chapter 8

Discussion and conclusion
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General discussion

The studies in this thesis have shown that among short-term travelers the risk of malaria was low and adherence to chemoprophylaxis high. Four travelers with anti-circumsporozoite seroconversion had been adherent to chemoprophylaxis and did not develop fever. Especially travel to Africa, using mefloquine, use of DEET and travel duration of 14-29 days in endemic areas were associated with good adherence. The risk of influenza virus infection was much higher than suspected based on reported symptoms. Fifty percent of symptomatic influenza patients could have imported the virus into the Netherlands and have caused further spread of disease.

The risk of travelers’ diarrhea was confirmed to be high both among immunocompetent short-term and long-term travelers. The clinical course tended to be mild / ‘watery’, suggesting no role for the prescription of routine stand-by antibiotics. If needed, travelers found appropriate treatment abroad. Female sex and tourism as travel purpose were risk factors for diarrhea in both short-term and long-term travelers. In long-term travelers both the incidence rate for a first episode of TD and the mean quarterly incidence for all TD episodes decreased significantly between the first and second quarter, the proportion who were diarrhea free increased, and the proportion experiencing multiple episodes decreased. Unprotected casual sex was reported commonly among long-term travelers, but was not associated with syphilis and HIV, possibly because the size of the cohort was too small compared to the incidence of syphilis and HIV. And finally, HIV infected children and children on immunosuppressive medication for rheumatic diseases responded well to a full series of combined HAV and HBV vaccine, though response after a single dose was relatively poor.

In this chapter the study findings are discussed and their practical relevance for pre-travel health advice presented.
Knowledge prior to this study

Risk estimates for malaria infection among travelers are based on infections in returned travelers, on transmission rates in the endemic population or both (1;2). Both estimates are likely not accurate for travelers from non-endemic countries (1). Prospective studies on P. falciparum infection combined with information on adherence to chemoprophylaxis and other anti-mosquito preventive measures are most informative to estimate the risk for travelers. Detecting anti-circumsporozoite antibodies can be used in non-immune travelers to estimate P. falciparum infection as shown in several studies (3-8). There are only a few other prospective studies on malaria infection using anti-circumsporozoite antibody tests in non-immune travelers using chemoprophylaxis (3;6;7). Cobelens et al found in 1991-1992 an AR of 1.3%, and an IR of 1.7 per 100 person-months, Nothdurft et al found in 1999 an AR of 4.96% and Knappik et al found an AR of 0.95%, also in 1999.

Since most clinical or symptomatic malaria infections occur in travelers not using or incorrectly using the appropriate chemoprophylaxis (9-16), adherence to chemoprophylaxis is important in the protection against malaria. Travelers to Africa are found to be more adherent to chemoprophylaxis than travelers to other destinations (17-19), and travelers who are more adherent to one preventive measure were likely to be more adherent to other preventive measures (20;21).

What this study adds

This is one of the few prospective studies estimating P. falciparum infection in combination with chemoprophylaxis and other preventive measures. We found anti-circumsporozoite antibody seroconversion in four out of 938 travelers and estimated an AR of 0.4% and an IR of 0.8 per 100 person-months. All 4 had been adherent to chemoprophylaxis; two visited Africa, one Suriname, one India, and none reported fever. Ten subjects with fever were tested for malaria while abroad and of these, three received treatment. All three had been adherent to chemoprophylaxis and tested negative for anti-circumsporozoite antibodies. Self-reported
adherence to chemoprophylaxis was good, 84% took at least 75% of recommended prophylaxis during travel. Travelers to Africa, travelers using mefloquine as chemoprophylaxis, travelers who spent 14-29 days in endemic areas and travelers who were more adherent to use of DEET showed a better adherence. The combination of chemoprophylaxis and other preventive measures were sufficient to protect this cohort of travelers from clinical malaria.

Discussion and recommendations.
Results showed that none of the travelers to low-endemic areas where only anti-mosquito preventive measures but no chemoprophylaxis is recommended contracted malaria, and consequently there is no reason to adapt the Dutch national guidelines in their recommendations for these low endemic countries.
The high numbers of adherent travelers found in this study suggests that travel advice had been effective, and that adherence with chemoprophylaxis in combination with other preventive measures was good enough to protect all travelers in this cohort from clinical malaria. Both our study and previous studies showed that better adherence to anti-mosquito preventive measures was associated with better adherence to chemoprophylaxis. Risk perception of travelers in our study seemed accurate as travelers to Africa, where malaria risk is highest, showed better adherence. Based on risk factors for adherence, one could target specific groups of travelers in pre-travel health advice and discuss information on adherence to anti-malarial chemoprophylaxis with these target groups. In future studies reasons for non-adherence in certain groups could be studied. Because longer travel duration is a known risk factor for non-adherence, the travelers’ advice and vaccination clinic of the GGD Amsterdam is currently studying risk factors for adherence among a cohort of long-term travelers.
Chapter 3
Influenza risk among short term travelers

Knowledge prior to this study
In the Netherlands, only risk groups for severe disease are advised on influenza virus infection. Several prospective studies found respiratory tract infections to be the second most frequent infectious disease contracted during travel (22-24) and influenza is one of the most frequently acquired infectious travel-related diseases (25). Other studies have shown that influenza, through travelers, could rapidly spread across borders (26-31), causing epidemics worldwide (29). Only one other prospective study estimated the attack rate and incidence rate of influenza virus infection during travel based on seroconversion, which showed an overall AR of 1.2% with an IR of 1.0 per 100 person-months, and an AR for symptomatic infection (symptomatic defined as only fever) of 0.9%. Travelers visiting the Indian subcontinent were most affected by influenza compared to other regions.

What this study adds
This prospective study has been unique in testing a complete study population for influenza virus infection in order to estimate an accurate risk for travelers. We found an AR for influenza virus infections of 7% and an IR of 8.9 per 100 person-months. The AR and IR of symptomatic (influenza-like illness [ILI], defined by fever and a sore throat and/or cough) serologically confirmed influenza virus infection for all travelers was 0.8% and 0.9 per 100 person-months. The AR for serologically confirmed influenza virus infection with fever only (no other symptoms) was 2% (95% CI 0.7%–2%). Persons born in Africa and Latin America were more likely to have contracted influenza virus infections during travel than those born in Western countries, which was also found in the study by Mutsch et al. South-central and Western Asia showed the highest AR and IR of all regions (11%; 14.4/100 person-months). Of the 15 travelers with confirmed influenza virus infection with fever or ILI, 7 were considered contagious during the flight or after return from travel, and could consequently have imported and spread influenza virus in the Netherlands. As asymptomatic travelers also could be infectious, the number of travelers who import influenza virus is probably underestimated.
Discussion and recommendations

This study supports earlier studies that show that influenza is one of the most frequently acquired infectious travel-related disease (see figure 1), and that travelers play an important role in the further spread of influenza virus across borders. In order to reduce the risk of infection and further spread, pre-travel health advice should consist of general information on personal hygiene, e.g. regular hand washing and coughing hygiene. The association between country of birth and risk for certain infections was also found in other studies (32-35). Possibly travelers who visit friends and relatives (VFR) have a higher risk for influenza because they tend to have closer contact with the local population (33;36;37). Another possibility to prevent infection and further spread of influenza is vaccination. In the Netherlands, as in many other countries, influenza vaccination is recommended to risk groups for severe disease, irrespective of travel. Vaccination of travelers against influenza has been discussed. Freedman describes benefits of influenza vaccination for travelers, varying from individual benefit because of protection against influenza during travel to prevention of outbreak or further spread of new antigenic drift variants. Freedman suggests to consider influenza vaccine not only for risk group travelers but for any tropical, cruise ship, tour group, influenza-season temperate traveler who wishes to decrease the risk for influenza illness, or who wants to diminish the risk of having respiratory symptoms mistaken for severe acute respiratory syndrome (SARS) (38). Because travel per se is not a risk factor for severe disease, and influenza can be contracted worldwide, we do not share Freedmans opinion and believe that as long as influenza vaccine is not recommended to healthy people in the home country, there is no rationale to recommend influenza vaccinations for all healthy travelers. However, in case of an influenza pandemic, rapid spread of disease could also occur. In that case, and if a vaccine can be produced for the pandemic type of influenza virus quickly, vaccination could be used for public health reasons to slow down the spread of the virus by travelers.
Chapters 4 and 5
travelers' diarrhea risk among short- and long-term travelers

Knowledge prior to these studies

Travelers’ diarrhea (TD) is the most common infectious health problem among travelers to developing countries (39-47), with attack rates (ARs) varying between 25% and 57% (43;44;47-49). A previous prospective study among travelers from Amsterdam in 1999 found an incidence rate (IR) of 3.14 per 100 travel days (40). Factors associated with TD and most consistently found are destination, age, sex and country of birth. Risk areas for TD are the Indian subcontinent, followed by African regions (40;42-44;50-52) Within Latin America regional variations in AR and IR are found (40;43;44;50-52). Variations in risk could be due to differences in circulating pathogens (39), differences in hygienic standards between countries (53), differences in study population or a combination of these factors: women were found to have more risk for TD (54), and persons born in non-Western countries show less risk for TD, probably because of conferred immunity caused by increased exposure to infection in the past (42;55). Several studies have shown an increased risk of TD in younger age groups (41;44;46). Furthermore, Cobelens et al found fecal blood loss and concomitant abdominal and systemic symptoms in subsequent episodes more often present than in first episodes, and also that subsequent episodes lasted longer than first episodes.

Research concerning TD among long-term travelers is scarce; only a few prospective studies among expatriates and Peace Corps Volunteers, a review among military personnel and a retrospective study among travelers (mean travel duration of 14.7 weeks) showed longer travel duration to be associated with increased or persistent health risks, including travelers’ diarrhea (42;56-60). Another retrospective study among travelers with a travel duration >2 months showed an AR of TD of 83% (61). Although persistent risk for TD exists up to 2 years of travel (59), longer travel duration is possibly associated with developing immunity (56;57;62). Steffen et al showed that visiting a tropical country in the 6 months prior to a trip, protected against TD during that trip (46). The association between risk for TD and younger age groups has been reported (40;46;57;60;62;63), possibly because of different risk behaviors (46).
Chapter 4: travelers’ diarrhea among short-term travelers

This prospective study is the first that estimated IRs for first as well as subsequent episodes, besides information on risk and risk factors for short-term travelers. The median age in this cohort was 38 years (interquartile range [IQR] 29-51). We found an AR of 50%, and the observed incidence rates did not differ between first and subsequent episodes of TD (2.49 and 2.75 per 100 travel days, respectively). The AR and IR were highest in the Indian subcontinent and Western Asia, followed by Middle, Western and Northern Africa and Central America and the Caribbean. Our study confirm earlier findings that female sex, a Western country of birth, tourism as the purpose of travel and the Indian subcontinent were risk factors for TD. Female sex was also an independent risk factor for subsequent episodes of TD, country of birth and purpose of travel were not. We found no differences in severity between first and subsequent episodes, and subsequent episodes had a significant shorter median duration than first episodes, which was not found in an earlier study of Cobelens et al. Possibly this could be explained by changes in circulating microorganisms and/or increased hygienic circumstances in the visited countries over the years (53). In the Netherlands, standby antibiotics are only advised to travelers at increased risk, such as immunocompromised travelers and travelers to very remote areas. In 5% (36/781) of all TD episodes antibiotic treatment was used, of which half was purchased locally without a prescription.

Chapter 5: travelers’ diarrhea among long-term travelers

The median age in this cohort was 25 years (IQR 23-30). As expected, we found a higher AR of TD among long-term travelers of 83% than among short-term travelers, with 66% reporting 2 or more episodes while traveling. The overall IR was 1.5 per 100 travel days (95% CI 1.3 - 1.6) for first TD episodes which was lower than in the cohort of short term travelers. Both the IR for first TD episodes and the mean quarterly IR of all TD episodes decreased significantly between the first and second quarter of travel; the proportion who were diarrhea free increased, and the proportion experiencing multiple episodes decreased. Independent determinants for having a first TD episode included: female sex, younger age, holiday as travel purpose, and visiting Asia, and all variables, except for travel purpose, were also determinants for having multiple episodes. Altogether, risk factors found for TD, regardless of first or subsequent episodes, did not seem to differ by travel duration among this cohort of long-term travelers. Of TD episodes 82% was ‘watery’ and 18% ‘febrile/dysenteric’, as defined by symptoms of fever and/or bloody or mucous stools. We found no difference in proportion of
watery versus febrile/dysenteric TD or other symptoms between first and subsequent episodes. In 10% of all episodes (119/1146) antibiotics were used: of which half was purchased locally without a prescription.

**Discussion and recommendations (chapter 4 and 5)**

Both studies among short- and long-term travelers confirmed the high ARs of TD in previous studies, despite pre-travel advice on personal hygiene. The AR among long-term travelers was even higher than among short-term travelers, probably due to longer travel duration and therefore longer exposure time.

The overall IR for first episodes among long-term travelers was lower compared to our study among short-term travelers. However, because of differences in study design, travelers’ characteristics and differences in definitions of TD and TD episodes, the results should be interpreted with care. For example, in the short-term travelers cohort, younger age showed highest TD AR’s and IRs (although younger age was not significant in multivariable analysis) and in the long-term travelers, a risk factor for first and subsequent episodes was younger age. Because median age in long-term travelers was much lower than in short-term travelers, besides travel duration, this could partly explain higher ARs. Similarly, a risk factor for first episodes of TD among short-term travelers was a Western country of birth, whereas all long-term travelers were of Western ethnicity. Furthermore, the IRs cannot be compared because of a difference in study design: because long-term travelers filled out their diary weekly, we did not know the exact start date of diarrhea and therefore not the exact follow up time for subsequent episodes. Instead, we estimated the mean IR of TD episodes over time.

Study results among long-term travelers suggest that the IR of TD episodes decreases as their travel progresses, which could suggest development of immunity or behavioral change of travelers over time. Other studies also suggested a possible association between longer travel duration and developing immunity (56;57;62). Possibly in short-term travelers follow up time was too short for travelers to develop immunity.

Risk factors for first episodes TD among short-term travelers were female sex, a Western country of birth, tourism as travel purpose and several destination regions including South-Central and Western Asia compared to South America. The only risk factor for subsequent episodes among short-term travelers was female sex. In long-term travelers risk factors for
first episodes were female sex, younger age, holiday as travel purpose and Asia as travel destination. Risk factors for subsequent episodes in long-term travelers were female sex, younger age and Asia as travel destination. For both long- and short-term travelers, female sex, holiday as travel purpose and Asia(n regions) as travel destination were risk factors for first episodes and female sex was the only consistent risk factor for subsequent episodes in both cohorts. As risk factors female sex, younger age, holiday as travel purpose, and Asia as travel destination are also consistent with prior studies, these factors should be mentioned in pre-travel health advice, with the intention to enhance risk perception in travelers and emphasize compliance with hygiene health measures.

As we found an overall mild / 'watery' course of TD among both short- and long-term travelers, a short median duration of TD among short-term travelers, and low percentages of travelers reporting having used antibiotics for TD, we believe prescriptions for standby antibiotics should remain limited to travelers at high risk, such as those who are immunocompromised or are visiting very remote areas. Compared to short-term travelers, long-term travelers more frequently reported use of antibiotics, 10% (95% proportion confidence limits 8.7-12.3) of all episodes among long-term travelers compared to 5% (95% confidence limits 3.3-6.3) of all episodes in short-term travelers. Almost 70% (82/119) of antibiotics use in long-term travelers was for subsequent episodes compared to 14% (5/36) in short-term travelers. Because of differences in study design and traveler characteristics these results are difficult to compare. Short- and long-term travelers both show a comparable proportion of antibiotics bought over the counter.

Travelers who required treatment were all able to obtain antibiotics locally. Also, in short-term travelers no hospital admissions because of TD were recorded, in long-term travelers in 1% (14/1146) of TD episodes a (short) hospital admission for rehydration and antibiotic treatment was reported. Our results support Dutch national guidelines in not providing all travelers with standby antibiotics and based on our findings these guidelines do not have to be adjusted. If studies of this kind are to be repeated, more precise details of TD should be recorded, e.g. the duration of TD in days, the diarrhea free days, the exact frequency of stools per 24hr and the degree of disability travelers experienced. On the other hand, asking too many details and daily entries could lead to non-compliance, especially in long term travelers. Having more precise information about the reason of antibiotics use during travel could be valuable to define differences in use between short- and long-term travelers. Finally the IR could be decreasing because of increasing levels of hygienic in travel destinations. Also, circulating
microorganisms may change over time. Repeating this study, e.g. in ten years, could be useful to follow trends in attack rates and incidence rates and combined with information on hygiene in travel destinations, to monitor possible changing risks and risk factors.

Compliance with hygiene measures has been found to be poor (46;64), and one can question the effectiveness of communicating these measures. On the other hand, what would attack rates be without pre-travel advice on preventive measures? In pre-travel health advice one can discuss these results with travelers, especially those at highest risk, which may increase adherence to preventive measures.

**Chapter 6**
**Sexual risk behavior among long-term travelers**

**Knowledge prior to this study**
Knowledge on sexual risk behavior among long term travelers may be used in pre-travel health advice. Studies have shown that 5% to 50% of travelers worldwide engage in casual sex while traveling, particularly young and single men, those traveling without a partner, and long-term travelers (65;66). Bloor et al found that patterns of condom use in female travelers varied with the ethnic background of their sexual partner: female were less likely than men to have safe sex with local partners (67). Knowledge on behavioral risk factors is scarce and limited to specific groups such as expatriates, specific occupational groups or travelers to specific destinations (68-75). Croughs et al studied a cohort of short-term travelers and found traveling without a steady partner to be the most important risk factor for casual sex while traveling (76).
What this study adds

Our study showed that 35% of long term travelers reported having casual sex while traveling. Half of those who had casual sex had unprotected casual sex. Single, male travelers (heterosexual and homosexual) had a higher number of casual sexual partnerships, which is consistent with earlier studies (67;76). The risk of unprotected sex increased with the number of casual partnerships and was higher among single travelers. Dutch or other Western partners were reported more frequently as casual partnerships than casual partnerships with locals from the travel destination. Neither travel destination nor the ethnicity of the casual partner was a significant factor in predicting condom use. We found no difference in condom use between heterosexual men and women with local or Dutch partners. Although MSM had more casual partnerships than heterosexual men or women, they did not have more unprotected partnerships in general. No HIV or syphilis seroconversions were recorded after travel.

Discussion and recommendations

Long-term travelers frequently engage in casual sex while traveling, both protected and unprotected, with risk for STIs such as HIV, syphilis, hepatitis B, and other STIs. Because the median age in our cohort was 25 years and age was found to be a risk factor in previous studies, this could explain the high number of travelers engaging in casual sex in our study. In pre-travel health advice, all single travelers should be advised on safe sex during their travel. Because of the high proportion of travelers in our study who had engaged in unprotected casual sex with both other tourists and locals, in future studies one could consider testing other, more common STIs, such as Chlamydia and Gonorrhea, to obtain more information on sexual risks in long-term travelers. DNA sequencing could give additional information on the epidemiology of STI’s in travelers. Also, it is unknown whether the risks of casual travel sex are indeed higher than to the risks of casual sex in those who do not travel, especially because populations migrate and mix increasingly. Therefore future studies are recommended where sexual behavior of travelers are compared with non-travelers, or when a cohort is prospectively followed for sexual behavior at home as well as during travel so sexual behavior can be compared.
Chapter 7
Immune responses to a combined hepatitis A and B vaccine among immune compromised children

Knowledge prior to this study

Because immune compromised children have increased survival and improved quality of life due to better treatment options, they may over time engage more in travel than in the past. For evidence based health advice to immunocompromised children, one needs information on immune responses to vaccination. Two studies evaluating protective antibody response after a first hepatitis A dose of vaccine in HIV-infected children found responses of 86% and 69% (77;78). Immune response to hepatitis A after the second dose of vaccine in HIV-infected children varied from 85% found by Siberry et al (79), to >97% in other studies (77;78;80;81). Higher CD4+ T-cell count and younger age (<12 years) in HIV-infected children were found to be associated with antibody response to HAV (79).

No data exists on anti-HAV immune response after the first dose of vaccine in children on immunosuppressive medication for treatment of rheumatic diseases. In children with juvenile idiopathic arthritis with or without immunosuppressive medication an overall immune response to hepatitis A of 92% was found, with lower rates in children on anti-TNF-α treatment (82). Two previous studies among HIV-infected children found low seroconversion percentages (60–71%) after hepatitis B vaccination (83;84). In these studies and also in studies among HIV-infected adults, low viral load, high CD4+ T-cell count, and cART were found to be positively associated with seroconversion (83–85). One study among children on immunosuppressive medication for JIA showed an immune response of 97% for hepatitis B (86).

What this study adds

This is the first interventional study that studied immune responses to the combined hepatitis A and B vaccine. We found a low initial immune response to HAV after the first dose of vaccine in both HIV-infected children and children on immunosuppressive medication for
rheumatic diseases treatment: 71% and 55% respectively developed a protective antibody response. After the second dose of vaccine, the immune response to hepatitis A was much better: 99% and 100% respectively. We did not find associations between immune response to hepatitis A and type of medication in children on immunosuppressive medication for rheumatic disease; neither did we find association between CD4+ T-cell count and younger age in HIV-infected children and immune response. Immune response to HBV after the first dose of vaccine in both HIV-infected children and children on immunosuppressive medication for rheumatic diseases was low: 27% and 17% responded, respectively. After the second dose of vaccine in both groups, we found an immune response for hepatitis B of 97% and 93% respectively. In our study HIV-infected children had a high median CD4+ T-cell count (858 cells/mm3), low median viral load (39 copies/mL), and almost all children (89%) used cART in our study. We found a larger proportion of children on cART and children with a viral load <50 copies/mL to be responders. Not surprisingly, all children not on cART had a viral load >50 copies/mL. Furthermore, a significantly higher geometric mean concentration (GMC) was found in the same two groups.

Discussion and recommendations

Immune responses after a full series of combined HAV and HBV vaccine in the two groups of children was excellent. Because we found a substantial proportion of HIV-infected children and children on immunosuppressive medication for rheumatic diseases not protected for HAV after the first dose of combined HAV and HBV vaccine, this has practical implications. Especially in travel health and postexposure prophylactic treatment for HAV, the following measures are suggested: HIV-infected children and children on immunosuppressive medication should be serologically tested for anti-HAV prior to travel to ensure they are protected if there is no time to await the second dose of vaccine; and, children who cannot be protected before travel and those who need postexposure prophylactic treatment for HAV should receive immunoglobulines.

Testing anti-HBs positive after a full series of vaccine maybe considered to ensure protection, in particular in HIV-infected children who are not receiving cART and in children with a viral load >1000 copies/mL. A follow up study in these two groups of children is advised to acquire more information on long-term protection. Also, if studies of this kind are repeated, having exact GMC’s could contribute to a better comparison with other studies.
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