Infectious souvenirs: the toll of travel?
Baaten, G.G.G.

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Chapter 1

Introduction
General introduction to travel medicine

Travel is as old as mankind. Homer’s epic poem The Odyssey, one of the oldest extant works of Western literature, already centres on the hero Odysseus’ long journey home following the fall of Troy. Nowadays, we live in a far more mobile world than past generations. Unlike Odysseus, we arrive back in our home country from the most distant locations on earth within two days. Thanks to low-cost airline travel, leisure and business travel have become part of our lifestyle. Yet, being able to travel is one thing; returning in good health is another. Since biblical times we have recognised that when we move from one environment and climate to another, this may have consequences for our health, ranging from trivial illness to death. Nowadays, travellers may still face health risks while on travel. This is particularly true for those venturing into the developing countries in tropical and subtropical regions, where other diseases may be encountered, and where health standards and the health system are suboptimal.

In recent years, international travel has increased enormously, including travel to countries in the developing world. The increase has been estimated at approximately 6% per year, and similar trends are expected in the future. Some 80 million individuals from developed nations travel to the developing world each year, and it is estimated that more than 200 million people now reside outside their country of birth. The estimated annual number of Dutch travellers to developing countries also increased: from 996,000 per 15.4 million inhabitants (6.5%) in 1995 to 1,943,000 per 16.3 million inhabitants (11.9%) in 2006. This increase largely reflects travel to the North African and West Asian region, including its popular destinations of Turkey and Egypt. The number of travellers with a pre-existing medical condition such as diabetes mellitus, inflammatory bowel disease, or an immunosuppressive disorder, has probably also increased, although exact numbers remain unknown. Due to improved awareness and support for these travellers, their overall health improves, and so does their motivation and physical fitness for travel. For these individuals, travelling to the developing countries may complicate their medical condition and may require special considerations and advice.

With the increasing ease of travel of both healthy persons and persons with pre-existing medical conditions, the need to provide evidence-based medical care for travellers also increased. Travel medicine is the interdisciplinary field developed to protect travellers from disease and death. It encompasses: the identification and epidemiology of travel-associated diseases and disorders and their geographical distribution; the pre-travel prevention of these conditions through education, vaccination, chemo-prophylaxis, and self-treatment; and the care of the returned ill traveller.

Risk assessment in travel medicine

The risk of infectious diseases during travel may differ from that at home for several reasons. First, the endemicity of the infectious agent may be higher at the destination than at home due to differences in socio-economic conditions, which primarily results in increased exposure to faecal-orally transmitted diseases such as hepatitis A, shigellosis, and typhoid fever, and
respiratory infections; and 2) differences in climatic, physical or geographical conditions, which primarily results in increased exposure to vector-borne diseases such as dengue fever and filariasis, or water- or soil-transmitted diseases such as schistosomiasis and strongyloidiasis. Second, the endemicity of infection may be higher at destination than at home due to insufficient herd immunity. Lower coverages of routine immunisations result in increased susceptibility for both locals and (unprotected) travellers. This primarily concerns faecal-orally and respiratory transmitted childhood infections that confer lifelong immunity, such as poliomyelitis and measles. Finally, transmission occurs only or more easily due to behaviour that is more frequent at the destination than at home (behaviour-related transmission). This primarily concerns sexually transmitted and blood-borne diseases, such as hepatitis B and C.

In order to advise travellers about preventive measures, evidence-based information on travel-related health risks is needed. In travel medicine, risk analysis for a specific infection is generally based on expert consensus, geographical distributions, and disease occurrence in travellers from surveillance or prospective studies.

Expert consensus is straight-forward, rather simple to create, and indeed widely used. However, ‘consensus’ is generic, imprecise and varies by policy body. It remains unknown if it really correlates to true risk, and it may leave the traveller (and the health provider) no choice. Risk assessment based on geographical distribution is widely available, and gives insight into regional risks. Yet, the quality of the data varies. Moreover, these data reflect the risk for the local population, often in a historical connotation. For the traveller, the risk is generic and may lead to excessive coverage, which is almost always accompanied by high costs on preventive measures.

The best evidence is provided by original study designs, which scientifically address the occurrence of disease and the effect of preventive measures in travellers. However, only 6% of the 5600 published scientific articles in the field of travel medicine report on original studies (PubMed Database, entry terms ‘Travel’ and ‘Medicine’; limits: clinical trial, randomised controlled trial, comparative study, or multicenter study; http://www.ncbi.nlm.nih.gov/pubmed. Accessed July 6, 2010), and although the quantity of these articles has increased since the 1990s, this does not necessarily apply to their quality.

**Characteristics of different study designs in travel medicine**

Each methodological approach has its strengths and limitations that can significantly influence risk estimates and the generalisability to all travellers. Some of these strengths and limitations are unique to travel medicine, as travellers generally have a defined and identifiable period of risk. The major study designs and their role in travel medicine research are discussed here, ranked in order from strongest to weakest empirical evidence.

1) **Experimental studies**

In experimental studies such as randomised control trials (RCTs), symmetry of potential confounders is maintained through randomisation; the researcher only controls the assignment of the exposure. This reduces spurious causality and bias. For example, McKenzie et al. conducted a randomized, double-blind, placebo-controlled trial to assess the immunogenicity and safety of an
oral, live-attenuated enterotoxigenic E. coli (ETEC) vaccine. Subjects received either vaccine or placebo. Then they were challenged with a virulent ETEC strain. The vaccine did not protect against moderate to severe ETEC illness, but it did prime subjects for a rapid antibody response after challenge.

RCTs are considered the ideal design for evaluating the effectiveness and the side effects of preventive or therapeutic interventions such as vaccines, malaria chemoprophylaxis, or self-treatment. As the allocation of exposure cannot be controlled by the researcher for logistical and ethical reasons, such studies cannot be used to inform about absolute risk estimates. Therefore, in travel medicine, most studies are observational.

2) Observational studies

a) (Prospective) cohort studies

Cohort studies are suitable to establish the absolute risk of a disease. In travel medicine, cohort studies generally select participants before exposure, i.e. before departure. The follow-up typically ends after return. These studies often use a questionnaire to collect data on travel itinerary, preventive practices and symptoms and signs of illness. In that case, they can only report on the occurrence of syndromes, for example travellers’ diarrhoea. For risk calculations of specific etiological diagnoses, laboratory tests have to be used.

Since cohort studies provide numerator and denominator data, they are the most common approach to acquire incidence estimates of illness. Incidence rates are specific and sensitive, and can serve the traveller and the health provider in making an informed decision. By comparing IRs, risk factors can be identified.

Although IRs are specific to travellers, they may not reflect all groups of travellers, and most of the time they do not give detailed regional risk assessment.

Cohort studies may have potential biases. For example, when the sample only comprises travellers seeking pre-travel health advice, those most at risk may be missed as they may be the least likely to seek pretravel health advice, for example young or budget travellers. Furthermore, cohort studies are often performed at a single site and a single point in time, and they may focus on travellers visiting specific high-risk destinations. Also, results are compromised when a lot of participants are lost to follow-up. If all these sources of selection bias cannot be avoided, they should at least be reported and commented on. As an example, Potasman et al. investigated the rate of seroconversion for antibodies against dengue virus infection in 104 young Israeli adults, who travelled to tropical countries for at least 3 months. The authors conclude that dengue fever is perhaps the most common mosquito-borne disease of long-term young travellers, particularly those visiting Southeast Asia. Most likely, participants were enrolled at a travel health clinic. However, place, setting, and year of enrolment were not stated, nor were the eligibility criteria or number and characteristics of participants lost to follow-up. Thereby, the validity of their study remains unknown, which seriously limits the interpretation and generalisability of its results. Bias in assessment of the outcome may occur when the person who decides whether disease has developed in a subject also knows whether that subject was exposed. Information bias may occur when the quality and extent of information obtained is different for exposed persons than for nonexposed persons.
Cohort studies are expensive and labour intensive, as they usually require large populations, in particular when the disease of interest is relatively rare. They cannot determine occurrence of diseases with incubation periods exceeding the duration of follow-up.

b) Cross-sectional studies (prevalence surveys)

In cross-sectional studies, exposure and outcome are determined simultaneously for each subject in the sample population. For illnesses with short incubation periods, they allow to calculate attack rates. Although they can assess potential risk factors by comparing ill and well travellers, they are not suitable to establish etiologic relationships. These studies can be used to assess people’s knowledge, attitudes, and practices regarding preventive measures. In travel medicine, these studies are often designed as airport surveys. For example, Van Herck et al. surveyed 5,465 passengers boarding an intercontinental flight to a developing country at the departure gates of nine major airports in Europe, to evaluate their travel health knowledge and practices. The authors conclude that more efforts to educate travellers to risk destinations are needed. However, the included participants may not represent the entire sample population, let alone the entire travel population. Bias might have arisen by the selection of destinations and flights. Also, certain specific groups of travellers might have been less likely to participate, as participation was voluntary, and questionnaires were distributed by interviewers knowing the study’s objectives. The number of persons refusing to participate was not stated. Cross-sectional studies lack any information on timing of exposure and outcome relationships and on disease duration. Also, those who died after the disease developed will not be included. As results apply to the specific population and time period being examined, the generalisability of findings is limited.

c) Studies based on cases

In travel medicine, many studies are based on ill travellers (cases). One can discern three different methodological approaches based on cases.

Case-control studies

In case-control studies the proportion of diseased travellers with a potential risk factor are compared to the proportion of travellers without the disease (controls) with the same risk factor. Although case-control studies cannot provide incidence rates, they can provide estimates of ratio measures of effect. Properly carried out, case-control studies provide information that mirrors what could be learnt from a cohort study, usually at considerably less cost and time. In travel medicine, these studies are particularly useful for rare conditions or for risk factors with long incubation periods and in the setting of disease outbreaks among a group of travellers. These studies may be subject to a number of potential biases. Selection bias may occur easily, as it is difficult to find similar travellers who have remained well. Measurement, screening or reader bias may occur when the degree of blinding, diagnostic suspicion, the measurement methods, or the interpretation made during inference of clinical information are consistently different between groups in the study.
Recall bias may occur when a subject is interviewed to obtain information on exposure after disease has occurred. For example, Frank et al. conducted a case-control study to identify the most likely infection vehicle after an outbreak of hepatitis A involving 278 German tourists returning from Egypt. Healthy hotel guests who stayed at the hotel during the minimum period of transmission who had neither been vaccinated against hepatitis A nor previously infected with hepatitis A were eligible as controls. The authors found that case-patients were significantly more likely to have drunk orange juice served at the breakfast buffet than were controls (odds ratio 2.6; 95% confidence interval 1.1–6.6). However, patients may be able to recall the many exposures more accurately than the controls, as the adverse outcome may have served as a stimulus to consider potential causes.

Notification data and data from surveillance networks for travellers

Some researchers have analysed cases and their characteristics by using surveillance data of notifiable diseases. This is only possible for infectious diseases of which reporting is indeed mandatory. Also, global and regional provider-based surveillance networks have emerged, involving collaborating clinics specialised in imported infectious diseases, which can provide data from large samples of diverse travellers, for example the GeoSentinel Surveillance Network, the European Network on Imported Infectious Disease Surveillance (TropNetEurop), and the European Travel Medicine Network (EuroTravNet) from the International Society of Travel Medicine. Although comparable to case series, the extent of the network enhances precision, reliability, and generalisability of findings. In both notification and network studies, risk factors for disease occurrence can be identified. For example, Lipner et al. collected demographic, travel, and clinical data concerning all cases of filariasis presented to the GeoSentinel Surveillance Network, and found clinical differences between cases among expatriates and those among immigrants. Of course, generalisability of results depends on the used case definition or coding system, and on the characteristics, destinations and behaviour of the included travellers. When estimates of the total numbers of travellers to a certain region are used as a surrogate denominator, these studies are suitable to examine trends of illness over time. Even then, a change in trend can also be attributed to a changed awareness and reporting, or, in network studies, a change in the number of reporting sites.

Case series or clinical series

Case series assess the range of diseases encountered, in particular the relative frequency of different diseases among ill travellers. These studies typically describe the manifestations, clinical course, and prognosis of a condition. They can provide country-specific risk information when limited to individuals returning from a single destination or when carried out by clinics that travellers attend during travel. Most of these studies are retrospective. They are relatively inexpensive, are easy to do, and require a relatively small number of subjects. For example, Libman reviewed the charts of 1,605 patients attending their clinic, to examine the clinical utility of eosinophil determinations, stool examinations, and serological studies for detection of schistosomiasis, filariasis, and strongyloidiasis. In their population, eosinophil counts contributed little in the screening for parasitic disease. However, because of the lack of comparability, such a study
provides weak empirical evidence, unless the findings are dramatically different from expectations. Also, studies that rely on chart review for study data have no control over how the disease and exposure variables are ascertained and recorded in the patient chart (ascertainment bias). All these factors seriously limit the generalisability of the findings. Unfortunately, the case series is the most common study type in travel medicine literature.

**General limitations of studies based on cases**

Results from these studies are based on the sociodemographic, behavioural and travel characteristics of persons who sought medical attention after travel, thereby missing persons who never had symptoms, whose symptoms resolved during travel, or whose disease was not severe enough (selection bias). Also, patient referral patterns may be different and coding of diagnoses may be inconsistent. Referral bias may occur when the cases are drawn from 1) a single institution, where an identified risk factor may be unique to the population seen at that hospital, or 2) only from tertiary care facilities which selectively admit severely ill patients. Much of the information relating to exposure involves retrospectively collecting data from subjects by questionnaires or interviews, raising limitations in remembering and reporting exposures. Details about itinerary and travel characteristics are often lacking or inaccurate.

In case series and network studies, risk estimates per destination can be made by calculating the proportionate morbidity: the number of patients with a given diagnosis divided by the total number of ill travellers to a destination. This gives some insight in the relative pattern of disease occurrence by region of exposure. However, the proportions are difficult to convert to and interpret as an individual risk, and a highly prevalent disease may make other diseases appear trivial, even if there are in fact significant absolute risks. Nevertheless, proportionate morbidities can guide differential diagnosis and decision-making in empiric therapy, and repeating analyses enables to describe trends.18

In studies based on cases, attack rates can only be calculated when estimates of the total numbers of travellers to a certain region are used as a surrogate denominator. Even then, true IRs cannot be calculated, as the numerator only represents cases from the notification system or from the network clinics, whereas the denominator represents (an approximation of) all travellers. Interpreting their findings is therefore difficult. These studies can be useful to describe trends in specific diseases among travellers.
Aim and outline of this thesis

Are infectious souvenirs the toll of travel? As the number of travellers to developing countries has increased, including those with a pre-existing medical condition, the need for evidence-based information on travel-related health risks and on how to prevent and manage these risks also increased. Unfortunately, the quantity, quality and generalisability of the available scientific data is disappointing. In many situations, guidelines on travel health advice are founded on expert opinion and consensus from limited data sources. More research is needed concerning the epidemiology of travel-related diseases, including the incidence, prevalence, and morbidity of these illnesses in specific groups of travellers, and the effectiveness of and adherence to travel health precautions.

The research described in this thesis addresses the epidemiology of several travel-related infections and the effect of preventive measures. It focuses on ‘short-term travel’, which generally refers to a travel duration less than 3 months. Most study objectives arose from the lack of evidence-based data in Dutch and international guidelines on travel health advice. Hence, the studies were specifically designed to enhance the risk management in pre-travel health advice settings. The secondary objective was to improve the assessment and (empiric) treatment of travellers in outpatient and inpatient clinics. The research has mainly been conducted at the Public Health Service of Amsterdam, Department of Infectious Diseases, Amsterdam, the Netherlands.

Overall, Western countries like the Netherlands are low-endemic for viral hepatitis. However, in urbanized regions like the city of Amsterdam, high-risk groups for viral hepatitis are more prevalent. Amsterdam, for example, has a large immigrant community, with people originating from countries endemic for hepatitis A, B, and C, such as Morocco, Surinam, and Turkey. In order to enhance screening practices and preventive strategies for viral hepatitis in a highly urbanized area, the prevalence of serological markers in relation to demographic and behavioural risk factors for hepatitis A, B, and C virus infection in a representative sample of the general Amsterdam population of 2004 was investigated, as described in chapter 2.

In industrialized countries, the incidence of travel-related faecal-orally transmitted infections, such as hepatitis A, typhoid fever, and shigellosis, has declined substantially. This decline is often attributed to pre-travel vaccination and improvements in hygienic and sanitary conditions at travel destinations. However, their absolute or relative contributions are unknown. To study if attack rates of faecal-orally transmitted diseases in travellers are influenced by improvements in hygienic standards at travel destinations, trends in vaccine-preventable hepatitis A and typhoid fever were compared to trends in non-vaccine-preventable shigellosis, in the study described in chapter 3. National surveillance data on all laboratory-confirmed cases of travel-related hepatitis A, typhoid fever, and shigellosis diagnosed in the Netherlands from 1995 to 2006 were matched with the number of Dutch travelers to developing countries to calculate region-specific annual attack rates. In addition, trends in attack rates of these three faecal-orally
transmitted infections were compared with trends in markers for hygienic standards of the local population at travel destinations, drawn from the United Nations Development Programme database: the human development index (HDI), the sanitation index (SI), and the water source index (WSI).

Travellers with a pre-existing medical condition such as diabetes mellitus and inflammatory bowel disease, and travellers using immunosuppressive agents are thought to have an increased risk of symptomatic infectious diseases when visiting a developing country. However, evidence for this is lacking. To improve travel advice for this substantial group, two prospective studies were conducted, with non-immunosuppressed travel companions serving as controls. Thus, the group of travellers with the condition of interest and the group of travellers without that condition were comparable for travel destination and travel duration, which minimized any differences in exposure to infectious agents between the two groups. These two studies are described in chapter 4.1 and 4.2.

Research on the prevalence and incidence of schistosomiasis, strongyloidiasis, filariasis, and toxocariasis among travellers is scarce. Also, studies on the predictive value of eosinophilia for asymptomatic helminth infection have shown different correlations, and its diagnostic relevance remains controversial. The study presented in chapter 5.1 prospectively estimated the prevalence and incidence of these infections based on serologic testing before and after travel in a cohort of short-term travellers to endemic areas. The study also assessed the diagnostic relevance of eosinophilia.

In the past few decades, dengue has emerged in tropical and subtropical countries worldwide. Also, the number of reported symptomatic dengue virus infections among international travellers has increased. This may reflect an increased incidence of dengue among travellers, an increased number of travellers to endemic areas, or both. The study presented in chapter 5.2 prospectively estimated the prevalence and incidence of dengue virus (DENV) infection based on serologic testing before and after travel, based on the same study sample as described in chapter 5.1.

In the general discussion, chapter 6, main findings are discussed and the strengths and limitations of the used study designs are considered. Also, the relevance and recommendations arising from our findings are presented.
References


