Infectious souvenirs: the toll of travel?

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General Discussion

In recent years, the number of travellers to developing countries has increased. Such travel may have health consequences, both for healthy travellers and for travellers with a pre-existing medical condition. To prevent and manage these risks, more and better evidence-based information is needed. The research described in this thesis addresses the occurrence of several travel-related infections and the effect of preventive measures, which will be discussed here in more detail. The strengths and limitations of the used study designs will be considered, elaborating on the review presented in the Introduction. The practical relevance and recommendations arising from our findings will also be discussed, with a focus on evidence-based medical practice. Financial and economic factors are not considered, as cost-effectiveness and cost-benefit analyses are not part of this thesis.

Chapter 2

The population-based study on the seroprevalence of hepatitis A, B and C virus infection in Amsterdam described in this chapter is a cross-sectional study. Such a study design is indeed suitable to assess the seroprevalence of hepatotropic viruses, as humans will sustain life-long detectable antibody titres after infection and the used serologic tests have a high sensitivity and specificity. Results of the study sample were weighted by sex, age, and ethnicity to minimise selection bias and to enhance representativeness. Nevertheless, the main finding of this study – the seroprevalences of hepatitis A, B, and C in an urban population are higher than nationwide, because high-risk groups are more present – is the very reason that the generalisability is limited: findings apply to the Amsterdam population of 2004. Repeating this type of study in the future, at other places, and in other settings is highly recommended.

Because of the cross-sectional design, there was only limited information on timing of exposure and infection versus outcome relationships, and on disease duration. Therefore, etiologic relationships were difficult to establish.

Findings of this study have several practical implications. In the Netherlands, vaccination against hepatitis A virus (HAV) is recommended to all travellers to HAV endemic areas, unless they are immune because of previous exposure or vaccination. Until August 2008, the Dutch travel health guideline on hepatitis A stated that natural immunity can be assumed in persons originating from a country where hepatitis A is common. The assumption arbitrarily concerned persons who had spent at least 15 years of their childhood in an African country, and persons born before 1970 who had spent at least 15 years of their childhood in a hepatitis A endemic region other than Africa.

In our study, indeed 100% of first-generation immigrants from Turkey and Morocco older than 15 years at the time of immigration was immune to HAV, reflecting the high risk of exposure during childhood. However, of all first-generation Surinamese & Antillean immigrants only 76% was immune; 24% was still susceptible. And of first-generation immigrants from other high-endemic ethnicities, 86% was immune, with 14% being still susceptible. Therefore, the Travel Health Clinic from the Public Health Service Amsterdam started a study on hepatitis A immunity among
travellers born in Turkey, Morocco, Surinam, or a country in Sub-Saharan Africa, to further evaluate how many travellers are considered to be immune to HAV according to the national guideline, while in fact they are susceptible. Although the results from the latter study are still awaiting, the Dutch Working Group on Traveller’s Health Advice has already adapted the national guideline on hepatitis A immunisation: since August 2008, natural immunity against HAV is no longer assumed in persons originating from Surinam or the Netherlands Antilles. Instead, for these travellers testing for anti-HAV antibodies or vaccination against HAV without prior testing for anti-HAV antibodies is recommended.

In the future, the increasing immigrant population, with its decreasing immunity to HAV and continuing visits to their country of origin, may necessitate more immunisation efforts, for both individual and public health reasons.

According to the Dutch travel health guideline on hepatitis B, vaccination against hepatitis B virus (HBV) infection is only recommended for high-risk travellers, including immigrants from HBV-endemic countries who want to visit friends and relatives in their country of origin. Vaccination is not necessary for individuals who have already been HBV infected. As HBV infection may be asymptomatic, screening for antibodies to hepatitis B core antigen (anti-HBc) prior to vaccination is recommended to individuals belonging to risk groups. According to Dutch guidelines, these include first-generation and second generation immigrants from HBV-endemic countries.

In our study, the anti-HBc seroprevalence was indeed significantly higher among first-generation immigrants of intermediate- or high-endemic areas, such as Turks (32%), Moroccans (21%), and Surinamese and Antilleans (21%), as compared to residents of low-endemic areas (4%). Anti-HBc seroprevalence was positively correlated with age at the time of immigration to the Netherlands: 25% among those older than 15 years at immigration versus 13% among those 15 years or less at immigration. However, adult second-generation immigrants with parents from intermediately or highly endemic countries did not have a higher seroprevalence than persons with parents from a low-endemic country. Thus, the current Dutch travel health guideline to screen second generation immigrants from HBV-endemic countries for antibodies to hepatitis B core antigen (anti-HBc) preceding vaccination seems irrational. To enhance travel health guidelines, more (national) information concerning this issue among travelling immigrants is needed. Therefore, the Travel Health Clinic from the Public Health Service Amsterdam started a study on hepatitis B immunity among immigrant travellers visiting friends and relatives in an HBV endemic country. Results are still awaiting.

Until now, universal hepatitis B immunisation has not been part of the Dutch National Immunisation Programme; apart from selective immunisation of travellers, hepatitis B vaccination programmes have only been set up to protect social groups having a raised risk of contracting hepatitis B. These include the children of mothers carrying HBV, behavioural risk groups such as men having sex with men and injecting drug users, and medical and paramedical staff. In 2003, immunisation was extended to infants with parents from intermediately or highly endemic countries, i.e. new-born second-generation immigrants. However, in our study, these second-generation immigrants did not have a higher seroprevalence than persons with parents from a low-endemic country. This finding suggests that the risk of horizontal transmission is low and that selective immunisation of second-generation infants only, is not justified. Rationally, either all
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children should be immunised or no children at all. In a low-endemic country such as the Netherlands, with a growing immigrant population and increasing contact between low-risk groups and high-risk groups, universal immunisation of all children should be considered. Indeed, in 2007 the Dutch Health Council recommended an immunisation programme that included general vaccination of all infants.\footnote{11} It was not until July 2010 that the Dutch Ministry of Health adopted this advice; hepatitis B immunisation for infants will be part of the National Immunisation Programme from 2012 onwards.

The seroprevalences of antibodies to hepatitis C virus (HCV) and HCV RNA among adult Amsterdam residents in 2004 was higher (0.63% and 0.62%, respectively), than the anti-HCV seroprevalence found in a nationwide study (0.1%).\footnote{12} Studies conducted in the urban populations of other Western countries have found seroprevalences of approximately 0.4%, and up to 0.7% in urban areas.\footnote{13}-\footnote{16}

As chronic HCV infection frequently results in progressive liver disease which can be halted by eradicating the virus with antiviral treatment, active case finding and preventive strategies for HCV are particularly needed in urban populations, where already identified risk groups, including persons who have injected drugs, first generation immigrants from high-endemic countries and their children, and HIV-infected men who have sex with men, are more present.\footnote{17,18}

As natural immunity against HAV and HBV, and the risk of HCV will probably change in the decades to come, repeating this type of study in future is recommended.

Chapter 3

The study relating improved hygienic standards at travel destination to the overall decline in attack rates of faecal-orally transmitted diseases among visiting travellers described in this chapter is based on national notification data of ill travellers. The number of annually reported cases was put into perspective by using estimated numbers of travellers as denominators. The advantages of using these data is that the sample size was large enough for statistical analysis, the results were generated relatively rapidly, and the costs were generally lower than the costs of primary data collection.

The used study design has some limitations, as discussed in the Introduction. For example, neither the notification system on hepatitis A, typhoid fever and shigellosis cases in the Netherlands nor the travellers’ statistics from the Continuous Holiday Survey provided information on travel characteristics, such as the purpose of travel, travel circumstances, travel duration, and preventive measures taken. However, there are no reasons to believe that the impact of these factors changed during the study period. Thus, they have led only to an underestimation or overestimation of the absolute annual attack rates, without affecting trends in attack rates over time.

Although not all physicians and laboratories report notifiable diseases as mandated by law, completeness of reporting has improved during recent years, because of the increasing use of laboratory diagnostic tests in identifying new cases and the implementation of automated,
electronic laboratory-based reporting. Thus, the decline in absolute annual number of cases might have even been bigger than we have estimated.

In this chapter, the decline in shigellosis despite the lack of preventive vaccination shows that a concurrent decline in hepatitis A and typhoid fever cannot be attributed solely to an increase in pre-travel vaccination. Improved hygienic standards at travel destination (also) contributed. Although these findings are in accordance with the fact that many European travellers (58%) still travel without vaccination against hepatitis A,\textsuperscript{19} it would be impudent to assert that the current practice to vaccinate travellers to high-risk areas against hepatitis A and typhoid fever\textsuperscript{6,20} has become obsolete. Nevertheless, as hygienic standards at popular travel destinations will probably continue to improve, the risk of faecal-orally transmitted diseases will further decline. Consequently, in the future, the risk of infection with hepatitis A and typhoid fever at some destinations will equal the risk of infection in developed countries, and vaccination of travellers to these destinations will no longer be necessary. For that matter, the current Dutch policy not to recommend typhoid fever vaccination for short-term travellers to Latin America, Eastern/ Southern Sub-Saharan Africa, Turkey, and Thailand/ Malaysia, has already proven to be justified as the median attack rates for these destinations were very low, i.e. less than 0.2 per 100,000 travellers. Repeating this type of study in the future is recommended.

Logically, if hygienic standards of the local population contribute to the decline in travel-related faecal-orally transmitted diseases, improving hygienic behaviour of travellers can also contribute. So, in countries where sanitation is poor it remains advisable not to drink tap water unless it has been treated. Hands should be washed after visiting the toilet, and always before preparing or eating food.

Chapter 4

In the studies on symptoms of infectious diseases in travellers with diabetes mellitus, inflammatory bowel disease, or travellers using immunosuppressive medication, a non-immune-suppressed travel companion served as a matched control. Thus, situational specifics for travellers with the pre-existing medical condition and their controls were comparable, which minimized any differences in exposure to infectious agents between the two groups. As far as we know, such a study design has never been used in travel medicine research before. With this design, small differences in exposure could still not be controlled for. A randomised controlled trial would have been a better design. However, as in travellers the allocation of exposure cannot be controlled by the researcher for logistical and ethical reasons, our approach is probably the most ideal and practical one for evaluating differences in risk of travel-related infectious diseases. It is easy to perform, inexpensive, and without ethical problems.

Our two studies only gathered data on symptoms, and therefore, could only report on the occurrence of syndromes. However, expanding the study design by doing laboratory tests on blood samples drawn before and after travel, could enable to calculate risk estimates of specific etiological diagnoses.
Apart from controlling for pre-existing conditions, the study design can also be used to investigate the risk of infectious disease related to sex, age, ethnicity, previous immunity, a history of previous travel etc; or to evaluate the effectiveness and the side effects of preventive or therapeutic interventions such as vaccines, malaria chemoprophylaxis, or self-treatment.

Although findings of our studies represent persons who sought pre-travel health advice, and thus may not reflect all groups of travellers, they have some important implications.

Based on another study which suggested that patients with diabetes have a higher risk of infection and metabolic dysregulation while on travel, Dutch travel health guidelines used to recommend the usage of stand-by antibiotics for treatment of diarrhoea to all travellers with medication-dependent diabetes.

However, we found that travellers with medication-dependent diabetes do not have travel-related diarrhoea more often or longer than their travel companion without diabetes. Eighty-three percent of the travellers with diarrhoea did not use the stand-by antibiotic treatment, although its importance was emphasised by an experienced travel health expert and by means of information leaflets. Of 152 stand-by antibiotic courses provided, 141 (93%) were not used. Moreover, travellers with non-insulin-dependent diabetes (NIDD) only reported hyperglycaemias. Indeed, hypoglycaemia is uncommon when using only oral anti-diabetics. Thus, for NIDD, routine prescription of stand-by antibiotics for uncomplicated diarrhoea is not more useful than for healthy travellers. Stand-by antibiotics may still be useful for diabetic travellers to areas where health facilities are lacking in case of more severe illness, although this could not be assessed in our study. For travellers with insulin-dependent diabetes (IDD), monitoring blood glucose more frequently, and adjusting insulin dosage and diet accordingly, are probably more helpful in minimising metabolic dysregulation than carrying a stand-by course of antibiotics. However, the incidence of metabolic dysregulation among travellers with IDD and the merits of stand-by antibiotics should be evaluated in more detail.

Our recommendations were adopted by the Dutch Working Group on Traveller’s Health Advice. Since February 2010, the national travel health guideline on diabetes advises to prescribe stand-by antibiotics for traveller’s diarrhoea only to travellers with IDD going to developing countries and to travellers with NIDD going to remote areas in developing countries.

Other immunocompromised travellers, such as travellers using immunosuppressive agents (ISA) because of a rheumatic disease, a solid-organ transplantation, or an auto-immune disease, and travellers with an inflammatory bowel disease (IBD) are also thought to have an increased risk of infection. Indeed, Dutch, British and Canadian travel health guidelines, recommend that these travellers should be prescribed stand-by antibiotics for treatment of diarrhea. However, as for travellers with medication-dependent diabetes, we found that ISA and IBD do not have travel-related diarrhoea more often or longer than their non-immunocompromised travel companion. Seventy-one percent of ISA with travel-related diarrhoea and 86% of IBD with travel-related diarrhoea did not use the stand-by antibiotic treatment, although its importance was emphasised by an experienced travel health expert and by means of information leaflets. Of 146 stand-by antibiotic courses provided, 131 (90%) were not used. Thus, also for ISA and IBD, routine prescription of stand-by antibiotics for uncomplicated diarrhoea is not more
useful than for healthy travellers, although they may be useful for immunocompromised travellers to areas where health facilities are lacking in case of more severe illness. Yet, this could not be assessed in our study.

We found that the incidence and burden of signs of travel-related skin infection were higher among ISA than among controls. A higher risk of skin and soft tissue infection among patients using immunosuppressive agents has been reported before, in particular following anti-TNF alpha drugs.\textsuperscript{30,31} Because bacterial skin infection can be life-threatening, the merits of stand-by antibiotics for skin infection among ISA should be assessed in future studies.

### Chapter 5

In the studies assessing the incidences of and risk factors for schistosomiasis, strongyloidiasis, filariasis, and toxocariasis (chapter 5.1), and dengue virus infection (chapter 5.2), a cohort of Dutch travellers to endemic areas was followed prospectively. Participants donated venous blood samples for serology and blood cell count before and after travel, and kept a structured travel diary.

This design has some limitations. First, results represent persons who sought pre-travel health advice. Second, the risk of travel-related infection depends on the endemicity and the outbreak rate in a particular country during a particular time of travel. The exact contribution of these factors on our findings is unknown, as they vary from year to year. Third, false-negative and false-positive test results may have occurred, even though the used serologic tests had a high sensitivity and specificity. Unfortunately, there is no true gold standard for confirming or ruling out these infections. These problems also arise in other studies.

In future studies, samples could be collected during travel to gain more insight into the time of infection. For example, the traveller can collect dried blood filter paper samples by finger stick at standardised time points during travel as an alternative to venipuncture before and after travel. However, proper blood collection procedures are essential for assay accuracy. Also, performing a finger stick, during travel and at several time points, may keep eligible participants from participation. As far as we know, such a design has not been carried out yet.

In conclusion, although time-consuming and relatively expensive, performing prospective studies as we did, is the best methodological approach for estimating incidence rates of clinical and subclinical travel-related infections.\textsuperscript{32} Although our studies were performed in a general cohort of short-term travellers, such studies can also be applied to more specific cohorts of travellers, such as expatriates, travellers visiting friends and relatives, or persons travelling for work or education.

Our two studies have the following implications. Current preventive education and post-travel follow-up strategies concerning helminth infections arise from risk estimates from retrospective and cross-sectional studies based on travellers who sought medical attention after return. Thus, these risk estimates are biased. We estimated the prevalence and incidence of \textit{schistosomiasis, strongyloidiasis, filariasis, and toxocariasis}, and assessed the diagnostic relevance of eosinophilia, by conducting a prospective study among healthy travellers. In our study, the risk of schistosomiasis, strongyloidiasis, filariasis, and/ or
toxocariasis during one short-term journey to an endemic area was low, ranging from 1.1 to 6.4 per 1000 person-months of travel. We therefore concluded that routine serological testing of returned travellers is of no value. Surprisingly, most of the recent infections were contracted in India and Southeast Asia, while in other studies, most parasitic infections, in particular schistosomiasis and filariasis, were contracted in sub-Saharan Africa. Although these differences may be explained by differences in study design and study population, the endemicity of the studied diseases might have changed. Differences may also be explained by differences in risk behaviour: as the risk of infection is subject to the travellers’ expectations about endemicity and their own risk behaviour, travellers to Africa may have been more cautious than those to Asia. Although the risk of infection during one short-term journey was low, previous stay or travel lead to a cumulative risk of infection. This may necessitate more efforts on prevention and education. At the moment, there is no vaccine available against any of the four parasites, although an antischistosome vaccine is under development. Chemoprophylaxis with diethylcarbamazine and ivermectin to prevent filariasis may be successful for indigenous populations in highly endemic areas, but is not recommended routinely for travellers, because their risk of acquiring filariasis is low. Generally, there is no need for travellers to carry stand-by medications for self-treatment: because most of these parasitic infections do not require urgent treatment, there is enough time to seek medical attention, even until after return. The only available way to minimise risk is to prevent exposure. To prevent schistosomiasis, contact with fresh water in endemic areas should be avoided. Avoiding contact with soil can prevent infection with strongyloidiasis and toxocariasis. For filariasis, insect bites should be avoided, by wearing proper clothing, using insect repellent containing N,N-diethyl-meta-toluamide (DEET) on exposed skin, using a mosquito net, and sleeping in an air-conditioned room with screened windows. Although these advices are simple to give, they may be difficult to carry out consistently.

In our study, the positive predictive value (PPV) of eosinophilia was low. In hospital-based case studies, eosinophilia has been found in 38-65% of patients with filariasis, strongyloidiasis, and/or schistosomiasis, and even then, its PPV was low. As the PPV is generally proportional to disease occurrence, the PPV of eosinophilia was expected to be even lower in our cohort of asymptomatic travellers with a low incidence of infection. We concluded that routine screening for eosinophilia of asymptomatic travellers after return has a very poor positive predictive value, and is therefore of no use.

In conclusion, our study showed that frequent travel can lead to a considerable cumulative risk of helminth infection, including schistosomiasis, strongyloidiasis, filariasis, and/or toxocariasis. Nevertheless, true infection rates are difficult to assess; they depend on geographic distribution of helminths, travel behaviour and pre-existing immunity of travellers, and the characteristics of diagnostic assays. To improve preventive education and post-travel follow-up strategies, more prospective studies using more sensitive and more specific diagnostic tests are needed.

In the past few decades, the number of reported symptomatic dengue virus (DENV) 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. Until now, there have only been two prospective cohort studies. Both were performed in the 1990s. One study yielded an incidence rate (IR) of 11.0 per 1000 person-months in 104 long-
This IR is comparable to our short-term travellers (14.6 per 1000 person-months), although our study differed in travellers’ destination and duration of exposure and also in test characteristics. The other study yielded an IR of 36.9 per 1000 person-months in 447 short-term Dutch travellers to Southeast Asia. In our study, the IR in travellers to Southeast Asia was lower (18.5 per 1000 person-months), which may reflect different test characteristics and differences in exposure and risk behaviour related to factors like travel destination and preventive measures taken against mosquito bites. Despite these differences, the incidence rate of recent DENV infection in short-term travellers to endemic areas seems not to have increased during the last two decades. The increase in annually reported dengue cases from network studies is more likely related to the increase in international travel, the expansion of DENV and its vector to new areas, and the increased number of reporting sites.

Nevertheless, the incidence rate of DENV infection in short-term travellers to endemic areas is substantial, which is confirmed by the cumulative risk of infection from previous stay or travel of 6.5%, in our sample of travellers.

At the moment, there is no effective and safe vaccine available that provides long-term immunity against all four serotypes of dengue. The only useful preventive measure for travellers in areas where dengue is endemic is to avoid mosquito bites by wearing proper clothing and using insect repellent containing DEET on exposed skin, in particular during the rainy season. However, in our sample of travellers seeking pre-travel health advice, the average use of insect repellent containing DEET was only 45% of travel days, and 17% of participants used no repellent at all, despite receiving oral and written travel advice and learning about the study objective. More efforts on effective prevention and education are needed.

For travellers to Sub-Saharan Africa, the risk of infection appeared to be higher than expected (13.4 per 1000 person-months), although the 95% confidence interval was wide (3.4 to 36.5). African dengue endemicity may have changed, and the risk for travellers may thus be higher than expected. This needs further investigation.
Concluding remarks

The research described in this thesis addresses the epidemiology of several travel-related infections, including the incidence, prevalence, and morbidity of these illnesses in specific groups of travellers, and the effectiveness of and adherence to travel health precautions. Our findings will enhance both the risk management in pre-travel health advice settings and the assessment and (empiric) treatment in outpatient and inpatient clinics. The practical relevance of the performed research does not only benefit travellers, but also health providers, researchers, and policy makers. Indeed, specific recommendations arising from the results have already found their way to the Dutch travel health guidelines, as described in the Discussion.

Are infectious souvenirs the toll of travel? The answer is: it depends. We found that the risk of infection is related to previous immunity, which is related to ethnicity (chapter 2); to hygienic standards at travel destination (chapter 3); to the frequency of (previous) travel to developing countries (chapter 5); and to travel destination and travel season (chapter 6). The risk of infection appears not to be higher for travellers with medication-dependent diabetes mellitus, inflammatory bowel disease, or using immunosuppressive medication (chapter 4).

The art of travel medicine lies in the careful selection of necessary preventive and therapeutic strategies, avoiding measures that may cause unnecessary adverse events, expense, fear, or inconvenience. However, physicians, epidemiologists, policy makers, and travellers each may view risk differently, and may have different levels of risk tolerance and different ways of dealing with uncertainty. Particularly in travel medicine, the traveller’s own perception of risk and his/ her attitude towards the reassurance provided by the intervention measure versus its potential side effects or costs is important. Also, what we believe to be ‘truth’ today, often turns out to be transient; tomorrow a study may appear that may invalidate or extend the best scientific information available to us today. As the Roman poet Ovid wrote: everything changes, but nothing is truly lost.

Travel health guidelines can assist the health practitioner in this difficult and changing process of risk assessment and selection of interventions, provided that these guidelines identify, summarise, and evaluate the best evidence and most current data. More efforts to quantify travel-related health risks and to evaluate guidelines are needed. Risk assessment should be destination-specific and should take into account individual factors, such as age, illness, and personal preferences. Only such an approach can provide improved and prioritised preventive and therapeutic strategies and evidence-based guidelines.
References

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