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Non-adherence to malaria prophylaxis: The influence of travel-related and psychosocial factors

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ABSTRACT

Background: The effectiveness of malaria chemoprophylaxis is limited by a lack of compliance in travellers. This study assesses the demographic, travel-related, and psychosocial determinants of non-compliance with chemoprophylaxis.
Methods: 715 adults, who received a pre-travel malaria prophylaxis prescription, were invited to complete a post-travel digital questionnaire on non-compliance, demographics, travel-related and psychosocial variables.
Results: 330 travellers (53% response) reported 32% non-compliance with malaria chemoprophylaxis. Logistic regression analyses revealed that 3/11 assessed psychosocial variables uniquely predicted non-compliance: 'negative attitude towards chemoprophylaxis' ($\beta = 0.694$, OR 2.0, $p < 0.01$), 'low perceived severity of malaria' ($\beta = 0.277$, $p = 0.04$) and 'fatigue during travel' ($\beta = 2.225$, OR 9.3, $p < 0.01$). Furthermore, the age and education of the traveller were uniquely predictive of non-compliance ($\beta = -0.023$ ($p = 0.02$) and $\beta = 0.684$ ($p = 0.04$)). None of the travel-related variables predicted non-compliance.
Conclusions: About one-third of the travellers in our study were non-compliant with malaria prophylaxis, especially young travellers and highly educated travellers. Fatigue during travel seems to lead to non-compliance. Further research should focus on addressing the psychosocial factors in pre-travel consultation, since these appear to be better predictors for intention to comply than travel-related variables.

Introduction

The number of travellers visiting tropical countries continues to rise, with a disproportionate increase in visits to areas where malaria transmission may occur [1,2]. Indeed, malaria is the most frequently imported preventable disease in international travellers [3,4]. More than 6000 cases of malaria were confirmed by the European Centre for Disease prevention and Control (ECDC) in 2014, of which 99.9% were travel-related [5]. The worldwide decrease in malaria incidence did not yet result in a decrease of travel-related cases [5]. Furthermore, compared to other travel-related diseases, malaria has a high mortality [6,7].

Malaria can be prevented effectively through protection against mosquito bites and through chemoprophylaxis [8]. In the Netherlands, atovaquone-proguanil and mefloquine are the most prescribed medications for chemoprophylaxis for travellers. Several studies demonstrate that malaria often occurs in travellers who do not use chemoprophylaxis, or who are not compliant to the prescribed regimen [9–13]. Indeed, non-compliance rates of malaria chemoprophylaxis are considerable, ranging from 11 to 38% in travellers [14–18].

A large number of studies has shown that non-compliance of malaria prophylaxis is related to demographic variables (e.g. a younger age), travel-related variables (e.g. destination or travel duration), as well as the type of chemoprophylaxis [8,14,15,19–24]. However, the impact of psychosocial or behavioural variables on non-compliance is a rather new field of interest. Until now, only a few studies have addressed psychosocial variables, and found that a low perceived susceptibility to contract malaria, a low perceived severity of malaria, and a negative social norm (negative peer advice) are related to non-compliance [16,25–27]. Thus far however, no studies have assessed demographic, travel-related

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and psychosocial variables together in relation to non-compliance using a quantitative approach.

Therefore, the purpose of this study was to, first, assess the proportion of travellers to risk areas for malaria who were non-compliant with chemoprophylaxis, and second, to determine which demographic, travel-related and psychosocial variables were related to non-compliance.

Materials and methods

Study setting

In the Netherlands, most regional Public Health Services (PHS) have a travel clinic for advice and vaccinations. These and other travel clinics in the Netherlands operate by using the guidelines of the Dutch National Coordination Centre for Travellers' Health Advice (LCR). At the time of study, malaria chemoprophylaxis was indicated for all high risk areas in Africa, Asia and the Americas. Atovaquone-proguanil (once daily), mefloquine (once weekly) and proguanil (once daily) were first choice prophylactic drugs [28]. After leaving the high risk area, continuation of the prophylaxis is advised for seven days (atovaquone-proguanil) or for 4 weeks (mefloquine and proguanil).

Study design and data collection

Five PHS travel clinics in the eastern part of the Netherlands participated in this study. Through a cross-sectional design, all clients who were prescribed malaria chemoprophylaxis according to the LCR-guidelines were asked to participate if they were 16 years or older. If they agreed, participants received pre-travel information by e-mail, stating that the study was about their health and health behaviour during travel in general, to prevent influencing their intention to comply to the chemoprophylaxis regimen. Age and sex were recorded for non-responder analysis. About four weeks post-travel, participants were invited to fill out an online questionnaire (via www.formdesk.nl). For non-responders, a reminder e-mail was sent after 7 and 14 days. The data were collected between November 2014 and October 2015. Travellers who eventually did not visit a high risk area, were excluded from further analysis (n = 11). The final sample for analysis consisted of 330 travellers (54% female, Mean age 41.8 years, SD = 16.3 years).

Measures

Non-compliance

Compliance with the chemoprophylaxis regimen was recorded retrospectively by self-reported use. Participants were considered 'compliant' to chemoprophylaxis if they reported to have taken 100% of their prescribed tablets. All other participants were classified as 'non-compliant'. Non-compliant travellers were asked whether they stopped deliberately.

Demographic and travel-related variables

The questionnaire contained three demographic and seven travel-related variables (including type of prophylaxis). Visited countries were grouped in three continental regions: Africa, Asia, and the Americas (see Table 1). For logistic regression analysis, nominal variables (education, continent and type of prophylaxis) were recoded into dichotomous variables.

Psychosocial variables

Several social cognitive models are available to identify beliefs, attitudes, and behavioural intentions, which are predictive of health behaviour [15,24,29,30]. For the current research, we based our choice of psychosocial variables on the Health Belief Model (HBM). In particular we included questions on risk perception (susceptibility and severity) and risk evaluation (benefits, perceived barriers and costs) [29,31]. Moreover, we based items on variables included in the Reasoned Action Approach (RAA), in particular on items measuring affective and cognitive attitudes, and social norms [30,32]. These variables have been shown to predict intentions to perform a certain behaviour, which in turn is associated with actual behavior [30]. For a full overview of all questions and the constructs derived from them, consult Table S1 in the Supplemental Materials.

Data analysis

Data were entered and analysed using IBM SPSS statistics version 19. We computed sum scores for all (psychosocial) variables, based on Cronbach's alpha or Pearson's correlation; see Table S1. In order to create a positive relationship with *non*-compliance, positively worded items were reversed-scored. Non-compliance was computed retrospectively and based on self-reported compliance, used for the analysis of demographic, travel-related and psychosocial variables, and used as an outcome variable in multivariate logistic regression analysis.

Ethical approval

In accordance with the 1964 Helsinki declaration and its later amendments, written consent was obtained from all participants and opting-out was possible at all times. Approval from the local Board of Medical Ethics was not obligatory (confirmed by the Board of Medical Ethics of the Radboud University Medical Centre, file number 2014–1345), as this study was not subject to the Law of Medical Scientific Research (WMO).

Results

Descriptives

Study population and non-responders

Between December 2014 and October 2015, 715 travellers were sent a pre-travel digital questionnaire, of which 53% were filled out (see Fig. 1). Non-responders (n = 318; 47%) were more often male ($p < 0.01$) and younger ($p < 0.01$).

The study population had an average age of 42 years, 46% of the respondents were men, and 64% was highly educated. The most visited continent was Africa (visited by 58%) and the mean total travel duration was 24 days. 86% of respondents used atovaquone-proguanil as chemoprophylaxis.

Non-compliance

The overall non-compliance of the 330 included travellers was 32%. Of all non-compliant travellers (n = 107), 15 travellers (14%) never started taking prophylaxis, and 39 travellers (36%) stopped deliberately taking the prophylaxis, although 20 of 39 travellers stopped after leaving the high-risk area.

Differences between compliant and non-compliant travellers

Demographic and travel-related variables

When comparing the demographic and travel-related variables between compliant and non-compliant travellers, we found significant differences between the two groups. Non-compliant travellers were significantly younger (mean 38 years old) than compliant travellers (mean 44 years old) (t (328) = 3.37, $p < 0.01$). Further, they were higher educated ($t = 2.130$, $p = 0.03$) and had a significantly longer travel duration (mean 32 days) than compliant travellers (mean 20 days; t (133) = 3.81, $p < 0.01$). Further,

Table 1
Descriptives of and differences between compliant and non-compliant travellers on demographic and travel-related variables.

	Compliant travellers (n = 223)	Non-compliant travellers (n = 107)	Differences between groups
Demographics	**Mean (95%CI)**	**Mean (95%CI)**	
Age (years)	44 (42–46)	38 (35–41)	$t = -3.37$, $p < 0.01$
	N (%)	**N (%)**	
Gender			$X^2 = 0.005$, $p = 0.95$
Male (n = 152)	103 (68%)	49 (32%)	
Female (n = 178)	120 (67%)	58 (33%)	
Education			$t = 2.13$, $p = 0.03$
Low (n = 18)	15 (83%)	3 (17%)	
Middle (n = 101)	73 (72%)	28 (28%)	
High (n = 210)	135 (64%)	75 (36%)	
Travel factors	**Mean (95%CI)**	**Mean (95%CI)**	
Travel duration (days)	20 (18–22)	32 (26–38)	t = 3.811, $p < 0.01$
	N (%)	**N (%)**	
Continent			
Africa (n = 189)	144 (76%)	45 (24%)	$\chi^2 = 15.37$, $p < 0.01$
Asia (n = 107)	62 (58%)	45 (42%)	
The Americas (n = 32)	16 (50%)	16 (50%)	
Duration of stay in high risk area			
<1 week (n = 73)	47 (64%)	26 (36%)	t = 0.77, p = 0.44
1–2 weeks (n = 165)	121 (73%)	44 (27%)	
>2 weeks (n = 91)	55 (60%)	36 (40%)	
Purpose of travel			
Tourism, independent (n = 138)	86 (63%)	52 (38%)	$\chi^2 = 3.63$, $p = 0.30$
Tourism, organised (n = 100)	70 (70%)	30 (30%)	
Business or education (n = 57)	43 (75%)	14 (25%)	
Visit friends/relatives (n = 34)	24 (71%)	10 (29%)	
Travel style			
Hotels (n = 168)	117 (70%)	51 (30%)	$\chi^2 = 0.73$, p = 0.87
Hostels or pensions (n = 94)	60 (64%)	34 (36%)	
With locals (n = 50)	34 (68%)	16 (32%)	
Camping (n = 17)	12 (71%)	5 (29%)	
Malaria prophylaxis			
Atovaquone-proguanil (n = 283)	206 (73%)	77 (27%)	$\chi^2 = 12.03$, p < 0.01
Mefloquine (n = 25)	16 (64%)	9 (36%)	
Paludrine (n = 6)	1 (17%)	5 (83%)	
Doxycycline (n = 1)	0 (0%)	1 (100%)	
No prophylaxis started (n = 15)	0 (0%)	15 (100%)	
Previous use of prophylaxis			
No, never (n = 168)	115 (69%)	53 (32%)	$\chi^2 = 0.099$, p = 0.95
Yes, once/more than once (n = 160)	107 (67%)	53 (33%)	

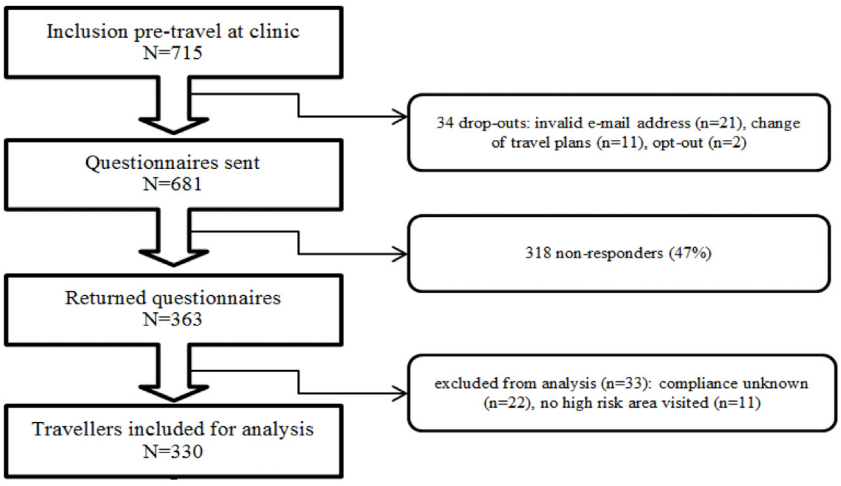

Fig. 1. Inclusion flow chart.

of the non-compliant travellers, only 43% visited Africa, compared to 65% of compliant travellers ($\chi^2 = 15.37$, $p < 0.01$). Finally, non-compliant travellers used atovaquone-proguanil less often: 72% versus 92% of compliant travellers used this chemoprophylaxis ($\chi^2 = 44.10$, $p < 0.01$). See Table 1 for an overview of all results.

Psychosocial variables

Comparing non-compliant with compliant travellers revealed that there were significant differences in t-tests for seven of the psychosocial variables. Specifically, non-compliant travellers reported higher scores on: negative social norm of local peers (t (164) = 4.418, $p < 0.01$), a negative cognitive attitude towards

Table 2
Descriptives of and difference between compliant and non-compliant travellers on psychosocial variables.

	Compliant travellers (n = 223)	Non-compliant travellers (n = 107)	Differences between groups
Psychosocial factors	Mean sumscore (SD)	Mean sumscore (SD)	
Negative social norm (0–2)	0.33 (0.55)	0.69 (0.74)	$t = 4.418$, $p < 0.01$
Negative cognitive attitude (0–2)	0.28 (0.51)	0.65 (0.67)	$t = 5.045$, $p < 0.01$
Low perceived severity (2–8)	4.35 (1.15)	4.64 (1.04)	$t = 2.209$, $p = 0.03$
Low perceived susceptibility (2–8)	4.96 (1.53)	5.39 (1.34)	$t = 2.474$, $p = 0.01$
Affective attitude: fear for adverse events (1–4)	1.95 (1.03)	2.29 (1.12)	$t = 2.672$, $p < 0.01$
Affective attitude: dislike taking pills (1–4)	2.05 (1.17)	2.27 (1.19)	$t = 1.600$, $p = 0.11$
Behavioural control: financial barriers (2–4)	3.15 (0.79)	3.19 (0.90)	$t = 0.353$, $p = 0.72$
Behavioural control: adverse events (0–18)*	0.41 (0.93)	0.63 (1.35)	$t = 1.507$, $p = 0.13$
Behavioural control: fatigue (1–4)	1.01 (0.12)	1.18 (0.53)	$t = 3.175$, $p < 0.01$
Behavioural control: illness (1–4)	1.51 (1.05)	1.96 (1.28)	$t = 3.169$, $p < 0.01$
Did not use reminder (1–4)	2.73 (1.35)	2.79 (1.33)	$t = 0.343$, $p = 0.73$

Note: *75% of respondents did not experience any effects; the maximum number of reported side effects was 7.

prophylaxis (t (154) = 5.045, $p < 0.01$), a low perceived severity of malaria (t (328) = 2.209, $p = 0.03$), a low perceived susceptibility to contract malaria (t (328) = 2.474, $p = 0.01$), a fear for adverse events (t (193) = 2.672, $p < 0.01$), fatigue during travel (t (111) = 3.175, $p < 0.01$) and illness during travel (t (177) = 3.169, $p < 0.01$). On the other four psychosocial variables, the two groups did not differ; t's <1.6 and p's >0.10. For a full overview of the differences between groups, see Table 2.

Variables influencing non-compliance

Only variables with a significant correlation with non-compliance ($p < 0.05$) were included in this analysis. For Pearson's correlations, see Table S2 in the Supplementary materials. The logistic regression analysis contained three models: model 1, which contained only psychosocial variables; model 2, which contained psychosocial and travel-related variables; and model 3 which contained psychosocial, travel-related and demographic variables. We used the enter-method, with non-compliance (coded 0 = compliant; 1 = non-compliant) as the outcome variable. All results are listed in Table 3, with OR and 95% CI of all significant variables.

This analysis revealed that the unique predictors of non-compliance in the final model (i.e. model 3) were: A younger age of the traveller ($\beta = 0.023$, $p = 0.02$, OR 0.98, CI [0.96–1.00]); a high education ($\beta = 0.684$, $p = 0.04$, OR 1.98, CI [1.0–3.8]), a negative cognitive attitude towards prophylaxis ($\beta = 0.694$, $p = 0.01$, OR 2.0, CI [1.2–3.3]); a low perceived severity of malaria ($\beta = 0.277$, $p = 0.04$, OR 1.3 CI [1.0–1.7]); and fatigue during travel ($\beta = 2.225$, $p < 0.01$, OR 9.3 CI [2.1–39.9]). For a full overview of all results, see Table 3.

Discussion

The aim of the current research was to assess the level of non-compliance with malaria chemoprophylaxis among travellers from the Netherlands, and to identify which demographic, travel-related, and psychosocial variables were related to non-compliance. The results showed that the level of non-compliance of malaria prophylaxis was 32%, and that a young age, a high education, a negative attitude towards chemoprophylaxis, a low perceived severity of malaria, and fatigue during travel were associated with increased odds for non-compliance with malaria chemoprophylaxis.

The proportion non-compliance in our study (32%) appears to be in line with proportions reported in similar studies (11–38%). However, the more recent studies demonstrate lower proportions of non-compliance as compared to older studies [14–18]. This might be due to increased use of atovaquone-proguanil (with fewer adverse events) in recent studies as compared to older studies [16,17]. Thus, our observed proportion of 32% is actually a rather worrisome outcome, as 86% of our subjects used atovaquone-proguanil.

Our study is among the first to assess the relationship between demographic, travel-related and psychosocial variables with non-compliance. Further, we made sure the travellers were unaware of the subject of the study during travel, to prevent socially desirable behaviour. As well as previous studies reported [15,21,23,24], we found an association between non-compliance and travel-related factors: the duration of travel, the visited continent and the type of malaria prophylaxis were related to non-compliance. However, in the multivariate model, this association became insignificant. An explanation can be that travel-related factors are not predictive themselves, but reflect a certain type of traveller, with a certain attitude towards the prevention of malaria.

Psychosocial variables that have been found to be related with non-compliance in previous research, are mainly the individuals' perceived susceptibility to contract malaria, the perceived severity of malaria, and a negative social norm of local peers towards using malaria prophylaxis [16,26,27,33]. These variables differ between compliant and non-compliant travellers in the univariate analysis of the current study as well. In addition, non-compliant travellers had a more negative cognitive attitude towards chemoprophylaxisand more fear for adverse events than compliant travellers. However, in the multivariate logistic regression analysis, a low perceived severity of malaria was found to be an unique significant predictor of non-compliance together with an individuals' (negative) cognitive attitude towards chemoprophylaxis. Unexpectedly, experiencing fatigue during travel was an unique predictors of non-compliance.

Of the demographic variables, our data demonstrated that a young age and a high education are predictive of non-compliance, which is in line with previous findings in the literature [14,19,34,35]. With regard to travel-related factors, previous studies have described that visiting moderate risk areas in Asia and the Americas were major risk factors for non-compliance [8,13,16,36]. Visiting such areas might, in turn, be related to a negative local peer advice against using malaria prophylaxis [16]. However, although we did find differences between compliant and non-compliant travellers and the visited continent, as well as their perceptions of a negative social norm of local peers, both variables did not show to be unique predictors in the multivariate logistic regression analysis predicting non-compliance.

Even though a traveller has the intention to comply, several barriers encountered during travel could lead to non-compliance. Barriers described in literature are adverse events, forgetfulness, the cost of prophylaxis, and disliking the tablets [16,23,26]. Of those factors, we studied financial barriers, adverse events, and disliking to take pills, but none of these showed a relation with non-compliance. However, we found that 'fatigue' is a significant physical barrierwith a negative impact on the likelihood of being

Table 3
Logistic regression models. Model 1: Psychosocial variables; Model 2: psychosocial and travel-related variables; Model 3: psychosocial, travel-related and demographic variables.

	Model 1		Model 2		Model 3	
Determinant	B (*p*-value)	OR (95%CI)	B (*p*-value)	OR (95%CI)	B (*p*-value)	OR (95%CI)
Negative social norm	0.595 (<0.01)	1.8 (1.2–2.8)	0.444 (0.07)		0.403 (0.10)	
Negative cognitive attitude	0.752 (<0.01)	2.1 (1.4–3.3)	0.676 (<0.01)	2.0 (1.2–3.2)	0.694 (<0.01)	2.0 (1.2–3.3)
Low perceived severity	0.263 (0.04)	1.3 (1.02–1.7)	0.256 (0.05)		0.277 (0.04)	1.3 (1.0–1.7)
Low perceived susceptibility	0.175 (0.08)		0.108 (0.30)		0.146 (0.18)	
Fear for adverse events	0.060 (0.66)		−0.028 (0.85)		−0.053 (0.72)	
Fatigue	1.878 (<0.01)	6.5 (1.8–24.4)	2.045 (<0.01)	7.7 (2.0–29.6)	2.225 (<0.01)	9.3 (2.1–39.9)
Illness	0.249 (0.03)	1.3 (1.0–1.6)	0.197 (0.12)		0.187 (0.15)	
Travel duration			0.015 (0.04)		0.012 (0.13)	
Continent [1)]			0.194 (0.54)		0.163 (0.61)	
Type of prophylaxis [1)]			0.647 (0.17)		0.845 (0.08)	
Age					−0.023 (0.02)	0.98 (0.96–0.997)
Education [1)]					0.684 (0.04)	1.98 (1.04–3.8)
Nagelkerke R^2	0257		0263		0296	
Cox&Snell R^2	0183		0183		0206	
−2 Log likelihood	334,913		303,894		295,172	
Chi-square	64,902		62,126		70,848	

1) For multivariate logistic regression analysis, dummy variables have been made for the variables 'Continent'(Africa versus other continents), 'type of prophylaxis' (atovaquone-proguanil versus other prophylaxis) and 'education' (high versus middle or low), in order to create dichotomous variables.

compliant to the prophylaxis. This might be due to perceptions that the chemoprophylaxis will cause or increase this fatigue. To our knowledge, no other study has addressed this specific barrier.

Limitations

As with any cross-sectional research, one should be cautious in the interpretation of the results and in drawing causal conclusions. Moreover, we had to rely on self-report of compliance, which is the most common and feasible method for assessing compliance with medication or prophylaxis. However, this method can be prone to recall bias and social desirability bias. We have tried to prevent such bias by revealing the actual subject of the study at the moment the post-travel questionnaire was sent, four weeks after the traveller's return to The Netherlands. However, this long period of time between travel and filling out the questionnaire might have increased recall bias, since travellers may not have been attentive to their compliance until they received the questionnaire.

The questionnaire was completed by 53% of the travellers we contacted. Additional inspection of the data indicated that non-responders were younger than responders, and more likely to be male. In our study, as well as in other studies, a younger age was a significant predictor of non-compliance [18,19,35]. This could have influenced our results. The gender-difference between responders and non-responders is regarded as not relevant, since it is not related to non-compliance [23].

It is well known that malaria is often diagnosed in people who travel to visit relatives in malaria-endemic countries [7,26,37–40]. In our study, as well as in other studies, travellers visiting friends & relatives (VFR) did not differ in their non-compliance from the other travellers. We assume that a substantial part of the VFR do not visit a travel clinic pre-travel, and therefore this group is under-represented in our study. A second risk group that does not visit a travel clinic before departure, are last-minute travellers. Non-compliance is known to be high among these travellers [7,39]. This group is probably also underrepresented in our study sample. When the VFR and last-minute travellers are significantly underrepresented, the true non-compliance in Dutch travellers might be underestimated in this study.

Implications and suggestions for future research

This study has shown that psychosocial variables are more important when predicting non-compliance than travel-related variables. Future research must address the mutual relationship between certain psychosocial variables, e.g. one's attitude, and demographic variables (age, education) or travel-related variables (e.g. adventurous travel).

Assuming that the intention to comply is in part based on psychosocial variables, further research should assess the possibility of increasing travellers' positive attitude towards compliance with, and importance of chemoprophylaxis. Furthermore, the actual severity of malaria seems to be underestimated by non-compliant travellers. This is a challenge for travel medicine to investigate and improve. Specifically, given the influence of some of the demographic variables on compliance, one can think of developing tailored (e.g, age-differentiated) health promotion materials.

Conclusion

Demographic and psychosocial factors can be important predictors of non-compliance, whereas in the current research, travel-related variables factors were not related to non-compliance. The intention to use the chemoprophylaxis as prescribed is, according to our results, related to the age and education of the traveller, and to the personal attitude towards chemoprophylaxis and to the perceived severity of malaria. Furthermore, fatigue of the traveller was an important physical barrier leading to non-compliance. This knowledge can be of use for further research on how to improve pre-travel counselling, in order to increase the intention of the traveller to use the chemoprophylaxis as prescribed.

Author contributions

J. Hoefnagel and J. Hautvast designed the study and wrote the study protocol. J. Hoefnagel collected the data under supervision of J. Hautvast. The data were analysed and interpreted by all authors. The draft of the manuscript was written by J. Hoefnagel. All authors contributed to, and approved of, the final manuscript.

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Competing interests

None declared.

Ethical approval

Not required.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jiph.2019.10.004.

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