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ORIGINAL ARTICLE

Success of malaria chemoprophylaxis for outbound civil and military travellers in prevention of reintroduction of malaria in Sri Lanka

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Background: Sri Lanka was certified as malaria-free in September 2016. However, the continuous presence of the malaria vector poses serious risks of reintroduction of the disease. Chemoprophylaxis and advice on malaria preventive behaviour for international travellers is a key strategy adopted to reduce the risk of imported malaria.

Methods: We conducted an efficiency study of malaria chemoprophylaxis for civilian and military travellers who requested travel advice from the Anti Malaria Campaign (AMC) prior to departure. The AMC is the only agency that can issue malaria chemoprophylaxis to travellers and hence this sample is representative of all such individuals seeking travel advice in Sri Lanka.

Results: A total of 544 (400 civilians and 144 military) travellers were interviewed prior to departure and after return. The majority travelled to African destinations (516/544 [94.8%]) and were prescribed mefloquine (517/544 [95%]). Chemoprophylaxis was well tolerated and discontinuation due to adverse events was minimal. Regular chemoprophylaxis was reported by 505 (92.8%) participants while overseas. The protective efficacy of chemoprophylaxis was 100% among those who complied with the full course.

Conclusions: The compliance with chemoprophylaxis and its protective efficacy were satisfactory in this study. It is an effective tool in preventing imported malaria to post-elimination Sri Lanka.

Keywords: adverse effects, chemoprophylaxis, imported malaria, malaria, mefloquine, reintroduction

Introduction

Currently 3 billion people in 91 countries are at risk of malaria infection. The morbidity (approximately 216 million infections annually) and mortality (455 000 deaths worldwide annually) of malaria are still very high as far as absolute numbers are concerned.[1] A meta-analysis of imported malaria cases worldwide showed that between 2005 and 2015, approximately 25 000 cases were reported in non-endemic countries.[2] This is a small but significant proportion of the total global malaria burden. The risks of imported malaria depend on the travel habits of the local population and immigration from endemic countries.[3,4] The risk of infection during travel can be reduced by the use of appropriate physical prevention measures and chemoprophylaxis.[5–7] The extent to which these measures are adopted depends on how well a traveller assesses the risks of infection.[8]

There are examples of malaria making a successful comeback after elimination or near elimination.[9] This is especially true in places where the vector remains abundant even though the parasite reservoir is reduced to zero.[10–12] The risk of reintroduction in these settings can only be reduced by remaining vigilant, raising awareness of imported malaria and by voluntary participation of travellers in screening programmes, as restriction of movement across borders is not practical for the sake of preventing malaria.[12–14]

With the last indigenous malaria case reported in October 2012, Sri Lanka has been certified malaria-free since September 2016.[15] However, the number of imported malaria cases reported in the country has increased since 2008, with the highest number of cases (95) reported in 2013.[16] Between 2013 and 2017, a total of 278 imported malaria cases were reported in Sri Lanka.[16] Surveillance for imported malaria is centrally coordinated by the government of Sri Lanka through the national Anti Malaria Campaign (AMC). A majority of the imported cases reported between 2013 and 2017 (185/278 [66%]) have been among Sri Lankans who had acquired the infection while travelling overseas for various purposes; these infections have originated mainly in India, Pakistan and African countries.[15] The imported malaria incidences reported for civilians and military personnel in Sri Lanka were considered separately, as their context of occurrence and the feasibility of implementing preventive strategies differ.[17–20] Currently Sri Lankan military personnel visit malaria-endemic countries in an official capacity as part of United Nations peacekeeping missions (e.g. South Sudan, Haiti, Central African Republic) or for military training (e.g. India).[21]

Malaria chemoprophylaxis and travel advice on malaria preventive behaviour to be adopted while overseas to minimize the risk of acquiring the disease is issued free of charge to travellers by the AMC and remains one of the most important strategies for preventing malaria in travellers. The current recommendations by the AMC for chemoprophylaxis are mefloquine 250 mg weekly for most travellers, including those visiting African countries, and chloroquine base 300 mg weekly, which is used only for a few countries. Both these drugs may have unpleasant side effects, and travellers usually ask about these adverse events and weigh the discomfort against the risk of contracting malaria.[22] It is plausible that the latter risk is often underestimated when they feel healthy and since malaria has become very rare in Sri Lanka.[23,24] In addition, to be effective, malaria chemoprophylaxis must be taken meticulously prior to departure, during travel and following their return to the country, which requires self-motivation and discipline.[25] There are no data regarding compliance with malaria chemoprophylaxis in civilian Sri Lankan travellers after malaria elimination in Sri Lanka. We have previously reported on the compliance of military travellers, but it was limited to an outbreak investigation.[26]

The present study aimed to document the self-reported adherence to malaria prophylaxis and adverse events among civilian and military travellers returning to Sri Lanka from malaria-endemic countries. The information presented here is important for the AMC to formulate necessary guidelines to prevent re-establishment of infections through imported infections. Globally, it is important for other countries that have recently eliminated malaria or are on the verge of elimination to follow Sri Lanka as a case study to structure their own prevention of reintroduction mechanisms.

Methods

Sample selection

Civilian travellers

This component of the study was conducted from March 2017 to October 2017. Sri Lanka is an island with only one international airport for overseas travel used by both civilians and military personnel. All civilian travellers visiting the AMC voluntarily to obtain chemoprophylaxis and travel advice prior to departure were sequentially included until the sample size was met. The sample size was calculated using the following formula:[27]

$$n = \frac{Z1\text{-}\alpha/2\, p(1-p)}{d2}$$

where n is the sample size; Z is the standard normal deviation, set at 1.96, which corresponds to 95% confidence limits; d is the degree of accuracy desired, specified as 0.05, and p is prevalence—in order to gain a larger sample size, a prevalence of 50% was used. The calculated sample size was 384 (403 when adjusted for a non-response rate of 5%).

Data collection was done by a pretested (in 25 travellers to malaria-endemic countries that was carried out during the study preparation stages) interviewer-administered structured questionnaire that collected information on participant demographics, their awareness of malaria, risk factors for developing malaria, pretravel advice, compliance with chemoprophylaxis and self-reported adverse events during chemoprophylaxis within 2 weeks of their return to the country.

Military travellers

All security forces personnel returning after 1 y of service in United Nations peacekeeping missions in malaria-endemic countries in 2017 were included in this study. Unlike civilian travellers, military travellers on peacekeeping missions are tracked by the AMC in coordination with the Ministry of Defence of Sri Lanka. Awareness programmes on the prevention of malaria are conducted before travel and all returning soldiers are screened at re-entry to the country. For this component of the study, a sample size calculation was not necessary, as all returning military travellers during the study period were included. The data collection was done with a different version of the pretested interviewer-administered questionnaire given to civilians but had more focused questions on self-reported mefloquine-related adverse events.

In both groups, compliance with chemoprophylaxis was considered as regular when the drugs had been taken for the entire duration spent overseas at the recommended dose and frequency, as irregular if chemoprophylaxis had been taken less frequently than recommended and as interrupted or not performed if chemoprophylaxis had been started but subsequently interrupted or never started.

Screening for malaria after return

Finger prick blood was collected under aseptic conditions from the study participants within 2 weeks of returning. According to the routine procedure, approximately 2 and 6 µL of blood was collected on a glass slide for the preparation of thin and thick blood smears, respectively. The smears were stained with 10% Giemsa stain for 10 min and examined under a microscope by a trained technical assistant. Five microlitres of finger prick blood was then used for the rapid diagnostic test (CareStart Malaria HRP2/pLDH [Pf/PAN] Ag Combo Test, product G0131, Access Bio inc. USA).

Data analysis

Data for both groups were entered in to an SPSS (version 23; IBM, Armonk, NY, USA) database and analysed as separate groups due to the differences in baseline characteristics and the use of separate questionnaires. Descriptive statistics were summarized as measures of central tendency (mean, median) and measures of dispersion (standard deviation, range) based on the frequency distributions.

Results

Civilian travellers

A total of 400 (males 284/400 [71%]) returning civilian travellers who obtained chemoprophylaxis prior to departure were interviewed after returning to the country. Demographic analysis showed that except for the <20 y age group, travellers were distributed in comparable proportions in other groups (Table 1, demographic data for civilians). All people who sought advice had received at least a secondary education. A majority of them had visited an African country (372/400 [93%]) and the remainder had visited an Asian or South American country (Supplementary Table 1). The duration of stay for most travellers at their destination was 1–4 weeks (293/400 [73.3%]). As expected, the most commonly prescribed chemoprophylaxis drug was mefloquine (373/400 [93.3%]), followed by chloroquine (15/400 [3.8%]) and doxycycline in case mefloquine was contraindicated (12/400 [3%]). Following their return, 361 (90.3%) participants reported regular chemoprophylaxis as advised by the AMC, while 19 (4.8%) and 20 (5%) reported irregular and non-initiation of chemoprophylaxis, respectively. A majority (364/400 [91%]) had started chemoprophylaxis in the 7 d prior to departure and 360/400 (90%) had continued it after arrival in Sri Lanka, as per medical advice, and none reported side effects. In 19 participants who reported irregular (or interrupted) intake, a minority (3/400 [0.8%]) had done so due to adverse events, while the most commonly cited reason for non-compliance was forgetfulness (10/400 [2.5%]) or the participants considering it unnecessary to take the given drugs once they arrived at their destination (6/400 [1.5%]). In the 20 participants who never started chemoprophylaxis after obtaining the drugs, not travelling as planned was the reason in 12 (3%), while 4 persons each gave reasons for not taking the drugs as fear of side effects or forgetfulness (1% each). None of the participants contracted malaria and all were screened negative for malaria parasites checked with microscopy or rapid diagnostic tests upon return to the country.

Military travellers

A total of 144 (90 Air Force personnel and 54 Army personnel, males 138 [95.8%]) security forces personnel who returned from their overseas deployments in 2017 were assessed. All were deployed in South Sudan and were prescribed mefloquine prior to departure. All had complied with regular chemoprophylaxis during deployment. A total of 121 (84%) reported that taking the drug had no adverse impact on their daily activities. A minority of subjects reported adverse events such as headaches (2 [1.4%]), hallucinations (1 [0.7%]), nightmares and inability to sleep (1 [0.7%]), loss of appetite (2 [1.4%]), diarrhoea (2 [1.4%]), nausea (2 [1.4%]), dark-coloured urine (1 [0.7%]) and abnormal sweating (21 [14.6%]) more than once during chemoprophylaxis. Eleven subjects had more than one adverse event. However, none of these events were serious enough to discontinue mefloquine. With the exception of one individual, the rest continued the chemoprophylaxis for a further 4 weeks after returning to Sri Lanka. No one reported symptoms of malaria during their overseas stay. All subjects were screened for malaria at the airport after returning and 6 weeks later and were reported as negative, except for a 37-year-old male who developed malaria symptoms on day 13 after returning and was diagnosed with falciparum malaria. He was treated with artemisinin-based combination therapy followed by a single dose of primaquine and made a full recovery. On further inquiry it was revealed that he was the only person who did not continue prophylaxis after returning to Sri Lanka.

Discussion

In this study, the compliance with prescribed prophylaxis was remarkably high (>90%) among civilian and military travellers returning from malaria-endemic overseas destinations. With the exception of one military personnel who did not complete the chemoprophylaxis following his return to Sri Lanka as advised and who thus developed malaria, chemoprophylaxis was effective, as none of the civilian and military travellers contracted malaria.

Although compliance is self-reported, the claim is supported by a zero imported malaria rate in those who complied with the drug regime. The high rate of self-reported compliance may be attributed to the proper awareness given before prescribing drugs by the medical staff of the AMC, higher education level in the travellers as well as institutional implementation in the case of military travellers, which led to a 100% compliance rate during deployment. Adherence to chemoprophylaxis might also have been influenced by a recent outbreak of malaria in a contingent of Sri Lankan security forces personnel deployed in the Central African Republic that resulted in the death of one person due to severe malaria.[26] At that time the contingent was prescribed doxycycline prophylaxis due to the unavailability of mefloquine. The lessons learned from that incident reinforced the drive to ensure that all military personnel deployed in malaria-endemic countries get first-line recommended antimalarials and that they strictly adhere to the prescribed chemoprophylaxis regimen. This also highlights the success of prophylaxis with mefloquine in preventing malaria cases and deaths.

Mefloquine is the first-line drug recommended by the AMC for prophylaxis in those who are travelling to countries with chloroquine-resistant malaria. The cost of mefloquine prophylaxis was approximately US$3 per person during the time of the study. All military personnel received mefloquine for 12 months by a directly observed treatment strategy. No serious adverse events leading to hospitalization or death following the use of long-term mefloquine were reported by the military personnel. Among the 23 military travellers who reported adverse events following ingestion of mefloquine, 21 complained of abnormal sweating, which could also have been due to other reasons, such as prevailing hot weather and heavy work. Only two people in this group developed neuropsychiatric adverse events such as hallucinations (1 [0.7%]) and nightmares and inability to sleep

Table 1. Characteristics of travellers seeking advice on malaria prophylaxis (civilian travellers n=400, military travellers n=144)

Characteristics	Civilian travellers, n (%)	Military travellers, n (%)
Gender		
Male	284 (71.0)	135 (95.8)
Female	116 (29.0)	9 (4.2)
Age (years)		
<20	21 (5.3)	0
21–30	83 (20.8)	12 (8.3)
31–40	75 (18.8)	84 (58.3)
41–50	97 (24.3)	45 (31.3)
>50	124 (31.0)	3 (2.1)
Level of education		
Primary or no education	0	0
Secondary education	138 (34.5)	118 (81.9)
Tertiary education	195 (48.8)	25 (17.4)
Postgraduate qualifications	67 (16.8)	1 (0.7)
Destination (region)		
Africa	372 (93.0)	144 (100)[a]
Asia	20 (5.0)	0
South America	8 (2.0)	0
Purpose of visit		
Leisure	217 (54.3)	0
Business	178 (44.5)	144 (100)
Other	5 (1.3)	0
Duration of overseas stay		
<1 week	54 (13.5)	0
1 week–1 month	293 (73.3)	0
1–3 months	23 (5.8)	0
3–6 months	30 (7.5)	
6–12 months		144 (100)[a]
Prescribed prophylaxis		
Chloroquine	15 (3.8)	0
Mefloquine	373 (93.3)	144 (100)
Doxycycline	12 (3.0)	0
Start of prophylaxis prior to departure		
Yes	379 (94.8)	144
No	21 (5.2)	0
Compliance during overseas stay		
Regular	361 (90.3)	144 (100)
Irregular or interrupted	19 (4.8)	0
Never started	20 (5.0)	0
Continuation of prophylaxis after return		
Yes	360 (90.0)	143 (99.3)
No	40 (10.0)	1 (0.7)

[a]All were deployed in South Sudan for 12 months.

(1 [0.7%)]. Three individuals from the civilian group gave a history of discontinuation due to adverse events. Overall, our observations are that long-term use of mefloquine was well tolerated and prevented imported malaria in Sri Lanka.

The good tolerance of chemoprophylaxis could have been due to the stringent selection criteria used by the AMC, excluding people with contraindications, and individual-level counselling before prescribing prophylaxis medicines. The need to take measures to avoid mosquito bites during their overseas stay, including sleeping under a mosquito net and applying repellents, is also emphasized during these counselling sessions, with instructions given in writing.

Notably, the frequency of adverse events reported was much less than similar studies conducted overseas.[28,29] Chemoprophylaxis with mefloquine has been under scrutiny recently after observations of a higher incidence of neuropsychiatric

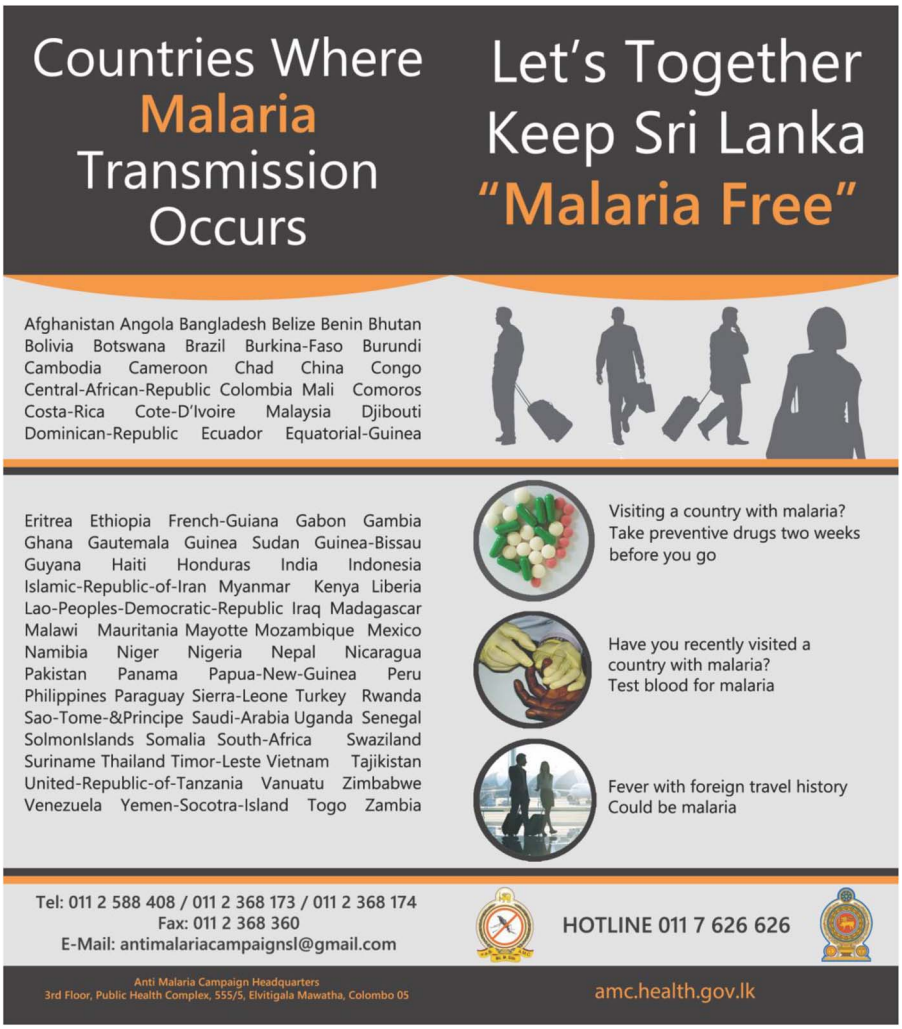

Figure 1. Leaflets handed out to travellers highlighting the importance of chemoprophylaxis.

side effects in travellers compared with those taking other antimalarials. In a large population-based study to quantify and compare the risk of psychiatric disorders during or after the use of mefloquine with the risk during the use of proguanil and/or chloroquine or doxycycline, it was reported that the absolute risk of developing psychosis or panic attacks was low and that there was no evidence to suggest an increased risk of depression in previously healthy individuals when compared with other antimalarials tested.[30] Mefloquine is also used as a first-line prophylactic agent in the UK, provided a doctor carries out a face-to-face risk assessment prior to prescribing.[31]

This study included only civilians who came to the AMC to obtain travel advice and chemoprophylaxis. Most of them were travelling to African destinations. This could be due to referrals by the port health office when travellers go to get a yellow fever vaccination, which is compulsory prior to travelling to Africa, and awareness of people regarding the serious nature of malaria in Africa, where the more virulent *Plasmodium falciparum* is highly prevalent. This is not representative of the general population of Sri Lankans travelling overseas. A high number of imported malaria cases between 2013 and 2017 originated from India (109/278 [39%]), and yet only 5% of our entire sample was travelling to an Asian destination. A previous study found that during the 6 y period from 2008 to 2013, a total of 1 352 140 Sri Lankans visited India.[32] The risk of acquiring malaria faced by travellers to India is probably underestimated by the general public. The prophylactic medicine prescribed for India is chloroquine, which is also available in the regional offices of the AMC, in contrast to mefloquine (given for African countries), which is not available in the regional offices. This could have also contributed to the lower percentage of people travelling to Asia reported in this study, which was conducted in the AMC head office. As health education in this regard is a priority, the AMC has taken efforts to carry out advocacy campaigns to promote the use of chemoprophylaxis for travellers prior to departure by issuing both ticketholders and advertisements (Figure 1) to travellers with a special focus on high-risk identified groups.

Our results are also subject to the limitations of recall bias and self-reports. Furthermore, we did not have facilities to measure biochemical evidence of compliance (serum mefloquine levels)

during the study. In addition, *Plasmodium vivax* and *Plasmodium ovale* malaria cases can present or relapse up to 1 y after the return of travellers, and this study did not assess late relapses or breakthrough infections. However, all patients were educated to see a doctor and mention their travel history in the case of fever. Furthermore, since malaria is a notifiable disease in Sri Lanka, any diagnosed cases would have been immediately reported to the AMC. None of the respondents in this study were reported to have malaria in the following year.

Conclusions

The protective efficacy of malaria chemoprophylaxis was 100% among the travellers who complied with prophylaxis following proper counselling by the AMC to exclude contraindications. There were no serious adverse effects reported among the military personnel who were on long-term prophylaxis with mefloquine. Even among civilians, adverse events due to prophylactic drugs were comparatively low. Although chemoprophylaxis is important, counselling travellers on preventive behaviour is equally important. Chemoprophylaxis with proper counselling is recommended as a key strategy for prevention of the reintroduction of malaria into Sri Lanka. Globally, it is of importance as an example for other countries that have recently eliminated malaria to structure their own prevention of reintroduction mechanisms.

Supplementary data

Supplementary data are available at International Health online (http://inthealth.oxfordjournals.org).

Authors' contributions: SDF, TW and RB planned and obtained funding to carry out the study in the military. SDF, DR, MD and HH planned and carried out the study at the AMC headquarters. CPM, MSW and CR collected the data and did the analysis. The manuscript was prepared by DF, DR, MSW and CR. All authors read and approved the final version.

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Ethical approval: Ethical approval for this study was obtained from the Ethics Review Committee of the Faculty of Medicine, University of Colombo, Sri Lanka (ERC: 15-077). In addition, permission to collect data from military travellers was obtained from the Ministry of Defence, Sri Lanka. Only investigators had access to the data collected for the purposes of this study. Informed consent was obtained from all participants prior to enrolment. Consent was obtained from the Ministry of Defence and all participants to publish the findings.

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