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A Smartphone App for Real-Time Assessment of Malaria Prophylaxis Adverse Events

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Abstract

Background: *Growth of international travel to malarial areas over the last decades has contributed to more travelers taking malaria prophylaxis. Travel-related symptoms may be wrongly attributed to malaria prophylaxis and hinder compliance. Here, we aimed to assess the frequency of real-time reporting of symptoms by travelers following malaria prophylaxis using a smartphone app.*

Method: *Adult international travelers included in this single-center study (Barcelona, Spain) used the smartphone Trip Doctor® app developed by our group for real-time tracking of symptoms and adherence to prophylaxis.*

Results: *Six hundred four (*n = *604) international travelers were included in the study; 74.3% (449) used the app daily, and for one-quarter of travelers, malaria prophylaxis was prescribed. Participants from the prophylaxis group traveled more to Africa (86.7% vs. 4.3%;* $p < 0.01$*) and to high travel medical risk countries (60.8% vs. 18%;* $p < 0.01$*) and reported more immunosuppression (30.8% vs. 23.1%* $p < 0.01$*). Regarding symptoms, no significant intergroup differences were observed, and no relationship was found between the total number of malarial pills taken and reported symptoms.*

Conclusions: *In our cohort, the number of symptoms due to malaria prophylaxis was not significantly higher than in participants for whom prophylaxis was not prescribed, and the overall proportion of symptoms is higher compared with other studies.*

Keywords: *m-health, medical apps, real-time health recordings, digital participatory surveillance system, malaria prophylaxis, adverse events, atovaquone–proguanil, telemedicine*

Introduction

The steady yearly international growth in tourism, the globalization of trade, and the increase of people working for international and nongovernmental organizations have contributed to a greater number of individuals from high-income countries visiting and working in tropical and subtropical destinations.[1,2]

Since 2013, between 6,000 and 8,000 cases of imported malarial infections have been reported per year by the European countries. Spain ranks fifth in Europe in imported *Plasmodium falciparum* cases, with a rate of 1.8 malarial cases per 100,000 inhabitants (~800 cases per year diagnosed since 2016).[3]

The growth in the frequency of international travel to high-risk malarial areas (e.g., sub-Saharan Africa[1]), the origin for most imported malarial cases around the world,[4] has led more travelers to take malaria prophylaxis, some of them for long periods.

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Current data and randomized controlled trials[5,6] focused on the symptoms associated with the drugs used to prevent malaria, for example, mefloquine, atovaquone–proguanil, and doxycycline among nonimmune travelers[6,7] are scarce. Most adverse events (AEs) of malaria prophylaxis are either modeled or reported after the trip,[7,8] incurring recall biases. The majority of studies on this issue are performed in selected populations, such as military personnel,[9] limiting the extrapolation of the results.[7,8] Furthermore, many symptoms occurring during the trip can be wrongly attributed to malaria prophylaxis, particularly those usually associated with antimalarial drugs, for example, mood disorders or gastrointestinal complications,[10] and this is probably due to the lack of specificity of some AEs of malarial drugs.[11] In most articles, the exact amount of drug taken is not quantified.

AEs to prophylactic use of antimalarial drugs are associated with a bad perception of health that may precipitate withdrawal[12–14] and consequently increase the risk of acquiring malaria.[13,15]

Our group developed a smartphone-based system called Trip Doctor®,[16] designed to engage travelers in the detection of symptoms of the main tropical infectious diseases and malaria prophylaxis AEs among travelers.

This study aimed to assess the frequency of real-time reporting of symptoms through Trip Doctor by comparing two groups of travelers: those to whom malaria prophylaxis was prescribed and those to whom it was not prescribed.

Methods

STUDY SETTING AND POPULATION

The study was conducted in the Hospital Clinic Barcelona Travel Clinic (Spain). Adult international travelers who attended our center before their trip for pretravel clinical consultation were invited to participate in the study between September 2017 and October 2018.

THE SMARTPHONE-BASED SYSTEM

The Trip Doctor platform includes a smartphone app that the traveler had to install on his/her mobile phone with a web-backend interface that allowed storing all the data captured automatically by the app in a cloud server from a web secure browser. The interface allowed physicians from the Travel Clinic to monitor patients in real time and remotely interact with them.

The app was free of charge (available in PlayStore® and Apple Store®), did not require an internet connection, and was activated by a code each participant received after being included in the study. The system monitored the health status of the traveler daily, providing specific medical advice and offering remote contact with the study physicians if needed (*Fig. 1*).

In addition, when malaria prophylaxis was prescribed to a participant, a notification with a reminder to follow the treatment was sent by the app.

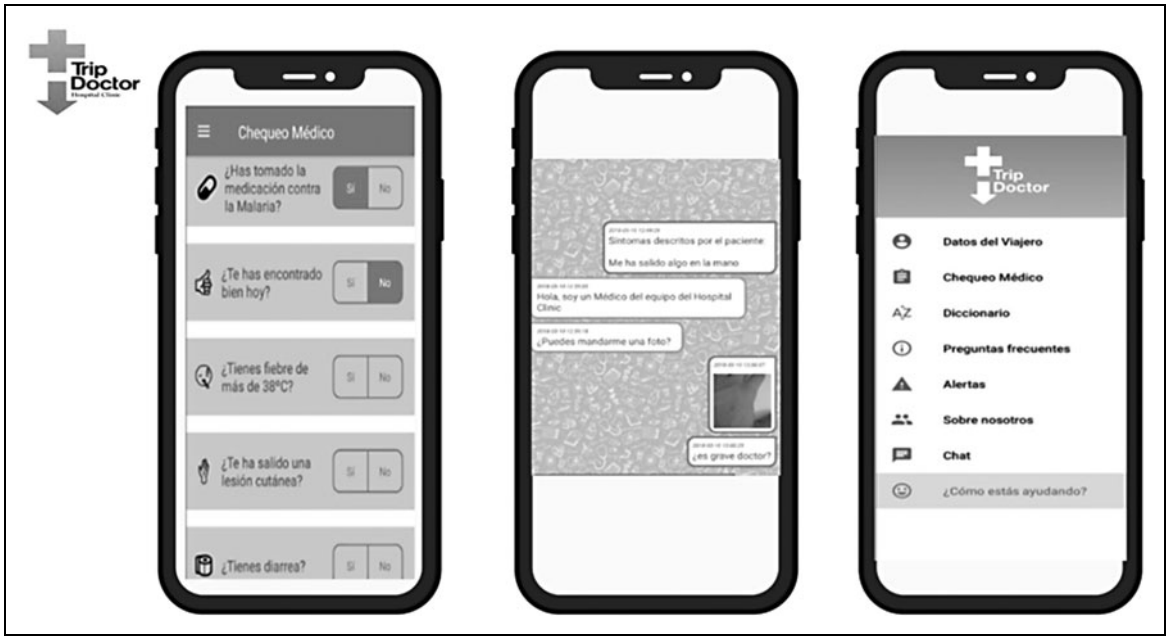

Fig. 1. App screen for the travelers.

COLLECTED DATA

1. Baseline characteristics: age, sex, chronic diseases, the status of immunosuppression (defined as any disease or treatment that significantly decreases or debilitates the immune system, e.g., cancer, HIV, radiotherapy, chemotherapy, transplantation, treatments for autoimmune diseases), malaria prophylaxis indication and intake, travel dates, destination (in addition, countries were classified by World Health Organization region and SOS International risk categories),[17] the purpose of travel, and estimated daily geolocation.
2. Symptoms were registered daily (diarrhea, abdominal pain, fever, joint pain, headache, cutaneous lesions) or every week (vaginal discharge, insomnia, nausea, anxiety or depression, seizures or dizziness). Weekly questionnaires were performed on all travelers as additional health questionnaires to limit biases when compared with the group to whom prophylaxis was not prescribed.

STATISTICAL ANALYSIS

Real-time recorded data of participants were transformed into aggregated data sets automatically for their analysis. Data management and descriptive analyses were performed using the R software.[18] Continuous data are presented as medians and interquartile ranges (IQR) and categorical data as frequencies and proportions. In an initial exploratory analysis for bivariate comparisons of continuous data, the Wilcoxon rank-sum test was used and for categorical data, chi-square tests were performed.

ETHICS

This study was approved by the Ethics Committee of Hospital Clinic Barcelona (Reference HCB/2015/0995) and the clinical investigation was conducted according to the principles expressed in the Declaration of Helsinki. The participants signed a digital informed consent and privacy and legal disclaimers before using Trip Doctor.

Results

Six hundred four international travelers were included in the study, from which 449 (74.3%) used the app and completed at least one daily symptom questionnaire. Travelers completed a median number of 16 daily questionnaires (IQR = 12–25; minimum of 1 and maximum of 381) (*Fig. 2*).

The median age of travelers, who used the app, was 34 years (IQR = 28–48) and 55.2% were female. Chronic diseases were reported by 20% of participants and 25.2% indicated some degree of immunosuppression. The most visited destinations were Southeast Asia (32.2%), Africa (26.6%), and the Americas (23.3%). Countries with medium or high travel medical

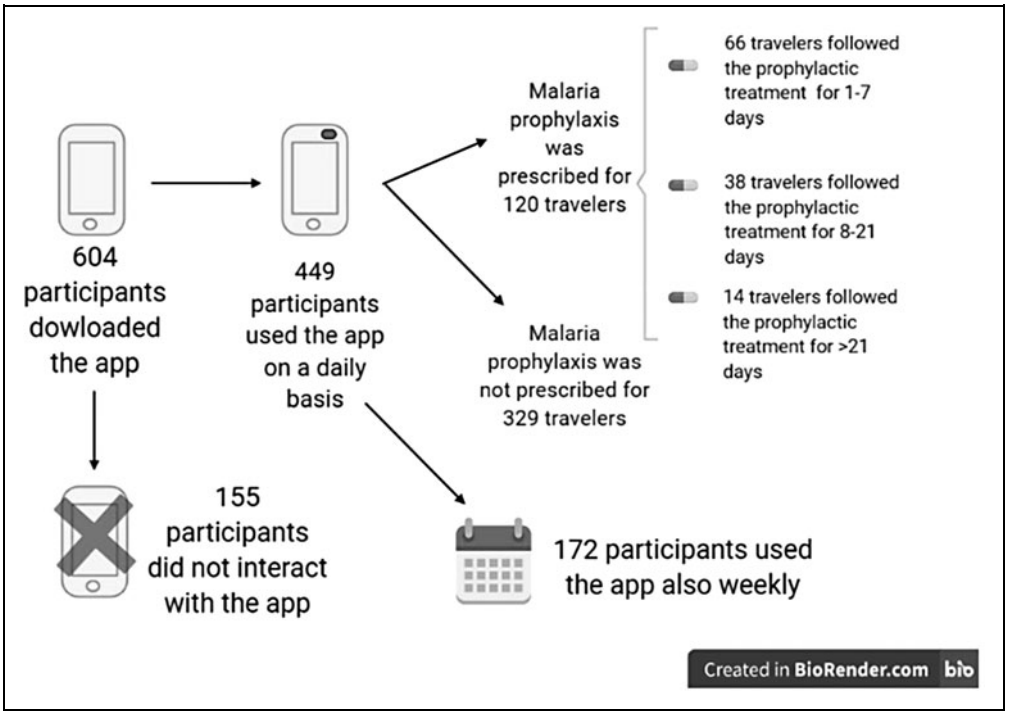

Fig. 2. Flowchart for study participants and malaria prophylaxis.

Table 1. Demographic and Travel-Related Characteristics of Participants Who Were Prescribed Malaria Prophylaxis Versus No Prophylaxis ($N=449$)

	SUBJECTS PRESCRIBED MALARIA PROPHYLAXIS ($N=120$)	SUBJECTS WITHOUT PRESCRIBED PROPHYLAXIS ($N=329$)	*P*
Age, years	38 (28–50)	33 (27–47)	0.622
Age groups, years			0.602
18–35	55 (45.8)	190 (57.8)	
36–60	50 (41.7)	120 (36.5)	
60+	15 (12.5)	19 (5.8)	
Sex			0.579
Male	60 (50.0)	141 (42.9)	
Female	60 (50.0)	188 (57.1)	
Duration of travel, days	21 (17–29)	18 (12–30)	0.025
The WHO regions of destination[a]			<0.001
Africa	104 (86.7)	15 (4.6)	
The Americas	2 (1.7)	102 (31.2)	
Eastern Mediterranean	–	6 (1.8)	
European	2 (1.7)	3 (0.9)	
Southeast Asia	7 (5.8)	137 (41.9)	
Western Pacific	5 (4.2)	61 (18.7)	
Southeast Asia+Western Pacific	–	3 (0.9)	
Health risk at the destination as per SOS International			<0.001
Low	5 (4.2)	14 (4.3)	
Medium	18 (15.0)	78 (23.9)	
High	73 (60.8)	59 (18.0)	
Very high	1 (0.8)	0 (0.0)	
Rapidly developing variable risk	23 (19.2)	176 (53.8)	
Travel purpose			0.168
Aid/volunteering	25 (20.8)	31 (9.4)	
Business	15 (12.5)	37 (11.2)	
Tourism	80 (66.7)	254 (77.2)	
Visiting friends and family	0 (0.0)	7 (2.1)	
Chronic condition	19 (15.8)	71 (21.6)	0.453
Immunosuppression or similar	37 (30.8)	76 (23.1)	<0.001

n (%) or median (IQR: P25–P75).

[a]Two missing.

IQR, interquartile range; WHO, the World Health Organization.

risk were visited by 51% of the study participants. The median duration of travel was 16 days (IQR = 11–25; minimum of 8 and maximum of 381). The main purpose of the trip was tourism in 74.4% of cases, followed by aid and volunteering in 12.5%, business in 11.6%, and visiting friends and relatives 1.6%.

Table 1 summarizes the characteristics of participants who were prescribed malaria prophylaxis (120, 26.7%) and of those who were not (329, 73.3%). The median duration of prescribed malarial drugs was 21 days (IQR = 17–29). All travelers who were prescribed malaria prophylaxis followed the treatment for at least 1 day; 66, 38, and 14 participants followed the treatment between 1–7, 8–21, and more than 21 days, respectively (*Fig. 1*). The most prescribed drug was atovaquone–proguanil (111, 92.5%), followed by doxycycline (4 participants, 3.3%) and mefloquine (5 participants, 4.2%).

Table 2 lists the symptoms captured from the 449 travelers who used the app on a daily and weekly basis. No clear correlation was observed between the number of days participants followed the prophylactic treatment and the reported symptoms (*Fig. 3*). No serious AEs associated with malaria prophylaxis were registered during the period of the study.

Discussion

Travelers to whom prophylaxis was not prescribed communicated more symptoms compared with the travelers to whom prophylaxis was prescribed, each reporting at least one symptom (56.6% vs. 40.4%, $p = 0.07$). Therefore, the use of antimalarial medications by our cohort does not cause more symptoms than those related to other travel risks. Furthermore, it should be noted that this result might be relevant as other similar studies do not have a comparator group.

In our cohort, 40.4% of the travelers to whom prophylaxis was prescribed reported at least one symptom, which is higher than that reported in other studies (5–18.8%)[19,20]; in the case of participants for whom prophylaxis was not prescribed, an even higher percentage of symptoms was communicated (56.6%). A reduction of the recall bias linked to our study methodology (real-time data) may explain this result. For extended-duration prophylaxis (>21 days), other studies[7,21] have reported a higher number of AEs (25–60%) in comparison with our group 28.6%. However, it should be considered that our extended-duration prophylaxis group included seven travelers.

The use of atovaquone–proguanil is associated with dizziness in comparison with other drugs, with no significant differences. Nevertheless, atovaquone–proguanil users reported fewer symptoms than the group to whom prophylaxis was not prescribed (56.6% vs. 38%), but again the difference was not significant.

Table 2. Symptoms Reported by Travelers With or Without Prescribed Malaria Prophylaxis

DAILY QUESTIONNAIRES (*N* = 449)	SUBJECTS NOT PRESCRIBED PROPHYLAXIS (*N* = 329)	SUBJECTS PRESCRIBED MALARIA PROPHYLAXIS (*N* = 120)	*P*	ATOVAQUONE–PROGUANIL (*N* = 111)	DOXYCYCLINE (*N* = 4)	MEFLOQUINE (*N* = 5)
Diarrhea	77 (23.4)	24 (20)	0.52	21 (18.9)	0 (0.0)	3 (60.0)
Skin lesions	27 (8.2)	11 (9.1)	0.89	10 (9.0)	1 (25.0)	0 (0.0)
Abdominal pain	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	0 (0.0)
Headache	21 (6.4)	9 (7.5)	0.84	9 (8.1)	0 (0.0)	0 (0.0)
WEEKLY QUESTIONNAIRES (*N* = 172)	**SUBJECTS NOT PRESCRIBED PROPHYLAXIS (*N* = 120)**	**SUBJECTS PRESCRIBED MALARIA PROPHYLAXIS (*N* = 52)**	***P***	**ATOVAQUONE–PROGUANIL (*N* = 50)**	**DOXYCYCLINE (*N* = 1)**	**MEFLOQUINE (*N* = 1)**
Vaginal discharge[a]	3 (4.5)	1 (4.5)	0.99	2 (4)	0 (0.0)	0 (0.0)
Nausea	7 (5.8)	2 (3.8)	0.69	2 (4)	0 (0.0)	0 (0.0)
Anxiety/depressed mood	4 (3.3)	2 (3.8)	0.99	2 (4)	0 (0.0)	0 (0.0)
Dizziness	5 (4.2)	6 (11.5)	0.23	6 (12)	0 (0.0)	0 (0.0)
At least one symptom	68 (56.6)	21 (40.4)	0.07	19 (38)	1 (100)	1 (100)

[a]Only female participants from the 449 travelers who used the app.

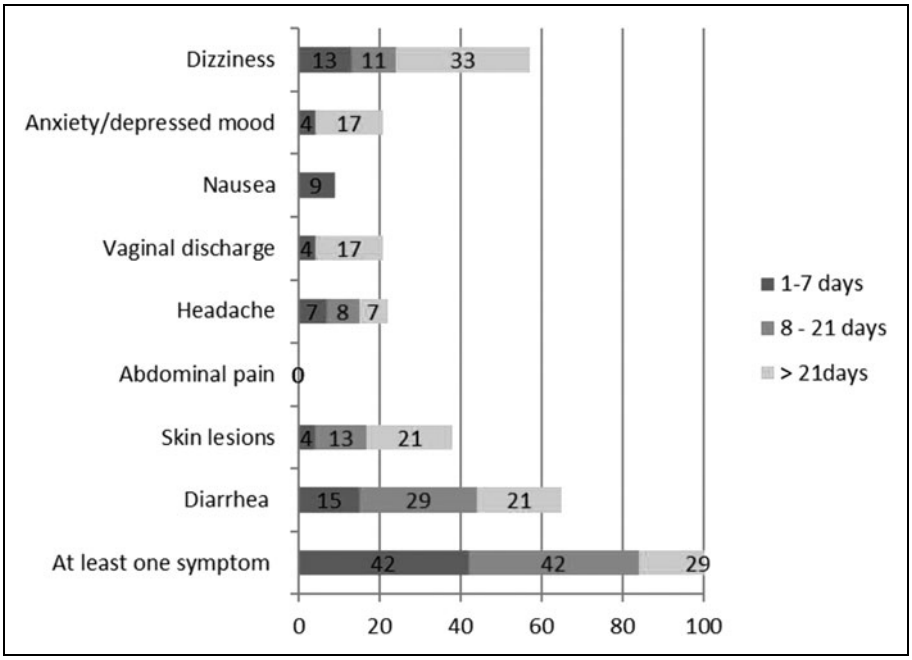

Fig. 3. The proportion of travelers reporting symptoms versus the number of prophylaxis days taken. $N = 449$.

The sample size of both study groups is small, and thus, the high percentages of skin lesions in the doxycycline group and diarrhea in the mefloquine group may be overrepresented.

Furthermore, travelers to whom malaria prophylaxis was prescribed communicated immunosuppression more frequently, which may indicate the concern of immunosuppressed patients when traveling to high travel medical risk areas such as Africa.

There are limitations to this study. First, missing data do not allow estimating adherence or determining a relationship with the reported symptoms or individual drugs. This study did not include children or a representative number of participants visiting friends and relatives, or travelers taking mefloquine or doxycycline.

Finally, 74% of the travelers included in this study used the app at least once. The median number of days of app use and duration of the trip was 16, which implies that the app was used daily during most of the trip. The use and acceptance of the app were good, shown by the high usage rates and completion of the symptom checker.

Conclusions

In conclusion, in this study, symptoms commonly interpreted as AEs of malaria prophylaxis (skin lesions, abdominal pain, headache, vaginal discharge, nausea, and anxiety/depressed mood) do not associate with the group of international travelers to whom prophylaxis was prescribed. Diarrhea and nausea occur more frequently in the group to whom prophylaxis was not prescribed and travelers report at least one symptom. A reduction of the recall bias linked to our study methodology (real-time data) may explain the higher number of symptoms reported in comparison with other studies.

In our study, and at the currently prescribed doses, malaria prophylaxis appears to be safe. However, this does not imply that prophylaxis should be given to subjects traveling to any malarial area regardless of the incidence.

Further studies using real-time data may provide more knowledge to patients and prescribers and may help improve adherence and compliance in areas with a high risk of acquisition where prophylaxis is needed.[22]

Disclosure Statement

No competing financial interests exist.

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REFERENCES

1. World Tourism Organization. 2017 Annual Report [Internet]. 2018. Available from: https://www.e-unwto.org/doi/pdf/10.18111/9789284419807 [Last accessed: December 1, 2023].
2. Tourism W, Unwto O. 2017 International tourism results: The highest in seven years. Adv Release 2018;16:1–7.
3. ECDC. Malaria Annual Epidemiological Report for 2017, vol. 393. ECDC: Stockholm; 2019.

4. Tatem AJ, Jia P, Ordanovich D, et al. The geography of imported malaria to non-endemic countries: A meta-analysis of nationally reported statistics. Lancet Infect Dis 2017;17(1):98–107; doi: 10.1016/S1473-3099(16)30326-7
5. Jacquerioz FA, Croft AM. Drugs for preventing malaria in travellers. Cochrane Database Syst Rev 2010;2010(4):CD006491.
6. Tickell-Painter M, Maayan N, Saunders R, et al. Mefloquine for preventing malaria during travel to endemic areas. Cochrane Database Syst Rev 2017; 2017(10):CD006491.
7. Schlagenhauf P, Nothdurft HD, Schwartz E, et al. Tolerability of malaria chemoprophylaxis in non-immune travellers to sub-Saharan Africa: Double blind, four arm study. Br Med J 2003;327:1078.
8. Toovey S, Smith PF. Comparative benefit of malaria chemoprophylaxis modelled in United Kingdom travellers. Travel Med Infect Dis 2014;12(6 Pt B): 726–732.
9. Saunders DL, Garges E, Manning JE, et al. Safety, tolerability, and compliance with long-term antimalarial chemoprophylaxis in American Soldiers in Afghanistan. Am J Trop Med Hyg 2015;93(3):584–590.
10. Nevin RL, Croft AM. Psychiatric effects of malaria and anti-malarial drugs: Historical and modern perspectives. Malar J 2016;15:332.
11. Jacquerioz FA, Croft AM. Drugs for preventing malaria in travellers. Sao Paulo Med J 2009;127(6):387.
12. Mccarthy AE, Coyle D. Determining utility values related to malaria and malaria chemoprophylaxis. Malar J 2010;9:92.
13. Landman: K., Tan KR, Arguin PM. Adherence to malaria prophylaxis among peace corps volunteers in the Africa Region, 2013. Travel Med Infect Dis 2016; 13(1):61–68.
14. Kain D, Findlater A, Lighfoot, et al. Factors affecting pre-travel health seeking behaviour and adherence to pre-travel health advice: A systematic review. J Travel Med 2019;216(6):taz059.
15. Laver SM, Wetzels J, Behrens RH. Knowledge of malaria, risk perception, and compliance with prophylaxis and personal and environmental preventive measures in travelers exiting Zimbabwe from Harare and Victoria Falls International airport. J Travel Med 2001;8(6):298–303.
16. Rodriguez-Valero N, Ledesma Carbayo M, Cuadrado Sanchez D, et al. Real-time incidence of travel-related symptoms through a smartphone-based app remote monitoring system: A pilot study. J Travel Med 2018;25(1):1–3.
17. SOS International. 2020. Available from: https://www.internationalsos.com/risk-outlook [Last accessed: August 17, 2023].
18. R Foundation for Statistical Computing. R: A Language and Environment for Statistical Computing. Vienna, Austria. Available from: http://www.R-project.org/ [Last accessed: December 1, 2023].
19. Depetrillo JC, Singer C, Bergagnini IA, et al. Assessment of adherence to atovaquone-proguanil prophylaxis in travelers. J Travel Med 2010;17(4):217–220.
20. Kato T, Okuda J, Ide D, et al. Questionnaire-based analysis of atovaquone-proguanil compared with mefloquine in the chemoprophylaxis of malaria in non-immune Japanese travelers. J Infect Chemother 2013;19(1):20–23.
21. Petersen E. The safety of atovaquone/proguanil in long-term malaria prophylaxis of nonimmune adults. J Travel Med 2003;10(Suppl 1):S13–S15.
22. Behrens RH, Hatz C, Med P, et al. Defining malaria risk: It is not only about epidemiology but also about perception and risk threshold of travellers and policy makers. J Travel Med 2018;25(1):tay043.

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