Traveling hosts and pathogens; Epidemiology of travel-related infections
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Introduction
General introduction

International travel has shown an uninterrupted growth over the last decades, with 1.035 million arrivals reported in 2012 (1). Compared to 2011, Asia and the Pacific recorded the strongest growth in 2012 with a 7% increase in arrivals, followed by Africa (+6%) and the Americas (+5%). According to long-term forecasts from the United Nations World Tourism Organization (UNWTO), the number of international tourist arrivals is expected to increase by 3.3% a year from 2010 to 2030 to reach 1.8 billion by 2030. Around 80 million travelers visit tropical and subtropical destinations yearly, who could consequently be faced with various health problems, varying from non-infectious events such as accidents, altitude illness or sun exposure to a broad range of infectious diseases (2-9), such as several vaccine preventable diseases, but also malaria, HIV, syphilis and travelers’ diarrhea. Health problems are frequently reported by 22-75% of travelers to developing countries, and mostly consisting of mild and self-limiting illnesses such as travelers’ diarrhea, respiratory infections or skin disorders (6,8-14). The risk of contracting an infectious disease depends on the endemicity in the country(ies) visited, and both travel characteristics (duration of stay, purpose of stay, season, hygienic standards) and traveler characteristics (individual behavior, healthy versus pre-existing condition, non-immune versus (semi-) immune), and can be limited by preventive health measures as behavioral change, vaccination or prophylaxis (8;13). Each year up to 8% of all travelers report becoming ill enough from health problems (both non-infectious and infectious) to seek health care during or after travel (4;15), in particular travelers to Africa and Asia (12). Besides impact from health problems on the traveler and his/her stay abroad, travelers can also contribute to the further spread of infectious diseases across international borders (16). Infectious travelers might, on return from travel, infect relatives, persons with whom they have close contact, or the community. Preventive travel health measures (vaccination, (malaria) chemoprophylaxis, self-treatment or health measures such as hygienic measures regarding food or respiratory illnesses, condom use or anti mosquito measures) thus not only benefit individuals, but occasionally public health as well. As international travel is expected to keep increasing, both increasing evidence based knowledge regarding travel-related illnesses and adherence to travel health measures will remain of great importance.
Travel medicine and guidelines

Travel medicine is the subspecialty of medicine that focuses on the prevention and management of health problems of travelers, involving risk assessment and risk management (17;18). It includes knowledge on epidemiology of health risks, vaccination, and malaria prevention and provides the most up-to-date accurate pre-travel advice (6;14;19-21). The World Health Organization (WHO) publishes the ‘International Travel and Health’ (ITH) book every year, on which many guidelines are based (21). Also, the Centers for Disease Control and Prevention (CDC) publishes the "yellow book" with guidelines every two years. (22).

In 1996, the Netherlands established a National Coordination Centre for Travelers Health Advice (Landelijk Coördinatiecentrum Reizigersadvisering; LCR) (23-26). In the Netherlands travel health advice is mostly provided by travel clinics run by Public Health Services and a few hospitals with tropical medicine departments. Also, some private travel clinics exist and both general practitioners and occupational health services provide their patients or clients with travel health advice. LCR has two aims: to improve the quality of travel clinics and to increase uniformity in travelers’ health advice. To do so, LCR publishes and updates national guidelines and quality criteria for travel clinics and general practices. LCR guidelines concern disease-specific information, including information on epidemiology of travel related diseases, possibilities for preventive measures such as hygiene, use of repellents and use of condoms and, if available, vaccination, chemoprophylaxis or stand-by treatment. Also, LCR guidelines comprise recommendations for specific risk groups, such as immune deficient travelers, pregnant travelers, and immigrants who visit friends and relatives in their country of origin. Guidelines are developed in various working groups, and based on information from WHO, CDC, scientific literature and local and national notification data on imported infectious disease. They include a list of countries with detailed advice per country on recommended vaccinations, anti-malarial chemoprophylaxis and extra information on the risk of specific infectious diseases. This 'country-list' can be used in individual pre-travel health advice. The list is a tool in obtaining more uniformity in travel health advice. Before publication, the guidelines are approved by a national LCR consensus group, consisting of diverse specialists working in different settings of travel medicine.
Pre-travel health advice seeking behavior

Not all travelers consult a health professional prior to travel. They may not be aware of the need to protect themselves from infectious diseases (27-33), consider the risks too low or vaccinations too expensive. Considerable variation exists in the proportion of travelers who sought pre-travel health advice from a travel specialist or travel clinic, ranging from as low as 4% among travelers departing from Australasian airports to Asia, Africa or South America (33), to 85-94% of those traveling to sub-Saharan Africa and Central and South America (30;34-36). Health advice seeking behavior is dependent on country of birth and residence. Heywood et al studied pre-travel health seeking behavior of travelers departing from Sydney or Bangkok airports. The studied travelers in both Sydney and Bangkok were Australian residents, residents from other Western countries or Asian residents. In both groups Asian travelers were significantly less likely to seek pre-travel health advice than Western travelers (29). Also, migrant Australian travelers (obviously) more likely visited friends or relatives but were half as likely to seek pre-travel health advice compared to Australian borne travelers. Wilder-Smith et al found among travelers departing from Australasian airports (Singapore, Seoul, Taipei, Kuala Lumpur, Melbourne) to Asia, Africa or South America, that travelers from Asian origin sought health advice less often than Western travelers. Those traveling longer, perceiving a high risk for malaria and travelers to rural places sought pre-travel health advice more often (33). Behrens stated that one of the most important factors in whether travelers seek health advice was perceived risk and severity of tropical diseases (37). Hamer et al showed that among international travelers from the United States to a hepatitis A high-endemic country, only 17% perceived themselves at risk for hepatitis A, and 73% of travelers to a high risk country for malaria perceived the risk as high (27).

Content of pre-travel health advice

Pre-travel health advice in the Netherlands is based on standardized LCR guidelines and during the consultation this standard advice is tailored to the individual traveler. The basic advice is personalized based on risk assessment for individual travelers using details of the person (age, sex, country of birth), medical history and planned destination (including information on purpose, duration and season of travel and way of travel). Most of the health advice consists of discussing health risks and advising specific preventive health measures. If applicable, vaccinations and prescriptions for anti-malarial chemoprophylaxis, altitude illness prophylactics or antibiotics for self-treatment are given during the consultation. If needed additional information is given to travelers, such as detailed information on the pros and cons of antimalarial chemoprophylaxis.
In case the travelers perceived risks do not match the actual risks, this is discussed in order to motivate the traveler to take the recommended preventive measures or vaccinations. Part of the pre-travel health advice concerns communication about evidence based information on infectious diseases, risks and/or preventive measures which can be taken to avoid acquiring infectious diseases. Because there are many possible subjects for discussion during pre-travel health advice, priorities regarding subjects are made depending on an individual risk assessment. The ‘risk-scale’ of Steffen et al (9) (see figure 1) is a handy tool in which one can clearly see differences in health risks during travel. This logarithmic scale was made using evidence based information on risks in incidence per month from different studies. Discussing risks during pre-travel advice can have a significant impact on the traveler’s choice to take anti-malarial chemoprophylaxis and on the type of chemoprophylaxis to use. In a study by Senn et al almost half of the travelers changed their initial medication preference. Discussing all information regarding chemoprophylaxis with the health provider seemed to put this information into perspective leading to a better informed decision (38). The authors suggested that communicating evidence-based information weighed more heavily than negative publicity on type of chemoprophylaxis. For instance, before consultation mefloquine was chosen by 44.7% and after pre-travel consultation by 50.2%, despite a priori concerns (38).

**Figure 1.** Incidence rates per month of health problems during stay in developing countries.
Evidence that preventive health measures reduce health risks

In general, prevention in travel medicine had proven its use. For instance, a number of studies showed that travelers who acquired malaria were those travelers not using antimalarial chemoprophylaxis (39-43). Also, the vaccine effectiveness of typhoid vaccination in travelers was estimated as 80% (44), and virtually all cases of hepatitis A are reported in unvaccinated travelers (45). The use of an insect repellent containing DEET was shown to be protective for dengue infection among travelers to tropical or subtropical countries (46). Balaban et al found that compliance with protective measures regarding respiratory disease was associated with less respiratory illness among travelers to the 2009 Hajj. Noticing health messages for influenza A during Hajj was positively associated with the number of protective measures people complied with and negatively associated with the incidence of respiratory illness (47). Shlim et al found that expatriates could safely eat locally bought food when they prepared it themselves taking appropriate hygiene precautions, but that they became sick when eating the same food prepared in restaurants (48). Matteeli et al found a lower risk of STI's in travelers who had pre-travel health advice compared to those who did not have such advice (49). Also, Muller et al found that, among travelers who consulted the International Travelers’ Medical Services in France, those who also consulted their general practitioner complied better with vaccination and malaria recommendations (50). Although these studies highlight the effect of pre-travel health advice and health messages, the effect of preventive measures on health risks could partly be due to the type of travelers: those who consult a pre-travel health clinic or who notice health messages could be those travelers who are more concerned about their health and therefore comply better with protective measures.

Receiving information on infectious diseases, risks and preventive measures can also help travelers in making choices: e.g. travelers who received pre-travel advice and suffered from diarrhea needed less medical assistance while abroad or post-travel and were more likely to use self-medication appropriately compared to those who did not receive pre-travel advice (51). Several other studies among travelers show a significant improvement in knowledge of infectious disease risk, more accurate risk perceptions and a higher level of intended risk-reducing behaviors after the travel advice consultation (52-57)
Adherence to preventive health advice

Farquharson et al studied travelers to malaria-endemic countries and found that perceived risk for malaria, perceived benefits from chemoprophylaxis and intention to adhere were increased and more realistic as a result of pre-travel health advice (58). Travelers who talked more during health advice and therefore engaged more in the discussion about adherence showed poorer adherence. Factors related to better adherence were perceived benefits of chemoprophylaxis, shorter travel duration, less discussion (about barriers and ways to facilitate adherence) and health professionals who answer travelers’ questions and providing them with information. Authors suggest conducting future studies including the impact of training for health professionals concerning discussion with the traveler about the benefits of taking chemoprophylaxis as well as resolving potential barriers to adherence, particularly focused on subgroups of travelers who are planning longer trips or who demonstrate concerns or ambivalence about adherence during the consultation.

In a study among travelers to malaria endemic regions three travel clinicians watched videotaped consultations and independently predicted adherence, rated the quality of the consultation with a 10-point scale, and gave reasons for their prediction/rating (59). Travelers were asked post-travel about adherence with a four-question telephone interview. Two of the three clinicians predicted adherence significantly better than chance and although they overestimated adherence, they rated the quality of the consultation where travelers subsequently adhered better significantly higher. Adherence to malaria chemoprophylaxis and/or anti-mosquito preventive measures also differ between subgroups of travelers: travelers visiting friends and relatives, on a short business trip or on a prolonged stay were less likely to adhere (60;61)

Reasons for non-adherence to health advice can be diverse, for instance inadequate pre-travel advice, inconsistent information from various sources, variation in risk perception or perception of severity of disease, poor recall, concerns about side effects, lack of belief in benefit from vaccinations or prophylaxis or costs (62;63).

Improve adherence: increase evidence and uniformity

In order to positively influence adherence to recommendations, motivational interviewing can be used in pre-travel health advice (62;64). In motivational interviewing, a patient-centered approach is used, in which questions and possible ambivalence of travelers towards health
preventive measures of travelers are explored and resolved. In order to reach informed shared decision, evidence based information is needed and tailored to individual circumstances. (62;64) As travelers are less likely to adhere to advice when information is inconsistent, uniformity and consistency of information and advice is expected to enhance adherence. Both Farquharson et al and Noble et al formulated characteristics of effective communication with emphasis on the importance of a defined structure for the consultation, taking a proactive approach to explore travelers’ perspective and responding to their concerns. Health professionals should demonstrate confidence and experience by anticipating concerns or questions, summarizing key issues and concerns, facilitating informed-decision making by providing information about risks, benefits and effectiveness of preventive measures, and being creative in problem-solving with a positive focus (59;62).

Aim and outline of this thesis

Risks for acquiring travel-related infectious diseases are related both to individual risk behavior and to the epidemiology of infectious diseases in the country of destination. The still increasing number of both healthy travelers and travelers with pre-existing medical conditions to tropical and subtropical countries are faced with travel related health risks, and can also be a vector and source for further spread of disease after return in their home country. Although research in travel medicine is increasing in quantity and quality, further research remains needed to increase knowledge on travel related risks, risk factors and individual behavior and to monitor changing epidemiology over time. Consequently, guidelines can be adjusted if needed and further improved. Evidence based information will provide uniformity in practical guidelines and travel health advice, which could reduce travel-related health risks by better compliance.

The aim of this thesis is to increase knowledge on the epidemiology of, risk factors for and protection against several travel-related infectious diseases. This is done by prospectively studying both short-term and long-term travelers to subtropical and tropical countries, with a focus on travelers’ diarrhea, influenza, malaria and sexual risk behavior. Also, the protection by combined hepatitis A and B vaccine in HIV-infected children and children on immunosup-
pressive medication was studied.
Almost all research described in this thesis was conducted at the Public Health Service Amsterdam (GGD Amsterdam). The travelers’ advice and vaccination clinic, part of the GGD Amsterdam, not only gives travelers tailored pre-travel health advice as described, but travelers can also be vaccinated or, if necessary, blood samples can be taken. As a large and diverse number of travelers are seen yearly and laboratory facilities are available, this renders a favorable setting for studies.

In chapters 2, 3 and 4, our study population is a cohort of short-term travelers, followed in 2006-2007. In chapter 2, we focused on malaria among short-term travelers from the Netherlands to tropical and subtropical countries and identified factors associated with adherence to chemoprophylaxis. We assessed the incidence rate of anti-circumsporozoite seroconversion, described symptoms associated with these seroconversions, and malaria treatment abroad, and discussed these results according to existing guidelines.

In chapter 3, we assessed the risk for influenza virus infection by serologically testing the short-term travelers for the epidemic influenza strains during the study period and we examined possible risk factors for influenza virus infections. Based on our study results, we estimated the risk for further spread of influenza after return in the Netherlands.

In chapter 4, we estimated the attack rate and incidence rate of travelers’ diarrhea (TD) among short term travelers and studied risk factors for acquiring first or multiple episodes of TD. Furthermore, we described duration and severity of symptoms, health seeking behavior for the treatment of TD and discussed the use of stand-by antibiotics.

In chapter 5, we estimated the attack rate and incidence rate of first and multiple episodes of travelers’ diarrhea (TD) among long term travelers, and studied risk factors for acquiring first or multiple episodes of TD. Furthermore, we described duration and severity of symptoms, health seeking behavior for the treatment of TD and discussed the use of stand-by antibiotics. Furthermore we estimated both the incidence rate of first TD episode per quarter traveled, and the mean incidence of all TD episodes per quarter traveled.

In chapter 6, we described casual sexual partnerships and condom use among long-term travelers.
In chapter 7, we evaluated the immune responses to a combined hepatitis A and B vaccine among HIV-infected children and children receiving immunosuppressive medication for treatment of rheumatic diseases.

In chapter 8 we discuss the findings of this thesis.

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