **hoofdstuk 6** en **hoofdstuk 7** worden de rol en eventuele gevolgen van antimicrobiële resistentie bij internationale reizigers onder de loep genomen.

Hoofdstuk 6 bevat een prospectieve studie waarin 370 volwassen Nederlandse reizigers van de LUMC Vaccinatiepolikliniek en GGD Hollands-Midden zijn onderzocht in hoeverre zij de resistente darmbacteriën genaamd extended-spectrum β-lactamase producerende *Enterobacteriaceae*

(ESBL-E) en carbapenemase producerende *Enterobacteriaceae* (CP-E) oplopen tijdens een buitenlandse reis. Ook werd onderzocht hoelang men deze bacterie bij zich kan dragen en wat de risicofactoren zijn. De reisduur was gemiddeld drie weken. Van de 370 reizigers bleek een beperkte groep (9%) voor vertrek al een ESBL-E "aan boord" te hebben. Van de resterende 338 reizigers heeft een derde een ESBL-E tijdens de reis opgelopen, waarvan bij een kwart de ESBL-E nog steeds werd aangetroffen zes maanden na terugkomst in Nederland. Er werd geen CP-E gevonden. Geen van de reizigers hoefde opgenomen te worden in een buitenlands ziekenhuis. De meeste ESBL-E's werden opgelopen door reizigers naar Zuid-Azië (73%) en Oost-Azië (67%). Deze reisbestemmingen zijn tevens de enige risicofactoren voor het verwerven van een ESBL-E die geïdentificeerd konden worden in dit onderzoek. Het advies dat voortkwam uit deze studie was dan ook om een actieve controle te hanteren voor ESBL-E en CP-E wanneer patiënten in een Nederlands ziekenhuis worden opgenomen en zij in de voorafgaande zes maanden een reis naar Azië hebben gemaakt.

In **hoofdstuk 7** is een deel van de gegevens van **hoofdstuk 6** (n=103) samengevoegd met vergelijkbare gegevens van twee andere studies onder Finse reizigers (n=196) en een andere groep Nederlandse reizigers uit Amsterdam (n=97). Omdat er steeds meer mensen naar Afrika reizen, lag de focus voor dit gecombineerde onderzoek op deze groep reizigers en het in kaart brengen van het oplopen van een ESBL-E en mogelijke risicofactoren. Oost- (47%) en West-Afrika (28%) waren de meest populaire regio's. Een kleine groep (6%) bezocht meer dan één Afrikaanse subregio. De gemiddelde reisduur was 19 dagen. Van de 396 reizigers heeft 15% een ESBL-E opgelopen en één reiziger naar Egypte een CP-E. De meeste ESBL-E's werden opgelopen door reizigers naar Noord-Afrika, gevolgd door Midden-Afrika en Oostelijk

Afrika. Vierenveertig reizigers (11%) gebruikten een antibioticum tijdens de reis, waarvan 17 reizigers een ESBL-E opliepen. Dit is drie keer zoveel als onder reizigers die geen antibioticum gebruikten. Opvallend was dat meer Finse dan Nederlandse reizigers een antibioticum gebruikten (34/196, 17% versus 10/200, 5%). Tevens werden er meer ESBL-E's gevonden bij reizigers die reizigersdiarree hadden gerapporteerd (20%) dan bij degenen die dat niet hadden (12%). Hoewel slechts zes reizigers opgenomen moesten worden in een ziekenhuis, verwierf 67% van hen een ESBL-E. In dit gecombineerde onderzoek kwamen reizen naar Noord-Afrika, een ziekenhuisopname in het buitenland, leeftijd, reizigersdiarree en gebruik van het antibiotica behorende tot de fluoroquinolonen groep, naar voren als risicofactoren voor het oplopen van een ESBL-E. Concluderend lijkt het risico op het oplopen van een ESBL-E tijdens een reis naar Afrika matig, behalve voor reizigers naar Egypte.

Conclusie

Resultaten van de studies in dit proefschrift vergroten de kennis over de ziektelast waarmee diverse groepen Nederlandse reizigers, zoals medisch studenten of oudere reizigers, te maken kunnen krijgen tijdens een verblijf in het buitenland. Naast het geven van meer inzicht in de ondervonden gezondheidsproblematiek en bijbehorende ongemakken, zijn er ook praktische adviezen naar voren gekomen die kunnen worden opgenomen in het huidige reizigersadvies. Beide genoemde aspecten dragen bij aan zowel een praktisch op maat gemaakt reizigersadvies voor de Nederlandse reiziger, maar kunnen ook interessante uitgangspunten zijn voor toekomstige onderzoeken in de zich continu ontwikkelende wereld van de reizigersgeneeskunde.

Appendices

Dankwoord

Curriculum Vitae

List of publications and portfolio

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Jessica Alexandra Vlot werd geboren op 4 juli 1988 in het toenmalig Academisch Ziekenhuis te Leiden (AZL), het huidig Leids Universitair Medisch Centrum (LUMC). In 2006 behaalde zij haar Gymnasiumdiploma aan het Herbert Vissers College te Nieuw-Vennep. In datzelfde jaar startte zij met de studie Gezondheidswetenschappen aan de Vrije Universiteit te Amsterdam. In 2009 behaalde zij haar Bachelor-diploma. Vervolgens voltooide zij haar vijf maanden durende masterstage op de afdeling Infectieziekten in het LUMC onder leiding van dr. D. Soonawala en prof. dr. L.G. Visser. In juni 2010 studeerde zij cum laude af in twee Health Sciences Master specialisaties: *Infectious Diseases & Public Health* en *Prevention & Public Health*.

In september 2010 startte Jessica als junior onderzoeker bij het onderzoek *Op Reis* van drs. H.J. Brockhoff en prof. dr. L.G. Visser op de afdeling Infectieziekten in het LUMC. Hieruit volgde begin 2013 de start van haar promotietraject.

Parallel aan haar promotiewerkzaamheden, is Jessica van augustus 2017 tot en met mei 2022 werkzaam geweest als clinical trial coördinator op de afdeling Reumatologie van het LUMC. Per juni 2022 is zij teruggekeerd naar de afdeling Infectieziekten om de nieuw opgezette functie als clinical trial coördinator binnen deze afdeling te gaan bekleden. Verder is Jessica sinds maart 2020 secretaris van de wetenschapscommissie voor COVID-19 WMO plichtig onderzoek van het LUMC.

Gedurende bovenstaande periode is Jessica getrouwd met Menno Lageweg en zijn zoon Owen (2019) en dochter Kate (2022) geboren. Tenslotte heeft zij 34 jaar na haar eigen geboorte in het vroegere AZL, haar proefschrift afgerond in het LUMC.

This thesis

Vlot JA, van Steenbergen JE, Luppino FS, Geary K, van Genderen PJJ, Visser LG. Hospital-based care and/or death followed by repatriation in Dutch travelers: the HAZARD study. *Travel Med Infect Dis*. 2022 sep-oct;49:102329. https://doi.org/10.1016/j.tmaid.2022.102329.

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Other publications

Daryl Geers, Roos S.G. Sablerolles, Debbie van Baarle, Neeltje A. Kootstra, Wim J.R. Rietdijk, Katharina S. Schmitz, Susanne Bogers, Lennert Gommers, Nella J. Nieuwkoop, Laura L.A. van Dijk, Eva van Haren, Melvin Lafeber, Virgil A.S.H. Dalm, Abraham Goorhuis, Douwe F. Postma, Leo G. Visser, Anke L.W. Huckriede, Alessandro Sette, Alba Grifoni, Rik L. de Swart, Marion P.G. Koopmans, P. Hugo M. van der Kuy, Corine H. GeurtsvanKessel, Rory D. de Vries the SWITCH research group. Ad26.COV2.S priming provides a solid immunological base for mRNA-based COVID-19 booster vaccination. *iScience.* 2023 Jan 20; 26 (1): 105753. https://doi.org/10.1016/j.isci.2022.105753

SWITCH research group LUMC mentioned in the supplementary appendix: ***J.A. Vlot****, P.H. Verbeek-Menken, A. van Wengen-Stevenhagen.*

R.S.G. Sablerolles, W.J.R. Rietdijk, A. Goorhuis, D.F. Postma, L.G. Visser, D. Geers, K.S. Schmitz, H.M. Garcia Garrido, M.P.G. Koopmans, V.A.S.H. Dalm, N.A. Kootstra, A.L.W. Huckriede, M. Lafeber, D. van Baarle, C.H. Geurts-van Kessel, R.D. de Vries, P.H.M. van der Kuy on behalve of the SWITCH research group. Immunogenicity and reactogenicity of booster vaccinations after Ad26.COV2.S priming.

N Engl J Med. 2022 Jan 19. https://doi.org/10.1056/nejmoa2116747

SWITCH research group LUMC mentioned in the supplementary appendix: ***J.A. Vlot****, P.H. Verbeek-Menken, K. Suijk-Benschop, J. Fehrmann-Naumann, A. van Wengen-Stevenhagen.*

Vyth EL, Steenhuis IH, **Vlot JA**, Wulp A, Hogenes MG, Looije DH, Brug J, Seidell JC.

Actual use of a front-of-pack nutrition logo in the supermarket: consumers' motives in food choice. *Public Health Nutr*. 2010 Nov;13(11):1882-9.

https://doi.org/10.1017/s1368980010000637

Presentations at (inter)national conferences and symposia

2019

ELDEST study: travel-related morbidity in older Dutch travelers to the tropics, a prospective cohort study, 16th Conference of the International Society of Travel Medicine (CISTM16), Washington DC, United States of America, oral presentation by co-author M. Vive.

2017

Health risks and travel preparation in medical students from Dutch and Belgian universities during an elective in the tropics, 15th Conference of the International Society of Travel Medicine (CISTM15), Barcelona, Spain, oral presentation.

ELDEST-study: pre-travel health status and vitality in elderly Dutch travelers, 15th Conference of the International Society of Travel Medicine (CISTM15), Barcelona, Spain, poster tour presentation.

2015

Undesired travel souvenirs – incidence and causes of traveler's diarrhea in Dutch travelers using cytotoxic drugs and/or monoclonal antibodies and in their travel companions after travel to the (sub)tropics, 14th Conference of the International Society of Travel Medicine (CISTM14), Québec City, Canada, oral presentation.

The use of hand sanitizers among Dutch travelers visiting (sub)tropical destinations, 14th Conference of the International Society of Travel Medicine (CISTM14), Québec City, Canada, poster presentation.

Member of the committee for the session "Highlights of the Congress", 14th Conference of the International Society of Travel Medicine (CISTM14), Québec City, Canada.

2014

Antibiotica resistentie van darmpathogenen, Boerhaave symposium Importziekten en reizigersadvisering, Leiden, the Netherlands, oral presentation.

2013

High acquisition rates of extended spectrum β-lactamase producing Enterobacteriaceae among Dutch travelers, 13th Conference of the International Society of Travel Medicine (CISTM13), Maastricht, the Netherlands, oral presentation.

Awards and grants

2015

CISTM14 Young Investigators Award travel grant $1,500 for the abstract *Undesired travel souvenirs – incidence and causes of traveler's diarrhea in Dutch travelers using cytotoxic drugs and/or monoclonal antibodies and in their travel companions after travel to the (sub)tropics*. Grant is to assist supporting attendance at the upcoming CISTM14 in May in Quebec City.

ISTM Research Award $11,000 for the application *ELDEST study: morbidity in elderly travelers during a short-term stay abroad, a prospective cohort study*.

2013

Third place of best oral presentation at 13th Conference of the International Society of Travel Medicine (CISTM13), Maastricht, the Netherlands.