HHS Public Access

Author manuscript

Travel Med Infect Dis. Author manuscript; available in PMC 2024 March 21.

Published in final edited form as:

Travel Med Infect Dis. 2017 ; 17: 50–55. doi:10.1016/j.tmaid.2017.05.003.

Long term health outcomes among Returned Peace Corps Volunteers after malaria prophylaxis, 1995–2014

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Abstract

Background: A primary reason for non-adherence to malaria chemoprophylaxis is fear of latent side effects. We examined latent effects of malaria chemoprophylaxis among Returned Peace Corps Volunteers (RPCVs).

Methods: During July 18−September 16, 2016, RPCVs who served during 1995–2014 with an e-mail address in Peace Corps' RPCV database were invited to take an internet-based survey on malaria prophylaxis and medical diagnoses. "Good adherence" meant taking prophylaxis "as prescribed" or "most of the time." Prevalence of diseases diagnosed after Peace Corps service was compared between users and nonusers of each antimalarial using log-binomial regression.

Results: Of 8931 participants (11% response rate), 5055 (57%) took chemoprophylaxis. Initial chemoprophylaxis was mefloquine 59%, chloroquine 13%, doxycycline 16%, atovaquone-proguanil 4%, and "other" 8%. Sixty percent reported good adherence. Mefloquine users had the best adherence (67% good adherence). Prevalences of most diseases were similar between exposed and unexposed groups. Certain psychiatric diagnoses were slightly more likely among mefloquine users (PR 1.14, 95% CI [1.04–1.25], P = 0.0048). When excluding those with prior psychiatric illness, there were no differences in psychiatric diagnosis rates.

Conclusion: Malaria chemoprophylaxis use by Peace Corps Volunteers is safe. Avoiding mefloquine use in those with prior psychiatric illness can reduce psychiatric side effects.

Keywords

Antimalarial side effects; Malaria prophylaxis; Long-term traveler

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Conflicts of interest

The authors report no conflicts of interest.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

1. Introduction

Malaria chemoprophylaxis, when taken as prescribed, effectively prevents malaria in travelers to malaria-endemic areas [1]. Prolonged malaria chemoprophylaxis is indicated in long-term travelers, such as ex-patriates or Peace Corps Volunteers, who travel to malaria-endemic areas for six or more months. However, long-term travelers have reported poor adherence to malaria prophylaxis. Studies of long-term travelers found that only 11–62% reported adhering to their malaria chemoprophylaxis [2–4]. Reasons cited for poor adherence have included fear of adverse events from the antimalarials [2]. A previous survey of 781 Peace Corps Volunteers (PCV)[1] posted in Africa found that 73% of PCVs were adherent to malaria chemoprophylaxis, and among those that were non-adherent, 54% reported fear of latent side effects, defined as diseases that might develop after taking antimalarials, as one of their top reasons for nonadherence [5].

The latent adverse effects of malaria chemoprophylaxis in long-term travelers are not well known. Much of the literature available on side effects of antimalarials in long-term travelers examines adverse events occurring while taking the antimalarial, not afterwards. Studies on latent side-effects of antimalarials are scant. There have been rare case reports of persistent dizziness despite discontinuation of mefloquine [6], and a study of adverse events reported with mefloquine raised the question of long-term mental health issues [7]. Chloroquine-related retinal disease is a latent side-effect reported in 0.65–1.0% of patients with rheumatologic conditions who took 250 mg or more per day for more than 5 years [8,9]. Data on latent adverse events from doxycycline use are limited and primarily derived from the dermatologic literature on use of other tetracyclines for years at a time, but do not suggest any latent adverse events [10]. There are no published studies on latent side-effects of atovaquone-proguanil (Malarone®). More evidence is needed to address a significant fear affecting adherence among long-term travelers, that is, the possibility of latent adverse effects following malaria chemoprophylaxis.

The multi-year deployment of PCVs to malaria-endemic areas requires them to use malaria prophylaxis for an extended period of time. Approximately 60% of the 71,435 returned PCV from 1995 to 2014 were given malaria prophylaxis during their service. We conducted a survey of Returned Peace Corps Volunteers (RPCVs) and compared the prevalence of certain conditions after Peace Corps service between RPCVs who took malaria prophylaxis and those who did not.

2. Methods

2.1. Survey

From July 18 through September 16, 2016, RPCVs who served during 1995–2014 and had an e-mail address in Peace Corps' RPCV database were invited to participate in an internet-based survey using the Survey Monkey platform (www.surveymonkey.com). The Peace Corps RPCV database has e-mail addresses for 47,328 of the 71,435 PCVs who served during 1995–2014. To maximize response rate, reminder e-mails were sent weekly

[1]PCV = Peace Corps Volunteer, RPCV = Returned Peace Corps Volunteer.

during the survey period, and contacted RPCVs were encouraged to invite other RPCVs who served during the time of interest to participate in the survey. In addition, e-mails were sent to select regional RPCV groups asking them to encourage participation among RPCV members. Sample size targets varied by the expected prevalence of specific diseases among the unexposed, and the estimated proportion of respondents exposed to each antimalarial. For example, in a disease with an expected prevalence of 1% in the unexposed, and assuming that 60% of the respondents took malaria prophylaxis, and that of these, 45% took mefloquine, in order to achieve a power = 0.80 and an alpha = 0.05 to detect a 50% difference in prevalence of disease between those exposed to mefloquine and those unexposed, the target sample size needed is 7099, which translates to a response rate of 17%.

The survey included questions about the country of service, type of assignment, whether or not malaria prophylaxis was required at the assigned site, and details about malaria prophylaxis regimens including the type of antimalarial, amount of time on the antimalarial, degree of adherence, and if applicable, reasons for switching prophylaxis. Respondents were asked to report what medical diagnoses they had before, during, or after Peace Corps. The survey also included questions about medications before, during, or after Peace Corps, as well as habits such as drinking, and demographics. Because self-reported symptoms might lack specificity, the survey asked for diagnoses made by a healthcare provider.

2.2. Definition of exposure groups and outcomes

Exposure groups were created for each antimalarial of interest: mefloquine, chloroquine, doxycycline, and atovaquone-proguanil. “Any” exposure was defined as reporting any use of the drug of interest for prophylaxis. Both the initial and second (for those who may have switched) antimalarial regimens were examined when categorizing participants into exposure groups. Those who did not take malaria prophylaxis or did not take the antimalarial of interest were in the “unexposed” group.

Outcomes were self-reported diseases diagnosed by a medical professional after leaving Peace Corps. Disease diagnoses of particular interest included those that might be related to known or perceived adverse events of antimalarials, and feared latent adverse events reported in a prior survey of PCVs [5]. The most-feared latent adverse effects due to malaria prophylaxis were: neuropsychiatric events (depression, anxiety, and insomnia), cancer (unspecified), and “sun sensitivity” [5]. From these, the outcomes of major depressive disorder, bipolar disorder, anxiety disorder, insomnia, psychoses, and cancers including skin cancer were derived. All disease outcomes were examined individually and some were grouped into a composite outcome. “Any psychiatric outcome” included all reported psychiatric outcomes such as major depressive disorder, bipolar disorder, anxiety disorder, schizophrenia, obsessive-compulsive disorder, and “other”. “Gastrointestinal disorders” included irritable bowel syndrome and inflammatory bowel disease. In total, more than 40 disease outcomes were examined for each antimalarial.

A sensitivity analysis further examined outcomes from more intense exposure to the drugs, taking into consideration adherence and duration of time on the antimalarial. Good adherence was defined as reporting use of the antimalarial prescribed on all or most

days. “Prolonged” exposure was defined as taking the anti-malarial of interest with good adherence for 6 or more months. “Prolonged-exclusive” exposure was defined as taking the anti-malarial of interest with good adherence, for 6 or more months, and having not taken other antimalarials for prolonged periods of time.

2.3. Analysis

2.3.1. Calculating response rate and description of respondents—The original e-mail invitation included a unique identification number for the recipient to use. The recipients were instructed to invite other RPCVs to also take the survey, using that same identification number. Response rates to the original email invitation were estimated by the count of unique identification numbers divided by the number of invitations emailed. The count of non-unique identification numbers was used to estimate the number of RPCVs invited by others.

Representativeness of our sample was examined by comparing select demographics of our sample to the aggregate demographic data of PCVs serving during 1995–2014. Demographics and characteristics of respondents were summarized using simple frequencies.

2.3.2. Examining prevalence of disease outcomes—Each antimalarial exposure group was examined for all outcomes. After disease outcome prevalence was measured by simple proportions, prevalence ratios were calculated, using log-binomial regression for diseases of interest. Possible confounders to any association between specific antimalarial exposure and outcomes of interest were examined, including sex, age at interview, family history of disease, past medical history, and habits such as drinking alcohol. To account for these confounders, multivariable analysis using log-binomial regression provided adjusted prevalence ratios (PR) of the disease outcomes. If the log-binomial regression model did not converge, Poisson regression was done. Data were analyzed using SAS v9.3 (SAS Institute, Cary, NC).

Informed consent was obtained from all participants. The protocol for this study was reviewed and approved by the Human Subjects Research Protection Office (protocol number 6752) at the Centers for Disease Control and Prevention.

3. Results

3.1. Respondents

Of the 47,328 RPCVs invited to take the survey, a total of 8931 RPCVs (13% of the RPCV population who served during the time of interest) responded. Of these, 5474 provided an identification code, of which 5386 were unique, suggesting that the response rate to the original email was at least 11%. There were 88 responses with non-unique identification codes, indicating that these respondents were invited by others.

Almost half, 47.1% of respondents, were between 30 and 39 years old, 31.1% were male, 82.9% were white, and 67.0% had a graduate or professional degree. Most had served in a rural assignment (78.3%), many in the Africa region (45.0%). A comparison of select

demographics between respondents and the larger population of PCVs who served from 2003 to 2014, the years for which this data are readily available (unpublished data, Peace Corps), demonstrated similar proportions (Table 1).

3.2. Description of antimalarial use

Of the 8931 respondents, 5055 (56.6%) reported taking any malaria prophylaxis during Peace Corps service. The initial anti-malarial drug taken for prophylaxis was mefloquine for 2981 (59.0%), chloroquine for 674 (13.3%), doxycycline for 831 (16.4%), atovaquone-proguanil for 183 (3.6%), and "other" for 386 (7.6%). Of the 5026 that reported their degree of adherence to the first malaria prophylaxis drug, specifically, taking prophylaxis medications "as prescribed" or "as prescribed most of the time", 3065 (61.0%) reported good adherence. The initial antimalarial was discontinued by 473 (9.4%) because of side effect.

Compared to RPCVs who used other antimalarials, RPCVs who used mefloquine had the best adherence, with 66.7% of users reporting good adherence (Table 2). Also, a higher proportion of mefloquine users, 44.4%, reported being on their antimalarial for two or more years compared to RPCVs who used other antimalarials (Table 3).

For those who switched antimalarials and reported which alternate antimalarial was given (N = 965), the top alternate antimalarial was doxycycline, 608 (63.0%) (Table 4). Of the 964 that reported a reason for switching to a second malaria prophylaxis, 762 (79.1%), switched to a second antimalarial due to "side effects" (Table 4). Overall, adherence to an alternate antimalarial was better than to the initial antimalarial, with 71.9% on an alternate anti-malarial reporting good adherence. Most (59.3%) reported being on the alternate antimalarial for more than six months.

3.3. Numbers in exposure groups

The numbers of respondents categorized in each exposure group is summarized in Table 5.

3.4. Disease diagnoses after Peace Corps service

Disease outcomes with statistically significant differences among those with any antimalarial exposure and those unexposed are presented for each drug below. Outcomes that were not significantly different between the exposed and unexposed for all antimalarial types are summarized in Table 6. Overall, there were very few disease diagnoses that were more prevalent among those who used certain antimalarials when compared to those who did not.

3.4.1. Mefloquine—The prevalence of having any psychiatric disease after Peace Corps service among those with any mefloquine exposure was lower than those with no mefloquine exposure (15.9% versus 18.8%, respectively). However, a closer look at these respondents revealed that among RPCVs with prior psychiatric illnesses that could pre-dispose them to adverse events with mefloquine (bipolar, depression, anxiety, and psychosis) compared to those with no prior history, a lower proportion had any mefloquine exposure (16.2% versus 44.0%, respectively), and a higher proportion had psychiatric diagnoses after

Peace Corps (55.1% versus 12.4%, respectively). Peace Corps screens for and avoids use of mefloquine in those who report having these select psychiatric illnesses. When controlling for prior history of psychiatric disease, family history of psychiatric disease, age, and sex, those with any mefloquine exposure had a slightly higher likelihood of having any psychiatric diagnosis after Peace Corps service (PR = 1.15, 95% confidence interval [CI] 1.07–1.23, p = 0.0001); however, if those with a previous psychiatric history (n = 847) were excluded from the analysis, there was no difference in prevalence of any psychiatric outcomes between those who had any mefloquine exposures and those who had none (PR = 1.07, 95% CI 0.95–1.21, p 0.2388). Furthermore, when comparing those with prolonged or prolonged-exclusive mefloquine exposure to those without any exposure, there was no difference in prevalence of any psychiatric disease.

Of women with any mefloquine exposure, 29.8% reported having yeast infections after Peace Corps service compared to 24.0% of those with no mefloquine exposure. When controlling for age, previous history of yeast infections, and diabetes, those with any mefloquine exposure had a slightly higher likelihood of yeast infection (PR = 1.28, 95% CI 1.17–1.39, p <0.0001). This association was not seen when the analysis was restricted to those with prolonged or prolonged-exclusive mefloquine exposure.

For those with any mefloquine exposure compared to those with none, there were no differences in prevalence of several disease diagnoses that might be related to side effects that have been reported with mefloquine use. These diseases include vestibular dysfunction, neurologic disorders, insomnia, arrhythmias, and other cardiac diseases.

3.5. Chloroquine

Gastrointestinal diseases were 1.40 (95% CI 1.10–1.79, p = 0.0070) times more prevalent among those who used any chloroquine [63 (9.1%)] than among those who did not [486 (6.7%)]. This increase in prevalence was not observed among those who had prolonged or prolonged-exclusive use of chloroquine.

Prevalence of several disease diagnoses that could be related to side effects previously reported with chloroquine use were similar in exposed and unexposed groups. These diseases include ocular toxicity and psoriasis. However, there were small numbers of respondents reporting ocular toxicity; only 4 (0.6%) of those who took chloroquine and 52 (0.7%) of those who did not take chloroquine.

3.6. Doxycycline

Insomnia was the only disease diagnosis more prevalent among those that used any doxycycline compared to those who did not (9.0% versus 5.4%, respectively, PR 1.27, 95% CI 1.02–1.59, p = 0.0343). There was no difference in prevalence of insomnia between those with prolonged or prolonged-exclusive doxycycline use and those with no doxycycline use.

For exposed and unexposed groups, there were no differences in prevalence of several disease diagnoses extrapolated from side effects previously reported or feared with doxycycline use. These diseases include recurrent yeast infections, allergic or contact

dermatitis (extrapolated from sun-sensitivity rash), and gastrointestinal diseases (irritable bowel syndrome, inflammatory bowel disease).

3.7. Atovaquone-proguanil

There were no differences in prevalence of post-Peace Corps disease diagnoses among those who had used atovaquone-proguanil compared to those who did not. This includes disease diagnoses derived from reported and feared adverse events with atovaquone-proguanil such as migraines based on reports of headaches, and fatty liver, cirrhosis, or liver failure.

4. Discussion

This large survey of RPCVs is one of the first studies to look at latent adverse effects of using antimalarials for prophylaxis over an extended period of time. Of the more than 40 disease outcomes examined across four different types of antimalarials, there were very few disease diagnoses that were more prevalent among those who had used specific antimalarials compared to those who did not. Almost all of the diseases possibly related to latent side effects reported as concerns by previously surveyed PCVs [5], including neuropsychiatric diseases, “cancer”, and “sun-sensitivity”, were found to be no different between exposure groups. In addition, of the four antimalarials of interest, the largest proportion of respondents who took antimalarials used mefloquine. Adherence to mefloquine was better than to all other antimalarials, and mefloquine was used for the longest amount of time. Other studies have similarly found better adherence to a weekly drug like mefloquine than other antimalarials; one study found adherence to mefloquine to be 80% while adherence to doxycycline, a daily drug, was 60% [4,11].

Mefloquine is known to cause neuropsychiatric adverse events in 1–10% of persons while taking it [4,12,13]. Because of this, mefloquine should not be prescribed to those who have a history of psychiatric disorders [14]. This survey found a 1.14 to 1.19 times increased likelihood of psychiatric diagnoses after Peace Corps among those who took mefloquine, which is consistent with the literature, yet, when those with a past psychiatric history were excluded from the analysis, there was no difference in psychiatric outcomes. This suggests that mefloquine use did not increase the risk of new psychiatric diagnoses among the Peace Corps Volunteers surveyed. A recent study examining neuropsychiatric outcomes in U.S. service members in the year after taking mefloquine or doxycycline prophylaxis had similar findings; those who took mefloquine had a 1.12–1.83 times risk of neuropsychiatric outcomes when compared to doxycycline, with risks being higher among those with a prior history of neuropsychiatric disease [15]. These data support that avoiding mefloquine use in those with a prior history of psychiatric problems can minimize latent psychiatric effects. In fact, the finding that RPCVs with a history of psychiatric illness were much less likely to have taken mefloquine when compared to those who did not have past psychiatric issues, may reflect good practice by Peace Corps’ screening for and avoiding use of mefloquine in those with past psychiatric disorders.

As early as 2004, Peace Corps technical guidelines for medical staff stated that mefloquine was contraindicated in persons with active depression, a recent history of depression, generalized anxiety disorder, psychosis, schizophrenia, or other major psychiatric disorders.

Peace Corps Medical Officers were cautioned from using mefloquine if a PCV had a previous history of depression. This screening depends on PCVs self-reporting a history of psychiatric disorders, so it would be expected that a small percentage of PCVs with a history of psychiatric disorders were not detected during screening and were given mefloquine.

It should also be noted that for U.S. travelers that are pregnant or children <5 kg, mefloquine is the only drug option for malaria prophylaxis when traveling to countries with chloroquine-resistant malaria [1]. When taking into consideration the previously discussed evidence for good adherence in users, and good tolerance especially when contraindications are taken into account, mefloquine is a useful drug for the prevention of malaria. Others have also supported the need to keep mefloquine as a viable option for malaria prevention [16].

Yeast infections were slightly more likely among those who had used mefloquine than those who had not. This has not been previously reported. Increased occurrence of yeast infection has been reported with use of antibiotics, but not with mefloquine. If the cause of yeast infections were due to an antibiotic mechanism, it would be expected for this finding to be consistent or even more pronounced with more prolonged exposure to mefloquine, but those with prolonged exposure to mefloquine in this study did not report increased prevalence of yeast infection when compared to those with no mefloquine exposure.

Findings of gastrointestinal disease and insomnia were more likely among those who had used chloroquine and doxycycline, respectively, than those who had not. These findings have not previously been reported and are surprising, considering the decades of experience using these two drugs for the prevention and treatment of malaria, and for the treatment of other diseases [17,18].

Notably, many of the disease diagnoses based on previously reported and known adverse effects of these antimalarials and those feared by PCVs in the earlier survey were no more common in the exposed groups. While mefloquine and doxycycline had robust sample sizes for most of the outcomes examined, the sample size was smaller for chloroquine and atovaquone-proguanil. It is possible that the small sample size for chloroquine and atovaquone-proguanil resulted in the study being underpowered to detect differences in the prevalence of disease in the exposed and unexposed groups for these two drugs.

4.1. Limitations

In addition to being underpowered to detect differences for chloroquine and atovaquone-proguanil exposure, and for rarer diseases, there are other limitations to this study. Selection bias is inherent in this survey, as those with health issues and concerns related to their history of antimalarial use might be more likely to respond. This would have biased the study towards having more significant findings for disease outcomes among those taking antimalarials. However, the opposite was true; few disease outcomes were found to be more prevalent even for the drugs with the largest sample size, doxycycline and mefloquine. Also, this was a convenience sample of those RPCVs with active e-mail addresses on file with Peace Corps, and contacts of RPCVs who were invited. A group of RPCV friends may be more similar than RPCVs who are not in the same social circle. To minimize the impact of

a large group of like-individuals influencing the results, the original invitation included an identification number to be re-used by others invited by the original invitee. Frequencies of these identification numbers were examined for any large groups that might influence these results, and answers within these groups were examined to see if they were uniform and might influence the results. With over 3400 respondents missing an identification number, it was difficult to know whether large social groups influenced the results. Another limitation is recall bias because the survey depends of self-reporting for antimalarial use and disease outcomes.

5. Conclusion

Malaria chemoprophylaxis is a safe intervention to prevent malaria with very few latent adverse effects. Psychiatric side effects of mefloquine can be minimized by avoiding use of mefloquine among those with a history of psychiatric illness. This information should be reassuring for the select group of people in whom long term prophylaxis is recommended.

Acknowledgements

The Peace Corps and the Centers for Disease Control and Prevention would like to acknowledge the Returned Peace Corps Volunteers who participated in this survey.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Table 1

Select characteristics of respondents compared to PCVs who served during 2003–2014.

Characteristic		Respondents n(%)	All PCVs 2003—2014[a] n(%)
Male		2312 (31.1)	37,572 (39.8)
Race	White	6439 (82.9)	69,988 (81.0)
	Hispanic or Latino	394 (5.1)	5159 (6.0)
	Black or African American	218 (2.8)	3415 (4.0)
	Asian	266 (3.4)	4384 (5.1)
	Other	453 (5.8)	3480 (4.0)
Region	Africa	3563 (45.0)	34,004 (39.3)
	Europe, Mediterranean, and Asia (including North Africa)	2097 (26.5)	25,253 (29.2)
	Inter-America and Pacific	2251 (28.5)	27,311 (31.5)
Work	Education	2777 (35.2)	32,719 (34.7)
	Agriculture	593 (7.5)	4915 (5.2)
	Community economic development	918 (11.6)	13,543 (14.4)
	Youth in development	488 (6.2)	4311 (4.6)
	Environment	715 (9.1)	13,058 (13.8)
	Health	1774 (22.5)	21,926 (23.3)
	Other	632 (8.0)	4274 (4.5)

[a]From unpublished data, Peace Corps.

Table 2

Adherence to first antimalarial for prophylaxis of malaria.

Degree of Adherence	Mefloquine n (%) (N = 2972)	Chloroquine n (%) (N = 668)	Doxycycline n (%) (N = 828)	Atovaquone-proguanil n (%) (N = 183)	Overall n (%) (N = 5026)[a]
Taken as prescribed	1691 (56.9)	177 (26.5)	425 (51.3)	86 (47.0)	2547 (50.7)
Taken as prescribed most of the time	291 (9.8)	66 (9.9)	110 (13.3)	25 (13.7)	518 (10.3)
Taken half the time	128 (4.3)	58 (8.7)	54 (6.5)	11 (6.0)	263 (5.2)
Rarely taken	236 (7.9)	207 (31.0)	81 (9.8)	34 (18.6)	628 (12.5)
Never taken	61 (2.1)	67 (10.0)	30 (3.6)	10 (5.5)	208 (4.1)
Stopped then switched because of side effects	365 (12.3)	23 (3.4)	64 (7.7)	9 (4.9)	473 (9.4)
Other	200 (6.7)	70 (10.5)	64 (7.7)	8 (4.4)	389 (7.7)

[a]"Overall" includes those who reported taking any of the four antimalarials of interest or other antimalarial, and provided information on degree of adherence.

Table 3

Length of time on first antimalarial for prophylaxis of malaria.[a]

Time (months)	Mefloquine n (%) (N = 2887)	Chloroquine n (%) (N = 624)	Doxycycline n (%) (N = 780)	Atovaquone-proguanil n (%) (N = 173)	Overall n (%) (N = 4811)[a]
<6 months	621 (21.5)	297 (47.6)	225 (28.9)	64 (36.7)	1379 (28.7)
6–11 months	424 (14.7)	95 (15.2)	96 (12.3)	25 (14.5)	675 (14.0)
12–23 months	561 (19.4)	88 (14.1)	172 (22.1)	41 (23.7)	903 (18.8)
24 + months	1281 (44.4)	144 (23.1)	287 (36.8)	43 (24.9)	1854 (38.5)

[a]"Overall" includes those who reported taking any of the four antimalarials of interest or other antimalarial, and provided information on time on the antimalarial.

Table 4

Alternate antimalarial use and reasons for switching.

Alternate Antimalarial (N = 965)	**n(%)**
Mefloquine	98 (10.2)
Chloroquine	19 (2.0)
Doxycycline	608 (63.0)
Atovaquone-proguanil	173 (17.9)
Other	67 (6.9)
Reason for switching (N = 964)	
Side effects	762 (79.1)
Deployment to a different area	27 (2.8)
Other	175 (18.2)

Table 5

Numbers of respondents in each exposure group, and in sensitivity analysis.

Antimalarial type	Any		Prolonged		Prolonged-exclusive	
	Exposed	Unexposed	Exposed	Unexposed	Exposed	Unexposed
Mefloquine	3401	5530	2070	5530	1734	5494
Chloroquine	715	8216	215	8216	190	7869
Doxycycline	1743	7188	1015	7188	708	7123
Atovaquone-proguanil	429	8502	249	8502	173	8206

Table 6

Outcomes not significantly different between exposure groups for all antimalarial types.[a]

Neuropsychologic: Dementia, migraines, seizures, tinnitus, vestibular disorder, “other” neurologic disorder, “any” neurologic disorder
Cardiac: Arrhythmia, congestive heart failure, myocardial infarction, “any” cardiac disorder
Ophthalmologic: Macular degeneration, retinopathy, “any” ophthalmologic disorder
Dermatologic: Allergic dermatitis, eczema, psoriasis, “other” dermatologic condition, “any” dermatologic condition
Reproductive: Miscarriage
Gastrointestinal: Cirrhosis, esophageal ulceration, fatty liver, liver failure, peptic ulcer, “any” liver dysfunction
Infectious: Amebiasis, giardia, “other” gastrointestinal infection, “any” gastrointestinal infection
Hematologic/Oncologic: breast cancer, gastric cancer, leukemia, liver cancer, lymphoma, prostate cancer, “other” cancers, “any” cancer

[a]“Any” means that the diagnoses previously listed were aggregated into one outcome.