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Research Article

Non-Adherence to Malaria Chemo-Prophylaxis in Travelers: Mind to the Care Gap!

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Abstract

Background: Travelers are at risk of contracting malaria when moving to endemic areas. Yet, despite effective malaria chemoprophylaxis, imported cases of malaria still occur worldwide. Indeed, some studies have shown a varied adherence level; consequently, a traveler care gap could occur.

Methods: A prospective cohort study was carried out in 2017 to evaluate the rate of malaria chemoprophylaxis adherence among Spanish travelers.

Results: A post-travel questionnaire was completed by 402 travelers to malaria endemic areas that were prescribed chemoprophylaxis: 67 (16.7%) did not take any dose of chemoprophylaxis and 41 (10.2%) had not even carried it while travelling abroad. The adherence of chemoprophylaxis was 68,7% of travelers, being statistically different according to travel duration, onset of adverse events and type of drug prescribed. The non-adherent travelers reported not continuing with administration mainly because of forgetfulness, fear of side effects and low perceived risk because itinerary changes.

Regarding the onset of the medication's secondary adverse events, one in three (35.2%) reported at least one, being more frequent among patients that took mefloquine than atovaquone-proguanil (p=0.01). The main adverse events reported by chemoprophylaxis users were gastrointestinal or sleeping disorders.

Conclusions: The suboptimal compliance of chemoprophylaxis is a major lost opportunity to achieve malaria prevention, so it is an important contributor to the traveler care gap.

INTRODUCTION

According to the World Health Organization (WHO) World Malaria Report of 2017, there were about 216 million cases of malaria estimated in 2016, with less than half a million of deaths [1]. As is known, travelers represent a selected population at risk when moving to endemic zones, such as large areas of Africa, Latin America, Asia (including South Asia, Southeast Asia, and the Middle East), and the South Pacific [2].

The care taken by travelers to avoid malaria could present some gaps which may be explained by sub-optimal patient access to a travel clinic; non-prescription of proven chemoprophylaxis when needed; poor adherence to chemoprophylaxis, and inadequate diagnosis of the presence of malaria overseas or in developed countries [3]. Adherence to prevention strategies such as avoiding mosquito bites and to chemoprophylaxis are keys components of success in preventing malaria in travelers [4], as well as to reduce imported malaria infections in countries of origin and transit [5]. Nevertheless, compliance with protective measures amongst travelers is still sub-optimal [6,7], embodying a substantial, well-recognized global public health problem sustained by an important avoidable rate of malaria among people travelling abroad. This is also associated with mortality and increased health-care expenses [8-11]. Such a poor level of adherence to malaria chemoprophylaxis may be influenced by several factors: lack of knowledge about the disease, low risk perception, onset of secondary adverse effects, the long duration of treatment or the travel characteristics. These could differ markedly according to the traveler's country of origin [12].

Malaria chemoprophylaxis adherence demands perseverance and is a mutually agreed component in the traveler-provider covenant, following professional indication, recommendation and prescription of evidence-based therapy. In contemporary traveler-centered care, a concordant understanding of indication, prescription and consent of the risks and benefits of possible malaria chemoprophylaxis are highly desired outcomes of the bilateral discussion between professionals and travelers as they seek a mutually determined malaria prevention strategy. In the short term, the compliance components of adherence refer to travelers' understanding and commitment to specific indication, or prescription requirements [13].

Some studies about malaria prevention were conducted in the airports and consisted of a questionnaire with no subsequent follow-up of any type. One of these studies conducted in our region [14] showed that 34.8% of travelers carried antimalarials, but no idea about adherence.

The adherence of malaria chemoprophylaxis could vary across the evidence [12], also depending on adherence definition. Much of the literature defines malaria chemoprophylaxis adherence in terms of whether all pills were taken as prescribed (63-89%) [15-19]. Adherence to chemoprophylaxis (CP) was defined in previous studies as travelers who took at least 75% of their prescribed pills during their stay; and non-adherence to those who took less than 75% [16,20].

Although recommendations for the length of chemoprophylaxis course have been defined, for some medication there is contention over what proportion of a recommended chemoprophylaxis course is necessary to provide detection [21].

The main reasons for non-adherence include forgetfulness, fear of side effects, low perceived risk, even related to unseen flying mosquitoes [20]; or high cost of provider visits and chemoprophylaxis, and cultural barriers [22].

In this research field, despite the presence of some information available addressing travelers' adherence to chemoprophylaxis, an in-depth knowledge of this issue is of special relevance, in particular regarding changes over time. Furthermore, current literature on this subject is still lacking in our region.

Therefore, the goals of this prospective cohort study were to assess the level of adherence towards chemoprophylaxis among travelers, highlighting the main predictors.

METHODS

Study design and setting

Travelers who consecutively attended a travel clinic and were travelling to countries with endemic malaria were invited to participate in a prospective cohort study about their adherence to malaria chemoprophylaxis.

Travelers who had completed their journey after the 31st of December 2017 were excluded from the study. The information was gathered by two questionnaires: one that was completed face-to-face prior to the trip and during the medical visit *(baseline questionnaire)* and another that was completed by phone or email from 3 to 4 weeks after the expected return date *(post-travel questionnaire).*

The study was conducted at the Travel Health Clinic at the Hospital Universitari de Bellvitge (HUB), in Barcelona, Spain.

Participants

Travelers seeking medical advice at the travel clinic, between January 2017 and December 2017, before travelling to areas with endemic malaria, who agreed to participate in the study and to be contacted after their trip, were included. Exclusion criteria were as follows: aged younger than 3 years, people not travelling to areas with endemic malaria or finally not travelling anywhere, patients with contraindications to the chemoprophylaxis (in particular people with severe renal impairment [creatinine clearance <30 mL/min], pregnant women, women breastfeeding infants weighing <5kg, or a history of hypersensitivity to antimalarial drugs), patients that receive chemoprophylaxis and stand-by emergency treatment for the same travel, and patients refusing chemoprophylaxis prescription or not willing to participate in the study. Those individuals included were asked to provide their phone numbers and email addresses, for the follow-up purpose of this research. Involvement was voluntary, and no incentives were offered to complete it. Travelers were informed that all information gathered would be anonymous and that confidentiality would be maintained by omitting any personal identifying information from the analysis. A written informed consent was obtained, and the Institutional Review Board of HUB granted approval for carrying out this research.

Participants were provided with information about malaria and its preventive measures; they were also instructed in how/when to self-administer chemoprophylaxis. Depending on the travelers' characteristics, type of journey and a bilateral decision between traveler and provider [23], the participants were prescribed atovaquone 250 mg and proguanil 100 mg, mefloquine 250 mg, or doxycycline 100 mg. Implementation of other interventions to avoid mosquito bites, such as a mosquito net, repellent and appropriate clothes, were also recommended.

Research instruments and outcomes measures

For the purpose of this survey-based prospective cohort study, two structured administered questionnaires were designed, as baseline and post-travel surveys.

The pre-travel questionnaire, completed face-to-face during the pre-travel medical visit, assessed the socio-demographic characteristics of the participants, which were collected as follows: age, gender, self-reported medical history, and information about travel, such as destination and duration. The previous use of anti-malarial drugs and if participants had ever experienced adverse effects were also investigated.

The post-travel information was gathered by an online questionnaire, which was delivered to all participants via professional online survey software (Google® Forms), between 3 and 4 weeks after the expected returns. All travelers received an email inviting them to complete the survey, accessible via an embedded URL link. Non-respondents received a reminder 2 weeks later. A clear preliminary statement provided information to the cohort about the study and instructions, and also allowed participants to confirm their own informed consent to carrying out the survey. The second research instrument, designed for capturing information about participants' compliance with and behaviors towards chemoprophylaxis, comprised a question whether travelers had gone to the pharmacy to buy the CP and if they have carried anti-malarial medication during their travel abroad. According to National Health Service CP prescription is a part of it, so once the traveler is attended in our Travel Clinic he has the prescription to buy the CP and the maximum cost to pay for it is the 40% of its price. On the other hand, we have verified if patients had gone to the pharmacy to collect it by informatics traceability of prescription. If participants answered "Yes, I have carried my anti-malarial medication", they were invited to provide information regarding self-administration of the prescribed prophylaxis. This included how long patients took the drugs, when they started and finished, if any adverse effects were experienced, and if chemoprophylaxis was suspended before the indicated period and why (cost, disbelief in efficacy, concern of side effects, forgetfulness, or misunderstanding about how and

when to take it). If participants answered "No, I have not carried my anti-malarial medication", they were invited to provide information regarding main reasons to it.

Both questionnaires were pre-tested and piloted with a convenience sample of 25 travelers similar to the study population, who were asked for their feedback of surveys acceptability in terms of length, clarity, and question format. Based on these suggestions, some minor revisions included changes to the questionnaire items wording and format. After collection, data were automatically stored in an electronic spreadsheet and were cleaned in order to reduce the risk of measurement error.

Statistical analysis

The statistical analysis was carried out using Stata version 13 [24] statistical software and consisted of two phases: descriptive and inferential analysis according to normal distribution studied by the Kolmogorov-Smirnov test.

Chi-square (χ^2) or Fisher's exact tests were used to assess differences between categories when needed; the Mann-Whitney U test was used to assess differences between independent means between participants who complied or did not comply. Univariate analyses were also conducted to determinate the effects on the travelers' suspension of chemoprophylaxis of the following independent variables: gender, age, prescribed chemoprophylaxis drugs, duration of travel, and the onset of adverse effects. Subsequently, these independent and uncorrelated variables were included in a mutually adjusted multivariate logistic regression model. Results were reported as odds ratios (ORs) and 95% confidence intervals (CIs).

All inferential tests were performed with significant statistical levels for *p*-values equal to or less than 0.05.

RESULTS

Of 1,025 travelers who attended the Travel Medicine Clinic of the HUB from January to December 2017, there were 869 (84,8%) that accepted to participate, finally travelled to endemic malaria areas and were prescribed only chemoprophylaxis. In fact, there were 32 (3.1%) travelers did not accept to participate, 68 (6.9%) did not go to malaria endemic areas, and 56 (5.6%) were prescribed with chemoprophylaxis and Stand-By Emergency Treatment (SBET). Selected characteristics of the overall study participants are presented in Table 1 and a flow-chart of the number of participants in the study was designed in Figure 1. Slightly more than half of the participants were female (n=494, 56.5%) and the mean age was 35.6 years (SD 13.0). There were 10.6% (n=92) of participants who reported pre-existing medical conditions and 16.7% (n=145) also declared regular medication consumption, with contraceptive (5.8%), antihypertensive (1.9%) and thyroid hormones (1.3%) as the most frequently used drugs.

Less than a fifth of the sample (n=155, 17.8%) had previously used antimalarial chemoprophylaxis in previous travels and 42 (27.1%) of these also reported adverse effects: most complained of symptoms that were gastrointestinal (mainly nausea and gastric pain or discomfort) and sleep disorders.

Regarding travel information, the vast majority of the study population travelled for a mean of 21.5 (SD 15.3) days to Africa (n=634, 73.0%), with Kenya (n=162, 18.6%), Senegal (n=93, 11.3%), and Tanzania (n=104, 12.0%) as the most popular destinations. Another group of patients (n=156, 17.9%) travelled to Asia, mainly to the south-eastern part of the continent (with Indonesia as the most visited destination, n=80, 9.2%). The remaining 79 subjects (9.1%) had planned to go to Central and South America.

Of the recruited participants, 402 completed the post-travel online survey for an overall response rate of 46.3%. The exact number of pills prescribed was available for 393 (97.88%) of 402 participants.

Regarding travelers that were prescribed CP alone, without SBET, 83.3% of them (n=335) took at least one dose being accurate its intake in 68.7% (n=230). However, 31.3% (n=105) of travelers prescribed CP did not take at least 75% of medication prescribed and were defined as non-adherent.

Table 1: Characteristics of study population (n=869).

	All sample (*n = 869*)	**Responders (*n = 402*)**	**Non responders (*n = 467*)**	**Comparison between groups (*p*)**
Gender *Male* *Female*	 375 (43.2%) 494 (56.5%)	 182 (45.3%) 220 (55.6%)	 193 (41.3%) 341 (56.9%)	*0.32*
Age°	35.6 ± 13.0 (3-77)	36.4 ± 13.1 (4-77)	34.9 ± 13.0 (3-75)	*0.01*
Area of destinations *Africa* *Asia* *Central and South America*	 634 (73.0%) 156 (17.9%) 79 (9.1%)	 300 (74.6%) 64 (15.9%) 38 (9.5%)	 334 (71.5%) 92 (19.7%) 41 (8.8%)	*0.71*
Duration of travel (in days)°	21.6 ± 14.9 (5-185)	20.9 ± 14.3 (5-96)	21.6 ± 15.1 (5-185)	*0.02*
Previous use of anti-malaria drugs	161 (18.5%)	79 (19.7%)	82 (17.6%)	*0.51*
Prescribed prophylaxis *Atovaquone/proguanil* *Mefloquine* *Doxycycline*	 800 (92.1%) 60 (6.9%) 9 (1.0%)	 373 (92.8%) 25 (6.2%) 4 (1.0%)	 427 (91.4%) 35 (7.5%) 5 (1.1%)	*0.13*

° Variables summarized by mean ± standard deviation (SD), and range.

No statistically significant differences were found between the adherent and non- adherent groups' characteristics, except for the duration of travel with the adherent participants travelling for less time than the non- adherent population (Table 2).

The non-adherent travelers to CP (n=105) reported not continuing with administration mainly because of the onset of adverse effects, concern about these effects and disbelief in efficacy (n=86, 81,9%); or because they forgot to keep taking the medication after their return (i.e., forgetfulness) (n=16, 15,2%); or because they changed the route of the voyage (i.e., the concern of adequate malaria chemoprophylaxis prescription according to final destination) (n=3, 2,8%). The odds of non-adherence were higher in the group prescribed with mefloquine compared with participants who were prescribed with other regimens (OR=3.13; 95% IC 1.09 - 10.12). In the adjusted multivariate analysis, the risk of non-adherence was 3 times higher in the mefloquine group than the other groups, if the traveler presented at least one adverse effect; in addition, there was a 3% higher risk of discontinuation per day of travel duration, independently of age and gender (Table 3).

One in three (35.2%) travelers that took at least one dose of CP (n=335) reported any adverse events, being significantly higher among patients that took mefloquine than atovaquone-proguanil (p=0.01). On the other hand, among subjects who reported a drug-related adverse event, the mean number of adverse event (±SD) per subject was 1.2±0.7 for subjects while receiving atovaquone-proguanil and 2.1+-1.9 for subjects while receiving mefloquine (p<0.05). The main adverse events reported by chemoprophylaxis users were gastrointestinal or sleeping disorders. Sleeping disorders were found more

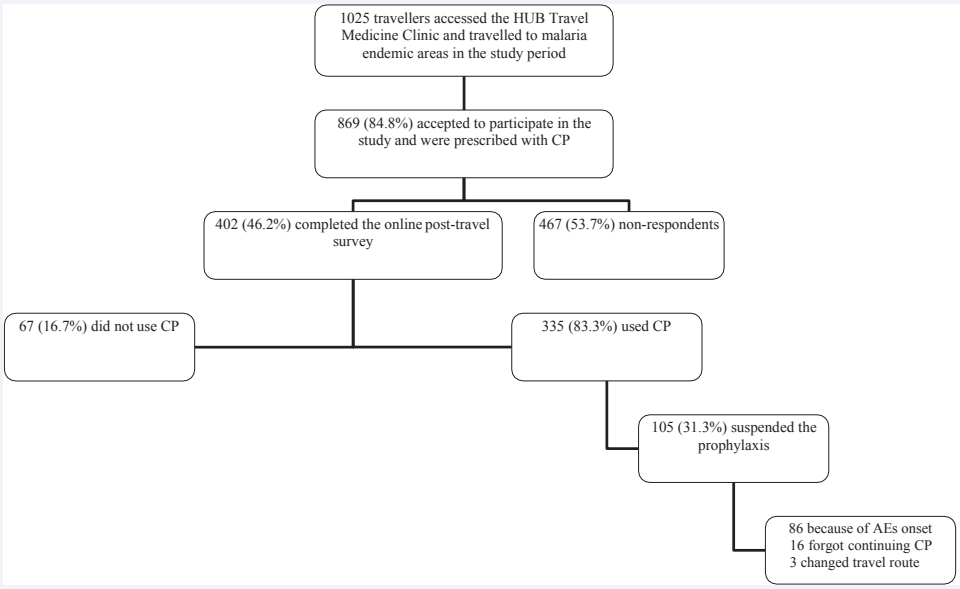

Figure 1 Flow-chart of number of participants in the study.

Table 2: Characteristics of chemoprophylaxis users by adherence (n=335).

	All group (*n = 335*)	Adherent group (*n = 230*)	Non adherent group (*n = 105*)	Comparison between groups (*p*)
Gender *Male* *Female*	 150 (44.9%) 185 (55.1%)	 102 (44.3%) 128 (55.7%)	 51 (48.7%) 54 (51.3%)	*0.60*
Age°	36.6 ± 13.5 (4-76)	37.0 ± 13.7 (4-76)	33.7 ± 12.5 (12-76)	*0.16*
Area of destinations *Africa* *Asia* *Central and South America*	 253 (75.5%) 54 (16.1%) 28 (8.4%)	 177 (77.0%) 35 (15.3%) 18 (7.6%)	 70 (66.7%) 22 (20.5%) 13 (12.8%)	*0.35*
Duration of travel (in days)°	20.5 ± 14.6 (5-93)	19.5 ± 12.8 (5-95)	26.1 ± 22.2 (5-93)	*0.01*
Previous use of anti-malaria drugs	72 (21.5%)	48 (20.8%)	27 (25.6%)	*0.63*
Prescribed prophylaxis *Atovaquone/proguanil* *Mefloquine* *Doxycycline*	 315 (94.1%) 18 (5.5%) 2 (0.4%)	 219 (95.3%) 10 (4.3%) 1 (0.4%)	 92 (87.2%) 13 (12.8%) 0 (0.0%)	*0.09*

° Variables summarized by mean ± standard deviation (SD), and range.

frequently in travelers prescribed with mefloquine (26.0% vs. 7.7%, p<0.05). Table 4 shows the adverse events reported by travelers, according to the prescribed prophylaxis. Doxycycline was indicated and taken by 4 travelers who did not complain any adverse events. Neither hospitalization nor emergency visits due to adverse events were reported.

To the best of our knowledge, no cases of malaria were observed in the sample.

DISCUSSION

First, it is worth emphasizing that, predictably, the 73.7% of enrolled subjects, for whom chemoprophylaxis was indicated, were travelling to African countries, which carry 90% of all cases of malaria and represent a relevant part of the global disease burden [1].

This survey-based prospective cohort study yielded interesting findings regarding the adherence to malaria chemoprophylaxis amongst travelers and the data from this research indicated that the current state of their compliance with protective measures is suboptimal. We found 68.7% of travelers took at least 75% of their chemoprophylaxis prescribed compared to 84% in a Dutch study [16] or 89% in an American study [20].

Only 7.3% of travelers who were completely in compliance with chemoprophylaxis. Our data also substantiates a low level of awareness and perception of malaria risk among travelers [12].

Analysis of the predictors of being more likely to lead to chemoprophylaxis non adherence showed that there was a significant difference in the level of discontinuation according to the type of prescribed drug, duration of travel, and development of one or more adverse effects independently of age and gender.

The associations found may be explained by the fact that the longer the duration of travel, the longer the period when chemoprophylaxis is indicated, and hence the most factors which could negatively influence adherence. Indeed, specific in-depth studies have analyzed this aspect, highlighting problems related to chemoprophylaxis continuation in long-term travelers,

Table 3: Univariate and multivariate analysis indicating associations between variables and chemoprophylaxis (CP) non-adherence.

	Crude		*Adjusted**	
	OR	**95% CI**	**OR**	**95% CI**
Gender *Male* *Female*	 1 0.83	 0.44 - 1.61	 1 0.86	 0.43 - 1.66
Age *(in years)*	0.98	0.97 - 1.01	0.98	0.96 - 1.01
Prescribed CP drugs *Atovaquone/proguanil Mefloquine*	 1 3.13	 1.09 - 10.12	 1 3.69	 1.12 - 12.54
Duration of travel (*in days*)	1.02	1.00 - 1.04	1.03	1.02 - 1.05
Onset of adverse effects *No adverse effects* *At least 1 or more*	 1 3.41	 1.79 - 6.53	 1 3.91	 1.87 - 7.83

CP, antimalarial chemoprophylaxis; *OR*, odds ratio; *95% CI*, 95% confidence interval
*Adjusted by gender, age, prescribed chemoprophylaxis drugs, duration of travel, and onset of adverse effects.

Table 4: Adverse events reported by chemoprophylaxis users (n=335)*°.

	No. (%) of subjects with adverse events who received		
	Atovaquone-Proguanil (n=312)	***Mefloquine (n=23)***	***P-value***
Any adverse event** Any gastrointestinal event	108 (34.6%) 77 (24.7%)	10 (43.5%) 5 (21.7%)	0.01
Nausea	17 (5.4%)	1 (4.3%)	
Vomiting	6 (1.9%)	0 (0%)	
Gastric pain or discomfort	49 (15.7%)	3 (13.0%)	
Diarrhoea	5 (1.6%)	1 (4.3%)	
Sleeping disorder** *	24 (7.7%)	6 (26.0%)	
Headache General malaise	12 (3.8%) 16 (5.1%)	2 (8.7%) 2 (8.7%)	
Others	5 (1.6%)	0 (0%)	

° Interviewees could choose more than one item
*Numbers of items may not add up to the total study population because of missing values.
**Among subjects who reported a drug-related adverse event, the mean number of adverse event (±SD) per subject was 1.2±0.7 for subjects while receiving atovaquone-proguanil and 2.1±1.9 for subjects while receiving mefloquine.
***Sleeping disorder comprises insomnia, strange or vivid dreams

including the possibility of discussing other measures in case of long stays (e.g. SBET, when also indicated) [25-28].

The frequency of adverse events in the chemoprophylaxis in the present study was quite similar to the frequency in previous studies [29]. Regarding the onset of adverse events, participants complained of the usual symptoms reported by chemoprophylaxis users, being more frequent among mefloquine users. The difference was especially pronounced for sleeping disorders in mefloquine users. Indeed, in the literature, it is well defined that this antimalarial drug has the highest proportion of neuropsychiatric adverse effects, especially that of insomnia. [29,30] On the other hand we have observed a larger gastrointestinal number of events in both chemoprophylactic courses (atovaquone-proguanil and mefloquine) than in previous studies that ranged between 16 and 19% [29]. Moreover, the fact of experiencing adverse effects may itself prompt users to stop the prophylaxis, as shown in the fully adjusted logistic regression model.

An interesting finding is that sixteen interviewees forgot to keep taking the chemoprophylaxis during the prescribed time. This behavior may result in part from a lack of knowledge about malaria and the possibility of its onset after returning home. This is because the disease's incubation period is 7 days or longer, depending on many factors, particularly which *Plasmodium* species is responsible for the infection [31-33]. Therefore, the idea of leaving countries and areas at risk of malaria transmission may falsely reassure travelers and during pre-travel consultation it is important to inform patients about malaria itself and to stress the necessity of using an antimalarial for all the prescribed period.

Regarding chemoprophylaxis length some recall bias could occur as we could not verify with the patient how many tablets do they still have at home. Furthermore, other potential limitations might affect the value of this research. The first is the cohort design of the study that does not make it possible to establish causal effects. In addition, participants were not allocated blindly and randomly to the study: the possibility that the association found may be explained by other confounders should be taken into account. However, cohort studies use broader inclusion criteria and less exclusion criteria compared to randomized studies, making results more generalizable to clinical practice. Furthermore, a possible non-response bias must be considered due to a rather moderate response rate, even though the absence of relevant differences between responders and non-responders allowed us assume an equal distribution of participants' characteristics, lessening this limitation. Finally, the study enrolled only travelers seeking pre-travel advice in our unit and does not include subject seeking it elsewhere or not seeking it at all, so this cohort might be inadequate for determining all the predictors of CP adherence or might make the sample not representative of the whole target population of travelers and results not completely applicable to other centers.

Despite these limitations, the strengths of this study were that the cohort was properly selected; the study design was appropriate and allowed us to meet the temporality criterion for causality. Moreover, the methodology of the study was accurate, reducing problems of bias.

CONCLUSIONS

In conclusion, this study resulted in providing useful information of travelers' adherence to malaria chemoprophylaxis and in fostering further research likely to be useful in global public health and for health-policy makers. Indeed, adherence to chemoprophylaxis is an important factor of success in preventing malaria [4] and its correct implementation should be the key message during pre-travel medical visits, particularly when factors found likely to be associated with chemoprophylaxis misuse are evaluated during consultations.

Health promotion about malaria prevention at a travel clinic needs some expansion to produce substantial health benefits and efficacy among travelers. It seems an outstanding opportunity to promote the importance of malaria prevention, particularly in population at greater risk for the disease [34].

KEY ISSUES

- The success of malaria chemoprophylaxis depends mainly on travelers' adherence.

- A suboptimal level of adherence to malaria chemoprophylaxis exists, which is influenced by several factors, such as the characteristics of the individual, the travel and the type of prescribed antimalarial drug.

- Onset of drugs' adverse effects may induce travelers to suspend the chemoprophylaxis for malaria.

- The longer the schedule of chemoprophylaxis, the more likely is an offset in the dose assumed by travelers.

- Further research is needed to investigate other predictors of travelers' behavior.

- Health promotion and malaria prevention concepts need to be stressed at travel clinics to foster health benefits and efficacy among travelers.

AUTHORS CONTRIBUTIONS

All authors conceived and designed the study. The study was conducted under the supervision of IRB at the Hospital de Bellvitge. All authors were involved in drafting, revising and finalizing the manuscript, and approved the final version which was submitted for publication.

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DECLARATION OF INTEREST STATEMENT

There was no external funding for this manuscript. The authors report no conflicts of interest. The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

AVAILABILITY OF DATA AND MATERIALS

Data and supporting materials associated with this study will be available from the corresponding author on reasonable request.

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