Aus der Klinik für Gastroenterologie, Hepatologie und Infektiologie
der Heinrich-Heine-Universität Düsseldorf
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# Clinical epidemiological study of 2314 ill returned travelers presenting to Heinrich Heine University Düsseldorf

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# Zusammenfassung

In den letzten Jahrzehnten hat internationales Reisen inflationär zugenommen. Fortschritte im Bereich der Luftfahrt führten zu einem zuverlässigen, schnellen Verkehrsnetzwerk, wodurch Reisen immer günstiger wird. Die Assoziation zwischen Reisen und Krankheit war nie so relevant wie heutzutage.

In dieser Studie wurde eine Population von 2314 Reisenden untersucht, die sich zwischen 2010 und 2012 aufgrund einer reiseassoziierten Erkrankung in der Klinik für Gastroenterologie, Hepatologie und Infektiologie der Heinrich Heine Universität Düsseldorf vorstellten. Das Hauptziel der Studie war die statistische Aufarbeitung der Assoziation von 10 klinischen Syndromen und 13 Weltregionen. Dieses erfolgte durch die Berechnung der proportionalen Morbidität sowie des Odds Ratios (OR). Krankheiten mit hoher globaler Morbidität (wie z.B. Malaria, Dengue Fieber und Lungentuberkulose) sowie dermatologische Syndrome wurden separat analysiert.

Die häufigsten Syndrome waren Reisediarrhoe (23.6%), gastrointestinale Syndrome ohne Diarrhoe (22.5%), dermatologische Syndrome (17%), systemische febrile Erkrankungen (16.9%) sowie respiratorische Syndrome (9.8%). Des Weiteren zeigten sich multiple signifikante Assoziationen zwischen den definierten Reisezielen und den erwähnten Syndromen. Das höchste OR konnte zum Beispiel für Durchfallerkrankungen bei Reisenden aus Südasien beobachtet werden (OR 4.26, $p < 0.001$). Systemische Fieberkrankheiten wurden mit Reisen im subsaharisches Afrika assoziiert (OR 6.35, $p < 0.001$). Auch die meisten Malariafälle wurden mit einem OR von 11.28 ($p < 0.001$) erwartungsgemäß aus dem subsaharischen Afrika importiert (80.8%). Wir konnten zudem die Entwicklung von Hautkrankheiten mit Reisen in das subsaharische Afrika, die Karibik oder ins südliche Asien in Verbindung setzen. Des Weiteren wurden Europareisende am häufigsten mit einer kutanen Leishmaniose infiziert.

Die vorliegenden Studiendaten erreichten eine hohe statistische Signifikanz und korrelieren gut mit der medizinischen Literatur. Die Studie liefert wichtige Informationen zu der reisemedizinischen Versorgung der Klinik. Zukünftige Studien könnten weitere Hinweise auf Reiseassoziierte Erkrankungen hervorbringen.

# Abstract

Over the last decades, international travel has been growing at an inflationary rate. The technological advances in the field of aviation have translated into a worldwide transportation network which is reliable, fast and increasingly cheap. The expansion of travel leads however to evolving challenges in medicine. The association between travel and disease has never before been so relevant.

This study characterized a population of 2314 ill returned travelers presenting to the department of tropical medicine of the gastroenterological clinic of Heinrich Heine University Düsseldorf between 2010 and 2012. The main objective of the study was to identify the association between the development of 10 broadly defined clinical syndromes and 13 world regions in a quantitative manner – through the calculation of the proportionate morbidity and the odds ratios (OR). Diseases with a high level of global morbidity (such as malaria, dengue fever and pulmonary tuberculosis) were studied separately Moreover, dermatologic syndromes were defined and analyzed in a similar manner.

The most common syndromes were traveler's diarrhea (23.6%), non-diarrheal gastroenterological disorders (22.5%), dermatological disorders (17%), systemic febrile illness (16.9%) and respiratory syndrome (9.8%). Moreover we could observe several significant associations between the region of visit and the mentioned syndromes. The highest odds ratio for the development of traveler's diarrhea, for instance, was observed in South Asia (OR 4.26, $p < 0.001$). Systemic febrile illness was associated with sub-saharan Africa (OR 6.35, $p < 0.001$). The majority of malaria cases were as expected imported from Sub Saharan Africa (80.8%) with an OR of 11.28 ($p < 0.001$). Finally, we could associate the development of skin disorders to regions such as sub-saharan Africa, the Caribbean or the southern part of Asia. Of note, the majority of patients presenting with cutaneous leishmaniasis were infected in Europe.

The data found in this study achieved high levels of statistical significance and correlates well with the medical literature. It provides important information concerning the practice of travel medicine in our institution. Future studies with more detailed datasets could provide interesting insights and associations.

# Abbreviations

Cutaneous leishmaniasis (CL)

Cutaneous larva migrans (CLM)

Lymph node tuberculosis (LKTB)

Lymphatic filariasis (LF)

Non-diarrheal gastrointestinal disorder (NDG)

Odds ratio (OR)

Pulmonary tuberculosis (PTB)

Robert Koch Institut (RKI)

Relative risk (RR)

Systemic febrile illness (SFI)

Skin disorders (SD)

Sexually transmitted diseases (STD)

Tuberculosis (TB)

Traveler’s diarrhea (TD)

World Health Organization (WHO)

# Content

# 1 Introduction

## 1.1 The relationship between travel and disease

International travel has been growing at an outstanding pace. Never before has travel been so intense – a growth from 25 million touristic international arrivals in 1950 to staggering 1087 million in 2013.[1] Motivation for travel include immigration, business trips, visit to friends and relatives, military interventions and volunteer work.[1] Travel leads not only to the exchange of capital, goods and ideas – it is also unfortunately associated with disease. Steffen et al.[2] have reported that 22 to 64 percent of travelers to the developing world self-report health problems, most of which are of benign nature. If we consider the ever increasing number of travelers to these regions, it is clear that travel – beyond its mostly positive nature – generates a considerable level of morbidity.

Travel medicine represents a relatively new field in medicine, which began organizing itself over the last 20 to 30 years.[3] The increase in global travel has led ultimately to the organic development of sites with a high level of specialization in travel medicine. In contrast to tropical medicine - which classically provides treatment for disease acquired in the tropics - these sites provide pre-travel advice (importantly immunization or chemoprevention), treatment of still travelling patients and therapy after returning home.[3] number of initiatives, including the GeoSentinel Survaillance Network, the International Society of Travel Medicine, the German Society of Tropical Medicine, the German Society of Travel Medicine, among others, research continuously the relationship between travel and disease.[4] An important multi-center study by Freedman et al.[5] analyzing a population of 17353 patients presenting to 30 centers distributed worldwide set a landmark for the epidemiologic characterization of the ill returned traveler, presenting proportionate morbidity according to discrete world regions. A further study by Harvey et al.[6] could show the most frequent travel related syndromes: acute diarrhea (22%), other gastrointestinal (15%), febrile or systemic illness (14%), and dermatologic (12%) with a detailed description of the most common causative agents.

Epidemic episodes such as the rapid spread of influenza in 2006[7], the dengue

outbreak in Madeira in 2012,[8] the Chikungunya virus outbreak in the Caribbean in 2014,[9] the reemergence of schistosomiasis in Europe[10] and the Ebola epidemic which continues to spread as we write this study[11] are very recent examples which remind us of how travel can alter the disease landscape within a given region or be associated with epidemics which have serious consequences around the planet.

## 1.2 Historical aspects

The origins of travel medicine can be traced to the field of tropical medicine, which is a branch of infectology.[3] The field has evolved to a distinct specialty over the last 20 years. The international Society of Travel Medicine was founded in 1991 – its goals comprehend the promotion of travel health, the development of guidelines for the practice of travel medicine, specialized training of health care professionals, among others.[3] Locally, the *Deutsche Fachgeselschaft für Reisemedizin* has been established to pursue the same goals. Travel medicine today is an interdisciplinary field which is not only dedicated to the treatment of the ill returned traveler, but also to the assessment of pre-travel risk, the evaluation of immunization before travel, and the reduction of environmental risk during travel.[3] The *Journal of Travel Medicine* and *Travel Medicine and Infectious Diseases* (founded in 1994 and 2003, respectively) are among the first journals dedicated exclusively to the field.

## 1.3 Travel in numbers

International travel has grown at an explosive rate: from 25 million touristic international arrivals in 1950 to 278 million in 1980, 528 million in 1995 to over one billion in 2013.[1] A recent report of the world tourism organization presents following numbers: in 2013, Europe was the preferred destination with 52% of all international arrivals and a growth of 5% in this year. Importantly, 80% of travelers remain in their geographic region.[1] Touristic growth varies worldwide but is expected to be maintained at a rate of 4%. Even though tourism represents the main reason for travel, it displays a decreasing trend on the overall amount of travelers: from 56% in 2000 to 51% 2001. The percentage of travelers visiting friends and relatives grew from 20 to 27% and business trips account for about 14% of travel.[1] Moreover, the ever growing touristic market (over one trillion dollars'

worth in 2013) stimulates new motivations for travel, such as medical tourism[12] or sex tourism.[13]

## 1.4 Challenges of research in travel medicine

Several studies sought to analyze the association between travel and disease in an evidence based manner. This growing body of knowledge has generated the first international guidelines, allowing a more standardized practice.[3] However, research in travel medicine is faced with following challenges:

- The study population: millions of people travel through the globe every day[1]. Beyond travel by air, naval and terrestrial transports are forms of transportation which are more difficult to account for. Research within this highly complex system is a challenge in itself.

- Under-reporting: most diseases such as mild diarrhea or discrete skin disease are self-limited, as these patients do not seek medical assistance.[5]

- Socio-economic differences: there is an enormous variability in the quality of health care worldwide.[14,15] The epidemiology of travel and disease within the developing countries remains to be researched (for example, the impact on global health caused by refugee waves or by military interventions).

- Lack of service providers: travel medicine is a relatively new field in medicine. Few physicians have received specific training and specialized clinics are found most commonly in metropolitan areas.[3]

- Methodological differences: most data come from retrospective studies or questionnaire based investigations. Prospective studies in the field of travel medicine are rare.[3]

In most travel medicine studies, individual diseases are grouped into syndromes with similar characteristics and the visited country is translated into a “world region”.[5,6,16] This allows researchers to determine which kind of disease is seen

more frequently in each geographic region. There is some variation in the literature on how the syndromes and world regions are defined. This thesis used a similar system as described by the GeoSentinel Network, a reference in the field of travel medicine.[6,17] The following sections will review data related the most common conditions: how they are defined, the most relevant diagnoses within the syndrome group, the global regions in which these syndromes are observed more often.

## 1.5 Most common syndromes

### 1.5.1 Traveler's diarrhea

It is consensus in the medical literature that traveler's diarrhea (TD) and non-diarrheal gastrointestinal disorders (NDG) are the most common causes of travel related morbidity.[5,18,19] Diarrhea is commonly defined as the passage of 3 or more unformed stools over a period of 24 hours.[20] A report has shown that the incidence of TD in some regions may reach up to 50%.[21] Most cases are self-limited and do not require medical attention. Patients presenting with bloody stool, fever, persisting symptoms, nausea and vomiting or intense symptoms (e.g. weight loss) should undergo careful clinical evaluation.[18] Detailed travel history should be obtained, as causative agents differ according to the visited country. If needed, laboratory examinations may include stool examination (culture and smear in order to rule out ova and parasites), blood count, blood culture and smears, as malaria may be directly or indirectly associated with diarrhea.[22]

The most important risk factor for developing TD is the country of visit.[23] Risk areas include most of South Asia, Africa (specially the north) and parts of South America.[24] A Japanese study could identify the following risk factors for the development of TD: destination, age between 20 and 29, passengers traveling during the summer months. Eighty percent of cases returned from Southeast Asia, south-central Asia and North Africa.[25] Regarding causative agents, the enterotoxigenic *Escherichia coli* is reported to be the most common pathogen, as it may be responsible to up to 50% of all cases.[18] *Shigella, Campylobacter* and *Salmonela* spp. are further bacteria which can cause TD. Viruses such as noroviruses or rotaviruses and protozoa such as *Giardia duodenalis* and *Entamoeba histolytica* expand the list of causative agents even further.[18,26] There

is some level of specificity concerning pathogens and geographical region: bacterial diarrhea caused by *Campylobacter* spp., for example, is commonly observed in Southeast Asia.[5]

Chemoprophylaxis for TD is usually not indicated. Prophylactic measures in order to avoid contaminated foods should be pursued.[27] Travelers visiting high risk regions for a longer period of time should be instructed about a self-treatment regimen: an antimotility agent such as loperamide and an antibiotic (usually a fluoroquinolone) are commonly recommended.[24] Moreover, a novel recombinant inactivated cholera vaccine seems to reduce the risk of cholera for travelers visiting endemic regions over a period of 7 days or longer.[20]

### 1.5.2 Non-diarrheal gastrointestinal disorders

The broad group of NDG, on the other hand, comprehends several diseases which are not primarily associated with diarrhea. General abdominal pain, cholelithiasis, viral hepatitis, nematode infestation, echinococcosis are a few examples of this vast syndrome group. In opposition to traveler's diarrhea, diseases in this group are loosely related to each other. Diseases such as viral hepatitis, cholecystitis, nematode infestation or esophagitis are all included in the group NDG. Studies in travel medicine with a large number of patients use this broadly defined syndrome group in order to the epidemiological information. Nevertheless, NDG represents a major cause of travel related morbidity.[6]

### 1.5.3 Systemic febrile illness

Patients returning home with a systemic febrile illness (SFI) are a diagnostic challenge. Detailed travel history is crucial - not only the country of visit but also the activities performed (for example, insect bites, swimming in lakes or contact with ill people). Importantly, pre-travel advice can reduce the risk of development of most infectious diseases through chemoprevention, immunization or through behavioral measures[3].

A study by Wilson and et al.[28] could show that 26% of patients presenting with SFI had to be hospitalized (in contrast to 3% within the remaining population). SFI was

associated with diarrhea in 15% of cases and 14% had fever and respiratory symptoms. Malaria was the most common specific diagnosis.

A further investigation by Warne et al.[29] studying 5962 ill returned travelers highlights the importance of pre-travel advice: the highest level was observed by military personnel (95%) and the lowest by travelers visiting friends and relatives (21%). The most common infection was malaria (8.1%). Within the malaria population, over 95% of patients resided in Europe but were born in another country. Almost half (46%) were visiting friends and relatives. Moreover, 54 cases of vaccine preventable disease were identified, including 3 cases of measles in western Europe. Finally, the authors point out to other diseases preventable through advice and behavioral change: *Giardia* infection (3.7%), dengue fever (2.4%), and schistosomiasis (2.2%).

A French study performed on troops deployed abroad provides further insights: over an 11 year period 125 soldiers had to receive emergency evacuation back to France to receive medical treatment due to infectious diseases. Most of the soldiers were in duty in Africa or Afghanistan. *Plasmodium falciparum* malaria, fever of unknown origin, cerebro-meningeal infections, invasive amebiasis, and HIV primary infections were the top five diagnoses.[30]

Dengue fever is a further cause of travel related SFI with a very high level of morbidity. It is an endemic disease in the tropics with an annual incidence which has been recently estimated at 390 Million cases worldwide.[31] It is the most common arboviral disease as it is transmitted by the mosquito *Aedes aegypti*. The recent dengue outbreak observed in the Madeira Islands in 2012 is a cornerstone example of how travel and disease are associated.[8] It began in 2005, when, through shipping and cargo, the mosquito was reportedly imported to the island, where it could find a compatible ecosystem. In 2012 the outbreak was recorded: 2100 patients were diagnosed with dengue and 78 further cases recorded in 13 European countries in travelers departing from the Madeira Islands. Using a statistical “importation index” and Virus sequencing, the authors indicated that the disease was probably imported from Venezuela.[8]

It is beyond the scope of this thesis to describe every single travel-related infectious disease. Ideally, travelers presenting with fever should be treated in a specialized center or by physicians trained in travel or tropical medicine.

### 1.5.4 Skin disorders

Skin disorders (SD) is one of the leading causes of travel associated morbidity, usually reported to come in third place after TD and SFI. The exact frequency in which they are observed varies to some extent. This seems to depend on the type of study (retrospective, prospective), the type of study center (tropical medicine department, primary care), population characteristics (size, geographical localization), among others.[32] One study performed between 1989 and 1991 observed an incidence of SD of 8%.[33] Another report from 2008 showed that 18% of the study population developed dermatological illness, the third cause of disease after TD and SFI.[34] A newer retrospective report analyzing 34162 individuals returning to Munich reported an incidence of SD of 12.2%.[16] Field et al.[35] had a similar result within an European population (12%)[5].

Furthermore, a French group of patients presenting to primary care were diagnosed with SD at 11%, after gastrointestinal and respiratory disorders.[36] Taken together, these studies indicate that SD are an important aspect of travel medicine, with a proportionate morbidity commonly reported within the 10-20% range.

Data associating the destination of travel and overall risk of SD is rare. It is however important to point out that the development of certain diseases is almost like a “signature” which connects the traveler to its destination: for example, rickettsial infection and South Africa, where the disease is endemic.[34] A report from the GeoSentinel Surveillence Network has indicated further links: cutaneous larva migrans was connected to the Caribbean, dengue fever and dog bites to Southeast Asia and tunguiasis to Brazil and sub-saharan Africa.[32] Another dermatological study points to South America as risk destination for the development of skin disease.[37]

The etiology of SD is highly variable. As the outermost organ, it is subject to infection or infestation, trauma, UV damage, neoplasia, several types of

inflammation (allergy, autoimmunity), among others. In the context of travel medicine, the creation of syndrome groups allows better analytical interpretation of data. Herbinger et al.[16] observed 22.6% of insect bites, 21.6% of bacterial infections and 10.5% helminthic disease as the leading causes of dermatological disorders – about half of all cases. Further categories such as protozoan (6%), viral (5.7%), allergic (5.4%) accounted for the remaining causes. Freedman et al.[5] have also reported insect bites as the most common cause of SD. The list goes on with cutaneous larva migrans (especially in patients returning from the Caribbean), allergic reactions and skin abscesses. Of note, cutaneous leishmaniasis was primarily associated with travel to South America or Central America in the aforementioned study.

Nevertheless, it is important to note that the observed incidence of SD after travel is underestimated. The same study presents only 0.8% of patients returning with sunburn.[16] Most insect bites do not require medical attention. The levels of morbidity which are related to travel in a broader sense – such as the development of UV-induced skin cancer or latent infectious diseases such as Lyme disease would be extremely challenging to measure.

## 1.6 Other syndrome groups

The syndrome groups presented above accommodate the majority of travel related morbidity. In the report by Freedman et al.[5] 67% of the population were included in the groups TD, NDG, SFI and SD. In one of the largest patient series (with a total of 141.789 patients) the syndrome groups TD, NDG, SFI and SD were responsible for 71% of travel-related morbidity.[6] The same study includes further definitions: “respiratory”, “adverse events to medication”, “oral or dental”, “ophthalmologic”, “obstetric”, “nonspecific findings”, “psychological”, “neurologic”, “genitourinary”, “sexually transmitted disease”, Injury and musculoskeletal”, “chronic disease” and “cardiovascular”.

## 1.7 Objective of the thesis

The objective of this thesis is to describe the population of 2314 ill returned travelers presenting to the department of tropical medicine of Heinrich Heine University Düsseldorf. What demographic characteristics were observed? What were the most common syndrome groups in our population? Do they correlate well to the medical literature? Is there an association between the country of visit and the development of specific syndromes or diseases? Is it possible to observe traits which are specific for our clinic? Furthermore, we have separately studied the individual diagnosis malaria, dengue, pulmonary tuberculosis (PTB). Moreover, an emphasis on dermatologic conditions was pursued: are there risk regions for the development of SD? What were the most frequent dermatologic diagnoses observed by travelers? The individual diagnosis sexually transmitted diseases (STD), rickettsiosis, lymphatic filariasis (LF), cutaneous leishmaniasis (CL) and lymph node tuberculosis (LKTB) have been studied separately.

# 2 Materials and Methods

## 2.1 Study population

Patients from all ages and ethnicities presenting between 2010 and 2012 to the department of tropical medicine of Heinrich Heine University Düsseldorf were included in the study. International travel in the last 6 months was a prerequisite for inclusion. Patients presenting to the clinic seeking pre-travel consultation were not included in the study. The information of a total of 2314 patients was electronically entered into a database and analyzed in a retrospective manner. All personal data (name, date of birth) was pseudonymized before statistical analysis (registered with Study number 4622 on the local ethics committee).

## 2.2 Statistical variables

Following parameters were taken into account:

**Age at the time of visit:** age groups were created in order to represent patients under 18 and patients over 65 years.

**Visited world region:** the travel destination was converted into the “world region” (Figure 1) containing the country visited by the patient (for example, Brazil was converted to “South America”).

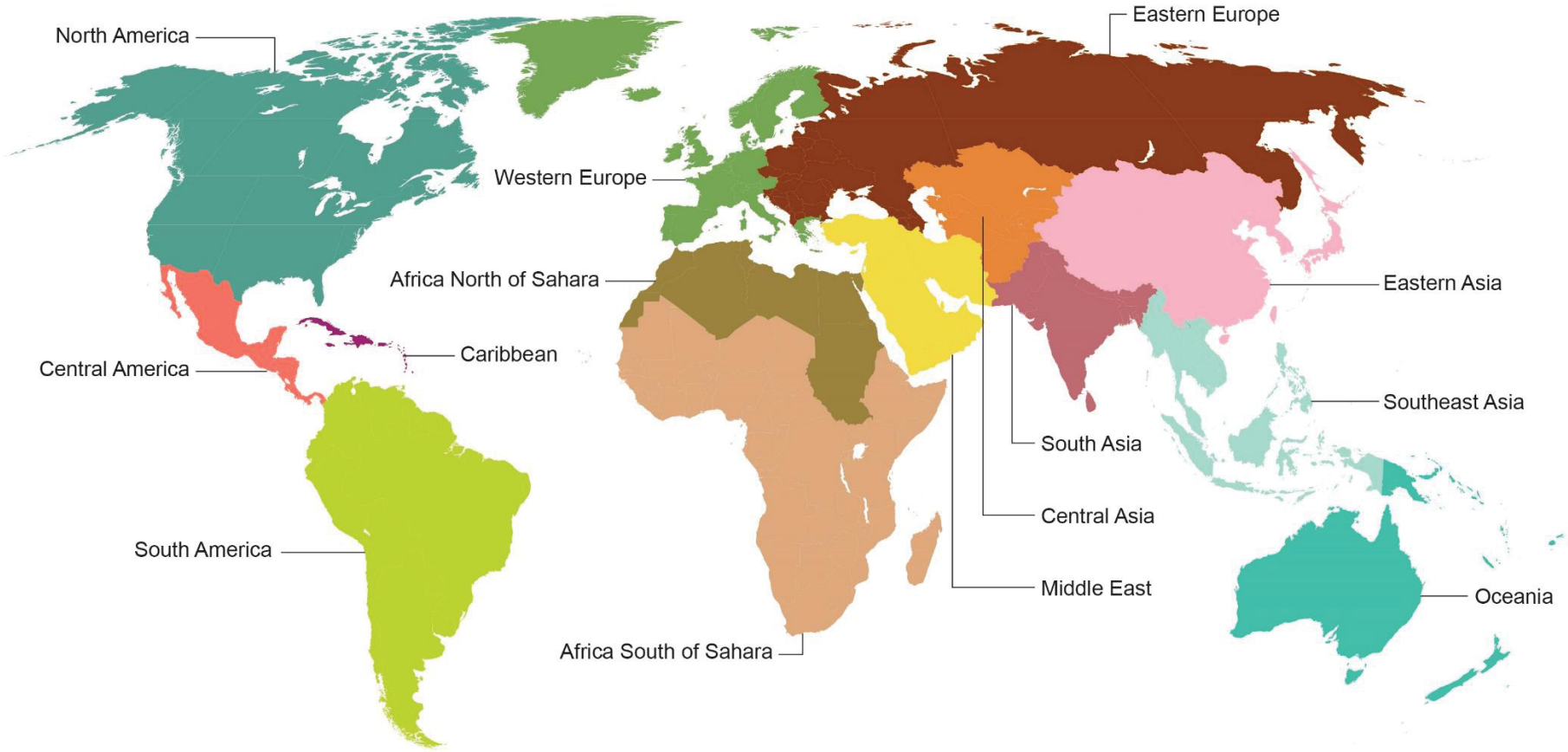


***Figure 1: World regions used in the present study:*** *the country visited by the patients was converted into a "world region". Travelers visiting two or more world regions within the same trip were added a separate group: "two or more" (not depicted).*

**Syndrome groups:** diagnoses obtained in the patient files were converted in 10 broadly defined syndrome groups (Table 1). The diganoses were made clinically or, when necessary, through diagnostic tests. Tables 2 to 6 show examples of diagnosis found in the syndrome groups: SFI (Table 2), TD (Table 3), NDG (Table 4), respiratory syndrome (Table 5) and SD (Table 6). We have chosen to give a detailed view of these five syndrome groups as they accounted for the majority of our patients. These examples do not include every single diagnosis encoutered during patient file analysis – they offer a broad view of the diseases commonly seen in the department of tropical medicine and were included for explanatory reasons.

| **Syndrome groups** |
|---|
| Systemic febrile illness (SFI) |
| Traveler's diarrhea (TD) |
| Non-diarrheal gastrointestinal disorders (NDG) |
| Skin disorders (SD) |
| Respiratory syndrome |
| Nonspecific symptoms |
| Genitourinary syndrome |
| Underlying chronic disease |
| Injury |
| Neurologic syndrome |

*Table 1: Syndrome groups used in the present study: the individual diagnosis were converted into a broadly defined "syndrome group". The clustering of diagnosis in syndrome groups is a method widely used in travel medicine studies.*

| **Systemic febrile illness** | | | |
|---|---|---|---|
| Viral | Bacterial | Protozoan | Other |
| Chikungunya fever | Bacterial meningitis | Chagas Disease | Fever, unknown |
| Dengue fever* | Brucellosis | African Trypanosomiasis | |
| O'nyong'nyong fever | Psittacosis | Malaria* | |
| EBV, CMV | Tsutsugamushi fever | Visceral leishmaniasis | |
| Ross River disease | Typhoid fever | | |
| Sindbis virus | | | |
| Viral meningitis | | | |

*Table 2: Systemic febrile illness: the most common diagnosis included in the group are presented according to etiology. *Dengue fever and malaria, due to their burden on global health, were studied separately. EBV denotes Epstein Barr virus. CMV denotes cytomegalovirus*

| **Traveler's diarrhea** | | | |
|---|---|---|---|
| Viral | Bacterial | Protozoan | Other |
| Adenovirus | *Campylobacter* spp. | *Entamoeba histolytica* | agent not identifiable |
| Astrovirus | *Clostridium difficile* | *Giardia duodenalis* | |
| Rotavirus | *Escherichia coli* | *Cyclospora cayetanensis* | |
| Norovirus | *Salmonella* spp. | *Cryptosporidia* spp. | |
| | *Shigella* spp. | *Blastocystis hominis* | |
| | *Yersinia* spp. | | |

*Table 3: Traveler's diarrhea: the most common causative agents included in the group are presented according to taxonomic classification. Patients presenting with diarrhea with no confirmed causative agent were included in the group "agent not identifiable".*

| **Non-diarrheal gastrointestinal disorders** | | | | |
|---|---|---|---|---|
| Viral | Nematodes | Cestodes | Trematodes | Other |
| Hepatitis A | Ascariasis | Echinococcosis | Fascioliasis | Cholecystitis |
| Hepatitis B | Enterobiasis | Teniasis | Paragonimiasis | Esophagitis |
| Hepatitis C | Gnathostomiasis | | Schistosomiasis | Helicobacter gastritis |
| Hepatitis D | Strongyloidiasis | | | Constipation |
| Hepatitis E | | | | |

*Table 4: Non-diarrheal gastrointestinal disorders: the most common diagnosis included in this group are presented according to etiology.*

| **Respiratory syndrome** | | | | |
|---|---|---|---|---|
| Viral | Bacterial | Fungal | Mycobacterial | Other |
| Influenza A | Bacterial pneumonia | Fungal pneumonia | Pulmonary TB | Upper respiratory tract infection |
| Influenza B | | Histoplasmosis | Atypical mycobacteria | Bronchitis |
| Influenza, other | | | | Asthma |
| | | | | Sinusitis |
| | | | | Allergic rhinitis |

*Table 5: Respiratory syndrome: the most common diagnosis included in this group are presented according to etiology. TB denotes tuberculosis.*

| Skin disorders | | | |
|---|---|---|---|
| Bacterial | Arthropod related | Ectoparasites | STD |
| Cellulitis | Insect bite | Myiasis | Chlamydia Infection |
| Pyoderma | Lyme disease | Cercarian dermatitis | Condylomata |
| Skin abscess | Lymphatic Filariasis | Lice infestation | Gonorrhea |
| Rickettsiosis | | Mite infestation | HIV |
| | | Tungiasis | HTLV |
| | | | Non-gonoccocal urethritis |
| | | | Syphilis |
| Protozoal | Helminthic | Animal related | Other dermatologic |
| Cutaneous leishmaniasis | Larva migrans | Animal bite | Herpes zoster |
| | | Marine envenomation | Rash, unknown |
| | | | Allergic related |
| | | | Fungal infection |
| | | | Lymph node TB |

*Table 6: Skin disorders: the most common diagnosis included in this group are presented according to etiology. TB denotes tuberculosis.*

**Dermatologic syndromes:** Out of the list of dermatologic conditions, we have selected broad syndrome groups ("arthropod related", "bacterial", "mite infestation", "animal related", "allergic related", "STD", "other dermatologic") or specific diagnoses ("cellulitis", "larva migrans", "lymph node tuberculosis" and "cutaneous leishmaniasis") to create 12 "dermatologic syndromes" (Table 7). Each individual case was added to the group with highest level of specificity: a patient presenting with rickettsiosis, for example, was included in the corresponding syndrome and not in the group "bacterial" or "arthropod related".

| Dermatologic syndromes | |
|---|---|
| Arthopod related | Celulitis |
| Bacterial | Mite infestation |
| Animal related | Larva migrans |
| Allergic related | STD |
| Lymphatic filariasis | Rickettsiosis |
| Cutaneous leishmaniasis | Other dermatologic* |

*Table 7: Dermatologic syndromes: the group of patients presenting with skin disorders was further divided into 12 dermatologic syndromes. *The subgroup "other dermatologic" included all diagnosis which did not fit into the other 11 dermatologic syndromes.*

## 2.3 Data analysis

In this study, the global proportionate morbidity was defined as a proportion between the total number of cases with a given syndrome by the total number of ill

returned travelers. The same step was performed for each individual region to calculate the local proportionate morbidity.

Furthermore, the odds ratio (OR) of acquiring each syndrome in each world region was calculated. The population traveling in western Europe was defined as the control population. All measurements with a corresponding *p* value below 0,05 were considered statistically significant. The confidence interval was defined at 95%.

Finally, we have estimated the relative risk (RR) as described by Herbinger et al.[16] This method divides the number of patients returning to Germany with any SD from a given world region by the number of patients flying from Germany to the same region (Ratio 1). Then division of the number of patients with any SD returning from overseas to Germany by the number of patients flying from Germany to overseas (Ratio 2). The RR is obtained by dividing Ratio 1 by Ratio 2.[16] The number of patients was obtained at the German Federal Bureau of Statistics (s*tatistisches Bundesamt*).[38–40]

All primary data was entered using the statistical software „Office Excel 2003“(Version 11.0, Microsoft Corporation). Further analysis (graphics, calculation of relative risks) was performed using „SPSS 15.0“of SPSS Inc. (Chicago, IL, USA).

# 3 Results

## 3.1 Demographics

We observed an almost 1:1 overall relationship between women (51.7%) and men (48.3%). The highest levels of female travelers were observed in Central America (66.7%) and the Caribbean (60.5%). Male travelers accounted for 65.5% of patients returning from eastern Asia and for 61.3% of patients returning from two or more world regions in the same trip (Table 8).

Concerning age, 87.7% of the collective was found in the age group 18 – 65 years. Patients under 18 accounted for 6.5% and 5.8% of travelers were older than 65. The mean age of the population was 38.5. The observed range was 0 - 89 years. The world region with the highest percentage of young patients was Central Asia (12.5%) and in Oceania 13% of travelers were older than 65.

| | Travel destinations | | | | | |
|---|---|---|---|---|---|---|
| **Variables** | North America (*n* = 26) | Central America (*n* = 48) | South America (*n* = 147) | Caribbean (*n* = 81) | Western Europe (*n* = 324) | Eastern Europe (*n* = 27) |
| Gender | | | | | | |
| female | 12 (46.2) | 32 (66.7) | 76 (51.7) | 49 (60.5) | 185 (57.1) | 16 (59.3) |
| male | 14 (53.8) | 16 (33.3) | 71 (48.3) | 32 (39.5) | 139 (42.9) | 11 (40.7) |
| Age (years) | | | | | | |
| Range | 19–67 | 17–70 | 3–74 | 0–75 | 1–89 | 5–59 |
| Mean | 38.6 | 37.8 | 37.9 | 36.5 | 44.0 | 37.2 |
| Median | 35.5 | 33.0 | 37.0 | 38.0 | 46.0 | 35.0 |
| Age group | | | | | | |
| <18 years | 0 (0) | 1 (2.1) | 7 (4.8) | 12 (14.8) | 20 (6.2) | 1 (3.7) |
| 18–65 years | 25 (96.2) | 44 (91.7) | 134 (91.2) | 67 (82.7) | 269 (83.0) | 26 (96.3) |
| >65 years | 1 (3.8) | 3 (6.3) | 6 (4.1) | 2 (2.5) | 35 (10.8) | 0 (0) |

| | Travel destinations (continued) | | | | | |
|---|---|---|---|---|---|---|
| **Variables** | Africa North of Sahara (*n* = 87) | Africa South. of Sahara (*n* = 737) | Central Asia (*n* = 32) | South Asia (*n* = 247) | Southeast Asia (*n* = 355) | Eastern Asia (*n* = 32) |
| Gender | | | | | | |
| female | 47 (54.0) | 370 (50.2) | 16 (50.0) | 120 (48.6) | 180 (50.7) | 11 (34.4) |
| male | 40 (46.0) | 367 (49.8) | 16 (50.0) | 127 (51.4) | 175 (49.3) | 21 (65.6) |
| Age (years) | | | | | | |
| Range | 3–77 | 0–85 | 13–62 | 2–76 | 1–78 | 19–72 |
| Mean | 40.7 | 37.0 | 37.2 | 40.1 | 35.8 | 36.7 |
| Median | 40.0 | 36.0 | 36.5 | 39.0 | 32.0 | 36.0 |
| Age group | | | | | | |
| <18 years | 6 (6.9) | 63 (8.5) | 4 (12.5) | 13 (3.7) | 13 (3.7) | 0 (0) |
| 18–65 years | 71 (81.6) | 633 (85.9) | 28 (87.5) | 221 (89.5) | 329 (92.7) | 31 (96.9) |
| >65 years | 10 (11.5) | 41 (5.6) | 0 (0) | 13 (5.3) | 13 (3.7) | 1 (3.1) |

| | Travel destinations (continued) | | | |
|---|---|---|---|---|
| **Variables** | Oceania (*n* = 23) | Middle East (*n* = 117) | Two or more (*n* = 31) | Total (*N* = 2314) |
| Gender | | | | |
| Female | 11 (47.8) | 59 (50.4) | 12 (38.7) | 1196 (51.7) |
| Male | 12 (52.2) | 58 (49.6) | 19 (61.3) | 1118 (48.3) |
| Age (years) | | | | |
| Range | 19–71 | 1–82 | 22–73 | 0–89 |
| Mean | 34.3 | 39.8 | 43.3 | 38.5 |
| Median | 30.0 | 40.0 | 42.0 | 37.5 |
| Age group | | | | |
| <18 years | 0 (0) | 10 (8.5) | 0 (0) | 150 (6.5) |
| 18–65 years | 20 (87.0) | 103 (88.0) | 29 (93.5) | 2030 (87.7) |
| >65 years | 3 (13.0) | 4 (3.4) | 2 (6.5) | 134 (5.8) |

*Table 8: Travel destinations: demographic data and travel destinations of a population of 2314 travelers presenting to the department of tropical medicine. Right to the absolute number of travelers the percentage value is displayed. Data has been split into 3 tables to simplify visualization.*

## 3.2 Travel destination

Sub-saharan Africa was visited by 31.8% of all ill returned travelers, followed by southeast Asia (15.3%), western Europe (14%) and South Asia (10.7%). The remaining regions are displayed in Figure 2.

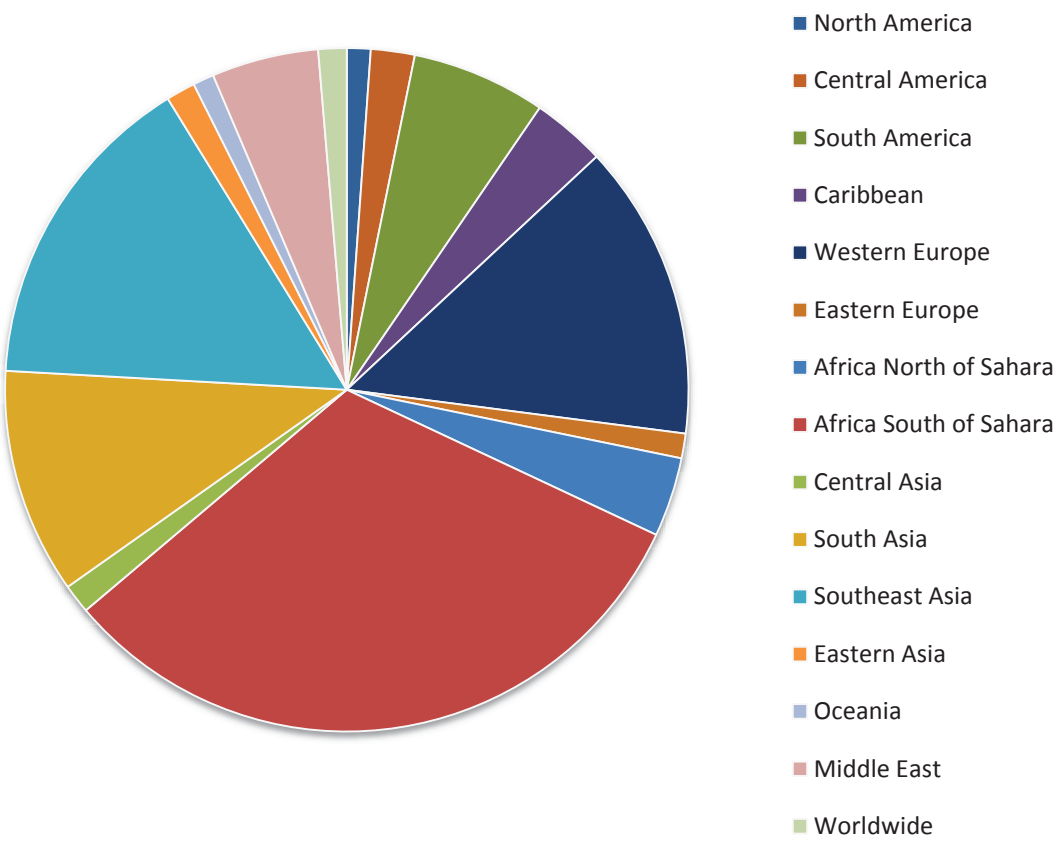


***Figure 2:Travel destinations:*** *the proportion of the visited world regions by the population of 2314 travelers is presented. Right to the absolute number of travelers (n) the percentage value is displayed. Travelers visiting 2 or more world regions were added to the group"Two or more".*

## 3.3 Global proportionate morbidity

The most common syndrome was TD (23.6%) followed by NDG (22.5%), SD (17%) and SFI (16.9%). Furthermore, a respiratory syndrome was diagnosed on 9.8% of the population, followed by non-specific symptoms (6%), underlying chronic disease (2.5%), injury (0.9%), genitourinary disease (0.7%), and neurologic disease (0.2%) (Fig. 3).

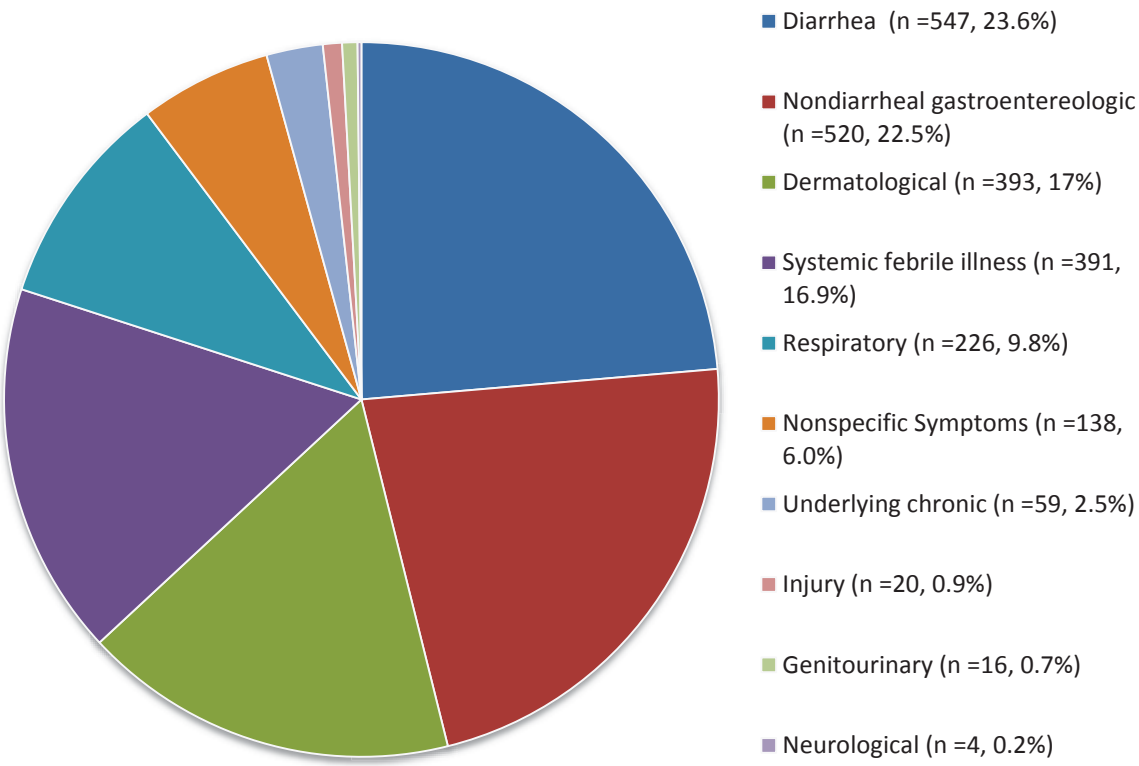


***Figure 3: Global proportionate morbidity:*** *the proportion of 10 the syndrome groups used in our study are represented. Right to the absolute number of travelers (n) the percentage value is displayed.*

## 3.4 Local proportionate morbidity

In a further step we calculated which syndromes were more commonly observed after travel to each travel destination (Table 9). Figure 4 allows visualization of the obtained data.

| Travel destination | SD | SFI | TD | NDG | RS | NSS | GU | UC | I | N |
|---|---|---|---|---|---|---|---|---|---|---|
| North America | 9 | 1 | 1 | 4 | 6 | 4 | 0 | 0 | 1 | 0 |
| Central America | 9 | 1 | 11 | 13 | 5 | 5 | 1 | 3 | 0 | 0 |
| South America | 20 | 31 | 47 | 25 | 9 | 8 | 0 | 4 | 2 | 1 |
| Caribbean | 16 | 10 | 16 | 24 | 11 | 2 | 0 | 0 | 2 | 0 |
| Western Europe | 76 | 19 | 58 | 80 | 46 | 31 | 2 | 8 | 2 | 2 |
| Eastern Europe | 8 | 1 | 0 | 13 | 1 | 3 | 0 | 1 | 0 | 0 |
| Africa North of Sahara | 11 | 5 | 36 | 20 | 7 | 4 | 2 | 1 | 1 | 0 |
| Africa South of Sahara | 115 | 209 | 137 | 171 | 49 | 32 | 6 | 13 | 4 | 1 |
| Central Asia | 0 | 2 | 3 | 26 | 1 | 0 | 0 | 0 | 0 | 0 |
| South Asia | 33 | 36 | 119 | 14 | 18 | 19 | 2 | 5 | 1 | 0 |
| Southeast Asia | 71 | 66 | 75 | 70 | 51 | 14 | 1 | 2 | 5 | 0 |
| Eastern Asia | 3 | 1 | 14 | 5 | 2 | 3 | 1 | 3 | 0 | 0 |
| Oceania | 9 | 1 | 4 | 5 | 1 | 1 | 0 | 1 | 1 | 0 |
| Middle East | 7 | 6 | 21 | 42 | 16 | 7 | 1 | 17 | 0 | 0 |
| Two or more | 6 | 2 | 5 | 8 | 3 | 5 | 0 | 1 | 1 | 0 |

***Table 9: Local proportionate morbidity:*** *syndrome groups plotted against the world regions. Only absolute numbers are shown. Following abbreviations were used: skin disorders (SD), systemic febrile illness (SFI), traveler's diarrhea (TD), non-diarrheal gastrointestinal disorders (NDG), respiratory syndrome (RS), non-specific symptoms (NSS), genitourinary (GU), underlying chronic (UC), Injury (I) and neurological (N).*

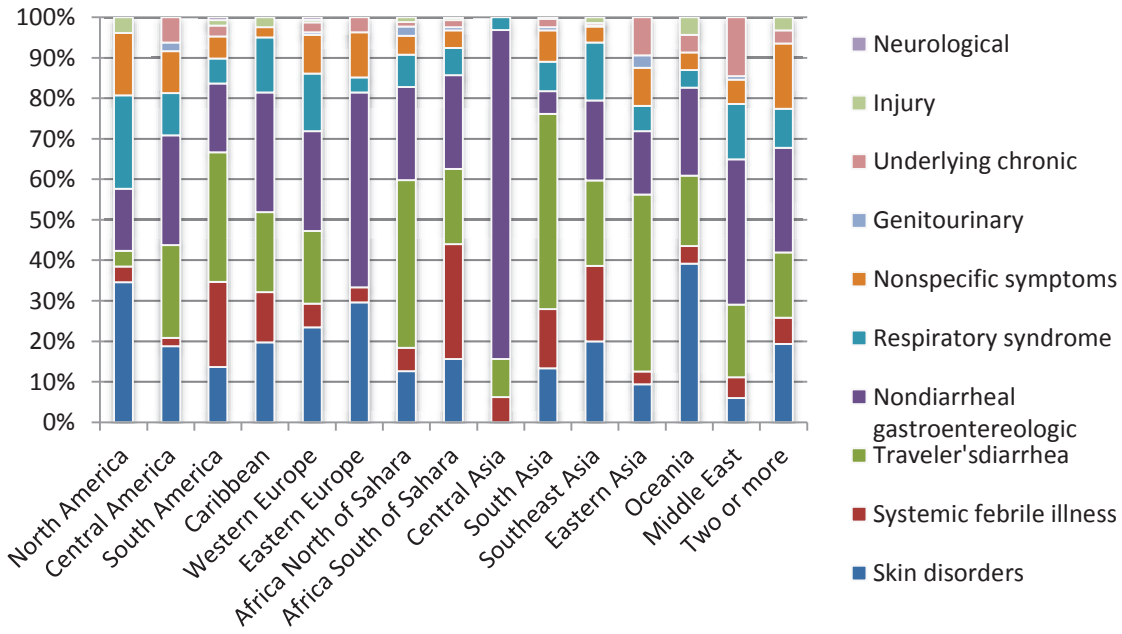


***Figure 4: Local proportionate morbidity:*** *distribution of the 10 syndrome groups in each world region.*

## 3.5 Odds Ratio of most common syndromes

### 3.5.1 Traveler's diarrhea

TD was the most common syndrome in our population (23.6%). The region of South Asia had the highest OR (4.26) with a high level of statistical significance ($p < 0.001$). Eastern Asia came second (OR 3.57, $p < 0.01$), followed by northern Africa (OR 3.24, $p < 0.001$) (Table 10).

| Travel destination | *n* | (%) | OR | | 95% CI | | *p* |
|---|---|---|---|---|---|---|---|
| Western Europe (reference) | 58 | (10.6) | | | | | |
| North America | 1 | (0.2) | 0.18 | | [0.02; 1.38] | | .10 |
| Central America | 11 | (2.0) | 1.36 | | [0.66; 2.83] | | .41 |
| South America | 47 | (8.6) | 2.16 | ** | [1.38; 3.37] | < | .01 |
| Caribbean | 16 | (2.9) | 1.13 | | [0.61; 2.09] | | .70 |
| Eastern Europe | 0 | (0.0) | | | | | |
| Africa North of Sahara | 36 | (6.6) | 3.24 | *** | [1.94; 5.40] | < | .001 |
| Africa South of Sahara | 137 | (25.0) | 1.05 | | [0.75; 1.47] | | .79 |
| Central Asia | 3 | (0.5) | 0.47 | | [0.14; 1.61] | | .23 |
| South Asia | 119 | (21.8) | 4.26 | *** | [2.92; 6.22] | < | .001 |
| Southeast Asia | 75 | (13.7) | 1.23 | | [0.84; 1.80] | | .29 |
| Eastern Asia | 14 | (2.6) | 3.57 | ** | [1.68; 7.58] | < | .01 |
| Oceania | 4 | (0.7) | 0.97 | | [0.32; 2.94] | | .95 |
| Middle East | 21 | (3.8) | 1.00 | | [0.58; 1.74] | | .99 |
| Two or more | 5 | (0.9) | 0.88 | | [0.32; 2.39] | | .81 |
| Total | 547 | (100) | | | | | |

* $p < .05$, ** $p < .01$, *** $p < .001$

***Table 10: Odds ratio (OR) of developing traveler's diarrhea (TD):*** *the OR for the development of TD was calculated for each region. The patients returning from western Europe were defined as the control population. P-values were defined as follows:* $p < .05$, ** $p < .01$, *** $p < .001$*

### 3.5.2 Non-diarrheal gastrointestinal disorders

The second most common syndrome in our population was NDG. The Region of Central Asia had the highest OR (OR 13.22, $p < 0.001$) in the group. Furthermore, patients returning from eastern Europe (OR 2.83, $p < 0.05$) and the Middle East (OR 1.71 $p < 0.05$) followed in the range of statistical significance (Table 11).

| **Travel Destination** | ***n*** | **(%)** | **OR** | | **95% CI** | | ***p*** |
|---|---|---|---|---|---|---|---|
| Western Europe (reference) | 80 | (15.4) | | | | | |
| North America | 4 | (0.8) | 0.55 | | [0.19; 1.66] | | .29 |
| Central America | 13 | (2.5) | 1.13 | | [0.57; 2.25] | | .72 |
| South America | 25 | (4.8) | 0.62 | | [0.38; 1.03] | | .06 |
| Caribbean | 24 | (4.6) | 1.28 | | [0.75; 2.20] | | .36 |
| Eastern Europe | 13 | (2.5) | 2.83 | * | [1.28; 6.28] | | .01 |
| Africa North of Sahara | 20 | (3.8) | 0.91 | | [0.52; 1.59] | | .74 |
| Africa South of Sahara | 171 | (32.9) | 0.92 | | [0.68; 1.25] | | .60 |
| Central Asia | 26 | (5.0) | 13.22 | *** | [5.25; 33.26] | < | .001 |
| South Asia | 14 | (2.7) | 0.18 | *** | [0.10; 0.33] | < | .001 |
| Southeast Asia | 70 | (13.5) | 0.75 | | [0.52; 1.08] | | .12 |
| Eastern Asia | 5 | (1.0) | 0.56 | | [0.21; 1.52] | | .26 |
| Oceania | 5 | (1.0) | 0.85 | | [0.30; 2.36] | | .75 |
| Middle East | 42 | (8.1) | 1.71 | * | [1.08; 2.69] | | .02 |
| Worldwide | 8 | (1.5) | 1.06 | | [0.46; 2.47] | | .89 |
| Total | 520 | | | | | | |
| * $p < .05$, ** $p < .01$, *** $p < .001$ | | | | | | | |

*Table 11: Odds ratio (OR) of non-diarrheal gastrointestinal disorders (NDG): the OR for the development of NDG was calculated for each region. The patients returning from western Europe were defined as the control population. P-values were defined as follows:* p < .05, ** p < .01, *** p < .001.*

### 3.5.3 Systemic febrile illness

The third most common syndrome in our population was SFI: Sub Saharan Africa (OR 6.35, $p < 0.001$) was the leading region with an absolute number of 209 patients (53.5% of the population). South America (OR 4.29, $p < 0.001$), Southeast Asia (OR 3.67, $p < 0.001$) and South Asia (OR 2.74, $p < 0.01$) were further risk regions (Table 12).

| **Travel Destination** | ***n* (%)** | **OR** | | **95% CI** | | ***p*** |
|---|---|---|---|---|---|---|
| Western Europe (reference) | 19 (4.9) | | | | | |
| North America | 1 (0.3) | 0.64 | | [0.08; 5.00] | | .67 |
| Central America | 1 (0.3) | 0.34 | | [0.04; 2.61] | | .30 |
| South America | 31 (7.9) | 4.29 | *** | [2.33; 7.89] | < | .001 |
| Caribbean | 10 (2.6) | 2.26 | * | [1.01; 5.07] | | .05 |
| Eastern Europe | 1 (0.3) | 0.62 | | [0.08; 4.80] | | .64 |
| Africa North of Sahara | 5 (1.3) | 0.98 | | [0.35; 2.70] | | .97 |
| Africa South of Sahara | 209 (53.5) | 6.35 | *** | [3.89; 10.38] | < | .001 |
| Central Asia | 2 (0.5) | 1.07 | | [0.24; 4.82] | | .93 |
| South Asia | 36 (9.2) | 2.74 | ** | [1.53; 4.91] | < | .01 |
| Southeast Asia | 66 (16.9) | 3.67 | *** | [2.15; 6.26] | < | .001 |
| Eastern Asia | 1 (0.3) | 0.52 | | [0.07; 4.00] | | .53 |
| Oceania | 1 (0.3) | 0.73 | | [0.09; 5.71] | | .76 |
| Middle East | 6 (1.5) | 0.87 | | [0.34; 2.23] | | .77 |
| Worldwide | 2 (0.5) | 1.11 | | [0.25; 4.99] | | .89 |
| Total | 391 | | | | | |

* $p < .05$, ** $p < .01$, *** $p < .001$

***Table 12: Odds ratio (OR) of systemic febrile illness (SFI):*** *the OR for the development of SFI was calculated for each region. The patients returning from western Europe were defined as the control population. P-values were defined as follows:* p < .05, ** p < .01, *** p < .001.*

## 3.6 Data analysis of specific diagnosis

### 3.6.1 Proportionate morbidity and odds ratio of malaria

The majority of malaria cases came from Sub Saharan Africa (80.8%). Southeast Asia (8.3%), South Asia (6.6%), South America (2.2%), Caribbean (0.9%), Africa north of Sahara (0.4%), eastern Asia (0.4%) and patients visiting two or more regions (0.4%) accounted for the remaining cases (Table 13).

| **Travel destination** | ***n*** | **(%)** |
|---|---|---|
| Western Europe (reference) | 0 | (0.0) |
| North America | 0 | (0.0) |
| Central America | 0 | (0.0) |
| South America | 5 | (2.2) |
| Caribbean | 2 | (0.9) |
| Eastern Europe | 0 | (0.0) |
| Africa North of Sahara | 1 | (0.4) |
| Africa South of Sahara | 185 | (80.8) |
| Central Asia | 0 | (0.0) |
| South Asia | 15 | (6.6) |
| Southeast Asia | 19 | (8.3) |
| Eastern Asia | 1 | (0.4) |
| Oceania | 0 | (0.0) |
| Middle East | 0 | (0.0) |
| Two or more | 1 | (0.4) |
| Total | 229 | (100) |

***Table 13: Malaria:*** *the absolute number of pateints (n) and the percentage value (%) are displayed for each world region*

The odds ratio (OR) of acquiring malaria after visiting southern Africa was 11.28 with a *p* value under 0.001 (Table 14).

| **Travel Destination** | **OR** | **95%CI** | ***p*** |
|---|---|---|---|
| Africa South of Sahara | 11.28*** | [7.98; 15.94] | <.001 |
| * $p < .05$, ** $p < .01$, *** $p < .001$ | | | |

***Table 14: Odds ratio (OR) of developing Malaria after travel to Sub Saharan Africa:*** *the OR for the development of malaria was calculated for Sub Saharan Africa. Patients returning from western Europe were defined as the control population.*

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### 3.6.2 Proportionate morbidity and odds ratio of dengue fever

Most travelers diagnosed with dengue fever returned from the endemic regions of South East Asia (45.5%), South Asia (22.7%). Sub Saharan Africa (15.9%), the Caribbean (11.4%), and South America (4.5%) (Table 15).

| **Travel destinations** | ***n*** | **(%)** |
|---|---|---|
| Western Europe (reference) | 0 | (0.0) |
| North America | 0 | (0.0) |
| Central America | 0 | (0.0) |
| South America | 2 | (4.5) |
| Caribbean | 5 | (11.4) |
| Eastern Europe | 0 | (0.0) |
| Africa North of Sahara | 0 | (0.0) |
| Africa South of Sahara | 7 | (15.9) |
| Central Asia | 0 | (0.0) |
| South Asia | 10 | (22.7) |
| Southeast Asia | 20 | (45.5) |
| Eastern Asia | 0 | (0.0) |
| Oceania | 0 | (0.0) |
| Middle East | 0 | (0.0) |
| Worldwide | 0 | (0.0) |
| Total | 44 | (100) |

***Table 15: Dengue fever:*** *the absolute numbers (n) and the percentage value (%) are displayed for each world region.*

Of note, the OR of acquiring dengue fever while traveling to Southeast Asia was 4.81 (Table 16). The p value was below 0.001.

| **Travel Destination** | **OR** | **95%CI** | ***p*** |
|---|---|---|---|
| Southeast Asia | 4.81*** | [2.63; 8.81] | <.001 |
| * $p < .05$, ** $p < .01$, *** $p < .001$ | | | |

***Table 16: Odds ratio (OR) of developing dengue fever after travel to Southeast Asia:*** *the OR for the development of dengue fever was calculated for Southeast Asia. Patients returning from western Europe were defined as the control population.*

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### 3.6.3 Proportionate morbidity of pulmonary tuberculosis

Regions without a single case were not included in the table. Most patients were exposed in sub-saharan Africa. South Asia, South America and the Middle East followed.The leading region was sub-saharan Africa (41.2%), followed by South Asia (17.6%). A total of 17 cases of PTB were observed (Table 17).

| **Travel destinations** | *n* (%) |
|---|---|
| South America | 2 (11.8) |
| Eastern Europe | 1 (5.9) |
| Africa North of Sahara | 1 (5.9) |
| Africa South of Sahara | 7 (41.2) |
| South Asia | 3 (17.6) |
| Southeast Asia | 1 (5.9) |
| Middle East | 2 (11.8) |
| Total | 17 (100) |

*Table 17: Proportionate morbidity of pulmonary tuberculosis: the absolute numbers (n) and the percentage value (%) are displayed for each world region.*

## 3.7 Skin disorders

### 3.7.1 Most common skin disorders

The most common dermatologic syndromes observed were: bacterial (28.2%), arthropod related (24.9%), STD (10.2%), cutaneous larva migrans (6.4%), rickettsiosis (6.1%), lymphatic filariasis (5.6%), among others. Data is displayed on Table 18.

| **Dermatologic syndromes** | *n* (%) | |
|---|---|---|
| Bacterial | 111 | (28.2) |
| Arthropod related | 98 | (24.9) |
| STD | 40 | (10.2) |
| Cutaneous Larva migrans | 25 | (6.4) |
| Rickettsiosis | 24 | (6.1) |
| lymphatic filariasis | 22 | (5.6) |
| Other dermatologic | 19 | (4.8) |
| Animal related | 17 | (4.3) |
| lymph node tuberculosis | 14 | (3.6) |
| Cellulitis | 9 | (2.3) |
| Allergic related | 7 | (1.8) |
| Mite infestation | 7 | (1.8) |
| Total | 393 | (100) |

***Table 18: most common skin disorders:*** *absolute numbers (n) and percentage values (%) for each dermatologic syndrome for the dermatologic population of 393 travelers.*

### 3.7.2 Most common skin disorders in each region

The next step was to analyze the relationship between the most important dermatologic syndromes and each world region. Only the 5 most frequent diagnosis were plotted in order to facilitate visualization of the obtained data (Fig. 5).

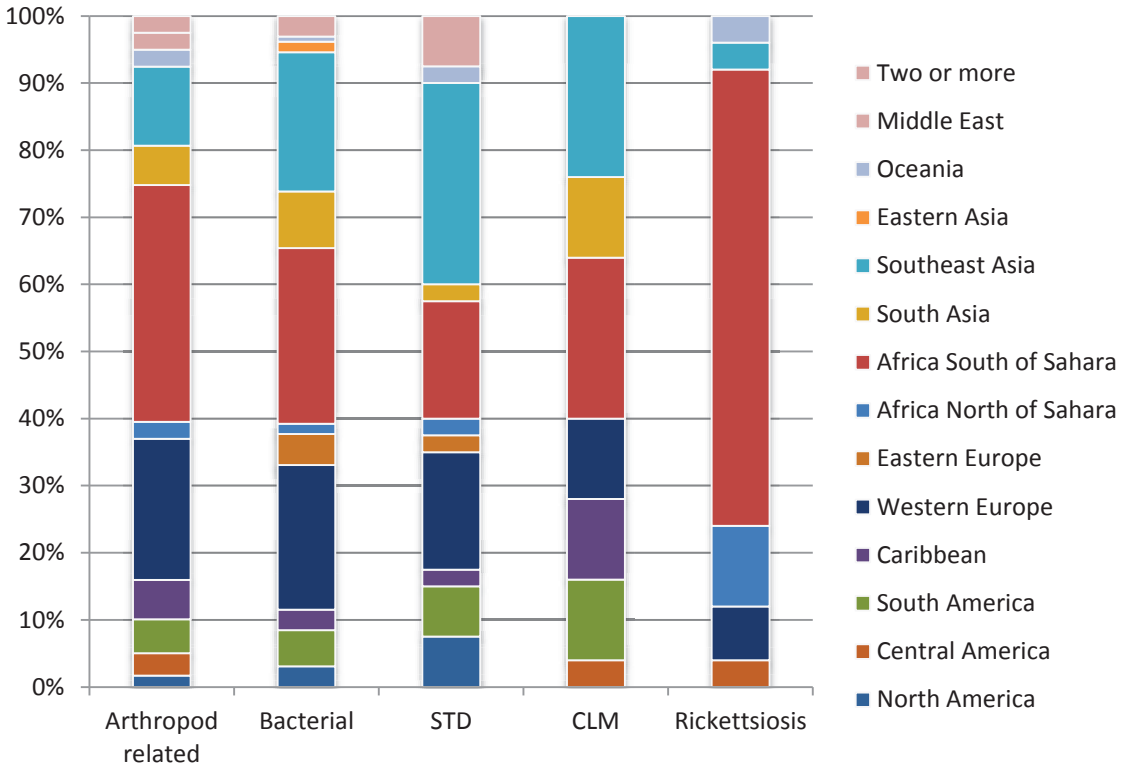


***Figure 5: most common dermatologic syndromes in each world region:*** *the 5 most frequent dermatologic syndromes were plotted against the geographic regions used in the study. STD denotes sexually transmitted diseases, CLM denotes cutaneous larva migrans..*

### 3.7.3 Relative risk of skin disorders

In a further step, we estimated the RR of developing SD after travel to each world region as described by Herbinger et al.[16] (Table 19).

| World Region | No of air passengers | Patients with SD | RR |
|---|---|---|---|
| North America | 11235595 | 9 | **0,40** |
| Central America | 2709303 | 9 | **1,68** |
| South America | 1300226 | 20 | **7,76** |
| Caribbean | 716549 | 16 | **11,26** |
| Western Europe | 130892767 | 76 | **0,29** |
| Eastern Europe | 15610678 | 8 | **0,26** |
| Africa North of Sahara | 3432500 | 11 | **1,62** |
| Africa South of Sahara | 1699422 | 115 | **34,12** |
| Central Asia | 371991 | 0 | **0,00** |
| South Asia | 1619118 | 33 | **10,28** |
| Southeast Asia | 2825474 | 71 | **12,67** |
| Eastern Asia | 3724901 | 3 | **0,41** |
| Oceania | 84407 | 9 | **53,77** |
| Middle East | 18929460 | 7 | **0,19** |

***Table 19: Relative risk (RR) of developing skin disorders (SD):*** *using the total numbers of passengers flying from Germany to overseas during the study period and the number of patients presenting with SD we calculated the RR of developing SD for each world region. The equation used is discussed in the section "Materials and methods".*

### 3.7.4 Proportionate morbidity and odds ratio of STD in each region

Thirty percent of travelers presenting with STD returned from Southeast Asia followed by Sub Saharan Africa (17.5%) and western Europe (17.5%) (Fig. 6).

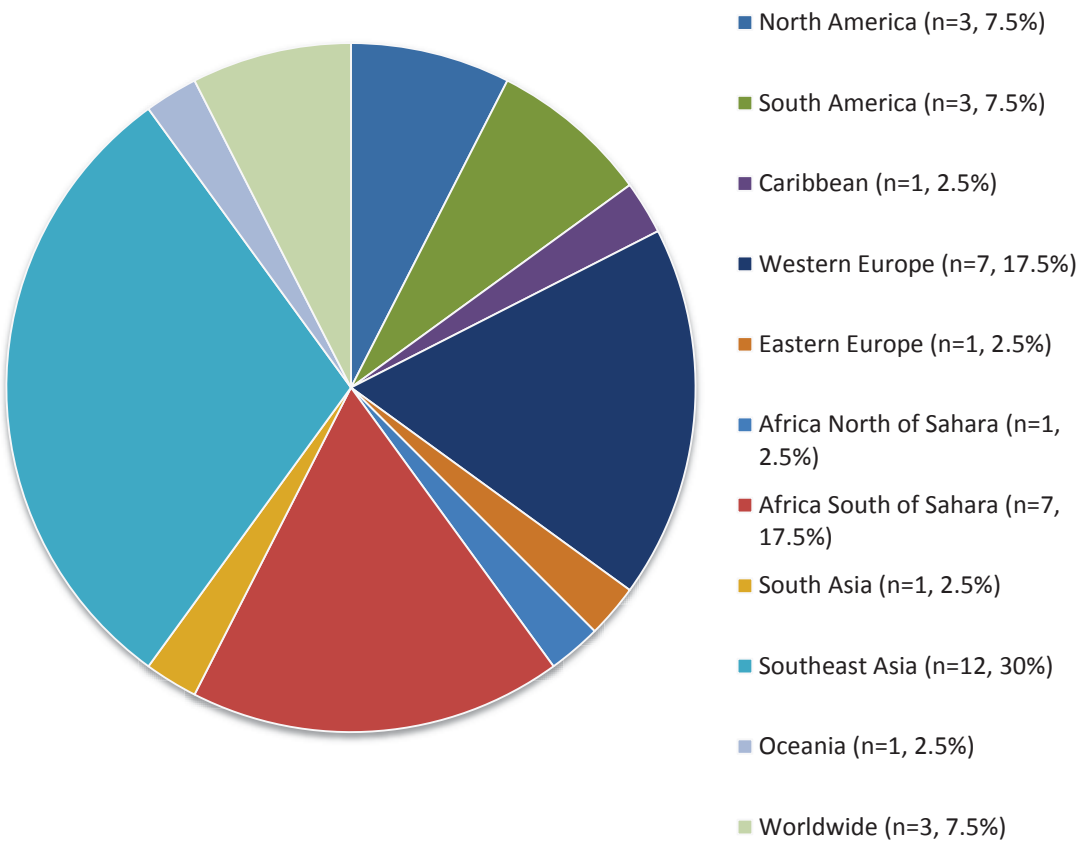


***Figure 6: Sexually transmited diseases (STD):*** *the proportion of travelers returning home with STD after traveling to each travel destination is displayed.*

The OR of developing STD after visiting Southeast Asia was 2.0. The *p* value was measured at 0.17. Furthermore, travelers returning from North America accounted for 7.5% of the STD population with an OR of 4.93. ($p < 0.05$) (Table 20).

| **Travel destinations** | ***n*** | **(%)** | **OR** | | **95% CI** | ***p*** |
|---|---|---|---|---|---|---|
| Western Europe (reference) | 7 | (17.5) | | | | |
| North America | 3 | (7.5) | 4.93 | * | [1.01; 24.15] | .05 |
| Central America | 0 | (0.0) | | | | |
| South America | 3 | (7.5) | 1.74 | | [0.41; 7.44] | .46 |
| Caribbean | 1 | (2.5) | 0.66 | | [0.08; 5.75] | .70 |
| Eastern Europe | 1 | (2.5) | 1.41 | | [0.15; 13.16] | .76 |
| Africa North of Sahara | 1 | (2.5) | 0.99 | | [0.11; 8.88] | .99 |
| Africa South of Sahara | 7 | (17.5) | 0.64 | | [0.21; 1.90] | .42 |
| South Asia | 1 | (2.5) | 0.31 | | [0.04; 2.61] | .28 |
| Southeast Asia | 12 | (30.0) | 2.00 | | [0.74; 5.42] | .17 |
| Eastern Asia | 0 | (0.0) | | | | |
| Oceania | 1 | (2.5) | 1.23 | | [0.13; 11.34] | .85 |
| Middle East | 0 | (0.0) | | | | |
| Two or more | 3 | (7.5) | 9.86 | * | [1.66; 58.40] | .01 |
| Total | 40 | | | | | |

* $p < .05$, ** $p < .01$, *** $p < .001$

***Table 20: Odds ratio (OR) of developing sexually transmitted diseases (STD):*** *the OR was calculated for each travel destination. Statistical significance (p < .05) was achieved for North America and for travelers visiting two or more regions on the same trip. The leading region of Southeast Asia (n = 12, 30%) failed to achieve statistical significance (OR = 2.0 p = .17)*

### 3.7.5 Proportionate morbidity of rickettsiosis

The majority of patients came from sub-saharan Africa (70.8%), followed by northern Africa (12.5%) and western Europe (8.3%). Southeast Asia and Oceania had respectively one case of rickettsiosis (Fig. 7).

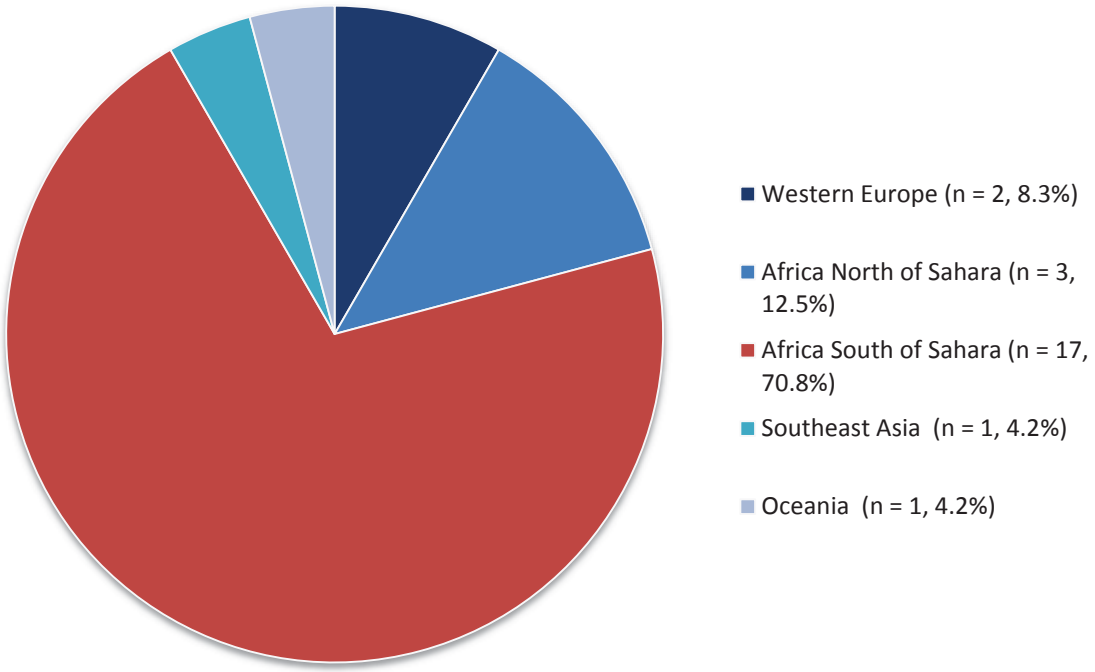


**Figure 7: Rickettsiosis:** the proportion of travelers returning home with rickettsiosis after traveling to each travel destination is displayed. T*he absolute numbers (n) and the percentage value (%) are displayed for each world region*.

### 3.7.6 Proportionate morbidity of lymphatic filariasis

Most patients came from sub-saharan Africa (59.1%), followed by Southeast Asia (22.7%) and South Asia (9.1%). The remaining cases came from South America and the Caribbean (Fig. 8).

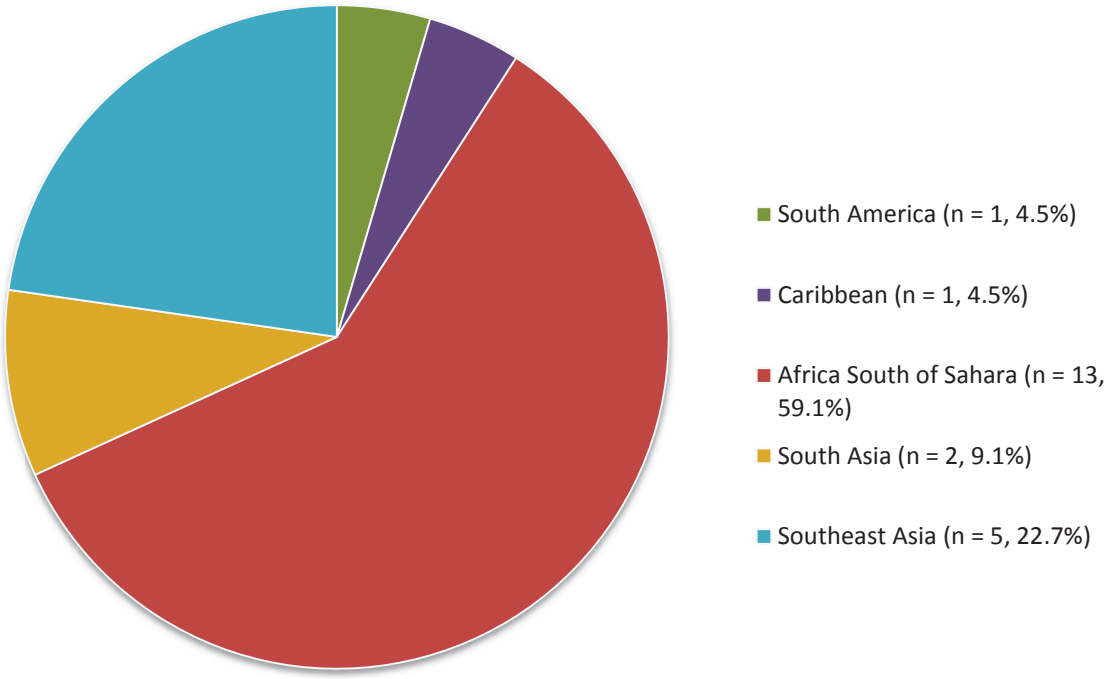


***Figure 8:Filariasis:*** *the proportion of travelers returning home with filariasis after traveling to each travel destination is displayed. The absolute numbers (n) and the percentage value (%) are displayed for each world region.*

### 3.7.7 Proportionate morbidity of cutaneous leishmaniasis

We observed that most of cases of CL (68.8%) were diagnosed on patients returning from western Europe (Figure 8). Central America (12.5%) came second followed by South America, Middle East and Sub Saharan Africa, with 6.3% each (Fig. 9).

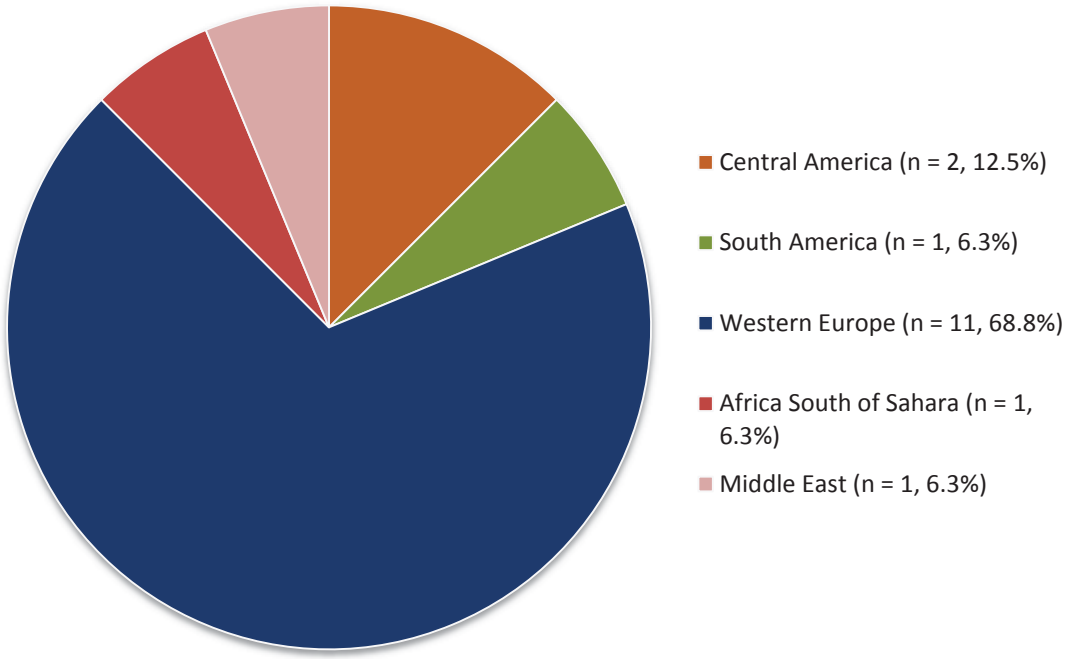


***Figure 9: Cutaneous leishmaniasis:*** *the proportion of travelers returning home with cutaneous leishmaniasis after traveling to each travel destination is displayed. The absolute numbers (n) and the percentage value (%) are displayed for each world region.*

### 3.7.8 Proportionate morbidity of lymph node tuberculosis

Out of 14 cases, 8 cases came from Africa – 4 from North Africa and 4 from sub-saharan Africa. The remaining cases of LKTB came from South Asia, western Europe and Southeast Asia (Fig. 10).

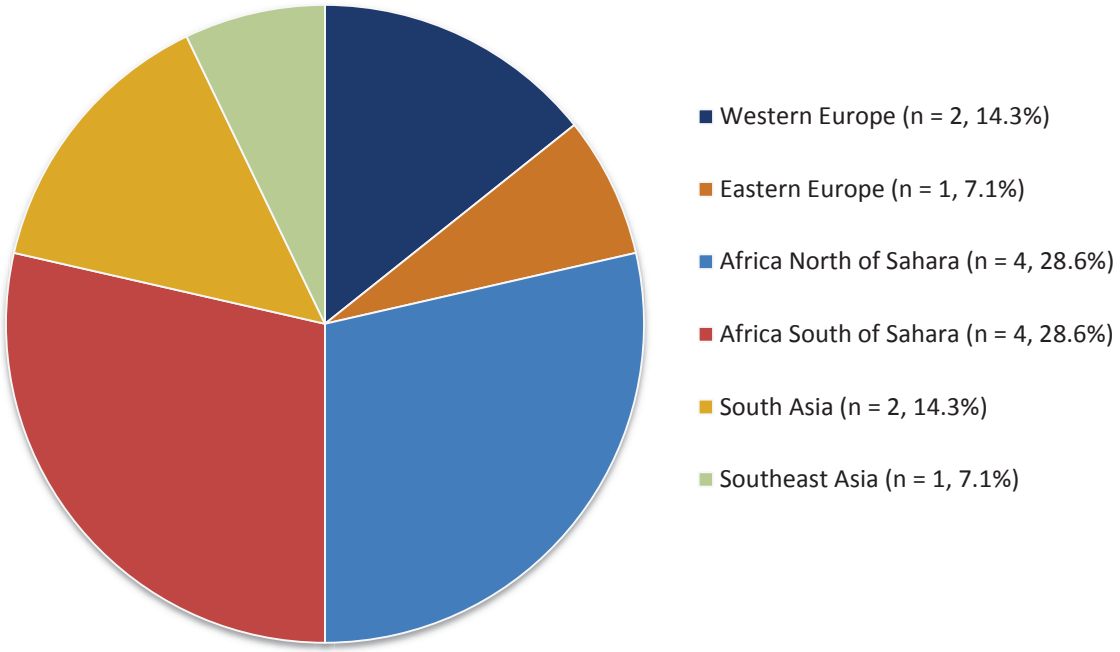


***Figure 10: lymph node tuberculosis:*** *The absolute numbers (n) and the percentage value (%) are displayed for each world region.*

# 4 Discussion

## 4.1 Demographics

We observed an almost equal number of female (51.7%) and male (48.3%) travelers in the present study. There is, however, some variation in selected world regions. The highest proportion of female travelers were observed in Central America (66.7%) and the Caribbean (60.5%). A similar trend has been reported by Freedman et al: of all regions, the Caribbean received the highest proportion of female travelers (54%).[5] The first scientific report highlighting specifically this phenomenon was published by Pruitt et al.[41] The authors describe the emerging phenomenon of sex tourism (defined as travel for the purpose of or in expectation of having sex with local men) pursued by women visiting the Caribbean. It remains speculative whether similar motivations were present in our population. We did not observe increased levels of STD in this region. An in-depth review of the topic is offered by Bauer et al.[42]

Male travelers accounted for 65.5% of patients returning from eastern Asia. This region encompassing China, Japan, Hong Kong, North and South Korea is not a primary destination for male sex tourism.[42] Men on business trips are the more probable motivation, as these countries have intense commercial relationship with Germany. As the reason for travel was not documented in this study, this interpretation remains speculative.

The mean age was 38.5 and the median age was 37.5. The median ages reported by Freedman[5] (33), Harvey[6] (34) and Herbinger[16] (37.4) stays in the same range of our population. The majority of patients was 18 – 65 years (87.7%). Patients under 18 accounted for 6.5% and 5.8% of travelers were older than 65. Again here, similar figures have been reported by the authors mentioned above.

## 4.2 Travel destination

In the present study, the region of sub-saharan Africa was visited by 31.8% of the population, followed by Southeast Asia (15.3%), western Europe (14%), South Asia

(10.7%), South America (6.4%), Middle East (5.1%), northern Africa (3.8%) and the Caribbean (3.5%). The full results can be seen in Figure 2. These findings differ from those observed in a large worldwide multi-center study[6]: sub-saharan Africa (23%), Central America (15%), South America (12%), the Caribbean (9%), South Central Asia (8%), South East Asia (7%) and western Europe (5%) were the leading regions in this larger population. It is important to highlight the fact that this study was performed in Germany leads to a certain level of "concentration" of travel in the region around Europe. About 80% of individuals travel within the boundaries of their geographic region.[1] It is crucial to take this into consideration when comparing our data to studies centered around the United States, for instance.

## 4.3 Most common syndromes

The most common syndromes within the study population were observed as follows: TD (23.6%), NDG (22.5%), SD (17%), SFI (16.9%), respiratory syndrome (9.8%), non-specific symptoms (6%), underlying chronic disease (2.5%), injury (0.9%), genitourinary disease (0.7%), and neurologic disease (0.2%).

The observed data correlates well to medical literature on the topic. The most frequent diagnostic groupings according to Harvey et al[6]. were TD (22%), NDG (15%), SFI (14%), and SD (12%). Field et al.[35] reported in 2010 following data: TD (24%), NDG (9%), SFI (20%), and SD (12%). These four syndrome groupings are also the leading causes of morbidity in study performed among expatriates.[43]

There is, however, an individual trend in our data. Taken together, TD and NDG account for 46.1% of all patients, which is more than has been observed in some international multicenter studies.[6, 43] We interpret this finding in three ways: first, our population contains a proportionately high number of patients coming from the endemic regions of Africa (35.6%) and southern Asia (26%). Second, our results are in line with a study of 5965 travelers of European origin (where TD and NDG accounted for 41% of all diseased travelers).[29] Finally, the department of tropical medicine is a part of the gastroenterological clinic, certainly increasing the input of patients with overall gastrointestinal problems.

## 4.4 Proportionate morbidity and odds ratio of most common syndromes

### 4.4.1 Traveler's diarrhea

TD is the most common cause of travel associated morbidity.[18,22,25,44] In endemic areas, 50- 90% of travelers may develop symptoms.[45] Several factor influence the risk of the disease. The most important variable has been consistently reported to be the travel destination.[23,24] Diemert et al.[24] have proposed that high risk regions for the disease include southern Asia, Africa and South America[8,24]. Medium risk regions include southern Europe, the Middle East and South Africa while northern European countries, the United States and Australia are described as low risk regions.[24] Furthermore, traveling during summer or rainy periods has been indicated as a further risk factor.[46]

TD was the most commonly observed condition in our study with a cumulative incidence of 23.6%. Values around 20% have been observed by other authors.[6,35] The highest rate of traveler's diarrhea in our study has been observed in South Asia where out of 247 patients seeking medical assistance in our department 119 had diarrhea (48%). The OR was measured at 4.26. The link between the disease and South Asia is well documented.[47,48] Further regions where a statistically significant increased OR was measured include eastern Asia (OR = 3.57), northern Africa (OR = 3.24) and South America (OR = 2.16). Our data is in line with the classification proposed by Diemert et al.[24] with the exception of eastern Asia, which in our data was associated with morbidity comparable to that of the endemic region of South Asia.

### 4.4.2 Non-diarrheal gastrointestinal syndrome

This category of diseases includes all gastrointestinal disorders which are not primarily associated with diarrhea. Examples among this broad group include viral hepatitis, nematode infestation (including strongyloidiasis and ascariasis), general abdominal pain, echinococcosis among many others. It comprehends a vast number of individual diseases with individual features in each world region. It was the second most commonly observed broad syndrome in our study (22.5%). It also comes second in a large study of the GeoSentinel Group[6] (15% of all patients)

although other authors have reported lower levels.[35] Before proceeding with the discussion of our findings, it is important to make a few remarks.

It may be helpful to compare this disease group with TD, where several gastrointestinal pathogens lead to a more or less homogenous diarrheal syndrome which is labeled as “traveler’s diarrhea”. There are differences in the incubation time, severity and therapeutic measures related to the condition, but the overall similarities in the clinical picture allow the publication of consistent papers and guidelines.[22,49,50]

The group of NDG, in contrast, is represented by individual diseases which share more differences than similarities. For this reason, our data can only be discussed case by case. There are a few remarks which can explain some of our findings:

First, we have measured a very high OR (13.22, $p < .001$) for NDG disease in the region of central Asia. The absolute number of travelers to the region of Afghanistan, Azerbaijan, Kazakhstan, Kirgizstan, Uzbekistan was low (n = 32, 1.4%). Twenty six presented with NDG and these patients accounted for only 5% of the syndrome group. Reviewing our data, we have found 14 cases of echinococcosis in the region. Considering 32 travelers to the region, this explains the measured OR. The tropical medicine department is as a transregional center for the disease.[51] Echinococcosis is endemic zoonotic disease in the region of central Asia.[52–54] The pathogens *E. granulosus*, *E. multilocularis*, *E. oligarthrus* and *E. vogeli* cause cystis commonly localized in the liver or less frequently in the lungs. Symptoms include weight loss, abdominal pain, jaundice, fever or cough. Our data highlights the importance of this differential diagnosis for patients with unspecific symptoms with a travel history to central Asia. Rarely, autochthonous transmission in Germany can occur.[55]

Second, patients returning from eastern Europe presented a high OR for non-diarrheal gastrointestinal disease. Reviewing the data, we saw a considerable number of cases of viral hepatitis. This is in line with other studies which emphasize the high prevalence of viral hepatitis in this region.[56,57] Moreover, echinococcosis is an endemic disease in Russia[58] and it has been diagnosed in

patients returning from eastern Europe.

Finally, the reference population of travelers voyaging within Europe had levels of NDG (24%) which were comparable to the overall population (22.5%). Reviewing the data, helmintic infections were a common place within this group. We assume exposure in southern Europe, where endoparasites are more frequent than in northern Europe.[59]

### 4.4.3 Systemic febrile illness

Among the syndrome groups in the context of travel medicine, patients presenting with SFI require the highest level of medical attention. A study by Wilson et al[28]. showed that 26% of patients presenting with fever had to be hospitalized. Detailed medical history and knowledge of endemic infectious diseases in the visited region is of crucial importance to guide diagnostic and therapeutic decisions. Importantly, this syndrome group is represented by diseases which are characterized by fever as a primary symptom (such as malaria, dengue, Chagas disease or typhoid fever) and not by conditions where it is an associated symptom (for example, febrile diarrhea, measles or an infected wound).

SFI was observed on 16.9% of our patients. The majority of patients (n = 209, 53.5%) were returning from sub-saharan Africa. Second came southeast Asia (n = 66, 16.9%) followed by south Asia (n = 36, 9.2%) and South America (n = 31, 7.9%). In all the above mentioned regions, a statistically significant increased OR could be measured – the highest in southern Africa (OR = 6.35, $p > .001$). Our data correlates well with published data. Harvey et al.[6] observed 14% in the group febrile/systemic disease. Malaria was the most frequent single diagnose in the group (3% of the overall population). Malaria was also the most common diagnose within the SFI population returning from the developing world of a further important study.[5]

## 4.5 Data analysis of specific diagnosis

### 4.5.1 Malaria

About 2000 people die each day in Africa due to malaria, most of them children.[60] Measures such as chemoprophylaxis[61], use of insecticides[62] and new drugs such as artesunate[63] are helping to decrease disease burden. The difficult objective of eradication of malaria has been gaining new impulse in some regions of the world.[60,64,65] Imported cases of malaria are becoming more frequent in Europe due to increased tourism in the tropics, immigration, and travelers visiting friends and relatives, especially in the african continent.[66]

The majority of malaria cases in the present study came from sub-saharan Africa (80.8%). southeast Asia (8.3%), south Asia (6.6%), South America (2.2%), Caribbean (0.9%), northern Africa (0.4%), eastern Asia (0.4%) and patients visiting two or more regions (0.4%) followed. To put this data in perspective, a few concepts have to be reviewed.

As mentioned in the above sections, the reason for travel also plays a role in the assessment of risk of a given traveler. Travelers visiting friends and relatives are less prone to seek pre-travel consultation.[29] They frequently assume they are familiar with the health risks in the visited region or that they possess long-lasting immunity against endemic infectious diseases. A large study has shown, that most travel-related malaria infections in sub-saharan Africa were associated with a visit to friends or relatives.[6] African immigrants residing in Europe who travel to Africa are a major source of malaria in Europe.[66]

Here, one limitation of this study becomes apparent: the reason for travel was not documented in our population. We do assume, however, that most of the malaria patients have an immigration background or were visiting friends and relatives. Out of the 229 malaria cases present in this examination, 185 came from sub-saharan Africa, generating an OR of 11.28 ($p < .001$).

Nevertheless, it is important to note that our data indicates clearly that malaria is an important diagnosis for travelers returning to Europe from Africa with SFI.

### 4.5.2 Dengue fever

Dengue fever represents a further leading cause of morbidity in the southern half of the globe. In most of South America, northern Africa, on parts of the Mediterranean and southern Asia it is possible to find the vector A*edes aegypti* which transmits the RNA virus of Flaviviridae family. Dengue fever is the most common arboviral disease in the world with an incidence which could reach 390 million annual infections worldwide.[31] Dengue fever represents an important differential diagnosis to malaria.[67] Poverty and housing conditions are the main risk factor for the disease.[68] In the last few years there has been considerable advance in the development of a vaccine, but to this date none has been approved for commercial use.[69]

We have observed a total of 44 patients with dengue fever in our population or 11% of the population presenting with SFI. The exact same level has been reported by Harvey et al[6]. The distribution of dengue fever in our study was observed as follows: Southeast Asia (45.5%), South Asia (22.7%). sub-saharan Africa (15.9%), the Caribbean (11.4%) and South America (4.5%). The OR was highest at southeast Asia (OR = 4.81, $p < .001$). This highlights the widespread distribution of the disease.

### 4.5.3 Pulmonary tuberculosis

PTB represents a major health care challenge worldwide. The incidence of the disease was estimated at 7.5 million new cases in 2013, and it was the cause of death of about 1.3 million in the same year.[60] The disease has a worldwide distribution, but disease burden is especially high in the developing world.[70] Recently, attention has been drawn to the spread of tuberculosis (TB) in african prisons.[71] TB screening before travel has been suggested for health care workers working abroad in order to reduce the risk of infection.[72] Moreover, data generated in our clinic indicate that the diagosis of TB in immigrants to Germany is often delayed.[73]

We have identified a total of 17 patients presenting to the department of tropical medicine with a positive travel history to an endemic zone. The majority of the

patients had a travel history to sub-saharan Africa (7 patients), followed by south Asia (3 patients), South America and the Middle East (both 2 patients). Beyond PTB, LKTB is a further clinical form of TB which will be discussed in the corresponding section of this manuscript. It is naturally impossible to confirm the country of infection of PTB, but as exposition in Germany is rare, infection abroad is the most likely explanation. It is an crucial differential diagnosis in patients presenting with cough, weight loss and low fever with travel history to an endemic zone, especially after long periods of travel.[74]

## 4.6 Skin disorders

### 4.6.1 Most common skin disorders

Skin disorders are a major cause of travel related morbidity[5]. The overall level of SD in this study was measured at 17%. Our data stays in the same range as presented by Lederman et al.[34] (18%) and Herbinger et al.[16] (12.2%). These are the largest studies dedicated to specifically study SD within the context of travel medicine. This data correlates well to other studies that have shown results which stay in the 10-20% range.[33,35]

Within the SD group, the dermatologic syndromes were observed as follows: bacterial (28.2%), arthropod related (24.9%), STD (10.2%), cutaneous larva migrans (6.4%), rickettsiosis (6.1%), LF (5.6%), other dermatologic(4.8%), animal related (4.3%), LKTB (3.6%), cellulitis (2.3%), allergic related (1.8%) and mite infestation (1.8%). The leading cause of SD reported by Herbinger et al.[16] were arthropodal skin disorders (22.6%) followed by bacterial (21.6%), helminthic (10.5%), protozoan (6%) among other causes. Lederman et al[34] had following numbers: cutaneous Larva migrans (9.8%), insect bite (8.2%), skin abscess (7.7%), superinfected insect bite (6.8%), allergic rash (5.5%), rash of unknown etiology (5.5%), among others.

Here, methodological differences become apparent. A few examples: the mentioned authors did not include STD in the dermatological population, as we did. We have included the diagnosis LKTB in the dermatologic group as it is our

experience that patients often seek assistence by dermatologists. Lederman does not include a syndrome group “bacterial disease” but uses the definitions “skin abscess”, “superinfected insect bite” and “cellulitis” when classifying SD.[34] Interestingly, the levels of the specific syndrome “larva migrans” observed by Herbinger (7.9%) and Lederman (9.8%) stay in the same range as measured in our study (6.4%). The same applies to animal bites (3%, 4.3% and 4.3%, respectively). Apparently, the level of correlation increases for conditions which are clearly defined and allow no room for interpretation or differences in definition. Overall, our data has similar results to by Herbingeret al.[16] as compared to Lederman et al.[34]

The RR measured in this study indicates that the regions of South America, the Caribbean, sub-saharan Africa and southeast Asia are risk locations for the overall risk of developing SD during travel. The unusually high RR measured for Oceania should be interpreted as an statistical artefact in this small population of travelers. Our data correlates well with Herbinger et al.[16], even though he uses a different system for world regions.

The estimation of the RR presented in this study uses the equation proposed by Herbinger et al.[16] We are aware of the limitations of his method: it does not strictly follow the definition of RR, where the presence or absence of a given disease is plotted against the presence or absence of a risk variable. We do assume that the number of international travelers acquired at the German Federal Bureau of Statistics[38-40] (statistisches Bundesamt) is accurate. However, we are aware that it is not possible to know with certainty the real number of travelers returning home with SD. Moreover, the vast majority of travelers which did develop SD did not seek assistance at our center. Nevertheless, the proportion of international travelers traveling from Germany to each world region allows the creation of a profile against which data can be plotted. The measured risk values remain, as discussed above, an estimation.

### 4.6.2 Sexually transmitted diseases

Thirty percent of travelers presenting with STD returned from southeast Asia,

followed by sub-saharan Africa (17.5%) and western Europe (17.5%). The OR of developing STD after visiting southeast Asia was 2.0. As the *p* value was 0.17, no statistical significance was achieved for this region. Moreover, travelers returning from North America accounted for 7.5% of the STD population with a statistically significant OR of 4.93. Travelers visiting two or more world regions in the same trip accounted for 7.5% of the population with an odds ratio of 9.86. The following remarks may allow better interpretation of results.

First, we acknowledge that the control population (western Europe) could be biased. A Norwegian study[75] pointed out that 41% of patients seeking medical assistance due to STD in a specialized clinic had casual sex abroad, mainly in Europe. Other countries mentioned in the study include USA, Brazil and Thailand. Moreover, some regions of Europe are associated with sex tourism.[76] Finally, the absolute number of travelers presenting with STD returning from western Europe (7 out of 324) was equal to the much larger population of travelers returning from sub-saharan Africa (7 out of 737).

Second, the OR measured for travelers returning from North America and patients visiting two or more regions (4.93 and 9.86, respectively) have to be interpreted with care. Travelers returning from North America (n = 26%, 1.1%) or two or more regions on the same trip (n = 31, 1.3%) were a small fraction of our population. We have a relatively small population of 40 STD cases, meaning these results are probably statistical artefacts. Our data does not allows us to affirm with certainty if these are risk destinations. There is however data associating travel to the United States and STD.[75,77]

Importantly, we observed that the majority of patients presenting with STD returned from southeast Asia. The OR of 2.0 measured in this region could be an underestimation. Sex tourism is a well-documented phenomenon in this region.[77–80].

### 4.6.3 Rickettsiosis

Rickettsiosis is a disease caused by obligate intracelular bacteria of the familiy

*Rickettsiaceae*. The bacteria can survive not only in the cells of arthropods such as mites, lice, ticks and fleas but also in vertebrates such as dogs, cats, goats, sheep and humans. The disease has a widespread distribution around the planet, as some species are specific for some world regions (*R. Rickettsii* are common in the Americas, *R. coronii* around the mediterranean basin, among 26 different species)[81]. Symptoms include fever, lymphadenopathy, rash with disseminated erythematous maculae and, in most cases, a typical necrotic lesion with erythematous borders referred to as eschar or *tache noire*. Importantly, different pathogens lead to different clinical syndromes.[82] Rickettsiosis has been associated with travel[83] and, in some cases, atypical presentation can lead to delay in the diagnosis and severe clinical findings.[84] Not every patient with rickettsiosis develops skin changes.[82] Neverthless, we have included the disease in this group because patients presenting with a rash frequently consult a dermatologist and in order to compare the levels in our population to other studies.[16]

We have observed a total of 24 cases of rickettsiosis in our population. As expected, most patients had travel history to sub-saharan Africa (17 total). Out of this group, 12 traveled to South Africa, two to Namibia, one to Kenia, one to Uganda and one to the Republic of Congo. The remaining cases were observed in North Africa (two in Tunesia and one in Algeria), Europe (Spain and Italy with one case each), Australia (one case), Costa Rica (one case), and Singapore (one case). Our data highlights that most cases of Rickettsiosis observed in Germany are imported especifically from South Africa. The remaining cases show the widespread presence of the disease. Herbinger et al.[16] have observed a proportion of 1.3% of rickettsiosis in their dermatologic population, most patients returning, as in our study, from southern Africa. Lederman et al.[34] has seen rickettsiosis in 1.5% of cases. The most probable explanation for the relatively high levels of rickettsiosis in our study (6.1%) is the high number of travelers returning from the endemic region of sub-saharan Africa (31.8%) in our population (Lederman et al., for instance, had 18% of travelers returning from the same region).

### 4.6.4 Lymphatic filariasis

LF is a parasitic disease caused most commonly by the roundworm *Wuchereria*

*bancrofti* and fess frequently by *Brugia malayi* or *Brugia timori.*[85] Several mosquito species of mosquitos from the genera *Anopheles, Aedes, Culex, Mansonia* are responsible for the transmission of the disease, which is endemic in Sub Saharan Africa, South and Southeast Asia and some regions of the Caribbean, South and Central America.[86] The World Health Organization (WHO) has targeted the disease for global elimination through the mass administration of albendazole to whole populations in endemic regions.[87] The disease is highly debilitating, leading to lymphatic swelling and hydrocele.[88]

Our LF population reflects well the global distribution of the disease: 13 patients presenting with LF had travel history to sub-saharan Africa, 5 to Southeast Asia, two to South Asia, one to the Caribbean and one to South America. Early diagnosis and treatment is crucial to prevent chronification of LF.[89]

### 4.6.5 Cutaneous leishmaniasis

Leishmaniasis is a vector-borne protozoan disease which is a major concern for public health in several countries. The clinical forms include cutaneous, mucosal and visceral leishmaniasis. The type of infection depends on the causative agent (the genus Leishmania include over 20 species that can infect mammals[90]) and immune status of the host.[91] CL has been estimated to account for 80% of all imported leishmaniasis cases.[92] A study published by the German survaillance network for imported diseases (Surveillance Importierter Infektionen in Deutschland, or SIPMID) could show that almost half of all cases of leishmaniasis they treated were cutaenous (23 out of 42).[93]

In this study, most cases were imported from mediterranean European countries. Another recent study describes three cases of mucosal leishmaniasis caused by *Leishmania Infantum* acquired in southern Europe.[94] A recent study by Alvar et al.[95] which sought to estimate the incidence levels of leishmaniasis in each global region, indicated that the incidence of CL in Mediterranean region is one of the highest worldwide, coming after the region of the Middle East to Central Asia. The authors point out that underreporting is a major challenge to determine real disease burden. It is estimated that about one-third of CL infections take place around the

Mediterranean basin, the remaining two-thirds in the Americas and western Asia.[95]

The majority of patients presenting with cutaneous leishmaniasis (CL) were traveling in western Europe (68.8%). This value corresponds to more than the double of the rest of the world combined. CL is endemic in several regions of southern Europe, which comprehends only the northern part of the Mediterranean basin. This finding is unusually high, as only 14% of our population travelled in Europe. The majority of CL patients came indeed from southern Europe, many from Mallorca, where the abundand wild life act as reservoir for the disease.[96] Freedman et al.[5], in contrast, reported that most of the CL patients in their study were returning from South or Central America. His study, however, is centered around the United States. Our data highlights the importance of CL as an imported dermatologic disease observed by patients returning from southern Europe. Importantly, due to climate change CL is expected to advance in Europe.[97]

### 4.6.6 Lymph node tuberculosis

The diagnosis LKTB was included in the dermatologic section of this study because patients often present to the dermatologist with subcutaneous nodes on the neck, armpits or groin. The disease can easily be misdiagnosed as epidermal cyst, skin abscess, neoplasia or acne inversa.

The most common clinical form of TB shows regional variation. According to the Report on tuberculosis Control presented 2011 by the WHO[98], 14.8% of worlwide TB cases were extrapulmonary. In Camboja, in contrast, the same study showed that the proportion of extrapulmonary TB reached 55.3%. A recent mexican study reporting from a high incidence region also observed a high proportion of extrapulmonary TB: 60.5% of all cases.[99] Lymphadenitis was the most common clinical presentation (42%). Lymphadenitis was again the most common clinical form in a study from our clinic[73] (37.1%). Further clinical forms included bone (20%), neurologic (14.3%) and pulmonary (8.6%).The delay in the diagnosis is highlighted by the aforementioned study: out of 35 cases, TB was suspected in only 5 cases, while malignancy was the initial diagnosis in 17 cases (48.6%).

Out of 14 cases of LKTB, 8 came from Africa and 3 from the southern part of Asia. The levels of LKTB in our population are comparable to the levels of PTB (17 cases). Ou data highligts the unusually high levels of LKTB observed by travelers or immigrants in Germany.

# 5 Conclusion

The present study sought to characterize a population of 2314 ill returned travelers presenting to the department of tropical medicine of Heinrich Heine University between 2010 and 2012. The association between broadly defined syndrome groups and region of visit was studied through the estimation of the proportionate morbidity and the odds ratios (OR). The diagnosis malaria, dengue fever, pulmonary tuberculosis (PTB), sexually transmitted diseases (STD), rickettsiosis, filariasis, cutaneous leishmaniasis (CL) and lymph node tuberculosis (LKTB) were studied separately.

The levels of traveler's diarrhea (23.6%) and non-diarrheal gastroenterological disorders (22.5%) accounted for almost half of all patients. Similar levels have been reported by other authors.[6] In our study, high risk regions for the development of traveler's diarrhea include South Asia, eastern Asia and northern Africa. This reflects the precarious hygienic situation in food handling in these regions. The unusual high level of non-diarrheal gastrointestinal disorders in Central Asia (OR = 13.22, $p < 0.001$) was observed due to several cases of echinococcosis which are referred to the department of tropical medicine as a transregional referral center for the disease.

The regions of South America (OR = 4.29), sub-saharan Africa, (OR = 6.35), South Asia (OR = 2.74) and Southeast Asia (OR = 3.67) were risk regions for the development of a systemic febrile syndrome (16.9% of the population). All above mentioned OR achieved statistical significance. As expected, the vast majority of imported malaria cases came from sub-saharan Africa (80.8%). Although this was not systematically assessed in the present study, it was the clinical impression that most travelers to Africa who became infected were immigrants or their children, supporting data published by the RKI[100]. These patients did not take malaria prophylaxis either because they were not aware of the risk of getting a symptomatic malaria due to the drop of their concomitant immunity after leaving their endemic home country or because of the cost of antimalarial medication. There is an urgent need of financial coverage by their health insurances which applies specially to the children, who cannot decide on their travel destinations.

Skin disorders were observed by 17% of all travelers. The most common dermatologic syndromes were: bacterial (28.2%), arthropod related (24.9%), STD (10.2%), cutaneous larva migrans (6.4%), rickettsiosis (6.1%), LF (5.6%), other dermatologic (4.8%), animal related (4.3%), LKTB (3.6%), cellulitis (2.3%), allergic related (1.8%) and mite infestation (1.8%). Many patients with bacterial skin infections presented to the tropical medicine department with the suspicion that there could be an underlying specific tropic disease or because practitioners, underestimating the virulence of the bacteria, were reluctant to prescribe systemic antibiotics. Using the model proposed by Herbinger et al.[16] we could identify following risk regions for skin disorders: South America, the Caribbean, sub-saharan Africa and southern Asia.

Five dermatologic conditions were analyzed separately: STD, rickettsiosis, filariasis, CL and LKTB. The number of patients presenting with STD was highest after travel to Southeast Asia (n = 12), where sex tourism is a known phenomenon in some countries.[80] The majority of patients with rickettsiosis and filariasis returned from sub-saharan Africa, where both diseases are endemic. Moreover, we have observed that, even though CL is endemic in several world regions, 68.8% of CL infections took place in Europe. Several patients were returning from Mallorca, Spain, were the disease is endemic.[96] Finally, 14 cases of LKTB were identified, most patients returning from Africa and the southern part of Asia. Our findings give further support for the high levels of LKTB observed amongst immigrants in Germany.

Our study has limitations. The purpose of travel – which impacts behavior in the travel destination and the probability of seeking pre-travel advice – was not documented. Nevertheless, it provides valuable information concerning the practice of tropical and travel medicine in our institution. Moreover, it provides valuable correlations and insights into the frontier between travel and medicine.

# 6 Literature


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Eidesstattliche Versicherung

Ich versichere an Eides statt, dass die Dissertation selbständig und ohne unzulässige fremde Hilfe erstellt und die hier vorgelegte Dissertation nicht von einer anderen Medizinischen Fakultät abgelehnt worden ist.

Düsseldorf 04.04.2016

Rodrigo Marques da Mota