Health problems and risks encountered among healthy and vulnerable Dutch travelers

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PART III

Discussion and summary

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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]

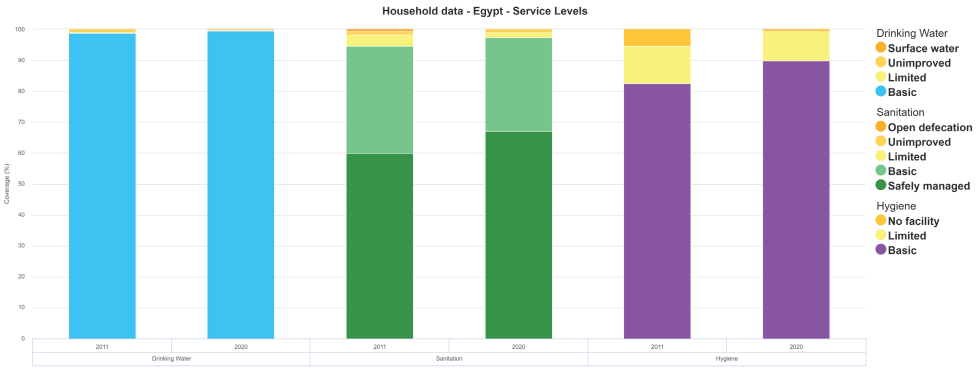
Extended-spectrum ß-lactamase producing Enterobacteriaceae (ESBL-E)

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

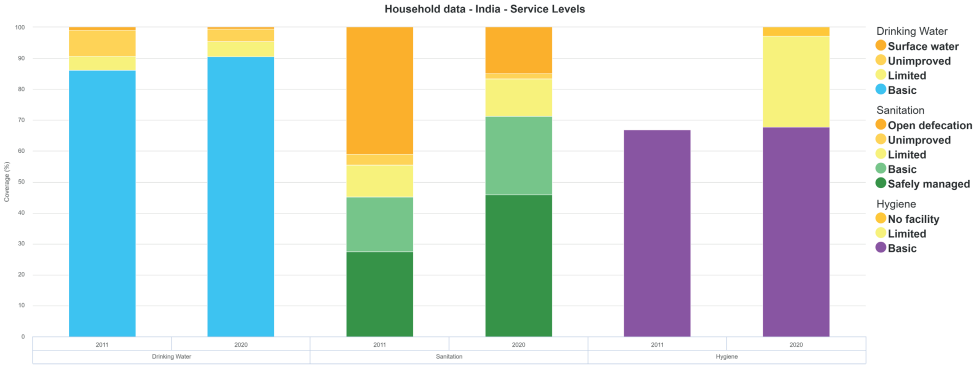
and self-limiting illness (e.g. upper respiratory tract infection, urinary tract infection or gastrointestinal complaints) in South America and Asia. Interestingly, pharmacists in Thailand are legally allowed to provide some type of antibiotics without the need of a prescription. [49]

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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