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Malaria in long-term travelers: Infection risks and adherence to preventive measures – A prospective cohort study

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A B S T R A C T

Background: Chemoprophylaxis and anti-mosquito measures are key to preventing malaria in travelers. Long-term travelers are at higher risk than short-term travelers, but their adherence to preventive measures is lower. Our aim was to determine malaria exposure risks and predictors for adherence to malaria-preventive measures in long-term travelers.

Methods: Long-term travelers (>12 weeks) completed a weekly questionnaire about preventive measures, symptoms, and malaria treatment abroad. Blood samples were tested for seroconversion to *Plasmodium falciparum* anti-circumsporozoite (*Pf*CSP) antibody. Adherence to preventive measures was defined as number of weeks of their usage divided by number of weeks in malaria-endemic areas.

Results: Of 561 travelers, the median travel time was 20 weeks (IQR 16–25). Eighteen were treated for malaria, all in sub-Saharan Africa. Sixteen *Pf*CSP seroconversions were found, of whom only 3 had traveled to high-endemic areas. Of the 18 travelers treated for malaria, only one seroconverted. No associations were found between covariates and seroconversion. Neither treatment abroad nor seroconversion were reliable predictors for exposure. 'Full adherence' to chemoprophylaxis was reported by 52% (218/417) and was associated with travel to Africa, use of mefloquine, lack of prior travel history, shorter duration of travel, and use of DEET.

Conclusions: The risk of malaria in this long-term travelers cohort was low. Our data confirm that anti-*Pf*CSP seroconversion is not a reliable method to retrospectively identify incident infection, or probably exposure. Prevention efforts should focus on more experienced travellers and longer travel duration, for whom mefloquine should be considered as the first-choice chemoprophylaxis.

1. Introduction

Malaria chemoprophylaxis and anti-mosquito measures are key to preventing malaria in travelers. *Plasmodium falciparum* is the species that causes most fatalities [1]. Prevention of fatal disease is the main goal of chemoprophylaxis.

Between 1998 and 2018, in a cohort of more than 100,000 travelers returning ill to Europe, falciparum malaria was among the most-frequently diagnosed illnesses and was the most frequent cause of death [2].

Adherence to chemoprophylaxis in travelers is generally poor [3,4], mostly due to the cost, alleged adverse effects, and unawareness of the risks and life-threatening potential of malaria [5,6]. Most patients with travel-related malaria had used their chemoprophylaxis incorrectly or not at all [7,8]. Non-adherence is associated with longer travel duration [4,9], putting long-term travelers at even higher risk than short-term travelers.

Long-term travellers are a heterogeneous group that can consist of tourist travelers (often backpackers), immigrants visiting friends and relatives in their country of origin (VFR), people who travel for study or work, each with their special risks and concerns [10].

Whether chemoprophylaxis should be recommended depends on the balance between the risks and benefits [11], such as level of endemicity; travel duration, itinerary, quality of accommodation and local health

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care access and quality, adverse effects of, and adherence to, chemoprophylaxis, as well as adherence to anti-mosquito measures [12–19]. Personality traits possibly play a role in adherence to preventive measures [20]. The malaria risk for travelers does not always correspond with the risk for the local population [12], and surveillance of travel-related malaria is incomplete because only travelers diagnosed after return are reported [17]. Underreporting is especially relevant for *P. falciparum,* with its short incubation period, acute onset and resulting necessity of immediate local treatment [21].

Several studies have used anti-*P. falciparum* circumsporozoite protein (*Pf*CSP) antibodies in nonimmune travelers to estimate the incidence of *P. falciparum* exposure [22–27], although this method is probably of very limited sensitivity.

The aim of this study was to determine malaria exposure risks and predictors for adherence to malaria-preventive measures in long-term travelers in order to optimize malaria-preventive recommendations, and to add to the limited data on *Pf*CSP measurements in travelers.

2. Methods

The Medical Ethics Committee of the Academic Medical Center Amsterdam approved the study protocol (MEC 08/064). All participants provided written informed consent. STROBE criteria were followed.

2.1. Study population and procedures

This study is part of a larger prospective study conducted at the Public Health Service Travel Clinic in Amsterdam from December 2008 through September 2011 [28–32]. The clinic is accessible for anyone and sees 30,000–40,000 travelers per year. Vaccinations must be paid by the traveler unless they have insurance that covers travel medicine. In the main study, all clients aged ≥18 years and planning to travel >12 weeks to Africa, Latin America, or Asia were invited to participate. Partaking travelers who spent at least one week in a malaria-endemic area were selected for the present sub-study. Participants traveling to low-, intermediate-, and high-endemic malarious areas were advised to take preventive measures against mosquito bites and given oral and written information about these measures. Participants traveling to intermediate- and/or high-endemic areas were additionally prescribed chemoprophylaxis. All participants were seen pre-travel by a physician or nurse specialist in travel medicine and were advised according to the then-valid highly standardized "Dutch National Guidelines on Traveler's Health Advice" (LCR) [33]. In the Netherlands at the time of the study, atovaquone/proguanil, mefloquine, doxycycline, proguanil in combination with chloroquine, or combinations thereof were recommended as chemoprophylaxis against *P. falciparum* malaria. Generally, with some exceptions, for multi-drug resistant malarious areas, atovaquone/proguanil, mefloquine and doxycycline are considered equally effective. At the time of the study, mefloquine was officially the first choice for travelers traveling >4 weeks, because atovaquone/proguanil was not registered for more than 4 weeks usage. The choice of chemoprophylaxis however depended on travel destination, but also travelers' individual preferences including costs, and characteristics. Mefloquine is contra-indicated for individuals with psychiatric disturbances. All travelers are provided with oral and written information about intake schedules and possible adverse effects of chemoprophylaxis.

Before departure, data on socio-demographics, prior travel history to (sub)tropical countries, and purpose of travel were collected using standardized questionnaires.

Travelers were asked to keep a structured weekly diary during their trip to record their itinerary, symptoms of disease, use of insect repellent containing a minimum of 30% N,N-diethyl-*meta*-toluamide (DEET), use of impregnated bednets, and use of malaria chemoprophylaxis. Participants were given a thermometer (Huikeshoven Medical, Tiel, The Netherlands) and asked to take their temperature if they felt feverish and to record physician visits, diagnoses, and (self)-treatment for malaria. Diaries were filled out on paper or digitally, and travelers received a weekly email as a reminder. We collected blood samples by venepuncture at the pre-travel study visit and in a time window of 2–6 weeks following return. Samples were tested for *Pf*CSP antibodies.

2.2. Laboratory methods

Blood samples were immediately stored at 6 °C and centrifuged (Hettich Rotixa 50 S, see APP/407: program 1, 10 min. 3000 rpm (210 g)), then frozen at −80 °C within 24 h. The *Pf*CSP-ELISA (*P. falciparum* circumsporozoite protein enzyme-linked immunosorbent assay) was used to test for *Pf*CSP antibodies according to standard protocol [34]. The optical density (OD) was read at 450 nm (reference filter 620 nm). Included in each plate were pooled plasma samples from Tanzanian individuals as a positive, and pooled plasma samples from Dutch individuals as a negative control.

The threshold for positivity for *Pf*CSP antibodies was calculated as the mean OD of the seven negative control plasma samples plus three standard deviations. If the OD in post-travel serum samples tested positive and showed a >2-fold increase compared to the pre-travel OD value, they were defined as *Pf*CSP seroconversions. This *Pf*CSP seroconversion was considered indicative of exposure to *P. falciparum* during the travel just completed.

2.3. Definitions

We categorized destinations into three continents: Asia, Latin America, and Africa. Most areas in Africa are highly-endemic, whereas most areas in Latin America and Asia are intermediate- or low-endemic. Adherence to preventive measures was quantified in percentages, taking the number of self-reported weeks of their usage divided by the number of weeks spent in malaria-endemic areas. We defined 100% as 'full adherence'. Fever was self-reported and defined as 'feeling feverish' or >38 °C fever.

2.4. Data analysis

We initially used *Plasmodium* infection (i.e., *Pf*CSP seroconversion or malaria diagnosis/treatment abroad) as an endpoint. We modeled the probability of having *Plasmodium* infection using Poisson regression with robust standard errors. We added covariates allowing us to compare probabilities across levels of determinants, which can be interpreted as a prevalence ratio (PR). PR was calculated along with 95% confidence intervals (CI).

We next examined three separate endpoints for full adherence to (i) chemoprophylaxis, (ii) DEET, and (iii) use of impregnated bednets. These endpoints were likewise modeled using Poisson regression with robust standard errors analysis, which included covariates.

Finally, we used time until discontinuation of chemoprophylaxis during travel as an endpoint, with discontinuation defined as not taking the recommended chemoprophylaxis for at least one week. We modeled this endpoint using a mixed-effects parametric survival model with a Weibull-distributed survival function. We included a random intercept for participants to account for their variation at inclusion. From this model, we calculated the hazards ratio (HR) and 95% CI comparing the hazards between levels of covariates.

For all models above, we initially conducted univariable analysis for each covariate separately. In multivariable analysis, we included all determinants with an overall p-value of <0.10.

Data analysis was performed with STATA Intercooled version 15 (College Station, TX, USA). Significance was defined by a p-value < 0.05.

3. Results

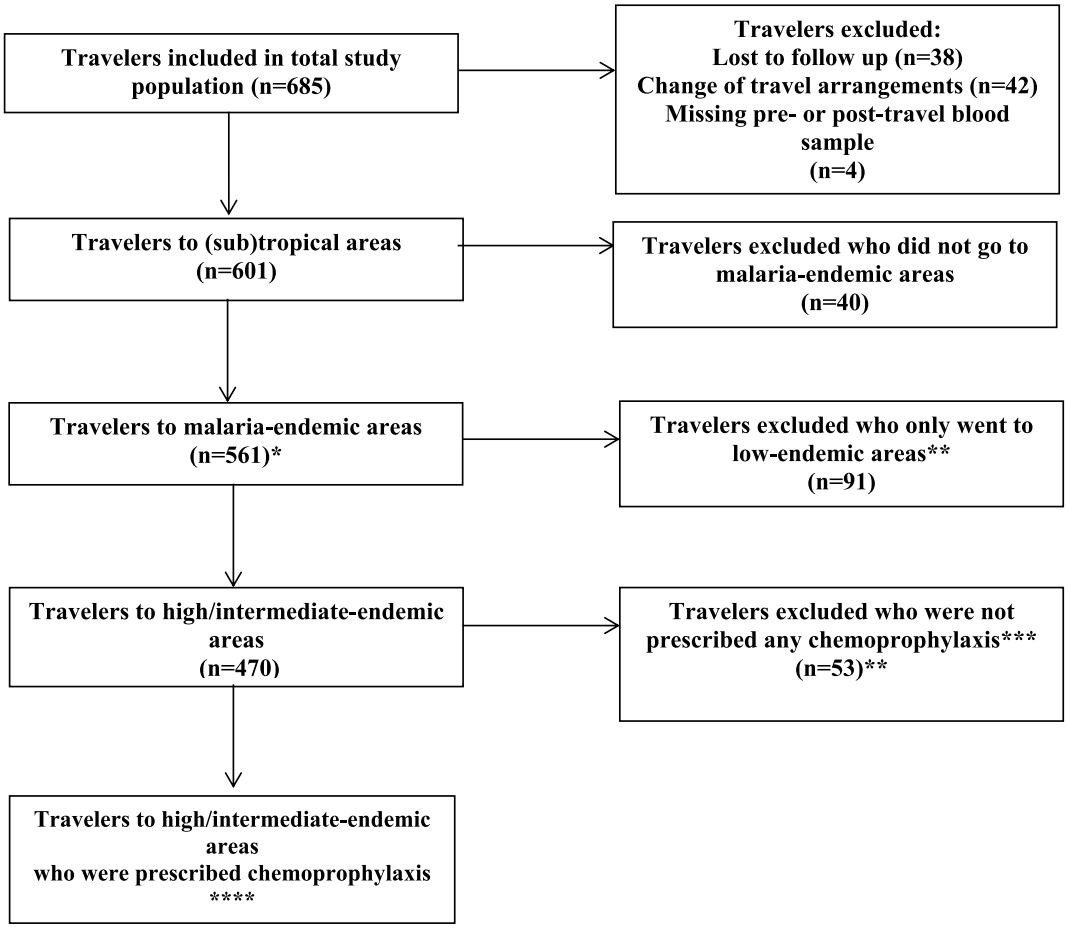
3.1. Study population characteristics

From December 2008 through September 2011, 685 travelers to (sub)tropical areas were recruited, 84 of whom were excluded upon completion of the study (Fig. 1) [28]. Of the remaining 601, 561(82%) traveled to malaria-endemic countries (Table 1). The average duration spent in malarial areas was 84 days (IQR 35–112 days). The median age of the 561 participants was 25 years (IQR 23–29), 64% were female, 80% had visited (sub)tropical countries before, 47% traveled to Asia, and the median travel time was 20 weeks (IQR 16–25).

Of the 561 participants, 91 (16%) were not prescribed chemoprophylaxis because they traveled to low-endemic countries, and 53 (11%) were not prescribed chemoprophylaxis for other reasons (Fig. 1). The remaining 417 were included in the analysis on adherence to chemoprophylaxis.

3.2. PfCSP antibody seroconversion

Of 561 travelers, 16 (2.9%) seroconverted for *Pf*CSP antibodies (Supplementary Table 1). Of these, 7 fully adhered to chemoprophylaxis, and 5 reported fever, of whom 4 visited a doctor but only 1 was diagnosed with malaria; 4 (25%) traveled only in low-endemic areas, 9



* These travelers are included in the analysis on adherence to DEET and to bednet use

**Travelers only to low-endemic malaria areas and travelers to high/intermediate-endemic areas not using chemoprophylaxis were excluded from adherence-to-chemoprophylaxis analysis.

***Travelers to high/intermediate-endemic areas who were not prescribed chemoprophylaxis for various reasons, such as change of itinerary during travel, or unwillingness to use chemoprophylaxis

**** According to Dutch National Guidelines on Traveler's Health Advice (LCR)

Fig. 1. Flow chart of our prospective study of malaria in long-term travelers: infection risks and adherence to preventive measures. * These travelers are included in the analysis on adherence to DEET and to bednet use, **Travelers only to low-endemic malaria areas and travelers to high/intermediate-endemic areas not using chemoprophylaxis were excluded from adherence-to-chemoprophylaxis analysis., ***Travelers to high/intermediate-endemic areas who were not prescribed chemoprophylaxis for various reasons, such as change of itinerary during travel, or unwillingness to use chemoprophylaxis, **** According to Dutch National Guidelines on Traveler's Health Advice (LCR).

Table 1
Characteristics of 561 travelers to malaria-endemic countries, including 417 who were prescribed chemoprophylaxis, who participated in prospective cohort of long-term travelers from the Netherlands, December 2008–September 2011; the prevalence ratios (PR) and determinants of full adherence[a] to prophylaxis.

	Travelers to malaria areas (%)	Travelers prescribed prophylaxis[b] (%)	Full adherence[a]	Univariable analysis PR (95% CI)	p-value	Multivariable analysis PR (95% CI)	p-value
Total	**561 (100%)**	**417 (74%)**	**218 (52%)**				
Sex							
Male	200 (36%)	155 (78%)	72 (46%)	1	0.0756	1	0.1347
Female	361 (64%)	262 (73%)	146 (56%)	1.2 (1.0–1.5)		1.2 (1.0–1.4)	
Age, years							
18–19	40 (7%)	30 (75%)	16 (53%)	1	0.5694		
20–29	385 (69%)	286 (74%)	154 (54%)	1.0 (0.7–1.4)			
≥30	136 (24%)	101 (74%)	48(48%)	0.9 (0.6–1.3)			
Country of birth							
Western country	547 (97%)	406 (74%)	214 (53%)	1	0.3559		
Non-western country	14 (3%)	11 (79%)	4 (36%)	0.7 (0.3–1.5)			
Reason of travel							
Tourism	358 (64%)	269 (75%)	130 (48%)	1	0.0857	1	0.8036
Visiting friends and relatives	10(2%)	8 (80%)	4 (50%)	1.0 (0.5–2.1)		1.1 (0.6–2.0)	
Work or education	152 (27%)	110 (72%)	64 (58%)	1.2 (1.0–1.5)		1.1 (0.9–1.4)	
Other[d]	41 (7%)	30 (73%)	20 (67%)	1.4 (1.0–1.8)		1.0 (0.7–1.4)	
Previous travel to a (sub)tropical country							
None	113(20%)	81 (72%)	52 (64%)	1	**0.0306**	1	**0.0419**
Less than 3 months	225(40%)	171 (76%)	86 (50%)	0.8 (0.6–1.0)		0.8 (0.7–1.0)	
More than 3 months	223(40%)	165 (74%)	80 (48%)	0.8 (0.6–0.9)		0.8 (0.6–1.0)	
Length of travel							
12–23 weeks	377 (67%)	283 (75%)	170 (60%)	1	**0.0002**	1	**0.0002**
24–35 weeks	144 (26%)	101 (70%)	40 (40%)	0.7 (0.5–0.9)		0.7 (0.5–0.8)	
≥36 weeks	40 (7%)	33 (83%)	8 (24%)	0.4 (0.2–0.7)		0.4 (0.2–0.8)	
Travel destination							
Africa	108 (19%)	104 (96%)	72 (69%)	1	**0.0000**	1	**0.0385**
Asia	263 (47%)	189 (72%)	99 (52%)	0.8 (0.6–0.9)		0.9 (0.7–1.1)	
Latin America	190 (34%)	124 (65%)	47 (38%)	0.5 (0.4–0.7)		0.7 (0.5–0.9)	
Preventive chemoprophylaxis							
Mefloquine	–	138 (25%)	93 (67%)	1	**0.0001**	1	**0.0000**
Atovaquone/ proguanil	–	199 (35%)	91 (46%)	0.7 (0.6–0.8)		0.6 (0.5–0.8)	
Doxycycline	–	16 (3%)	7 (44%)	0.6 (0.4–1.1)		0.6 (0.3–1.0)	
Proguanil	–	37 (7%)	12 (32%)	0.5 (0.3–0.8)		0.5 (0.3–0.8)	
Other	–	27 (5%)	15 (56%)	0.8 (0.5–1.1)		0.9 (0.6–1.4)	
DEET[c] use ('Full adherence'[a])							
Yes	182 (68%)	147 (81%)	95 (65%)	1	**0.0001**	1	**0.0208**
No	379 (32%)	270 (71%)	123 (46%)	0.7 (0.6–0.8)		0.8 (0.7–1.0)	
Bednet use (Full adherence[a])							
Yes	71 (87%)	62 (87%)	42 (68%)	1	**0.0024**	1	0.2796
No	490 (13%)	355 (72%)	176 (50%)	0.7 (0.6–0.9)		0.9 (0.7–1.1)	

PR = prevalence ratio.
[a] Adherence was quantified in percentages, taking the number of self-reported weeks of usage of the preventive measure divided by the number of weeks spent in malaria-endemic areas. We defined 100% as 'full adherence.'
[b] Traveling to high-endemic areas were 470, of whom 53 were not prescribed prophylaxis for various reasons.
[c] N,N-diethyl-*m*-toluamide.
[d] Doxycycline, chloroquine, or a combination of different chemoprophylactic regimens.

(56%) traveled in intermediate-endemic areas; 8 (50%) were tourists, and 7 (44%) traveled for work or education. Poisson regression did not reveal any association between covariates and seroconversion.

3.3. Diagnosis and treatment of malaria abroad

Of the 561, 18 were diagnosed with malaria while abroad and treated accordingly by local physicians (Supplementary Table 2). All 18 traveled in Africa, one had also traveled to Asia but was treated in Africa. Of this group, 11 had fully adhered to their chemoprophylaxis, 12 reported fever, and 8 traveled for work or education. Only one of these 18 seroconverted for *Pf*CSP antibodies.

Travelers born in non-Western countries and those who traveled to Africa were significantly more likely to be treated for malaria than travelers born in Western countries or travelers to Asia.

3.4. Adherence to chemoprophylaxis

Of the 417 travelers who were prescribed chemoprophylaxis, the largest group (35%) were prescribed atovaquone/proguanil, whereas 25% were prescribed mefloquine (Table 1). Of all 417, 218 (52%) were considered fully adherent because they reported having used chemoprophylaxis every week while in high- or intermediate-endemic areas. In multivariable analysis, travelers to Latin America (PR 0.7; 95%CI 0.5–0.9) were less likely to be fully adherent than travelers to Africa; those who traveled for 24–35 weeks (PR 0.7; 95% CI 0.5–0.8) and ≥36 weeks (PR 0.4; 95%CI 0.2–0.8) were less likely to be fully adherent compared to 12–23 weeks, and travelers using atovaquone/proguanil (PR 0.6; 95%CI 0.5–0.8) and doxycycline (PR 0.6; 95%CI 0.3–1.0) were less likely to be fully adherent compared to travelers using mefloquine.

Travelers who reported full adherence to DEET were likewise more often fully adherent to chemoprophylaxis compared to those less adherent to DEET (PR 0.8; 95%CI 0.7–1.0). Travelers with a prior travel history were less likely to use chemoprophylaxis than those with no such history.

3.5. Time until discontinuation of chemoprophylaxis during travel

In multivariable analysis, travelers to Africa were significantly more likely to continue chemoprophylaxis longer than travelers to Asia (HR 4.3; 95%CI 2.1–9.0) and Latin America (HR 11.1; 95%CI 5.0–24.7) (Table 2). Travelers using mefloquine were more likely to continue longer than those taking doxycycline, chloroquine, or other chemoprophylactics (HR 4.8; 95%CI 2.5–8.9), (HR 5.6; 95%CI 1.3–23.3), (HR 5.1; 95%CI 1.9–13.5), respectively.

Travelers who left and re-entered malaria-endemic areas were more likely to discontinue chemoprophylactics earlier than travelers who stayed in one endemic area: once re-entering a malaria-endemic area: (HR 1.5; 95% CI 1.2–1.8); twice re-entering: (HR 1.2; 95%CI 1.0–1.6).

3.6. Use of insect repellent

Of 561 travelers, 182 (32%) were considered fully adherent to DEET use (Table 3). In multivariable analysis, travelers who traveled 24–35 weeks (PR 0.7; 95%CI 0.5–1.0) and >35 weeks (PR 0.5; 95%CI 0.3–1.0) were less likely to fully adhere to DEET compared to those who traveled 12–23 weeks. Travelers to low-endemic areas (PR 0.6; 95%CI 0.4–0.9) and travelers who did not fully adhere to chemoprophylaxis (PR 0.7; 95%CI 0.6–1.0) were less likely to adhere fully to DEET than travelers to high/intermediate-endemic areas who fully adhered to chemoprophylaxis. Travelers who were less adherent to bednet use (PR 0.4; 95%CI 0.4–0.9) were also less adherent to DEET use.

3.7. Use of bednets

Of 561 travelers, only 71 (13%) reported to have fully adhered to using their bednets (Table 4). Travelers to Asia (PR 0.3; 95%CI 0.2–0.5) and Latin America (PR 0.4; 95%CI 0.2–0.7) were less likely to adhere to bednet use than travelers to Africa. Travelers who were not fully adherent to DEET use (PR 0.3; 95%CI 0.2–0.4) were likewise less likely to adhere fully to bednet use.

4. Discussion

In this cohort of 561 long-term travelers, 18 reported treatment for malaria abroad, all in Africa. Especially in high-risk areas, patients with fever are often treated for malaria without laboratory confirmation [23,35,36]. Unfortunately, we could not determine whether the diagnosis was laboratory-confirmed in the cases above. We found two predictors for receiving treatment abroad: travelers born in non-Western countries and travelers to Africa. We also tested *Pf*CSP antibodies and found 16 seroconversions. Only one traveler who was treated for malaria was amongst those with documented seroconversion. This person had traveled 14 weeks to study in Ghana and reported full adherence to mefloquine and provides the strongest cumulative evidence of exposure to falciparum malaria.

It is remarkable -but in line with earlier studies-that none of the other 17 travelers treated for malaria had seroconverted. Possibly, patients had been treated without falciparum malaria laboratory-confirmation, while they had contracted another febrile illness or non-falciparum malaria. Also, the brief time period between sporozoite inoculation and hepatic invasion (i.e. the disappearance of sporozoites from the bloodstream on first liver passage) is the only life-cycle stage at which *Pf*CSP is expressed. Most naturally-acquired malaria infections probably result from exposure to only a very low number of sporozoites. Parasites multiplying in the liver and then in the blood no longer express CSP. Thus, the total antigenic load of *Pf*CSP to which the immune system is exposed will only induce minuscule amounts of *Pf*CSP antibodies barely measurable with even highly sensitive methods.

Conversely, of the 16 travelers who seroconverted, 15 had not been treated for malaria, irrespective of their adherence to chemoprophylactics: one traveler to an intermediate-endemic area and four travelers to low-endemic areas had not been taking prophylaxis at all and were not diagnosed or treated for malaria abroad. This finding indicates the poor specificity of *Pf*CSP seroconversion. Since falciparum malaria is generally not a self-limiting disease, it is unlikely that these travelers were truly infected.

Table 2
Characteristics of 417 travelers who were prescribed malaria chemoprophylaxis; hazard ratios (HR) and determinants for discontinuing prophylaxis during stay in high-endemic country.

	Travelers prescribed prophylaxis (%)	Univariable analysis HR (95% CI)	p-value	Multivariable analysis HR (95% CI)	p-value
Total	417 (74%)				
Sex					
Male	155 (78%)	1	0.7312		
Female	262 (73%)	0.9 (0.5–1.6)			
Age, years					
18–19	30 (75%)	1	0.1284		
20–29	286 (74%)	1.8 (0.7–5.2)			
≥30	101 (74%)	2.9 (1.0–9.0)			
Previous travel to a (sub)tropical country					
None	81 (72%)	1	0.2052		
Less than 3 months	171 (76%)	1.6 (0.8–3.5)			
More than 3 months	165 (74%)	2.0 (0.9–4.3)			
Travel destination					
Africa	104 (96%)	1	**<0.0001**	1	**<0.0001**
Asia	189 (72%)	5.6 (2.8–11.5)		4.3 (2.0–9.0)	
Latin America	124 (65%)	16.4 (7.7–34.8)		11.1 (5.0–24.7)	
Preventive chemoprophylaxis					
Mefloquine	138 (25%)	1	**<0.0001**	1	**<0.0001**
Atovaquone/proguanil	199 (35%)	6.5 (3.5–12.2)		4.8 (2.5–8.9)	
Doxycycline	16 (3%)	3.5 (0.8–14.6)		5.6 (1.3–23.3)	
Proguanil	37 (7%)	12.0 (4.6–30.9)		5.1 (1.9–13.5)	
Other*	27 (5%)	2.1 (0.7–6.6)		1.6 (0.5–5.1)	
In and out of high-endemic area					
None	197 (47%)	1	**0.0006**	1	**0.0009**
Once	112 (27%)	1.5 (1.2–1.8)		1.5 (1.2–1.8)	
Twice	64 (15%)	1.2 (1.0–1.6)		1.2 (1.0–1.6)	
> Three times	44 11%)	1.0 (0.8–1.4)		1.0 (0.8–1.4)	

HR = hazard ratio.
**doxycycline, chloroquine, or a combination of various chemoprophylactic regimens.

Table 3
Determinants and prevalence ratios (PR) for full adherence[a] to repellent containing DEET[b] during travel in a prospective cohort of long-term travelers from the Netherlands, December 2008–September 2011.

	Travelers to malaria areas (%)	Full adherence[a]	Univariable analysis PR (95% CI)	p-value	Multivariable analysis PR (95% CI)	p-value
Total	561 (100%)	182 (32%)				
Sex						
Male	200 (36%)	51 (26%)	1	**0.0115**	1	0.0503
Female	361 (64%)	131 (36%)	1.4(1.1–1.9)		1.3(1.0–1.7)	
Age, years						
18–19	40 (7%)	11 (28%)	1	0.5949		
20–29	385 (69%)	130 (34%)	1.2(0.7–2.1)			
≥30	136 (24%)	41 (30%)	1.1(0.6–1.9)			
Country of birth						
Western country	547 (97%)	178 (33%)	1	0.7608		
Non-western country	14 (3%)	4 (29%)	0.9(0.4–2.0)			
Reason of travel						
Tourism	358 (64%)	106 (30%)	1	0.2223		
Visiting friends and relatives	10 (2%)	3 (30%)	1.0(0.4–2.6)			
Work or education	152 (27%)	56 (37%)	1.2(1.0–1.6)			
Other[c]	41 (7%)	17 (41%)	1.4(0.9–2.1)			
Previous travel to a (sub)tropical country						
None	113 (20%)	42 (37%)	1	0.2012		
Less than 3 months	225 (40%)	77 (34%)	0.9(0.7–1.2)			
More than 3 months	223(40%)	63 (28%)	0.8(0.6–1.0)			
Length of travel						
12–23 weeks	377(67%)	141 (37%)	1	**0.0029**	1	**0.0209**
24–35 weeks	144 (26%)	34 (24%)	0.6(0.5–0.9)		0.7(0.5–1.0)	
≥36 weeks	40 (7%)	7 (18%)	0.5(0.2–0.9)		0.5(0.3–1.0)	
Travel destination						
Africa	108 (19%)	42 (39%)	1	**0.0640**	1	0.0618
Asia	263 (47%)	90 (34%)	0.9(0.7–1.2)		1.4(1.0–1.9)	
Latin America	190 (34%)	50 (26%)	0.7(0.5–0.9)		1.1(0.8–1.6)	
Adherence to chemoprophylaxis						
High/intermediate-endemic area (full adherence[a])	218(39%)	95 (44%)	1	**0.0001**	1	**0.0222**
High/intermediate-endemic area (< full adherence[a])	199 (36%)	52 (26%)	0.6(0.5–0.8)		0.7(0.6–1.0)	
High/intermediate-endemic area (no prophylaxis prescribed)	53 (9%)	16 (30%)	0.7(0.5–1.1)		0.8(0.5–1.2)	
Low-endemic area (no prophylaxis required)	91 (16%)	19 (21%)	0.5(0.3–0.7)		0.6(0.4–0.9)	
Bednet use (full adherence[a])						
Yes	71 (87%)	49 (69%)	1	**0.0000**	1	**0.0000**
No	490 (13%)	133 (27%)	0.4(0.3–0.5)		0.4(0.3–0.5)	

pr = prevalence ratio.
[a] Adherence was quantified in percentages, taking the number of self-reported weeks of using the preventive measure divided by the number of weeks spent in malaria-endemic areas. We defined 100% as 'full adherence.'
[b] N,N-diethyl-*m*-toluamide (minimum use of 30%).
[c] Doxycycline, chloroquine, or a combination of various chemoprophylactic regimens.

Furthermore, no determinants for seroconversion were found, although traveling to high-risk areas, especially Africa, was a priori expected to be associated as these travellers have a much higher risk of infection than travelers to intermediate- and low-risk areas [37–42].

Since 2017, in the Netherlands, chemoprophylaxis is no longer prescribed for travelers to intermediate/low-endemic areas because of the very low risk. Thus, the fact that 13/16 of our travelers seroconverted in such areas renders it highly unlikely that *Pf*CSP seroconversion indicated true exposure under successful malaria chemoprophylaxis. Whilst *Pf*CSP antibody assays play an important role in pre-erythrocytic vaccine studies, our results re-confirm that they are not sufficiently reliable, and hence not suitable for identifying previous incident infections in returning travellers [43].

In our study, only 52% fully adhered to chemoprophylaxis; adherence to DEET (32%) and bednet use (13%) was even lower. Travel to Africa was associated with better adherence to chemoprophylaxis, and better adherence to bednets, but not to better adherence to DEET. Overall, travelers who were less adherent to DEET were also less adherent to bednets and to chemoprophylaxis. This aligns with the finding that personality traits play a role in adherence to preventive measures against malaria [6], rather than making deliberate choices between different prophylactic measures to reduce the risk. When time was included in the analysis, travelers to Africa were also less likely to stop chemoprophylaxis earlier during travel than travelers to other destinations. Overall, travelers to Africa comply best with preventive measures.

Several other studies showed that travelers to Africa adhere better to chemoprophylaxis than travelers to other malaria-endemic areas [5,6,8,44,45]. Awareness of differences in malaria risks between areas could play a role: most regions in Africa are highly-endemic. Also, in Africa, most travelers must take chemoprophylaxis consistently throughout their travel, whereas in Asia and Latin America, travelers often stop and start chemoprophylaxis as they move in and out of malaria-endemic areas. We found that staying in one malarious area throughout the entire trip is a predictor of full adherence.

Previous travel to (sub)tropical countries was associated with less adherence to chemoprophylaxis, and longer duration of current travel with less adherence to both chemoprophylaxis and DEET. Prevention efforts should focus on more experienced travellers and longer travel duration, for whom mefloquine should be considered as the first-choice chemoprophylaxis to improve adherence.

A modelling study in UK based on imported malaria cases, number of prescriptions and literature on adverse effects found that there was little benefit when mefloquine use is substituted by atovaquone/proguanil or

Table 4
Determinants and prevalence rate ratios (PRR) for 'full adherence'[a] to bednet use during travel among a prospective cohort of long-term travelers from the Netherlands, December 2008–September 2011.

	Travelers to malaria areas (%)	Full adherence[a]	Univariable analysis PR (95% CI)	p-value	Multivariable analysis PR (95% CI)	p-value
Total	561 (100%)	71 (13%)				
Sex						
Male	200 (36%)	22 (11%)	1	0.3835		
Female	361 (64%)	49 (14%)	1.2(0.8–2.0)			
Age						
18–19	40 (7%)	1 (3%)	1	0.2098		
20–29	385 (69%)	50 (13%)	5.2(0.7–36.7)			
≥30	136 (24%)	20 (15%)	5.9(0.8–42.6)			
Country of birth						
Western country	547 (97%)	69 (13%)	1	0.8515		
Non-western country	14 (3%)	2 (14%)	1.1(0.3–4.2)			
Reason of travel						
Tourism	358 (64%)	25 (7%)	1	**0.0000**	1	0.1648
Visiting friends and relatives	10 (2%)	1 (10%)	1.4(0.2–9.6)		0.8(0.2–3.9)	
Work or education	152 (27%)	35 (23%)	3.3(2.0–5.3)		1.8(1.0–3.1)	
Other[c]	41 (7%)	10 (24%)	3.5(1.8–6.8)		1.7(0.8–3.4)	
Previous travel to a (sub)tropical country						
None	113 (20%)	15 (13%)	1	0.4962		
Less than 3 months	225 (40%)	24 (11%)	0.8(0.4–1.5)			
More than 3 months	223(40%)	32 (14%)	1.1(0.6–1.9)			
Length of travel						
12–23 weeks	377(67%)	49 (13%)	1	0.9353		
24–35 weeks	144 (26%)	17 (12%)	0.9(0.5–1.5)			
≥36 weeks	40 (7%)	5 (13%)	1.0(0.4–2.3)			
Travel destination						
Africa	108 (19%)	39 (36%)	1	**0.0000**	1	**0.0001**
Asia	263 (47%)	17 (6%)	0.2(0.1–0.3)		0.3(0.2–0.5)	
Latin America	190 (34%)	15 (8%)	0.2(0.1–0.4)		0.4(0.2–0.7)	
Adherence to chemoprophylaxis						
High/intermediate-endemic area (full adherence[a])	218(39%)	42 (19%)	1	**0.0024**	1	0.4559
High/intermediate-endemic area (< full adherence[a])	199 (36%)	20 (10%)	0.5(0.3–0.9)		0.9(0.5–1.4)	
High/intermediate-endemic area (no prophylaxis prescribed)	53 (9%)	6 (11%)	0.6(0.3–1.3)		1.1(0.5–2.4)	
Low-endemic area (no prophylaxis required)	91 (16%)	3 (3%)	0.2(0.1–0.5)		0.4(0.1–1.4)	
DEET[b] use (full adherence[a])						
Yes	182 (68%)	49 (27%)	1	**0.0000**	1	**0.0000**
No	379 (32%)	22 (6%)	0.2(0.1–0.3)		0.3(0.2–0.4)	

PR = prevalence ratio.
[a] Adherence was quantified in percentages, taking the number of self-reported weeks of using the preventive measure divided by the number of weeks spent in malaria-endemic areas. We defined 100% as 'full adherence.'
[b] N,N-diethyl-*m*-toluamide (minimum use of 30%).
[c] Doxycycline, chloroquine, or a combination of various chemoprophylactic regimens.

vice-versa in preventing malaria [46], but did not take adherence into account. In our study, use of mefloquine was independently associated with full adherence when compared to other chemoprophylaxis, and mefloquine users were less likely to stop earlier during travel. A recent review likewise found that, although a similarly high percentage of adverse events were reported for both, more people reported to have stopped with mefloquine due to (perceived) adverse effects than with atovaquone/proguanil (5.5% vs 1.2%). Overal.compliance however was higher with mefloquine than with atovaquone/proguanil (81% vs 71%) [9]. In The Netherlands, atovaquone/proguanil was registered in 2000. Between 2000 and 2007, the number of mefloquine prescriptions decreased steadily, while atovaquone/proguanil prescriptions increased [47], making it now the most-frequently prescribed prophylactic. Although atovaquone/proguanil is much more expensive than mefloquine, especially for long-term travel, travelers often prefer atovaquone/proguanil because of the easier intake schedule before and after travel, and the reputation of mefloquine for adverse psychiatric effects. Mefloquine can indeed have adverse effects (abnormal dreams, anxiety, insomnia, and depressed mood), but atovaquone/proguanil also has these effects, though most occur with lower frequency [48,49]. Severe psychiatric adverse events are very rare, and mefloquine is generally well-tolerated compared to other chemoprophylaxis [9,50,51]. Screening travellers for psychiatric history before prescribing mefloquine is important to diminish its risk of severe adverse effects [51–53]. There is an ongoing discussion about the safety of mefloquine, and some researchers find it irresponsible to use this medicine for preventive purposes [54,55].

Although the study period ended in 2011 and malaria infections had been decreasing worldwide in the past 10 years [56], we believe the data are still worthwhile reporting as malaria is still the main cause of death from infections among travelers [2]. Also, disruption of services during the COVID-19 pandemic substantially impacted malaria prevention and control activities in sub-Saharan Africa. While international travel volumes are recovering, awareness of risks and access to affordable antimalarial chemoprophylaxis is more important than it has been in recent years [57]. Data on adherence to various preventive measures is scarce, especially data drawn from a relatively large and very comprehensive study among long-term travelers.

Our data should be interpreted with care, as most data were collected through self-reported weekly diaries. We chose weekly entries and weekly reminders instead of daily, assuming the weekly approach would be the most achievable. It could be more reliable for travelers using mefloquine, with its weekly intake schedule, but less reliable for travelers using other chemoprophylaxis or anti-mosquito bite prevention

with daily regimens, perhaps leading to underestimations in this group of travelers. Compared to travelers in general, our participants were motivated to visit a pre-travel clinic and participate in the study. Our participants are therefore likely to have been more adherent than travelers in general, which may have led to an overestimation of our estimates for adherence.

Because of better adherence profile and longer half-life compared to other prophylactics, mefloquine seems to be the most effective chemoprophylactic for long-term travelers. Travelers often refuse to try mefloquine because of alleged side effects, but their actual incidence is very low. Better education of travelers about predictors and risks of serious side-effects might increase mefloquine use, especially in experienced travelers, long-term travelers and travelers to Africa. Neither treatment abroad nor seroconversion were reliable predictors for exposure. It would be useful to find better methods to estimate the malaria risk in travelers, for example by collecting dried blood spots during travel. Also, qualitatively evaluating the behavior of long-term travelers could give more insight: in-depth interviews could help provide information about facilitators and barriers to following instructions provided at the pre-travel health clinic. *Pf*CSP antibodies are not suitable to reliably assess falciparum malaria exposure in travelers.

Authors contributions

FS data analysis and draft manuscript. FS, FO, and GvR inclusion of travelers, data collection, data cleaning and quality control, manuscript review; AM statistical advice and overview; manuscript review, MPG manuscript advice and review; MP data analysis and manuscript advice and review; MBBM laboratory assessments and manuscript review, GS study design and funding, manuscript review. All authors contributed to the writing and endorsed the final version of the manuscript submitted.

Disclosure

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Appendix A. Supplementary data

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