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INFECTIOUS DISEASES IN RETURNING SWEDISH TRAVELLERS

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ABSTRACT

The number of travellers to “tropical” parts of the world has increased substantially during the past decades. Identifying risk groups and providing preventive measures is important both to reduce the number of travellers falling ill and to prevent introduction of diseases into new countries. The aim of this thesis is to describe the epidemiology of imported infectious diseases in Sweden and to identify risk groups.

To investigate epidemiology and use of chemoprophylaxis in patients notified with *P.falciparum* malaria we studied compiled information on patients notified to the Swedish institute for infectious disease control (SMI) 1994-2001. Ninety percent of the patients had traveled to Africa. Malaria infection despite intake of adequate chemoprophylaxis decreased during the study period indicating more effective chemoprophylaxis at the later part of the study. Chloroquine/proguanil had been prescribed for travellers to Africa when it was no longer in line with the national recommendation.
To evaluate risk groups for malaria, we conducted an observational analytic study on all malaria cases notified to SMI 1997-2003 and compared them with data from the Swedish tourist and travel database (TDB). Malaria was more often diagnosed in men than in women (OR 1.7, 95% CI 1.3-2.3), in the age group 0-6 years (OR 4.8, 95% 1.5-14-8) and in travellers to sub Saharan Africa.
To evaluate the effectiveness and adverse events (AE) of malaria chemoprophylaxis in a high transmission area, we studied compiled information from Swedish soldiers (7,000 person months) in Liberia. The majority (81%) of the soldiers took mefloquine and the remaining part atovaquone/proguanil. After return to Sweden all soldiers completed a questionnaire about behavior and AE. No cases of *P. falciparum* malaria were notified. The AE were mostly mild.
To estimate risk groups for travel related hepatitis A infection in Sweden 1997-2005 we used notification data from SMI as nominator and TDB as a denominator. The highest incidence was seen in the age-group 0-6 years and in travellers to east Africa, Middle East and India where a majority of the travellers had been going to see friends and relatives in their country of origin (VFR-travellers).
To investigate causes of travel related fever we included febrile patients returning from malaria endemic areas to five Swedish hospitals 2005-2008. Additional paired sera were analyzed for influenza virus, dengue virus, chikungunya virus, *Brucella* spp., *Leptospira* spp., *C.burnetii*, and *Rickettsia* spp. In 21% of patients with unknown fever additional serology revealed a diagnosis. In 9% patients with a defined diagnosis, additional serology established a co-infection. Influenza was the most common serological finding followed by dengue fever, rickettsial infections and leptospirosis.

Conclusion: The chief problem with malariaprophylaxis is the failure to use them when really needed. VFR-travellers, and especially their children, constitute a high risk group for malaria and hepatitis A and preventive measures should be focused on this group. Influenza is an underestimated cause of fever in travellers returning from sub/tropical regions.

LIST OF PUBLICATIONS

This thesis is based upon the following papers, which will be referred to by their Roman numerals.

I. **Askling HH**, Ekdahl K, Janzon R, Braconier J-H, Bronner U, Hellgren U, Rombo L, Tegnell A. Travellers returning to Sweden with falciparum malaria: pretravel advice, behaviour, chemoprophylaxis and diagnostic delay. *Scandianvian Journal of Infectious Diseases 2005; 37:760-765.*

II. **Askling HH,** Nilsson J, Tegnell A, Janzon R, Ekdahl K. Malaria risk in travelers. *Emerging Infectious Diseases 2005;11:436-441.*

III. **Askling HH,** Rombo L, Andersson Y, Martin S, Ekdahl K. Hepatitis A risk in travelers. *Journal of Travel Medicine 2009;16:233-238.*

IV. Andersson H, **Askling HH,** Falck B, Rombo L. Well-tolerated chemoprophylaxis uniformly prevented Swedish soldiers from *Plasmodium falciparum* malaria in Liberia 2004-2006. *Military Medicine 2008;173(12):1194-8.*

V. **Askling HH*,** Lesko B*, Vene S, Berndtson A, Björkman P, Bläckberg J, Bronner U, Follin P, Hellgren U, Palmerus M, Ekdahl K, Tegnell A, Struwe J. Serologic analysis of fever in returned travelers, Sweden. *Accepted for publication in Emerging Infectious Diseases.*

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CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
CDC	Center for Disease Control and Prevention (USA)
CI	Confidence Interval
CMV	Cytomegalovirus
DEET	Diethyltoluamid
DHF	Dengue Hemorrhagic Fever
DNA	Desoxyribonucleic acid
DSS	Dengue Shock Syndrome
EBV	Epstain-Barr Virus
ECDC	European Center for Disease Control and Prevention
ELISA	Enzyme Linked Immuno Sorbent Assay
ER	Emergency Room
GP	General Practitioner
HAV	Hepatitis A Virus
HIV	Human Immunodeficiency Virus
HTLV	Human T-cell Lymphotropic Virus
ID	Infectious Diseases
IF	Immunoflourescens
IVDU	Intravenous Drug User
MARA	MApping malaria Risk in Africa
MAT	Microscopic Agglutination Test
OR	Odds Ratio
PCR	Polymerase Chain Reaction
RNA	Ribonucleic acid
SARS	Severe Acute Respiratory Syndrome
SCB	Statistics Sweden (Statistiska Central Byrån)
SFG	Spotted Fever Group
SMI	Swedish Institute for Infectious Disease Control
SSI	Statens Serum Institute
TDB	Travel- and Tourist Database
TG	Typhus Group
VFR	Visiting Friends and Relatives
WHO	World Health Organization
WTO	World Tourism Organization

1 INTRODUCTION

The possibility to travel to other countries and experience different cultures is a privilege for a growing number of people around the world. During the past decades there have been an increased number of tourists to international airports every year, including arrivals to “tropical areas” in sub-Saharan Africa, Asia, South America and Middle East (WTO).

In Sweden, travelling is often associated with pleasure, vacation and relaxation. For some, this implicates a sunny beach and for others hitch-hiking in the middle of nowhere. For all travellers, new perspectives and the opportunity to meet people living a different life than your own add an experience that influences the ordinary life long after returning home, hopefully in a positive way. Meeting new cultures also includes exposure to microbes and environmental hazards not formerly known to the traveller.

Travelling is a part of migration and immigration, whether voluntary or not.
People with their origin in another country than the one they are living in go back to see friends and relatives (VFRs = Visiting Friends and Relatives). This mode of travel differs a lot from “ordinary tourism” as the VFR-travellers are exposed to diseases in the similar way as the local population.

The importance of identifying risk groups and to provide preventive measures is crucial, both to reduce the number of travellers falling ill as well as to prevent introduction of diseases which are not endemic in the home country of the traveller. This is also important for the travel industry; a healthy traveller will return and recommend the destination to others.

Travel medicine emerged as a medical speciality in the end of the last century and covers a broad field of epidemiology, risk assessment, vaccination, primary care, public health and tropical medicine. The discipline links together medical doctors from different specialties and nurses specialized in vaccination and travel medicine.

The travel medicine society has a responsibility to ensure updated information and risk assessment based on relevant research for travellers.

2 BACKGROUND

2.1 TRAVEL RELATED MALARIA

2.1.1 Malaria pathogenesis

Malaria is caused by a parasite of the genus *Plasmodium.* Five species of *Plasmodium* are known to be capable of infecting humans: *P. falciparum, P. vivax, P. ovale, P. malariae and P. knowlesi.* The life cycle of malaria is complex and there are differences between the species. Transmission occurs during an infective bite by the female *Anopheles* mosquito. The infected mosquito saliva contains *sporozoites*, which are only present in the blood for a short period (minutes). The *sporozoites* enter liver cells (hepatocytes) where they multiply asexually to become *merozoites*. Eventually, after 1-2 weeks, the hepatocytes rupture and the merozoites enter the red blood cells (erytrocytic stage). Approximately four weeks after leaving a malaria endemic area, ≥ 98% of the *P. falciparum* parasites in the liver have proceeded to the erytrocytic stage. In *P. vivax* and *P. ovale* a certain form of the parasite, *hypnozoite*, can remain dormant in the liver for several months or even years before beginning the erytrocytic cycle. The human part of the parasites life cycle is completed by the formation of sexual forms, *gametocytes*. The *gametocytes* may be ingested by the mosquito, where the parasites undergo sporogony, i.e formation into the next generation of infective *sporozoites*.

P. falciparum causes a more severe disease than the other species. It has a capability to produce microvascular disease with peripheral sequestration of the red blood cells as well as a capability of a high parasite density, leading to cerebral malaria and/or multiorgan failure. The clinical manifestations of falciparum malaria differ in persons without immunity, e.g. travellers from a non endemic area, and semi immunes who may be asymptomatic even when parasites are detected. In the former group of patients detectable parasitemias virtually always cause significant symptoms and if not treated properly and in time it might be fatal (Strickland, 2004, Mandell, 2000). The clinical symptoms of falciparum malaria in non-immune patients are initially dominated by high fever, myalgia, sometimes combined with nausea, headache and/or diarrhea. The symptoms are often undistinguishable from influenza or septicemia the first days but the patient then quickly deteriorates due to cerebral or other organ failure. Also, *P. knowlesi* has recently been found to cause severe malaria with fatal outcome (Singh et al, 2004, Cox-Singh et al, 2008, Bronner et al, 2009) but the complete pathogenesis remains to be investigated. Lacking the mechanism for sequestration, *P. vivax, P. ovale and P. malariae* cause benign malaria with milder and non-fatal symptoms. However, recent reports indicate that *P. vivax* can cause significant morbidity and a mortality of 0.8-1.6% (Muhlberger, et al 2004, Barcus, et al 2007, Tjitra, et al 2008, Genton, et al 2008, Kochar, et al 2009).

2.1.2 Malaria epidemiology

The global burden of malaria disease is huge and the vast majority of those affected and dying are children below the age of five living in sub-Saharan Africa. In 2006, the number of estimated cases was 247 million and nearly 1 million deaths were reported. Malaria was endemic in 109 countries in 2009; 45 within the WHO African region (WHO World malaria report 2008). The transmission intensity in a malaria endemic country depends on the season (dry or moist) and the effectiveness of the vector. The transmission sometimes vary a lot within the same geographical area (WHO International Travel and Health 2009, Trape, et al 1996, Beier, et al 1999, Orlandi-

Pradines, et al 2009). The transmission rate of plasmodium falciparum is highest in Africa and particularly the western part of the African continent (MARA maps).

In some African countries, the number of malaria cases and deaths is reduced by a high coverage of a combination of malaria interventions (Bhattarai, et al 2007, Guerra, et al 2008). Furthermore, reports have demonstrated a major overestimate of malaria cases due to inappropriate diagnostic tools (Msellem, et al 2009, D´Acremont, et al 2009, Reyburn, et al 2004). This is valid also for travellers as proper malaria diagnostics at the destination is not always available and malaria remains a presumptive diagnosis in many cases. A study using serology in 105 returning travellers with a history of treatment for malaria during travel indicates that the majority of the cases (75%) had no antibodies against plasmodia trophozoites or schizonts (Miranda, et al 2008), thus the diagnosis was probably false-positive.

2.1.3 Malaria in travellers

Globally, malaria is the most common specific agent in patients with systemic febrile illness and the most common cause of death due to an infectious disease in travellers. Malaria in travellers have been estimated to occur in more than 25,000 cases and approximately 150 deaths per year (Wellems & Miller, 2003) Even with modern intensive care, case fatality rate of imported falciparum malaria varies from 0.6 to 3.8% and may be as high as 20% in elderly patients or patients with severe malaria (Schlagenhauf, 2008, Kain, et al 2001, Krause, et al 2006, Mühlberger, et al 2003). The vast majority of reported fatal cases of imported malaria had not used recommended chemoprophylaxis and had experienced a delay in seeking medical care or in diagnosis of malaria by the physician (Krause , et al 2006, Schlagenhauf, 2008, Newman, et al 2004).

The risk for malaria depends on several factors and has been shown to increase per day with longer stay (Kofoed & Petersen, 2003, Muehlbergher, et al 1998). Primitive accommodation, moist season of the year, non-compliance with chemoprophylaxis and male sex are associated with higher risk (Phillips-Howard, et al 1990, Muehlberger, et al 1998, Mölle, et al 2000, Jelinek, et al 2002). Increasing age has been identified as a risk factor for severe disease and fatal outcome (Greenberg & Lobel, 1990, Lewis, et al 1992, Schwartz, et al 2001, Gjorup & Ronn, 2002, Mühlberger, et al 2003, Krause, et al 2006).The VFR group has a higher risk for acquiring malaria than other groups of travellers (Phillips-Howard, et al 1990, Romi, et al 2001, Schlagenhauf, et al 2003, Leder, et al 2004, Brunvatne, et al 2002, Stäger, et al 2009).

The destination and the local malaria transmission are of major importance also for the traveler, but different living conditions makes the risk lower than in the local population in the same area (Rombo, 2005, Behrens, et al 2007). Several studies have assessed malaria risk in travellers by country of travel. The risk is high in Africa south of Sahara and New Guinea, intermediate on the Indian subcontinent and low in most parts of South-east Asia. The risks assessments are often based on incomplete national reporting data and lack of a homogenous denominator (Lobel, et al 1990, Phillips-Howard, et al 1990, Hill, et al 1996, Tada, et al 2008, Kofoed & Petersen, 2003, Mölle, et al 2000, Behrens, et al 2007, Behrens, et al 2008, Schmid, et al 2009). In recent

years, studies have shown a declining trend in the number of imported cases of falciparum malaria from South and Central America, West Africa and India (Behrens, et al 2007, Behrens, et al 2006, Behrens, et al 2008, Schmid, et al 2009). In Sweden, there has been a decline of imported cases since 1999. The last three years approximately 90 cases have been reported annually. The number of VFR travellers with imported malaria is unchanged. Thus, the decline is attributable to the non-VFR travellers.

2.1.4 Malaria prevention in travellers

The risk for malaria infection in travellers can be reduced by an adequate protection against mosquito bites and, when appropriate, use of a recommended chemoprophylactic drug.

2.1.4.1 Mosquito protection

Repellents and impregnated clothing reduce the number of mosquito bites and should, if possible, be used in areas of possible malaria transmission. Repellent must, however, be applied several times a day to be effective. Impregnated bed-nets reduce the risk for malaria, especially in children in endemic areas. The effect is best when transmission occurs indoors at night, which is not always the case. In hotels or houses with high standard and air-condition, bed nets are usually not necessary. (Sexton, 1994, Hewitt, et al 1996, Schoepke, et al 1998, Goodyer & Behrens, 1998, Govere, et al 2000, Smith, et al 2002).

2.1.4.2 Chemoprophylaxis

Malaria chemoprophylaxis is primarily recommended to prevent falciparum malaria. When used properly it is effective in preventing illness and death. (Krause, et al 2006). In several European studies, low adherence to malaria chemoprophylaxis has been demonstrated, even when the travellers had reported a high perception of malaria threat (Cobelens & Leentvaar-Kuijpers , 1997, Laver, et al 2001, Lobel, et al 2001, Muehlberger, et al 1998, Mölle, et al 2000, Kofoed, et al 2003, Behrens, et al 1998, Weber, et al 2003). In one study, men were found to be less adherent with chemoprophylaxis than women (Phillips-Howard, et al 1990). Other studies have found that the VFR travellers use chemoprophylaxis less frequently than other groups (Phillips-Howard, et al 1990, Blystad, 2000, Mölle, et al 2000, Jelinek, et al 2002, Bacaner, et al 2004). In Sweden, SMI distribute guidelines on malaria prophylaxis annually and the National Board of Health and Welfare recommends travellers returning from the tropics with fever to be examined at an infectious diseases clinic.

A short overview of the currently most used drugs for malaria prevention is following below:

Chloroquine has been used for treatment and prophylaxis for more than half a century. The action site of the drug is on the blood stage of the parasite. The tablets are taken weekly and have to be taken four weeks after leaving the endemic area. Due to widespread global use the malaria parasites have developed resistance in a vast majority of the endemic areas. Chloroquine is considered safe during pregnancy and in children.

Proguanil has mostly been used daily, in combination with weekly chloroquine, but is now rarely effective due to the development of resistance. Therefore, the national Swedish guidelines for malariaprophylaxis (SMI) to travellers to Africa were changed in 1998 from the combination of chloroquine and proguanil to other alternatives. However in case of no other alternative, this combination might still be prescribed. Even though this is not a safe strategy onset of disease can be delayed and result in a milder disease.

Mefloquine is an effective drug both for treatment and prophylaxis. Mefloquine acts as chloroquine, on the blood stage of the parasite and therefore the weekly dose has to be continued for at least four weeks after departure. Mefloquine is well documented for long-term use. It is used in areas where chloroquine resistance is well developed, i.e Africa South of Sahara, South America and Asia. Resistance to mefloquine has been reported, especially in the border area of Thailand/Myanmar and Thailand/Cambodia. Mefloquine might be used during pregnancy even though there are conflicting advice not to become pregnant during and three months after use of mefloquine. Children tolerate mefloquine well. (Palmer, et al 1993, Hellgren, et al 1991, Ohrt, et al 1997, Vanhauwere, et al 1998)

Doxycycline is an antibiotic with well documented prophylactic effect against malaria. The effect is primarily on the blood phase and the daily dose has to be continued four weeks after departure from a malaria endemic area. Doxycycline is an alternative to mefloquine in chloroquine resistant areas as well as an alternative in mefloquine resistant areas in Thailand/Cambodja/Myanmar. The use of doxycycline in pregnant women is not recommended according to WHO. Children below 8 years should not take doxycycline due to effects on the growing teeth. (Pang, et al 1987, Andersen, et al 1998, Ohrt, et al 1997).

The combination of **atovaquone/proguanil** has been available for malariaprophylaxis the last ten years. This combination is effective both on the liver- and the blood stage of the parasite. The intake is daily and has to be continued for seven days after leaving a malaria endemic area. Atovaquone/proguanil is another alternative to mefloquine in chloroquine resistant areas. Long-term use (> 1 month) has not been fully evaluated. It is registered for use in children but limited data prevents use in pregnant and lactating women. No serious adverse events have been reported and there are only a few reports on prophylactic failure due to resistance so far. (Lell, et al 1998, Högh, et al 2001, Overbosch, et al 2001, Ling, et al 2002, Petersen, 2003, van Genderen, et al 2007, Boggild, et al 2007)

The adverse events reported for the above mentioned drugs are generally mild and similar in frequency. Severe events are rare. Travellers, and especially women, using both cloroquine+proguanil or mefloquine prophylaxis experience more neuropsychological problems (including headache and sleep disturbances) than those taking other drugs. These side effects are, even though not graded as severe, perceived as disturbing for the daily life. (Petersen, et al 2000, Croft & Garner, 2001, Lobel, et al 2001, Schlagenhauf, et al 2003). Atovaquone/proguanil is a more recent drug compared to the other prophylactic alternatives and rare adverse events might still be reported.

For the same reason, experience from long-term use is scarce. Considering this limitations, available data show that this is a safe and well tolerated combination.

2.2 TRAVEL RELATED HEPATITIS A

2.2.1 Hepatitis A pathogenesis and epidemiology

Hepatitis A is transmitted via contaminated food and water by a virus, classified as a hepatovirus in the family Picornaviridae. The virus is transported through the gastrointestinal system and transported by the blood to the liver, which is the major site of replication, and causes damage to the hepatocytes. Blood transmission is possible even though the short period of viremia limits this possibility. The incubation period is 2-6 weeks, with an average of one month. In adults, the initial symptoms are non-specific including fever, malaise, nausea and abdominal pain. After 2-7 days the patient usually notices dark urine followed by general jaundice. Hepatitis A infection is mostly a mild and self-limited disease with a case-fatality rate of less than 0.5%. In children below the age of 5 years the infection is asymptomatic in 50-90% and jaundice is comparatively rare. The most severe and fatal cases occurs in the older age-groups. The case-fatality rate in US during 1983-1989 was 3% in persons > 50 years of age. Complications include relapses, cholestatic forms and immunologic manifestations. Infection results in life-long immunity. The diagnosis is based on the identification of anti-HAV IgM antibodies in serum. (Strickland, 2000, Plotkin & Orenstein 2004, Vogt, et al 2008).

Hepatitis A virus is found globally but is highly endemic only in areas with poor hygiene and sanitation conditions. During these circumstances children are infected early in life and the infection passes silently in the majority of the cases. In regions with higher socioeconomic standard, children grow up without encountering the virus and hence without development of protective immunity. According to WHO and CDC, regions considered as highly endemic for hepatitis A (determined as percentage of the population with antibodies against hepatitis A) are Greenland, Africa, South and Central America, Middle East and Asia except Malaysia and Japan. Southern and Eastern Europe, Russia and Malaysia are defined as having an intermediate endemicity. All other countries have low or very low natural anti-HAV prevalence. During the past decades with better living conditions, improved hygiene and sanitation measures have led to a seroepidemiological shift in Asia, Middle East and Latin America (Chatproedprai, et al 2007, Tufenkeji, 2000, Sacy, et al 2005, Jacobsen & Koopman, 2004, Tanaka, 2000). There, a growing proportion of young adults lack natural immunity implicating greater potential for outbreaks. The importance of travel related hepatitis A is, apart from morbidity in adults, mainly the risk for transmission from asymptomatic children to non-immune adults or immunocompromised individuals. (Christenson, 1985, Diel & Schneider, 2001, Postma, et al 2004, Bell, et al 1998).

2.2.2 Hepatitis A immunization

Protection against hepatitis A virus can be achieved by passive or active immunization. Passive immunization is obtained by injection of immunoglobulin derived from a pool of human sera. Protection lasts for 2-3 months depending on the dose and amount of

HAV-antibodies in the immunoglobulin used. Active immunization is done by vaccination. An inactivated hepatitis A vaccine has been available for commercial use since the beginning of the 1990s. The vaccine is safe and efficient (Werzberger, et al 1992, Innis, et al 1994) and after two doses the protection lasts for at least 20 years. National vaccination policies have differed between countries depending on endemicity, incidence rate and travel patterns. In 1999, childhood hepatitis A vaccination was recommended in communities with historically high rates of hepatitis A in the US. Local outbreaks continued to cause morbidity and mortality and a universal childhood vaccination was later recommended, as was also the case in Israel. As a result the annual incidence has declined significantly, also in cohorts of not vaccinated children and adults, due to marked herd immunity effect (Dagan, et al 2005, Wasley, et al 2005, Arumugan & Ahmed, 2005, Vogt, et al 2008). In countries where the decision and the cost of vaccination is up to the traveller, the immunization level in travellers to highly endemic countries has been relatively low (Prazuck, et al 1998, Van Herck, et al 2004, Wilder-Smith, et al 2004, Hamer & Connor, 2004, Toovey, et al 2004). The immunization rate in 588 Swedish travellers in 2002 was 40%, which is a quite high percentage compared to international figures (Dahlgren, et al 2006). In Sweden, hepatitis A vaccine is provided as a pre-travel service at vaccination clinics at a cost of approximately 45E per dose.

2.2.3 Hepatitis A in travellers

Hepatitis A has long been considered as one of the most common vaccine-preventable travel-related diseases globally. Incidence in travellers has been estimated to 3-20 cases/1000 travel months (Steffen, et al 1994), 6-28 cases/100,000 person months (Mutsch, et al 2006) and most recently 39/100,000 travel months in Danish travellers (Nielsen, et al 2008). The regions of exposure are mainly sub-Saharan Africa, Asia, Middle East and South and Central America. The studies have to a certain extent been hampered by the lack of a homogenous denominator or underreporting of cases. Data on epidemiology and risk of hepatitis A in Swedish travellers were published before the introduction of vaccines and have not been updated (Iwarson & Wahl, 1983, Christenson, 1985, Nordenfeldt, 1992).

2.3 TRAVEL RELATED FEVER

Fever is an important reason for seeking post-travel health care and many febrile illnesses have unspecific and overlapping signs and symptoms. A total of 2-3% of returned travellers present with fever (Steffen, et al 1987, Bruni & Steffen 1997, Hill, 2000) Fever has been estimated to account for 2-44% of all consultations in returning travellers. Diagnosis is not established in a considerable proportion of the febrile episodes which therefore remain as “unknown fevers”, despite modern diagnostic methods (Doherty, et al 1995, O´Brien, et al 2001, D´Acremont, et al 2002, Casalino, et al 2002, Antinori, et al 2004, Stienlauf, et al 2005, Ansart, et al 2005, Parola, et al 2006, Bottieau, et al 2006, Freedman, et al 2006, Fenner, et al 2007, Wilson, et al 2007, Bottieau, et al 2007). Most studies describing the general spectrum of travel related fever have been descriptive or observational single-centre studies with no standardized diagnostics. Studies from the international network of travel medicine, Geosentinel, has generated two large multicenter studies in recent years (Freedman, et al 2006, Wilson,

et al 2007). These data, however, are mostly derived from specialized travel- and tropical medicine units. Recent studies, and major findings, of travel related fever in returning adult travellers are displayed in table 1.

Table 1. Compilation of studies, published the past ten years, of travel related fever in adult travellers returning from the tropical and subtropical regions

Author	Journal and year	No. of febrile patients	VFR(%)	Destination sub-Saharan Africa (%)	Inpatients (%)	Unknown fever (%)	GE (%)	Malaria (%)	Dengue (%)	Rickettsiosis (%)	Influenza (%)	HIV (%)
O´Brien et al.	CID 2001	232	27	15	100	9	14	27	8	2	5	0.4
D´Acremont et al.	AmJTMH 2002	336	NA	65	21¥	21¶	18¶	29	1¶	1¶	NA	NA
Casalino et. al	Arch Intern Med 2002	783	50	79	NA	55	12	18	NA	NA	NA	NA
Antinori et al.	JTM 2004	147	18	61	100	12	5	48	3	0.7	NA	4.5≠
Ansart et al.	JTM 2005	272	34*	58*	0	5	23	21	6	1.2	4	0.8
Steinlauf et al.	JTM 2005	163	8	34	100	21	6	33	17	0		NA
Bottieau et al.	Arch Intern Med 2006	1842±	14	68	27	24	6#	28	3	3	0.8	0.3
Parola et al.	Trav Med and Inf Dis 2006	613	59	84◦	100	8	1	75	2	<1	NA	<1
Wilson et al	CID 2007	6057	21	41	26	22	15	21	6	2	1	NA
Fenner et al.	EID 2007 (non-VFR)	217§	0	20	15	3	26	3	1	NA	NA	4
Fenner et al.	EID 2007 (VFR)	121§	100	22	29	0.5	11	8	0.5	NA	NA	8

*Out of 622 travellers (both febrile and non-febrile)

Only bacterial enteritis.

± All ages

§ Fever as primary symptom in only 108

≠1/22 who were tested

◦ of which 53% travelled to the Comros archipelago

¥ of malaria patients

¶ out of 239 nonmalaria cases, unknown fever = flulike syndrome

GE = gastroenteritis, VFR = visiting friends and relatives

2.3.1 Other diagnoses of travel related fever

2.3.1.1 Dengue fever

Dengue fever is transmitted via mosquitoes, primarily by the *Aedes aegypti,* living in urban areas and in close association with humans. The infectious agent is a flavivirus which is grouped into four different serotypes. Endemic areas include most tropical and subtropical parts of the world. The incubation period is 3-14 days. Dengue fever is sometimes referred to as "break-bone fever" which describes the most common symptoms of fever, myalgia and arthralgia. Other symptoms include rashes, nausea, frontal headache, altered taste sensation and cutaneous hypersensitation. The most serious form of the infection is Dengue Hemorrhagic Fever (DHF) which occurs primarily in people living in endemic areas. The attack rate of DHF has been estimated to 4.2% in persons with prior dengue infection. One of the main hypotheses explaining this fact is that DHF occurs when someone is reinfected with another serotype (Guzman, et al 2000). DHF might occur in primo-infected and serious cases have been reported in travellers (Jensenius, et al 2007). DHF might proceed to severe shock in the Dengue shock syndrome (DSS). In endemic areas dengue causes considerable morbidity, especially in children (Gubler, 2002). The case-fatality rate in severe DHF-DSS is high but depends to a great extent on availability of adequate health-care. If treated promptly and with good medical management, less than 1% of the patients die.

Dengue has been diagnosed in an increasing proportion of febrile travellers returning from the tropics, estimated to be the cause of fever in 2% in the early 1990s to 16% more recently (Wilder-Smith & Schwartz, 2005, Freedman, et al 2006, Jelinek, 2000). Among travellers, dengue is most often seen in visitors to South East Asia, the Caribbean and South America (Freedman, et al 2006). The attack rate has been estimated to 3.4/1000 in travellers to Thailand (Schwartz, et al 2000). A big proportion of infected travellers does probably not require health-care and are therefore not reported. Prospective studies of seroconversion rates have shown positive IgM antibody test in 2.9% after a mean travel duration of one month (Cobelens, et al 2002) In a Swedish study, risk factors for dengue fever in returning travellers were: travel to Malay peninsula, age 15-29 years and travel duration > 25 days (Lindbäck, et al 2003). In 1997-2006, annual morbidity in travellers increased from 50 dengue cases/1,000 returned travellers in nonepidemic years to an average of 159/1,000 travellers during epidemic years (Schwartz, et al 2008). Treatment is supportive. No vaccine is currently available.

2.3.1.2 Rickettsial infections

Rickettsiae are intracellular gramnegative bacterias. *Rickettsia, Ehrlichia, Coxiella* and *Orientia* cause human infection. Distribution, reservoirs, transmission and clinical signs vary according to species. Rickettsial diseases are divided into the Spotted Fever Group (SFG), Typhus Group (TG) and other. With the exception of louse-borne typhus, all are zoonotic diseases and humans are only infected when inadvertently exposed to the vector. The pathogenesis of the different species generally includes vasculitis in any form. Clinical signs and symptoms can differ a lot but typically includes fever and rash or eschar. Leukopenia and thrombocytopenia are often present. Diagnosis is usually made with serologic tests. The bacteria are sensitive to tetracycline. The diseases are often self-limited after 2-3 weeks but complications like hemorrhagic manifestations, hepatitis and endocarditis might occur (Strickland, 2000). A few rickettsial infections of importance for travellers are described in table 2.

Table 2. Clinical disease and if applicable group (SFG or TG), etiologic agent, vector, risk exposure, geographical distribution and main symptoms of five different rickettsial infections.

Disease/Group	Etiologic agent	Vector	Risk exposure	Distribution	Main symptoms
Murine typhus*/TG	R. typhi	fleas	sub/urban areas where rats are common	Global, most sub/tropics coastal areas	Rash, fever
Mediterranean spotted fever/SFG	R. conorii	ticks	peridomestic/dogs	Southern Europe, Africa, Asia	Eschar, fever
African tick-bite fever/SFG	R. africae	ticks	camping/safari, farming	Southern and East Africa	Eschar, rash, fever
Scrub typhus	O. tsutsugamushi	larval mites (chiggers)	plantations, river banks etc	Asia	Eschar, rash, fever
Q fever	C. burnetii	NA	cattle	Global	Fever, headache

*also called endemic- or flea-borne typhus

Rickettsial infections in travellers are usually imported from Southern Africa (Freedman, et al 2006) where the incidence has been estimated to 4.0-5.3% (Jensenius, et al 2003) or 1/1600 travellers compared to the incidence of 1/140,000 in other destinations outside Europe (Rahman, et al 2003). The presenting symptoms can be non-specific and flu-like, and far from all recall a tick-bite during the travel. The serological response is often delayed (Jensenius, et al 2003, Raoult, et al 2001, Jelinek & Löscher 2001).

2.3.1.3 Influenza

Influenza is a cosmopolitan respiratory infection caused by influenza A or B virus. It is an acute febrile illness and the most common clinical manifestations are fever, cough and myalgia but the range of symptoms is wide; from subclinical to mild to "classical" influenza syndrome. Especially in elderly individuals, fever may be the only symptom. (Mandell, 2000). Influenza is now considered as the most frequent vaccine preventable travel related disease among travellers to tropical and sub-tropical countries with a monthly incidence estimated to 1.0-2.3% (Mutsch, et al 2005). In that study, approximately 30% of all influenza infections remained clinically undetected with seroconversion only but the authors could not establish if all were travel related cases. A study from Spain (Camps, et al 2008) revealed influenza virus in 18/118 (15%) of returning febrile travelers, from sub/tropical areas, with respiratory symptoms within 10 days post travel. Influenza attack rate in pilgrims to Makkah, Saudi Arabia, has been calculated to be as high as 38% (El Bashir EID 2004). Influenza in travellers has been associated with VFR-travel and trip duration > 30 days (Leder, et al 2003). The incidence of influenza shows a seasonal pattern in temperate areas, but little is known about influenza seasonality in tropical regions. Transmission seems to be perennial but most tropical countries report peaks associated with rainy seasons (Hampson, 1999, Dosseh, et al 2000, Beckett, et al 2004, Hasegawa, et al 2006, Nguyen, et al 2007, Moura, et al 2009). Two studies have shown that influenza is missed in hospitalized patients in Thailand and Singapore (Simmerman, et al 2006, Chow, et al 2006).

2.3.1.4 Leptospirosis

Leptospirosis is caused by a spirochete of the genus *Leptospira.* It is a zoonosis and transmission to humans occurs by contact with contaminated water or via direct contact with infected animal tissues. The symptoms include a wide range from subclinical to fever only and to fever with other symptoms (myalgia, conjunctivitis, rash, nausea etc) and at the extreme renal failure, jaundice, hypotension and pulmonary hemorrhages. The geographical distribution is worldwide and a classical aphorism is that the disease "is found wherever looked for". Reliable incidence data are not available due to unspecific symptoms and limited resources of diagnostics. (Mandell, 2000, Ricaldi & Vinetz, 2006). Occupational exposure of veterinaries, farmers, hunters and abattoir workers has been described. The risk is associated with male sex due to traditional male dominance in these professions. Recreational outbreaks have mostly been associated with water sports and wild life (Katz, et al 2002, Haake, et al 2002, Sejvar, et al 2003). No study has estimated the frequency of leptospirosis in travellers. In a study from the Netherlands 1994, 32 Dutch travellers with leptospirosis 1987-1997 were described. Signs and symptoms were not specific, 14 received adequate treatment but all patients recovered completely (van Crevel, et al 1994).

3 AIMS

3.1 GENERAL AIMS

To describe the epidemiology of imported infectious diseases in Swedish travellers and to identify risk groups.

3.2 SPECIFIC AIMS

- To describe the epidemiology, use of chemoprophylaxis and behaviour of returning Swedish travellers infected with *P. falciparum* malaria.
- To evaluate the effectiveness and adverse events of recommended malaria chemoprophylaxis in a high transmission area.
- To identify risk groups for malaria diagnosed in Sweden.
- To identify risk groups for imported hepatitis A in Sweden.
- To describe the etiologies of fever and evaluate additional information from systematic serology in Swedish travellers returning from malaria endemic areas.

4 METHODS AND MATERIALS

4.1 DATA SOURCES

4.1.1 The Swedish Communicable Disease Act

Fifty-six infectious diseases (June 2009), including the colonization with resistant bacteria, are included in the Swedish Communicable Diseases Act as notifiable diseases.

Most of these diseases are transmitted to humans from humans or animal reservoirs and a few from the environment (e.g. soil). Every suspected or confirmed case must be reported without delay to the County Medical Officer and the Swedish Institute for Infectious Disease Control (SMI). Notification is compulsory for the laboratory which identifies the pathogen and in most of the cases also for the physician treating the patient. The notification is based on the unique personal identification number of each Swedish citizen, which also prevents double-reporting. The notifiable diseases are divided into four groups: 1) notifiable diseases only, e.g. malaria, dengue, leptospirosis 2) diseases also subject to mandatory contact tracing e.g., brucellosis, legionellosis 3) diseases also dangerous to public health e.g., hepatitis A, typhoid fever 4) diseases also dangerous to society; SARS and smallpox. In the second group the patients must do their best to give information about how they contracted the infection and who else might have been exposed. The contacts are traced and asked to see a physician. In the third group every patient also gets personal guidelines in order to stop the spread of the disease. These guidelines are mandatory and might lead to isolation by force if not adhered to. The two diseases in the fourth group are considered as a public threat and patients or geographical areas could be subject to quarantine or isolation. When reporting a notifiable disease, the clinician is asked to provide relevant demographic and epidemiological data such as possible transmission route, country of infection, time and length of stay, animal contact and prophylaxis.

4.1.2 The Swedish Travel and Tourist Database

The Swedish Travel and Tourist Database (TDB) is run by a commercial company (Resurs Marknadsfakta) since 1989. It is an ongoing survey with the aim to collect and provide data on Swedish tourism, i.e. destinations, length of stay and purpose of travel. The data is extracted from 2000 randomly selected telephone interviews every month. The target population consists of all persons between 0 to 74 years of age living in Sweden. Telephone numbers are chosen from a national register of numbers where the last two digits are replaced by a random number between 00 and 99, so called Random Digital Dialing, RDD. The register is only providing access to non-mobile telephone subscriptions. If there is no answer, there will be a total of eight attempts at different times before the number is registered as “no answer”. When in contact, the interviewer first confirms that the telephone number is private and then asks about the number and ages of the people in the household. All members of the household between 0-74 years are then randomly selected by a computer for an interview. Children are represented by their parents and people with difficulty in speaking or understanding the Swedish language are asked to be assisted by someone at the household who can act as an interpreter. The interviews are conducted Mondays to Thursdays and Sundays between 5 and 9 p.m. and the selected persons are asked to provide details on all travels made the preceding month, both within Sweden and to foreign countries. The data is then weighted and extrapolated to reflect the whole Swedish population based on official demographic statistics such as regional population, size of households and age.

4.2 AIRPORT SURVEY OF IMMUNIZATION COVERAGE

To estimate the current vaccination coverage to some destination of special interest we conducted an airport based survey at the two main airports in Sweden, Arlanda and Landvetter. Between April and June 2007, Swedish travellers going to Thailand, Malaysia, Iran, Egypt and Morocco were asked to fill in an anonymous questionnaire while waiting for check-in. The participation was voluntary. The questionnaire was collected on site. The travellers were asked to report age, sex, destination, protection against hepatitis A (yes/no/don´t know) and, if applicable, a specification of the protection (previous illness/vaccine/gammaglobulin) including the number of vaccine doses and when administered. All travellers going with the same flight, except those who came very late, were approached. Parents were asked to fill in details about their children.

4.3 DIAGNOSTIC METHODS

The diagnostic methods used in paired sera (paper V) are described below. For a schematic overview and the order in which the different methods were undertaken see figure in paper V (last page).

4.3.1 Enzyme linked immunosorbent assay (ELISA)

A prepared antigen is forming a complex with a specific antibody linked to an enzyme. The enzyme is capable of convert to a detectable signal if the sample from the patient contains the antibody, after adding an enzymatic substrate. The sample antibody from the patient links the prepared anti-antibody together with the enzyme-antibody complex, and thus creates a colour that is indicative of the presence of human antibodies in the blood. We used ELISA for detecting antibodies against dengue virus (IgM, only if IF IgG was positive first), *Leptospira spp*. (IgM), influensa A and B virus (IgG), *Brucella spp*. (IgG, IgM) and *Coxiella burnetii* (IgG, IgM). Serology for influenza A and B was performed at the Department of Microbiology, Malmö University Hospital. All other analyses were performed at the Swedish Institute for Infectious Disease Control (SMI) in Stockholm.

4.3.2 Immunofluorescence (IF)

Infected cells are used as antigen and when fluorescein labelled antibodies are added they link together the antibodies present in the sample and create a fluorescent signal. We used IF for detecting antibodies against dengue virus (IgG), chikungunya virus (IgG) and *Rickettsia spp*. (IgG, Spotted Fever Group (SFG) and Typhus Group (TG)). For *Coxiella burnetii* we conducted IF as a confirmation test if antibodies were found with the ELISA. In patients with a travel history to Asia we conducted IF for detecting antibodies against *Orientia tsutsugamushi* (IgG) in all patients and antibodies against Japanese encephalitis virus (IgG, IgM) if dengue virus IF was IgG positive but ELISA IgM negative. All analyses were performed at SMI in Stockholm.

4.3.3 Polymerase chain reaction (PCR)

The PCR technique amplifies repeatedly a single or a few copies of a piece of DNA. The process needs a heat-stable DNA polymerase and primers containing sequences complementary to the target region. The method relies on thermal cycling, consisting of cycles of repeated heating and cooling of the reaction for DNA melting and enzymatic replication of the DNA. We used PCR for detecting *Leptospira spp.* only if ELISA IgM was positive. The PCR (Real-time, TaqMan) was targeted at specific sequences of the genes 16s RNA, LipL21 and LipL32. PCR for *Leptospira* spp were undertaken at Statens Serum Institute (SSI) in Copenhagen, Denmark.

4.3.4 Microscopic agglutination test (MAT)

MAT is based on the agglutination of antigen and antibody. Agglutination can be seen in a dark-field microscope and this is the most widely used serological method for detecting leptospiral antibodies (Cole, et al 1973). The MAT used in Paper V was targeted against 13 different serogroups and was undertaken at Statens Serum Institute (SSI) in Copenhagen, Denmark.

4.4 STUDY DESIGN AND METHODOLOGY

4.4.1 Paper I

To study the epidemiology, chemoprophylaxis and behavior of patients infected with falciparum malaria, we conducted a descriptive study of compiled information on patients notified 1994-2001. The malaria notification data was obtained from SMI and 408 questionnaires were passed on to the patients by the courtesy of the treating doctors, once every 6 months, from the 1st of January 1994 to the 31st of December 2001. Data on use of chemoprophylaxis were compared with the national Swedish guidelines and with statistics from the National Cooperation of Swedish Pharmacies (Apoteket AB).

4.4.2 Paper II

We evaluated risk factors for imported malaria by conducting an observational analytic study on all travel related malaria cases notified to SMI 1997-2003. We collected data from notified cases (n = 857) and from TDB on travellers going to malaria-endemic countries for the same years (n = 881), using the variables age, sex, year and month of infection (patients), year and month of travel (controls), country of infection (patients) and country/region of travel (controls).
To assess the association between risk factors (age, sex and travel destination) and outcome (being reported with malaria) we used multivariate logistic regression with the variables mentioned above and adding month of travel or infection. Each factor was first analyzed in a univariate model. The parameter with the lowest odds ratio (OR) in each category was used as a reference in the models. Likelihood statistics were used to assess whether each variable in the model contributed significantly to the model and to test for interaction. All analyses were performed with Stata 6.0 software (Stata Corporation, Collage Station, TX, USA). The risk for disease per 100,000 travellers, with 95% CI, was calculated by using reporting data as numerator and the estimated total numbers of travellers from the database as denominator. To evaluate data quality in the travel database, the weighted and extrapolated estimates of the total numbers of travellers to Thailand, India, the Gambia and South Africa were compared with in-flight or visa data for Swedish travellers. These figures were obtained by courtesy of the embassies of the respective country in Sweden, except for the Gambia, where the figures were supplied by the central statistics department of the Gambia (through the courtesy of the Swedish embassy in Senegal). For these four specific countries, the risk per 100,000 travellers was also calculated by using in-flight and visa data as a denominator. The latest available information on annual malaria incidence among the local population in the studied countries and regions were obtained from the WHO, to be compared with the risk estimates in travellers.

4.4.3 Paper III

To calculate incidence rates and estimate risk groups for travel related hepatitis A infection in Sweden 1997-2005 we conducted a population based study using the Swedish notification system as nominator and the TDB as a denominator. In order to be able to relate our findings to a fresh estimate of the immunization coverage among travellers, we also conducted an airport survey as

described earlier. In the notification data from SMI we identified the travel related cases and the subgroup of VFR travellers. The cumulative incidence of travel-related hepatitis A by region, age and sex per 100,000 travellers with 95% CI was calculated by dividing the notified cases with the estimated number of travellers from the TBD. Incidence rates, as cases per 100,000 person months with 95% CI, were calculated by dividing notified cases with length of travel to each specific region. The estimated proportions of unprotected travellers were calculated by multiplying the total number of estimated travellers with the percentage of travellers in the vaccination survey who were not protected or had unknown protection against hepatitis A.

4.4.4 Paper IV

To evaluate the effectiveness and adverse events of malaria chemoprophylaxis in a high transmission area, we conducted a descriptive study on compiled information from 1,170 Swedish soldiers in Liberia 2004-2006. Each contingent was deployed for six months. Before departure, all soldiers were informed by the same medical doctor about the importance of malaria protection with chemoprophylaxis and mosquito prevention. Chemoprophylaxis was prescribed according to ordinary routines and the majority (81%) of the soldiers took mefloquine. Atovaquone/proguanil was prescribed to the remaining part. Both health and military personnel encouraged the intake of the tablets during deployment in Liberia. Intake of tablets was done together and at the same time every day. The Swedish Medical Officer in Liberia examined all soldiers who fell ill with fever and was obliged to report possible cases of malaria diagnosed at the referral hospital. In Sweden, after deployment, a case of malaria would be notified to SMI. In addition, a follow-up routine meeting six months after return to Sweden ensured case finding. After return, all soldiers were asked to answer a questionnaire on living conditions as well as intake and possible adverse events of chemoprophylaxis and body weight. Each adverse event was graded on a severity scale from 1 to 5 as follows: 1 = very mild, 2 = rather mild, 3 = neither mild nor severe, 4 = rather severe and 5 = very severe. The soldiers were also asked to grade the influence the adverse events had on their everyday life on a scale from 1-5. Three contingents (n=609) were asked exactly the same questions and for that reasons only these answers were analyzed. The questionnaires were distributed to the soldiers when they came for a medical check-up directly after returning to Sweden, except for one contingent (n=161) to which the questionnaires were sent by mail.

4.4.5 Paper V

Study Population and Inclusion Criteria
To investigate the diagnosis of travel related fever in Sweden and evaluate additional serology we included patients at five Swedish hospitals (Karolinska, Malmö, Lund, Linköping, Jönköping) with departments of infectious diseases. The study period was between 14th March 2005 and 14th March 2008. The inclusion criteria were; travel to a malaria-endemic area as defined by the WHO within two months prior to consultation, age ≥18 years, a documented temperature of ≥38°C (oral, axillar or rectal) at admission or within the last two days (as reported by the patient) and the clinician's decision to perform a blood film examination for malaria.

Patients were identified either through prospective case finding at emergency rooms (ER) and out-patient clinics or through a retrospective case finding of eligible patients who had not been included in the prospective case finding, based on listings of all performed malaria diagnostics. All patients were examined and subject to diagnostic investigations according to normal routines and clinical needs by or with the assistance of an infectious disease specialist. The study population constituted of a mixture of referred and non-referred patients. According to the Swedish health-care system a referral is not needed if a patient suffers from acute symptoms. The following variables were recorded: age, gender, travel history (destination and duration), reason for travel, diagnosis, and if applicable days of hospitalization. Information on pre-travel

immunisations and time interval between return to Sweden and first signs of symptoms were available only in the group of prospectively included patients. Travel destinations were grouped into three regions; Africa, Asia and America. Reason for travel was divided into tourism, VFR or other. In the group of prospectively included patients paired sera were collected at the first visit and at a follow-up visit 1-3 months later.

Microbiology

Apart from the blood film for malaria, diagnostics (cultures, serology, x-rays etc) were performed in all patients according to routine practice in the hospitals. In prospectively included patients, additional paired sera were later analyzed for antibodies to influenza A and B virus, dengue virus, chikungunya virus, *Brucella* spp, *Leptospira* spp, *Coxiella burnetii*, *Rickettsia spp* Spotted Fever Group (SFG) and Typhus Group (TG), respectively. If the travel destination was Asia, also *Orientia tsutsugamushi* and Japanese encephalitis virus were included in the analysis. A fourfold or greater rise in reciprocal antibody titre against a relevant pathogen was considered as a positive result.

Diagnosis

A diagnosis was established by the doctor treating the patient. Microbiological confirmation was defined as demonstration of a relevant microorganism in a clinically relevant specimen or by seroconversion to an infectious agent considered to be the aetiology of the recent infection. The responsible infectious diseases (ID) consultant at each study site confirmed the diagnosis based on investigations performed and before results of the additional serology were available. Comparisons between groups were made using univariate statistics (chi 2 test). A p-value less than 0.05 was considered significant.

5 RESULTS AND DISCUSSION

5.1 TRAVEL RELATED MALARIA

Fifty-eight percent of the responding malaria patients (n=237) in paper I had consulted one or more medical institutions for pre-travel advice concerning malaria. Forty-two percent did not receive a medical advice. Ninety percent of the patients had travelled to Africa, the most common destination being Kenya followed by Tanzania and the Gambia. The majority (69%) of all travellers stayed at least one night in the countryside and the median length of stay was 23 days (range 1-545). Thirty-two percent of the travellers were tourist, 26% classified their trip as business, 21% had visited friends and relatives and 16% stated different combinations of the above alternatives. Twenty-one percent of all patients had used bed-nets during the travel but only 9% had used both bed-nets and repellents regularly. Most of the patients (71%) diagnosed with falciparum malaria reported intake of chemoprophylaxis during their travel.
However, this figure decreased from 79% 1994 -1997 to 56% in 1999-2001. Forty percent (96/237) of all patients took an adequate drug according to the national guidelines but this figure also decreased, from 55% to 12%, during the study period. A combination of chloroquine and proguanil was used by 23% of the malaria-infected travellers from Africa 1999-2001, despite the fact that this was not generally recommended by the SMI at the time. A majority of these cases had sought pre-travel advice at medical institutions. This indicates that the professional advice was not up-to date with the prophylaxis recommended. In a few cases, there might have been a medical reason for not using mefloquine. Doxycycline was not recommended and atovaquone/proguanil was not available during the study period.

The median time reported by the malaria patients from onset of symptoms to contact with the health care professionals was two days and the median time to treatment was less than 24 hours, which are both acceptable delays. Seventy (29%) of the cases had either contacted a hospital or a community health centre for telephone advice concerning their symptoms. Out of these, 15 (22%) had not been advised to go to a hospital, which is an unacceptable high proportion. The exact terms used in this telephone conversation can not be checked, but it underlines the importance of both pre-travel advice to inform the health care personnel about preceding visit to a malaria endemic area and the education of the health personnel to ask for such a visit. The possibility of incorrect pieces of advice exemplified by non-compliance to the national malaria chemoprophylaxis recommendations raises the question of how to reach travel medicine providers and medical society properly. How shall changes in malaria recommendation policies be communicated and provided?

The results were based on a limited amount of questionnaires which was sent out retrospectively, in some cases several months after the malaria episode. The response rate was rather low (237/408, 58%) and the ability to remember exact doses, telephone advices and type of pre-travel advice facility must be carefully interpreted. The problem of evaluating compliance with chemoprophylaxis has been addressed in a study were questionnaires were compared with electronic pill-boxes (Landry, et al 2006). In this study low adherence of malariaprophylaxis was confirmed, despite extensive information about the malaria disease and prevention. In paper I, declining use of chemoprophylaxis among patients who fell ill with falciparum malaria 1994-2001 indicates that the chemoprophylaxis used during the later period was more effective. This is also consistent with statistics from the National Cooperation of Swedish Pharmacies (Apoteket

AB), reporting a more than four-fold increase in the sale of mefloquine parallel to a decrease in the sale of proguanil in Sweden 1994-2001.
The effectiveness of malaria chemoprophylaxis, when properly used, is highlighted by the findings in paper IV where more than 99% of the soldiers took drug prophylxis regularly (81%) or almost regularly (18%). There were no cases of *P.falciparum* in the total group of 1,170 soldiers, corresponding to 7,000 person-months. Fourteen cases of *P. ovale* malaria were diagnosed between 2.5 and 12 months after the return to Sweden, making the crude attack rate of benign malaria 1.2%. All soldiers diagnosed with *P. ovale* had been taking mefloquine as chemoprophylaxis but the difference between the two drug regimen was not statistically significant ($p = 0.3$) and could partly be explained by the fact that 10/14 soldiers belonged to the contingent deployed first, in which all soldiers took mefloquine and slept in tents. The crude attack rate of *P. ovale* malaria confirms that mefloquine is not effective against hypnozoites but also reflects the effectiveness of chemoprophylaxis against *P. falciparum* as this species is ~ 10 times more common than *P. ovale* in Liberia (Björkman, et al 1985). Our result can be compared with the *P. falciparum* attack rate of 44% in U.S Marine soldiers deployed to Liberia without taking malaria chemoprophylaxis and spending at least one night ashore (Fox, ProMed mail 2003). Another paper reported 35.7 malaria cases per 1,000 person months in French troops deployed to Ivory Coast (Migliani, et al 2003).
In paper IV, out of soldiers who took mefloquine (n=491), 57% reported at least one adverse event, nightmares and sleep disturbances being the most frequent. In the group taking atovaquone/proguanil (n=161), 34% reported adverse events, the most common was also sleep disturbances, followed by stomach pain. In general the adverse events were mostly mild; the mean severity score for the atovaquone/proguanil and mefloquine groups were 2.0 and 2.2 respectively, i.e. without marked influence on work or other activities. Out of the soldiers who reported AE, thirty-seven percent in the meflouquine group and 24% in the atovaquone/proguanil group defined their adverse events as grade 4-5 on the severity scale ($p = 0.05$).
Neuropsychological adverse events were more common in the mefloquine group (1.12 per person) than in the atovaquone/proguanil group (0.23 per person). The larger number of reported neuropsychological adverse events with mefloquine has been documented before (Overbosch, et al 2001, Schlagenhauf, et al 2003). Forty (8%) soldiers changed from mefloquine to atovaquone/proguanil and 4 (3%) changed the other way around. No soldiers were hospitalized due to adverse events.

We conclude that mefloquine and atovaquone/proguanil were safe and efficient in our setting and that atovaquone/proguanil seems to be appropriate for long-term use. Experience of long-term use of atovaquone/proguanil has been documented in a few reports only (Boggild, et al 2007, Petersen, 2003) but is recommended with no limit in the U.S (Boggild, et al 2007). In our study, AE were also acceptable regarding severe events, as reported by the soldiers.
Mefloquine is associated with negative publicity with respect to AEs, even though studies show that severe events do not occur more frequently with this drug than with other comparable (Croft & Garner, 2001, Schlagenhauf, et al 2003). A study from 2007 showed that travellers most frequently choose mefloquine for chemoprophylaxis if provided with objective written information (Senn, et al 2007). In paper IV, with both drug regimens, there was a higher proportion of soldiers who reported AE in the lower weight class of 50-69kg (29% women) than in the middle weight class of 80-89 kg (mefloquine $p<0.01$, atovaquone/proguanil $p = 0.02$). For mefloquine this is consistent with earlier findings (van Riemsdijk, et al 2003, Ollivier, et al 2004) but to our knowledge this has not been shown with atovaquone/proguanil and should be confirmed with further studies.

The AE rates and severity, as reported by the soldiers, must be interpreted with caution since this descriptive study was neither blinded nor randomized. The soldiers probably influenced each other when discussing adverse events during the deployment and the fact that the questionnaire was distributed after return to Sweden might have overestimated the AE perceived as more severe, since they were probably easier to remember. Furthermore we lacked information about true compliance as well as actual drug concentrations. We do, however, believe that the high reported level of compliance was close to truth and promoted by the fact that all soldiers were living tight together with the same routines and taking the tablets at the same time of the day. Also, before deployment, the soldiers were informed, by the same medical doctor, that malaria is the only true medical life threatening disease in Liberia. The above described circumstances differ a lot from an "ordinary" traveller to the same high-transmission area.

Altogether, the chief problem with antimalarial prophylactic drugs is the failure to use them when needed. This emphasizes the importance of prescribing malaria chemoprophylaxis and to give reinforcing information to those who actually need it, i.e. in situations where possible adverse events can be accepted in return for prevention of disease. Furthermore, the declining number of reported malaria cases in travellers, both in Sweden and globally, highlights the question of who really needs prophylaxis and how the information shall be provided to be adhered to.

5.1.1 Risk groups

In Paper II we have analyzed all 857 patients with notified malaria in Sweden from 1997 to 2003, excluding newly arrived refugees or immigrants. Three-hundred forty-eighth cases were caused by *P. falciparum*, 178 by *P. vivax*, 47 by *P. ovale*, and 15 by *P. malariae*. In 269 patients information on species was lacking. Only small variations in number of cases occurred during this period except in the last year (2003), which had <65% of the mean of the reported cases for the preceding years. The latter was attributable to a decreased number of *P. falciparum* cases. According to the TDB, 881 persons had traveled to malaria-endemic areas, corresponding to 3.5 million travellers to these areas during the same time interval. In the multivariable analysis, travellers to sub Saharan Africa had the highest risk for malaria when returning home. The Indian subcontinent had an OR in the same "middle" range as southern Africa. Southeast Asia and South America had OR at the similar lower range. The malaria risk in the Arab countries did not differ significantly from the risk in the reference group of Central America and the Caribbean. Malaria was more often diagnosed in men than in women (OR 1.7, 95% CI 1.3-2.3) and in the age-group 0-6 years (OR 4.8, 95% CI 1.5-14.8) compared with other age groups. See table 3.

Table 3 Estimated number of travellers to malaria-endemic areas, respondents in the tourist database, and notified cases with travel associated malaria 1997–2003, with a multivariate odds ratios (with 95 % CI) for the risk factors age, sex and travel destination from a logistic regression model, and incidence per 100,000 inhabitants as reported to the WHO.
For definitions of regions see table 4 in paper II.

Age/Sex/Region	Estimated no. of travellers	Controls	Notified cases	Risk per 100,000	95% CI	Multivariate odds ratio	95% CI	Incidence per100,000 (WHO)
Total	3,560,000	881	857	24	22–26	–	–	36,865
0–6 years	70,000	18	38	54	31–95	4.8	1.5 – 14.8	No data
7–18 years	300,000	74	91	30	22–41	2.7	1.1 – 6.0	No data
19–45 years	1,630,000	404	506	31	27–35	4.1	1.9 – 9.0	No data
46–65 years	1,340,000	331	205	15	13–18	2.0	0.9 – 4.3	No data
65+ years	220,000	54	17	7.7	4–13	1.0	Reference	No data
Men	1,790,000	444	536	30	26–34	1.7	1.3 – 2.3	No data
Women	1,770,000	437	321	18	16-21	1.0	Reference	No data
Arab countries and Iran	220,000	44	4	1.8	0.7–5.1	1.7	0.5 – 6.4	1,279
Indian Subcontinent	120,000	31	74	62	41–94	57.4	23 – 141	366
East Asia	2,050,000	517	111	5.4	4.4–6.6	5.6	2.5 – 12.5	205
West Africa	80,000	22	242	302	196–468	277	112 – 683	13,356
East Africa	90,000	18	216	240	148–388	341	134 – 866	7,126
Central Africa	30,000	8	107	357	174–732	317	108 – 930	5,508
Southern Africa	170,000	42	78	46	32–67	49.6	21 – 119	7,742
Central America + Caribbean	550,000	43	7	1.3	0.6–2.7	1.0	Reference	155
South America	250,000	61	18	7.2	4.3–12.2	7.1	2.7 – 18.4	1,205

Our results that travel to sub-Saharan Africa is associated with a higher risk for catching malaria is well established as well as the fact that the risk for getting malaria when travelling to East Asia and South America is low. The exact odds ratios for the specific regions have to be carefully interpreted since different regions are not comparable in number of malariaendemic countries, i.e the Caribbean consist of malaria free countries but there are no such countries in West Africa. In the TDB classification, one region may include both malaria endemic and malaria free countries (e.g Asia) and hence travellers who visit malaria-free countries are also included in the

denominator for the region. Therefore the risk might be underestimated in a region which includes several malaria free-countries. However, many of these countries are comparatively rare as a tourist destination. For more detailed methodological considerations of the data collection in the TDB see 5.3.

The strength of this study is the sensitivity of the Swedish surveillance system of notifiable diseases as well as the well-defined denominator of the travel- and tourist database. The reliability of the TDB could be confirmed when we calculated malaria risk per 100,000 travellers in the four countries (see below) with alternative sources of denominator data and compared with the TDB. The comparison showed that the two sources had good agreement for Thailand and The Gambia/West Africa. For India/the Indian subcontinent and South Africa/Southern Africa the risk estimates were less in agreement which is explained by the fact that most travellers go to India and South Africa while the most malaria cases are from other countries in the region. When calculating OR for being diagnosed with malaria in Sweden we did not have information on the travel duration of the malaria cases. Length of travel is known to be positively associated with the risk for being diagnosed with malaria (Phillips-Howard, et al 1990, Kofoed & Petersen, 2003, Muehlbergher, et al 1998). In paper II, we only studied the risk for malaria when returning to Sweden and considering the average incubation period for *P.falciparum* malaria our OR mostly reflects the last month before returning home. The true risk for *P.falciparum* malaria in travellers during and after travel is probably higher than the post-travel risk only. The higher risk in children 0-6 years might be related to travel length assuming that this group is overrepresented by VFR-travellers, who tend to travel for longer periods (Schlagenhauf, et al 2003, Leder CID 2006). However, children are probably staying as long as their parents. Studies from other countries have indicated that correct adherence to chemoprophylaxis is low in VFR-children (Minodier, et al 2003, Huerga & López-Vélez, 2001, Matteelli, et al 1999).

In paper II we did not systematically collect data on country of origin and purpose of travel. However, notification data, which often includes this information, indicated that a large number of patients were VFRs who had visited countries outside usual tourist routes like Somalia, Uganda, Bangladesh and Ethiopia. Thus, our data support that VFR-travellers are a risk group for imported malaria and requires special attention both regarding pre-travel advice and, if fever, post-travel management. A high and increasing proportion of malaria in VFR travellers in relation to other purposes of travel has been documented in several countries (Bradley, et al 1994, Romi, et al 2001, Mattelli, et al 1999, Baas, et al 2006, Leder, et al 2004, Stäger, et al 2009) and is consistent with Swedish notification data, as mentioned in the background. A British study from 1990 (Phillips Howard, et al 1990), showed an incidence of malaria in VFR-travellers that was almost three times higher than that of tourists. Going back to friends and relatives implicates living together and in the same way. As a consequence the risk of exposure to malaria is approaching that of the local population, rather than the lower risk for tourists going for a short vacation with air-conditioned housing.

A limitation in paper II is that we did not have information on adherence of malaria chemoprophylaxis but considering the low adherence to appropriate drugs in malaria patients shown in paper I as well as the annual report from SMI 2003 (SMI, 2003) we assume that this limitation was not crucial for the results.
In 1997, the number of unspecified malaria species was very high (85%) probably due to introduction of a new electronic surveillance system at SMI. During the following study years (1998-2003), approximately 50% or more of the reported cases were due to *P. falciparum* and

there is no indication that 1997 was different. The risk calculations are based on all notified species, even though *P. falciparum* malaria is the prime target for chemoprophylaxis. The inclusion of all species in the calculation is motivated by the fact that other malaria species also contribute substantially to malaria morbidity in travellers (Muhlberger, et al 2004, Barcus, et al 2007, Tjitra, et al 2008, Genton, et al 2008, Kochar, et al 2009).

During recent years, Thailand has emerged as one of the most popular Swedish tourist destinations. The risk for *P. falciparum* malaria varies from none to very high. The transmission rate in popular tourist beaches and towns do not motivate chemoprophylaxis. The transmission rate is higher in forested areas and especially at the Myanmar and Cambodia borders, where mefloquine resistence is reported. A low risk for malaria in Thailand was confirmed with 2.1 cases/100,000 travellers in our study and corresponds well with 2.5/100,000 in a Danish study from 2003 (Kofoed & Petersen, 2003). A British study from 1996 (Hill, et al 1996) showed a slightly higher risk; 8.2/ 100,000. All Swedish travellers who contracted *P.falciparum* malaria in Thailand 1997-2003 had visited regions outside the usual tourist destinations. In January 2009, two Swedish tourists fell ill with *P. falciparum* malaria after independent short trips to a tourist area in southern Thailand. Both had spent a couple of days in a national park (Bronner, ProMed mail 2009) and none of them took chemoprophylaxis, which was in line with the national Swedish guidelines. This demonstrates that the risk of transmission exists nearby popular tourist resorts and that pre-travel advices with emphasis on mosquito-bite prevention and information on the importance of seeking health care immediately with symptoms of fever is essential.

5.2 TRAVEL RELATED HEPATITIS A

5.2.1 Incidence rates and risk groups

During the study period 1997-2005, 1,885 cases of hepatitis A infection were notified to the SMI. Six-hundred thirty-six cases were classified as travel related. Out of these, 331 (52%) were VFR travellers. The number of notified hepatitis A cases was decreasing during the study period but the proportion of travel related cases, and the VFR related, was slightly increasing. In 1997, due to the above mentioned introduction of a new electronic surveillance system at SMI, the number of cases of hepatitis A with unknown source of infection (domestic or travel related) was 396/693. This also coincided with a national outbreak in intravenous drug users (IVDU) and we assume that a great proportion of the unknown cases were of domestic origin, which should not affect the incidence calculations below. The denominator consisted of 22,673 persons recorded with international travel in the TDB, corresponding to 94,443,000 travel episodes by Swedish residents. The overall risk of travel associated hepatitis A was 0.67 per 100,000 travellers. By age-group the highest incidence was seen in children 0-14 years (3.1/100 000 travellers). We did not have information on travel length in different age groups and the higher incidence in the lowest age group might be a result of longer travel duration and therefore a higher risk of exposure. However, children and their parents probably travel together. Furthermore, considering the incidence rates by region, the percentage of VFR-travellers in the age-group 0-14 years and in the three regions with the highest incidence rates, our findings indicate that the most important factor for the high incidence in children is the region of exposure and purpose of travel (VFR). The overall incidence rate was 0.61 per 100,000 travel months and travel to East Africa was associated with the highest risk (14.1 cases/100,000 travel months) followed by the Middle East (5.8/100,000 travel months) and the Indian subcontinent (5.6/100,000 travel months). The lowest incidence rate in a high endemic HAV area, as defined by the WHO, was found in East Asia (0.3

cases/100,000 travel months) and is in the same low range as the incidence rate of Europe (0.2) and North America (0.15). The subgroup of VFR travellers constituted 91% of the cases infected in the Middle East, 83% from East Africa and 70% from the Indian subcontinent. In the age group 0-14 years, 88% of the cases were classified as VFR travellers. For confidence intervals and all regions see table 4.

Table 4 Estimated number of travellers 1997-2005 (from TDB) divided into sex, age and region (according to map in figure 1), notified cases of travel-associated hepatitis A 1997-2005, hepatitis A cases per 100,000 travellers with 95% Confidence Interval (CI), 100,000 travel months (total and per region), hepatitis A cases per region per 100,000 travel months with 95% CI and percentage VFR of total notified hepatitis A cases. For definition of regions see figure1 paper III

Sex/age/region	Est. no of travellers	Cases	Cases per 100 000	95% CI	100 000 months	Cases per 100 000 months	95% CI*	%VFR
Total	**94,443,000**	**636**	**0.67**	**0.6-0.7**	**1 047**	**0.61**	**0.56-0.66**	**52%**
Sex								
Men	50,867,000	364	0.72	0.6-0.8				45%
Women	43,576,000	272	0.62	0.6-0.7				62%
Age								
0-14	8,67,5000	271	3.12	2.8-3.5				88%
15-29	19,770,000	128	0.65	0.5-0.8				47%
30-44	22,478,000	123	0.55	0.5-0.7				18%
45-59	27,570,000	83	0.30	0.2-0.4				8%
60+	15,950,000	31	0.19	0.1-0.3				13%
Region								
Nordic countries	32,330,000	19	0.06	0.0-0.1	188	0.1	0.06-0.16	16%
Western Europe	21,173,000	45	0.2	0.2-0.3	185	0.2	0.18-0.33	7%
Southern Europe	15,641,000	34	0.2	0.2-0.3	213	0.2	0.11-0.22	6%
Eastern Europe (incl. Baltic Rep)	5,150,000	15	0.3	0.2-0.5	50	0.3	0.18-0.5	40%
Eastern Mediterranean	10,014,000	144	1.4	1.2-1.7	162	0.9	0.75-1.05	66%
Russia and former Soviet union	381,000	13	3.4	1.9-6.1	5	2.6	1.5-4.6	38%
Middle East	393,000	103	26.2	19.6-35.0	18	5.8	4.6-7.7	91%
India with neighbours	215,000	40	18.60	12.4-28.0	7	5.6	4.1-8.4	70%
East Asia	2,809,000	19	0.7	0.4-1.1	72	0.3	0.17-0.4	21%
North Africa	1,143,000	68	5.95	4.6-7.7	17	4.1	3.2-5.3	37%
West Africa	117,000	8	6.8	3.1-14.9	2	3.5	1.8-7.7	38%
East Africa	123,000	40	32.5	19.8-53.3	3	14.1	10.3-23.1	83%
Southern Africa	265,000	7	2.6	1.2-5.8	6	1.2	0.6-2.6	29%
North America	2,962,000	10	0.3	0.2-0.6	66	0.15	0.08-0.3	10%
Central America	219,000	12	5.5	2.9-10.2	6	1.8	1.05-3.4	8%
Caribbean	489,000	8	1.6	0.8-3.3	9	0.9	0.4-1.8	25%
South America	403,000	50	12.4	8.8-17.4	14	3.7	2.8-5.1	48%

*The lower level of the CI in this column is slightly different from the corresponding table in paper III (Table 2). This is due to a formula error detected after publication of the paper. The point estimates are the same and the conclusions of the paper are not influenced. In table 4 above, the correct values are shown. The mistake has been corresponded to the editor of *J Travel Med*.

Compared to previous studies (Mutsch, et al 2006, Nielsen, et al 2009), we have a more homogenous denominator and a sensitive surveillance system of notified hepatitis A cases in paper III. Our major finding is that the main risk group for acquiring travel related hepatitis A is VFR-travellers and especially children who constituted 42% of all cases during the study period with an incidence of 3.12/100,000 travellers. This strengthens the results in other studies (Behrens, et al 1995, Gosselin, et al 2006, Mutsch, et al 2006, Rendi-Wagner, et al 2007, Gungabissoon, et al 2007, Nielsen, et al 2009). The VFR group has been shown to travel to a greater extent to highly endemic HAV regions and to stay longer, compared to other group of travellers (DeSerres, et al 2007). Given an individual perspective, children normally have a mild or subclinical disease. However, older secondary cases can be critically ill and such outbreaks have been described (Diel & Schneider, 2001, Postma, et al 2004, Bell, et al 1998).

At the SMI, a separate analysis of hepatitis A outbreaks at Swedish paediatric day-care centres revealed 17 outbreaks during 2000-2007 with a total number of 97 people infected (76 children, 21 adults). The index case was a child in 11/17 and the source of infection was travel related in 13/17 outbreaks; 4 "tourist trip" and 9 VFR-travels (pers.comm M.Löfdahl SMI). Bearing these figures in mind and considering the fact that HAV vaccines are available and safe, it seems worthwhile to recommend national HAV immunization to all children with at least one parent born in a country highly endemic for hepatitis A. This is already the case for hepatitis B immunization, as recommended by the Swedish National Board of Health and Welfare. The cost-effectiveness for targeted hepatitis A vaccination to children of ethnic minorities has been favourably evaluated in the Netherlands (Postma, et al 2004). As with malaria prophylaxis, adequate pre-travel advice and the difficulties to reach the risk groups are highlighted again. If you have been growing up in an area highly endemic for HAV you do not perceive it as a health problem since the majority of the children have had a mild infection that is rarely recognized. As a consequence you may neither identify hepatitis A as an issue for your own children, when going back to see friends and relatives from the country of origin, nor understand the risk of transmission to other children and adults when returning home. This verifies the need for targeted information as well as routine immunization to children as suggested above.

At the other end of the scale, our findings indicate that the risk for contracting hepatitis A on a tourist trip to East Asia is very low. This is supported by the sero-epidemiological shift of HAV in Asia (Chatproedprai, et al 2007, Das, et al 2000, Mall, et al 2001, Barnett, et al 2003). The same shift has been demonstrated in South America and the parts of the Middle East (Tufenkeji, 2000, Sacy et al 2005, Jacobsen & Koopman, 2004, Tanaka, 2000). The impact of improved socioeconomic conditions and the subsequent decline in HAV prevalence during the last decades must be considered when estimating immunity in young immigrants who has earlier been considered naturally HAV immune.

In the airport survey, we collected information on HAV immunization from 399 travellers, 15% were children and 12% were classified as VFR-travellers. The median age was 26 years (range 0.5-73) and gender was equally distributed. In all, 79% stated that they hade been immunized against hepatitis A, 12% was not protected and 9% did not know their vaccination status. Travellers to Asia were significantly more often immunized than travellers to North Africa ($p<0.0001$). Travellers to the highly HAV endemic countries in North Africa have been shown to

be vaccinated to less extent than travellers to other HAV endemic countries (Nothdurft, et al 2007). This might be explained by the geographical proximity to Southern Europe, where HAV immunization is not routinely recommended. The group of VFR travellers in the age group 0-14 years was less often immunized than non-VFR children but the difference was not statistically significant. Approximately 10% of the travellers who were asked at the airports declined participation, the reasons being unwillingness to fill in a questionnaire or a sense of lack of time.

Even though our immunization data consist of a limited sample that was collected after the study period in paper III, they constitute the only updated available HAV immunization data in Swedish travellers. In 2002, a Swedish airport study revealed a hepatitis A immunization rate of 40% (Dahlgren, et al 2006), which was then a high figure compared to international studies (Prazuck, et al 1998, Wilder-Smith, et al 2004, Hamer, et al 2004) and probably a more adequate figure for the study period 1997-2005. A major drawback in these studies, as in our own, is that the figures are based on personal information and not on serological data. Furthermore, our immunization data are slightly overestimated as the non-responders as well as those with a late check in were probably immunized to a lesser extent. This is based on the assumptions that people who come late to a flight tend to come late to or miss other appointments, e.g. pre-travel vaccination, and that people who do not want to answer a questionnaire have a feeling that they should have been vaccinated and don't want to admit that they are not.

Considering these disadvantages, the incidence rates in unprotected travellers were estimated to 2 cases/100,000 travel months in East Asia, 12 in North Africa and 18 in the Middle East. See table 5.

Table 5. Estimated number of unprotected travellers 1997-2005, notified cases of hepatitis A 1997-2005, cases per 100,000 unprotected travellers with 95% CI, travel length in 100,000 months, cases per 100,000 unprotected person months with 95% CI and percentage VFR of total notified hepatitis A cases.

Region	Est. no of unprotected travellers	Cases	Cases per 100,000 unprotected travellers	95% CI	100,000 person months	Cases per 100,000 person months	95% CI	VFR%
Middle East (Iran)	129,690	103	79	59.4-106.1	5.9	18.0	13.1-23.4	91.0
East Asia	337,080	19	6	3.6-8.9	8.7	2	1.4-3.5	21
North Africa	388,620	68	17	13.4-22.8	5.6	12	9.2-15.7	37

The most striking finding in table 5 is the low incidence rate of hepatitis A in unprotected travellers to East Asia. The incidence rate is comparable to that of Southern Africa and Russia and confirms the reports on HAV sero-epidemiological shift in parts of East Asia. The relatively high incidence rate in travellers to North Africa supports the recommendation of HAV immunization even for shorter tourist trips to this region.

5.3 METHODOLOGICAL CONSIDERATIONS ON THE DATA COLLECTION IN THE TDB

The TDB data is weighted and extrapolated to estimate the total number of Swedish travellers. These calculations are based on size and structure of households from the national census of the population in 1990 as well as from annual official statistics of age, gender etc. There are several reasons to believe that the household composition has changed since 1990 and in consequence the estimations might not be fully reliable. Another complicating factor is that the household is defined as a one-person household in the TDB if the household contains two or more persons, of which only one is 75 years old at the most. According to a travel habit survey conducted by the Statistics Sweden (SCB) 2005-2006, persons in the age group 75-84 years old represent 3% of all travellers (both national and international). With an expected growing proportion of people over 75 years old the coming years, this proportion will probably increase.

The target population of all individuals in Sweden 0-74 years old differs somewhat from the selected population due to the selection criteria of a non-mobile private telephone subscription. This selection procedure gives an underestimation of people with mobile subscriptions only, which is a growing group. It also underestimates the number of people who are attached to a collective telephone subscription, e.g. mostly health-caring institutions.

Considering the process of randomly choosing persons to be interviewed in the household, the probability to be chosen for an interview correlates negatively to the size of the household. This is probably one of the explanations that children < 15 years are underrepresented and people > 60 years old are overrepresented in the TDB compared to official statistics. There is also a possible underestimation of frequent travellers who are not at home when their number is dialed. Furthermore, when weighting and extrapolating the data to reflect the whole Swedish population, the average individual statistical weight is around 4000 which gives disproportionate influence to unusual travel destinations undertaken by a few persons and it should also be emphasized that 1% of the interviewed persons represent 15% all travels. Based on a definition of response rate as "contact has been established but the selected person does not want to participate", the response rate in TDB is ~70% (Holmberg & Westberg, 2001).

Based on the estimation of an underrepresentation of frequent travellers with mobile telephones only in the TDB denominator, there might have been an overestimation of the incidence of hepatitis A and malaria.

5.4 TRAVEL RELATED FEVER

In paper V, 1,432 febrile travellers fulfilled the inclusion criteria; 514 patients were identified through prospective case-finding, 383 of those were tested with additional serology, and 918 patients were retrospectively identified. Base characteristic were similar in these groups, with exception of a slightly higher proportion of VFR among the retrospectively included as shown in table 6.

Table 6. Characteristics of all 1,432 patients divided into the groups of prospectively and retrospectively identified cases with and without additional paired sera.

	Patients with routine investigation only		**Prospectively identified patients with routine investigation + additional serology n=383 no.(%)**
	Prospectively identified n=131 no.(%)	Retrospectively identified n=918 no.(%)	
Age (median and range)	32 (18-65)	36 (18-84)	37 (18-76)
Female (%)	56 (43)	420 (46)	162 (42)
Travel to Africa (%)*	69 (53)	430 (47)	199 (52)
Travel to Asia (%)*	53 (40)	427 (46)	169 (44)
Travel to America (%)*	10 (8)	63 (7)	20 (5)
Tourists (%)	76 (58)	581 (63)‡	247 (64)
VFR (%)†	10 (8) p = 0.05[1]	126 (14)‡	20(5) p<0.0001 [1]
Duration of stay (median days)	20	21[§]	20
Pre-travel influenza immunization (%)	8 (6)	NA	53 (14)
Hospitalised after return to Sweden (%)	37 (28)	258 (28)	123 (32)

*A small number of travellers had been to more than one region, making the percent sum >100%
†VFR=Visiting friends and relatives= Swedish residents who were born in a malaria-endemic country and who had visited friends and relatives in their country of origin.
‡In 39 patient files information on type of travel is missing.
§In 115 patient files this information is missing
NA=Not Applicable
[1] Compared to retrospectively identified patients

In the whole group (n=1,432), unknown fever was diagnosed in 34%, followed by febrile gastroenteritis 24%, malaria 6%, influenza 3% and dengue fever 2.5%, before the results of additional serology was obtained. The proportion of patients with unknown fever, gastroenteritis and malaria did not differ between the prospectively included and the retrospectively included patients. For all diagnosis see table 7.

Table 7. Clinical and etiological diagnosis before results of additional serology (n=1,432).

Diagnosis	Patients with routine investigation only n=1432 (%)
Fever of unknown aetiology	491 (34)
Gastroenteritis pathogen verified	182 (13)
Gastroenteritis no pathogen verified	163 (11)
Malaria	92 (6)
P.falciparum	*56 (4)*
Upper respiratory tract infection	76 (5)
Pneumonia	73 (5)
Urinary tract infection	49 (3)
Influenza	46 (3)
Gram negative septicaemia non typhoid fever	41 (3)
Dengue fever	38 (2.5)
Non-infectious cause	33 (2)
Skin infection/ cellulitis	29 (2)
Rickettsial infection	22 (1.5)
Legionellosis	21 (1.5)
EBV/CMV	18 (1)
Mycoplasma	13 (1)
Aseptic meningitis	12 (1)
Gram positive septicaemia	10 (0.6)
Paratyphoid fever	9 (0.6)
Typhoid fever	7 (0.5)
HIV	6 (0.4)
Hepatitis*	5 (0.4)
Leptospirosis	4 (0.4)
Katayama fever	3 (0.2)
Enterovirosis	3 (0.2)
Tick Borne Encephalitis	1 (<0.1)
Nephropatia epidemica	2 (0.1)
Varicella zoster	2 (0.1)
Q fever	2 (0.1)
Parainfluenza virus	2 (0.1)
Endocarditis	2 (0.1)

* hepatitis A = 1, hepatitis E = 1, hepatitis B = 1, unspecified hepatitis n = 2

In the 383 prospectively included patients with additional serology, the diagnosis was unknown fever in 115/383 (30%) before results of serology. The serology established a diagnosis in 24/115 (21%) of these patient. The most common diagnosis was influenza (n=12) followed by SFG rickettsial infection (n=5 patients), dengue fever (n=3), leptospirosis (n=2), Q fever (n=1) and rickettsial infection due to *Orientia tsutsugamushi* (n=1). A positive result in the additional serology added a co-infection to a defined diagnosis other than unknown fever in 23/268 patients

(9%); influenza (n=14), dengue fever (n=3) TG rickettsial infections (n=2), SFG rickettsial infection (n=2), leptospirosis (n=1) and chikungunya fever (n=1). All undiagnosed cases were mild and self-limiting and the main symptom was fever without typical clinical signs.

After results of serology, we compared the final diagnosis in the groups with and without additional serology; fever of unknown aetiology was diagnosed in 23% and influenza in 9% of the patients with additional serology, compared to 35% and 4% in the group with routine investigations only. See table 8.

Table 8. Final diagnosis after result of both routine examination and additional serology (n=383), compared with the patients with routine investigations only (n=1,049)

Final diagnosis	**Patients with additional serology n=383 (%)**	**Patients with routine investigations only n=1,049 (%)**	**p-value**
Fever of unknown aetiology	91 (24)	372 (35)	<0.0001
Influenza	34 (9)	38 (4)	<0.001
Dengue fever	17 (4)	27 (3)	NS*
Rickettsial infection	17 (4)	15 (1)	<0.001
Leptospirosis	4 (1)	3 (0.2)	NS*
Q fever	3 (0.7)	0 (0)	0.004
Chikungunya fever	1 (0.3)	0 (0)	NS*

* NS = Not Significant

Overall, the proportion of patients with fever of unknown aetiology was rather high compared to previous studies (table 1). There might be several reasons, but the main factor was probably that our study population was less selected than studies where the patients are seen at more specialized tropical- and travel medicine centres. This is demonstrated by the fact that the study population in paper V derives from a catchment area of 3.3 million Swedish inhabitants (~1/3 of the Swedish population) who, if malaria has to be excluded, should be referred to one of the study hospitals with department of infectious diseases. There are no private alternatives. Considering the catchment area, the number of malaria in our study (n=92) corresponds well to the total number of notified malaria cases in Sweden during the study period (n=290). Another reason for the relatively high proportion of unknown fever might be that our study has mostly been conducted in an ER setting, with a high patient turnover, where febrile patients in good clinical condition might be sent home without extensive investigations or follow-up. A third hypothesis would be that Swedish ID doctors do not prioritise diagnostics in febrile returning travellers enough.

To analyze the latter hypothesis we did a separate minor analysis of the patients included at Karolinska/Solna up to December 2007 (n=172). We found that 39/172 (23%) of the patients had not been subject to blood culture and out of them 54% had a final diagnosis of unknown fever. Only 20/172 (12%) had been tested for HIV which is worrying as we found 6/1,432 patients with primary HIV among all patients with routine examinations only. HIV-serology was not included

in the additional serology due to the ethical concern of positive HIV-test in samples handled under code.

HIV should always be considered in febrile travellers, both as a primary infection and as an underlying condition. Primary HIV masquerading another tropical disease has been described before (Pendle & Sacks, 1998, Morrissey, et al 2001). In a study from Belgium (Bottieau, et al 2006) where 1,842 febrile travellers were included 2000-2005, 71/1,842 patients had "infectious mononucleosis-like syndrome". Out of them 36 had CMV, 16 *T.Gondii*, 15 EBV and 5 a primary HIV-infection. The authors reported that the four diseases were clinically indistinguishable. Casual sex has been estimated to occur in 5-51% of short-term travellers in different studies (Arvidson, et al 1995, Gillies, et al 1992, Hawkes, et al 1994, Gagneux, et al 1996, Daniels, et al 1992, Tveit, et al 1994). In a recent French study 2/49 returning travellers had primary HIV (Ansart, et al 2009). Altogether this emphasis that HIV-diagnostic should be a part of the routine procedure when investigating travel-related illnesses.

The proportion of malaria cases are lower in our study than other comparable (table 1) and strengthen the hypothesis of an unselected study population, due to lack of alternatives for the ill-returned travellers, as already mentioned. Another reason could be the lower proportion of VFR-travellers, who more often are returning with malaria than other travellers. A higher proportion of VFR-travellers in other studies might have an historical reason of colonialism, e.g. France and parts of Africa, which is not the case in Sweden. A lower frequency of malaria could also indicate a better adherence to and more effective malaria chemoprophylaxis in recent years as shown in paper I.

In Sweden, there are no private or out-patient alternatives for malaria diagnostics. There is, however, a possibility for a GP to send a blood test to the department of microbiology for malaria diagnostics. This is not recommended, due to a risk of considerable delay of diagnosis, and occurs only in a minority of the numbers of blood films for malaria.

The finding of undiagnosed rickettsial infections in patients with unknown fever was expected and in concordance with other studies (Jensenius, et al 2003, Rahman et al 2003) concluding that the presenting symptoms are often non-specific and flu-like and that the serological response is often delayed. The three verified TG rickettsioses in patients with other verified clinical conditions are neither surprising as TG rickettsiosis might be a subclinical or mild disease. Futhermore, the frequency of dengue infections was in accordance with or lower than other studies (Wilder-Smith & Schwartz, 2005, Freedman, et al 2006, Jelinek, 2000). Our results also indicate that leptospirosis is an underestimated cause of fever in returned travellers and not only related to extreme sports and adventurous travel.

Even though we found undiagnosed cases of rickettsial infections, dengue fever and leptospirosis, the limited additional yield of serology indicate that the cost-benefit of routine paired sera in this group of patients is most likely to be negative. Infections with *C.burnetii* and *Leptospira* spp. are treatable, but many of the cases are mild and subclinical and generally we do not recommend routine serology without an initial clinical suspicion. The key point should be epidemiological knowledge of the disease in combination with a careful patient history and examination.

Other illnesses of interest not included in the additional serology were; CMV/EBV, shistosomiasis and legionnaires disease.

Influenza

The major finding in paper V is that influenza was the most common cause of fever of unknown aetiology. In patients with additional serology (n = 383), 9% of patients had verified influenza. In the whole prospectively included group (n=514), 36 (7%) patients had influenza, diagnosed with both routine examination and additional serology. In this group, the median age was 33 years, and 20/36 was men. Four patients reported previous influenza vaccination. The median time from first symptom to health contact was 3 days. 18/36 patients fell ill with fever either just before returning to Sweden or within 1 day from arrival indicating that they had acquired the infection abroad, 5/36 patients had been home between 1 and 2 days indicating that the infection could have been acquired either during travel or after the return, and 13/36 patients had returned from travel more than 3 days before falling ill with fever, indicating that they had most likely been infected in Sweden. 25/36 influenza patients had verified influenza A and 11/36 had influenza B. 9/36 (25%) patients fell ill after returning from a trip well outside the influenza season in the northern hemisphere (May-September); 7/9 of them had visited Africa and two had travelled to Asia, one reported vaccination; 4/9 fell sick > 3days after return to Sweden.

Our findings confirm that influenza is a common cosmopolitan disease in travellers and highlights that it is often missed in routine diagnostics of febrile travellers returning from tropical areas. The possibility that another pathogen than influenza caused the febrile episode in the study patients, and that influenza occurred in between the paired sera, must be considered. The reports from tropical Asia of a significant proportion of missed influenza cases (Simmerman, et al 2006, Chow, et al 2006) and the assumed perennial transmission in tropical countries (Hampson, 1999, Dosseh, et al 2000, Beckett, et al 2004, Hasegawa, et al 2006, Nguyen, et al 2007, Moura, et al 2009) indicate, however, that the number of imported influenza cases from tropical countries are probably underestimated. One study found an association between influenza, VFR-travellers and travel > 30 days (Leder, et al 2003). We could not confirm this with our data.

6 GENERAL DISCUSSION

Gender aspect

In our studies of imported malaria we have found a predominance of men; 62% (146/237) in paper I and 73% (68/93) in paper V. This is also the case with hepatitis A; 57% males (364/636) and fever from malaria endemic areas; 55% males (794/1432). The explanation for this might be that men travel to a larger extent. We investigated TDB data on all travels abroad during 2008 (n=13,291,000) and found that 55% of the travels were undertaken by men. Travels to India, China and Thailand were overrepresented by men but travels to Egypt and South Africa showed a similar gender proportion (pers.comm H.Remvig, TDB). Considering the denominator, the risk for malaria and hepatitis A infection was higher in men than in women. The explanation could be differences in exposure and/or in prevention measures, such as immunization and chemoprophylaxis. However, we found no gender difference in immunization rate in paper III and in adherence to chemoprophylaxis in paper I. The hospitalization rate in paper V was 33% in men (97/296) and 29% (63/218) in women, but this difference was not significant ($p = 0.3$).

VFR/children

VFR-travellers often consist of people who have migrated from poorer to richer countries. "Visiting friends and relatives" is a commonly used term that is not standardized and could be interpreted as "the purpose of travel". However, in the literature of travel medicine, it has become a buzz word for travellers, with origin in a poor area of the world, now living in a new richer region of the world and going back to their country of origin to see family and relatives. Children to VFR-travellers are often included in this group even though they are born in the new country. The VFR-travellers have been shown to have higher rates of several travel related infectious diseases than other groups of travellers, to be less inclined to search pre-travel advice despite their knowledge of the diseases in the country, and to travel for longer periods and to more rural areas than an ordinary tourist (Angell & Behrens, 2005, Fulford & Keystone, 2005, Leder, et al 2006).

In this thesis we have found an increased risk for hepatitis A in VFR children and an increased risk for malaria in children that was probably often belonging to the VFR group. Among the adult malaria patients in paper V, 54% (50/93) were classified as VFR-travellers and 36/93 cases were male VFR returning from a travel in West Africa. Our findings, together with data from studies in other countries, implicate that pre travel advice to this group of travellers must be adjusted and targeted to the group that has most benefit of the advice. Further investigations on this subject are warranted.

Validity of our findings

The sensitivity of the Swedish notification system of communicable diseases is effective with more than 98% of patients with a confirmed diagnosis, according to microbiology, being picked up by the surveillance system (Jansson, et al 2005). The TDB has several shortcomings, but is nevertheless a reliable and homogenous source of national denominator data of Swedish travellers. Based on these two data sources we assume that the notification data from SMI and the risk calculations of hepatitis A and malaria are reliable. The combination of the sensitive notification system and active case finding in paper IV ensured knowledge of all possible *P.falciparum* malaria cases. In paper V, we believe that all febrile patients from areas endemic for malaria were identified in a catchment area representing 1/3 of Sweden 2005-2008. The serological methods in paper V are well defined and a diagnosis is based on a fourfold or greater rise in reciprocal antibody titre. However, the value of the compiled information from

questionnaires in paper I and IV are relatively low due to perceived recall difficulties by the respondents.

The notification system and the TDB are both representative for the whole country. In Sweden, the bulk of patients with symptoms after travelling are probably seen by a GP. However, fever after travelling to a malaria endemic area is a concern for the department of infectious disease and thus we believe that our findings ca be generalized to all Swedish patients at the infectious diseases departments, bearing in mind that children are often taken care of at the pediatric unit. An exception would be hepatitis A patients, who might not have to seek hospital care, even though an ID specialist is often involved at some stage concerning prophylaxis and exposure information. The risk estimates for malaria and hepatitis A as well as the finding of influenza as an underestimated cause of fever are probably valid for other western European countries. The diagnosis found in paper V can serve as a basis for development of Swedish guidelines for evaluation of fever in travellers from areas endemic for malaria. This has been done in other European countries (Bottieau, et al 2002, Spira, 2003, D´Acremont, et al 2003, Johnston, et al 2009).

Information aspect

All comes down to the important issue of how to provide updated information based on risk assessment to different sorts of travellers. Providing information is difficult and too much information makes it impossible for the traveller to extract the most essential parts. On the other hand immunization and prophylactic medication must be provided with caution and the risk for getting the disease must be higher than the risk of serious adverse events.

7 MAIN FINDINGS

Swedish malaria patients infected with *P.falciparum* had traveled to Africa in 90% of the cases and had a generally low adherence to recommended chemoprophylaxis and protection against mosquito bites.

Malaria chemoprophylaxis is effective in a high transmission area if encouraged and properly used.

Travellers to sub-Saharan Africa and children 0-6 years old have a higher risk for being diagnosed with malaria when returning to Sweden, compared to travellers to other regions and other age groups.

VFR travellers from East Africa, India and the Middle East, and especially children, constitute a high risk group for being diagnosed with hepatitis A after returning to Sweden.

Influenza is an underestimated cause of unknown fever in travellers from tropical and subtropical regions.

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