Infectious souvenirs: the toll of travel?
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Summary

Due to different socio-economic, climatic, physical or geographical conditions, or due to behaviour that is more frequent at the destination than at home, travellers may face several health problems, in particular when travelling to the developing world. Travellers with a pre-existing medical condition are expected to suffer the most from this.

To prevent and manage the travel-related health risks, evidence-based information is needed. The best evidence is provided by original study designs. Unfortunately, these are relatively scarce. Moreover, each methodological approach has its strengths and limitations that can significantly influence risk estimates and the generalisability to all travellers. The major study designs and their role in travel medicine research have been discussed in chapter 1.

In the population-based, cross-sectional study described in chapter 2, the seroprevalences of hepatitis A, B, and C in the adult population of Amsterdam and the related sociodemographic and behavioural risk factors were assessed in order to enhance screening practices and preventive strategies for viral hepatitis. Therefore, sera from a representative sample of 1,364 adult residents were tested for viral markers.

It was estimated that 57% of the general Amsterdam population was immune to hepatitis A virus (HAV) through prior exposure to the virus or through immunisation. Seroprevalence was significantly lower among residents of ethnicities associated with low-endemic areas (46%) than among first-generation immigrants of high-endemic ethnicity (up to 99%). The seroprevalence among second-generation immigrants did not differ from residents of Western ethnicities. Seroprevalence increased with age.

The seroprevalence of antibodies to hepatitis B core antigen (anti-HBc) and of hepatitis B surface antigen (HBsAg) in the general Amsterdam population were 9.9% and 0.4%, respectively. Both were highest among men with a sexual preference for men, and among first-generation immigrants of intermediate- or high-endemic areas. Anti-HBc seroprevalence was positively correlated with age at the time of immigration to the Netherlands, reflecting the contribution of sexual and horizontal transmission of hepatitis B virus (HBV) among the first-generation immigrants from endemic countries, in addition to perinatal transmission. The anti-HBc seroprevalence among second-generation immigrants was comparable to persons of Western ethnicities.

The seroprevalence of antibodies to hepatitis C virus (HCV) and the HCV RNA prevalence were 0.63% and 0.62%, respectively.

We concluded that, in a low-endemic country, the seroprevalence of viral markers for hepatitis A, B, and C may be higher in urbanized regions with many people originating from high-endemic countries than nationwide, indicating the need for differentiated regional studies and prevention strategies. More prevention efforts in cities like Amsterdam are warranted, particularly for hepatitis A and B among second-generation immigrants, for hepatitis B among men with a sexual preference for men, and for hepatitis C. Active case finding strategies are needed for both hepatitis B and C.
To study whether 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, as 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).

We found that the trends in attack rates of non-vaccine-preventable shigellosis among Dutch travellers to developing countries between 1995 and 2006 resembled the trends in attack rates of vaccine-preventable hepatitis A and typhoid fever. Region-specific analysis also showed that trends in attack rates of the three diseases correlated well: a decline for Latin America and the Arab region, including Turkey and Egypt, and stable trends for the Caribbean, Sub-Saharan Africa, Thailand/Malaysia, and the Indian subcontinent. We also found that declining attack rates of the three fecal-orally transmitted diseases correlated with improvements in socioeconomic, sanitary, and water supply conditions of the local population at travel destination. These findings suggest that improved hygienic standards at travel destination strongly contributed to the overall decline in attack rates of faecal-orally transmitted diseases among visiting travellers.

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, a prospective study was 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.

In chapter 4.1 it was investigated whether travellers with medication-dependent diabetes have symptomatic infectious diseases more often and longer than travellers without diabetes. In that study, no differences in travel-related diarrhoea, vomiting, fever, cough, rhinitis, or signs of skin infection were found when comparing 70 travellers with insulin-dependent diabetes (IDD) and 82 travellers with non-insulin-dependent diabetes (NIDD) with their respective controls. Although regular testing of blood glucose levels during travel was not part of the study protocol, only 3 of 70 IDD (4.3%) and 2 of 82 NIDD (2.4%) reported dysregulation of blood glucose levels during travel. Only 6 out of 31 IDD with diarrhoea (19%) and 5 out of 32 NIDD with diarrhoea (16%) used the stand-by antibiotics. Unfortunately, the effect of the use of stand-by antibiotics on the duration of diarrhoea could not be analysed due to small numbers.

We concluded that routine prescription of stand-by antibiotics for travellers with diabetes to areas with good health facilities is probably not more useful than for healthy travellers.
In chapter 4.2 it was investigated whether travellers using immunosuppressive agents (ISA) and travellers with an inflammatory bowel disease (IBD) have symptomatic infectious diseases more often and longer than non-immunocompromised travellers. As for travellers with medication-dependent diabetes, no differences in travel-related diarrhoea, fever, cough, rhinitis, fatigue and arthralgia were found when comparing 75 ISA and 71 IBD with their respective controls. Among ISA, the incidence and burden of signs of travel-related skin infection were higher. Among IBD, the incidence and burden of vomiting were higher.

Only 10 out of 35 ISA with diarrhoea (29%) and 5 out of 37 IBD (14%) used the stand-by antibiotics (properly). Also in this study, the effect of the use of stand-by antibiotics on the duration of diarrhoea could not be analysed due to small numbers.

We concluded that routine prescription of stand-by antibiotics for these immunocompromised travellers to areas with good health facilities is probably not more useful than for healthy travellers.

The study presented in chapter 5.1 prospectively estimated the prevalence and incidence of schistosomiasis, strongyloidiasis, filariasis, and toxocariasis 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.

Recent infection, defined as a seroconversion for any of the 4 parasites, was found in only 0.8% of 1,207 included travellers. They were largely contracted in Asia. The disease-specific incidences were low and ranged between 1.1 and 6.4 per 1,000 person-months of travel. However, as much as 9.3% of travellers had previous infection, defined as seropositivity for any of the 4 parasites in pre- and post-travel samples: schistosomiasis in 2.7%, strongyloidiasis in 2.4%, filariasis in 3.4%, and toxocariasis in 1.8%. This indicated that exposure from a previous stay raises risk of infection. Indeed, previous infection was related to a history of frequent travel to developing countries.

The positive predictive value of eosinophilia for serology suggestive for one of four parasitic infections was low, being 15% for diagnosis of previous infection and 0% for recent infection. None of the symptoms studied had any positive predictive value for recent or previous infection.

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.

Serology suggestive for recent infection, defined as a seroconversion for anti-DENV IgM and/ or IgG antibodies, was found in 14 of 1,207 travellers at risk (1.2%). Although the majority of seroconverted travellers had travelled to Southeast and Southwest Asia, 3 had travelled to Sub-Saharan Africa. The incidence rate (IR) was 14.6 per 1,000 person-months, and was significantly higher for travel during the rainy months. The IR appeared to be higher among travellers who were male, travelled for work or education, and inconsistently used insect repellent containing DEET, but differences were not significant (p>0.05). The presence of fever, retro-orbital pain, myalgia, arthralgia, and skin rash all had predictive value for recent infection. Dengue-like illness was the strongest predictor (in 5 of the 14 recent infections (36%).
As many as 6.5% of travellers had serology suggestive for previous infection, defined as seropositivity for anti-DENV IgG antibodies in both pre- and post-travel samples. The prevalence rate was strongly related to birth in a dengue-endemic country and a history of frequent travel to such countries. Previous dengue infection was also related to increasing age and the travel purpose of visiting friends or relatives.

We concluded that the risk of DENV infection for short-term travellers to endemic areas is substantial. However, the incidence rate found in this study is comparable to the IR found in two other serology-based prospective studies, performed in the 1990s.

In chapter 6, the major findings of the studies described in this thesis were put into perspective by discussing their strengths and limitations. Also, their relevance for daily practice was outlined. Specific recommendations arose from our studies, that will enhance both the risk management in pre-travel health advice settings and the assessment and (empiric) treatment in outpatient and inpatient clinics. Quantification of travel-related health risks as we did, is the only means to provide improved and prioritised preventive and therapeutic strategies, including evidence-based guidelines.