A cluster of *Plasmodium vivax* malaria in an expedition group to Ethiopia: Prophylactic efficacy of atovaquone/proguanil on liver stages of *P. vivax*

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**KEYWORDS**
Malaria; *Plasmodium vivax*; Prophylaxis; Atovaquone/proguanil

**Summary**  
**Objectives:** Complete prevention of malaria especially *Plasmodium falciparum* is the goal of prophylaxis. A survey, designed to ascertain reasons behind the choice of malaria prophylaxis, compliance and side effects, and to gather data on acquired malaria, identified a cluster of *Plasmodium vivax* infection in a cohort of 33 who travelled to Ethiopia on a scientific expedition.  
**Methods:** A questionnaire based survey of travellers who took part in a scientific survey and rafting expedition in Ethiopia between October and December 2005 on their return from the expedition and two years later.  
**Results:** 31 of 33 subjects completed the survey fully. Evidence was obtained on factors influencing choice of, and adherence to prophylaxis and the incidence and type of malaria related to prophylaxis. Over the two year follow up period 32% of travellers developed *P. vivax* malaria. Of those taking Mefloquine and Doxycycline 50% and 66% respectively developed malaria, compared to none taking Atovaquone/Proguanil as prophylaxis. Awareness and management of malaria was inadequate in several cases. Failure to use Primaquine led to second relapses.  
**Conclusions:** Within this cluster, prophylaxis against *P. falciparum* was successful. Widespread failure of prophylaxis against *P. vivax* malaria was documented despite the use of recommended regimes of known efficacy against the parasite. Atovaquone/Proguanil had the least side effects and afforded the highest protection. Atovaquone/Proguanil may provide previously unrecognised protection against liver stages of *P. vivax*.

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Introduction

Despite recent trends indicating a decline in incidence, infection with Plasmodium spp remains a serious hazard in travellers to much of the tropics. The UK Health Protection Agency reports 1–2000 cases diagnosed on return from overseas annually. In 2010 over 1000 cases of Plasmodium falciparum and 350 of Plasmodium vivax were imported into Britain.1 Surveys of imported infection provide important information about distribution of the parasite and vector and behavioural trends in prophylaxis among returning travellers. However they are inevitably large samples of individual cases which cannot be related accurately to one another in terms of environmental factors and exposure to infection. Clustered outbreaks of malaria are reported rarely. They have been noted amongst refugees,2–4 returning holiday makers,5,6 and expatriate students.7 A common feature is partial or complete adherence to advice on prophylaxis.8 Clusters of malaria have occurred following disease importation where the outbreak correlated geographically with specific breeding habitats of the anopheline vectors.9 There are very few publications on imported P. vivax malaria but the majority of sufferers appear to be travellers, expatriates, recent immigrants, or foreign visitors.10 We describe an unusual cluster of P. vivax infection acquired during a scientific expedition in Ethiopia. The participants were a group travelling from non-malarious areas, mainly the UK, to north-western Ethiopia between October and December on a two month scientific expedition. Prior to travel they individually took advice on prophylaxis against malaria. The close proximity of the group throughout a prolonged period in an endemic area and the high incidence of acquisition of malaria imply that every member of the party was exposed to infection. Malaria is present in all areas of Ethiopia, except Addis Ababa, and areas above 2600 m. P. vivax is highly prevalent in sub-Saharan Africa and in Ethiopia it is the second commonest cause of malaria morbidity, accounting for 30–40% of cases.11 This group of non-immune travellers was in Ethiopia during one of the main seasons for transmission of malaria (from September to December).12 Such a group provides an unusual opportunity to derive observational ‘controlled’ data on the comparative efficacy of prophylactic regimes and how they may be improved.

Methods

Study design

This was a questionnaire based study performed by one of us (AM) who was on the expedition, was responsible for health advice and for ensuring compliance with antimalarial medication. The cohort was contacted shortly after return from Ethiopia. All subjects were approached individually and consent obtained for their anonymised data to be included and analysed. Formal ethical approval was not sought. All were asked to contact the study leader if they developed malaria and complete a second questionnaire. All were contacted 2 years after return either via email or telephone to complete the data on malaria incidence.

Diagnosis of malaria

The single subject on no prophylaxis who acquired both P. falciparum and P. vivax was diagnosed locally in Addis Ababa by direct microscopic examination of thick and thin blood films (confirmed visually by author AM). One subject was diagnosed with P. vivax by thin and thick film examination in a hospital in New Zealand. These two have not been able to be definitively independently confirmed. All others were diagnosed in UK hospitals by thick and thin film examination. Samples from district hospitals were sent for confirmation to The London School of Tropical Medicine and Hygiene.

Main outcome measures

Evidence was obtained on efficacy of, and factors influencing choice of, and adherence to prophylaxis and the incidence and type of malaria.

Results

Of the total group of 33 people all consented to participate in the survey of whom 31 returned complete data. Two were lost to follow up. The age range was 22–74 years (mean 54). Advice on prophylaxis was obtained most commonly from family practitioners (40%) and specialist services and mostly was appropriate. Two of the subjects had travelled to Bolivia and one to Iraq in the 18 months prior to the Ethiopia expedition. None had contracted malaria.

Travel histories and treatment

Subject 1
Took doxycycline during trip and for subsequent 4 weeks. Developed malaria (reported as probable P. vivax) 4 months after return was treated with chloroquine and had relapse five weeks later.

Subject 2
Took doxycycline during trip and for subsequent 3 weeks (3 doses missed contributed to by admission to ITU for stridor ultimately necessitating tracheal resection). Developed P. vivax and Plasmodium malariae 6 weeks after return. Treated with Quinine.

Subject 3
Took doxycycline during trip missing 2–3 doses and for subsequent 4 weeks. Developed P. vivax malaria 9 months after return treated with Quinine and Primaquine.

Subject 4
Took doxycycline during trip missing no doses. Developed P. vivax malaria 9 months after return treated with chloroquine and Primaquine.

Subject 5
Took mefloquine during trip, missing no doses and for subsequent 4 weeks. Developed malaria (unspecified — no
Subject 6
Took mefloquine during trip and during subsequent 5 weeks missing no doses. Developed P. vivax malaria 4 months after return treated with Quinine then chloroquine and Primaquine.

Subject 7
Took mefloquine during trip and for 4 weeks subsequently missing one dose. Developed P. vivax malaria 5 months after trip treated with Quinine.

Subject 8
Took mefloquine during trip and for subsequent 4 weeks. Developed P. vivax malaria 6 months after return (treatment uncertain) and further relapse 2 years later treated with Atovaquone/Proguanil.

Subject 9
Took mefloquine during trip and for 4 weeks subsequently; one dose taken one day late. P. vivax malaria diagnosed 6 months after return. Treatment not certain.

Subject 10
Took mefloquine during trip and for subsequent 4 weeks; one dose taken late. P. vivax and Plasmodium ovale malaria diagnosed in teaching hospital (under care of AMLL) 4 months after trip (confirmed by second centre). Treated with Quinine then chloroquine and Primaquine.

Subject 11
Took homeopathic remedy. Developed P. falciparum and P. vivax malaria within one month of start of trip (diagnosed in Ethiopia visually confirmed by AM). Treated with Quinine and subsequently Atovaquone/Proguanil.

Prophylaxis

Recommended prophylaxis for this area of Ethiopia includes Doxycycline, Mefloquine, or Atovaquone/Proguanil. The breakdown of use is shown in Table 1. One person chose not to take any and one was given advice to take Chloroquine/Proguanil; this is not considered efficacious in this region. The reasons given for the specific choice varied. Advice given and cost were the most important factors in choosing the type of prophylaxis. The nature and incidence of side effects of chemoprophylaxis were predictable with the exception of an extremely high level of photosensitivity in those taking Doxycycline, 83% compared to previous reports of 4% and up to 15% in long-term usage. The sensitivity was self limiting. No one discontinued use due to this side effect.

Good drug compliance was recorded, uninfluenced by drug side effects with 50% reporting taking all prophylaxis on time. 33% of the group missed at least one dose (Table 2). The period of time that prophylaxis was taken after return varied within each group with some taking the prophylaxis for longer than the recommended time (Table 3). Failure to take prophylaxis did not correlate with subsequent P. vivax relapse.

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| Table 1 | Number of subjects developing malaria, and type, relative to prophylaxis. |
|---------|-----------------------------|-----------|-----------|-----------|-----------|
| Prophylaxis taken | Number developing antimalarial malaria | % of group developing antimalarial malaria | Specific type of malaria identified (may have been more than one type in an individual) | P. falciparum | P. vivax | P. ovale | P. malariae | Unknown type |
| Atovaquone/proguanil | 11 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Mefloquine | 12 | 4 | 33 | 1 | 4 | 33 | 1 | 2 |
| Doxycycline | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Chloroquine/proguanil | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| None | 1 | 1 | 100 | 1 | 1 | 100 | 1 | 2 |
| Total | 31 | 11 | 35 | 1 | 9 | 1 | 1 | 2 |
Malaria incidence

Sixteen malaria infections (including two relapses of \( P. \) vivax) were diagnosed in eleven subjects. One subject took no prophylaxis and acquired \( P. \) falciparum and \( P. \) vivax. Nine confirmed and one probable cases of \( P. \) vivax were diagnosed in subjects who took prophylaxis. In one each of these co-infection with \( P. \) ovale and \( P. \) malariae was detected. Infection did not correlate strongly with adherence to medication.

In total, over the two year follow up period 32% of travellers developed \( P. \) vivax malaria. Of those taking Mefloquine and Doxycycline 50% and 66% respectively developed malaria, compared to zero taking Atovaquone/Proguanil as prophylaxis (Table 1). From the start of the trip and hence the start of exposure to malaria, the average time to onset of symptoms was five months (range one–nine months) (Fig. 1). The only person to develop \( P. \) falciparum was not on any recommended malarial prophylaxis.

Table 2 Doses missed/delayed.

<table>
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<tr>
<td></td>
<td>Number</td>
<td>%</td>
<td>Number</td>
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<td>Number</td>
<td>%</td>
<td>Number</td>
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<td>1</td>
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<td>1</td>
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<tr>
<td>Mefloquine</td>
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<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Doxycycline</td>
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<tr>
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</table>

Table 3 Time taken after return.

<table>
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<th>Time taken after return</th>
<th>Number taking antimalarial</th>
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<td>2 weeks</td>
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<td>Mefloquine</td>
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<tr>
<td>Doxycycline</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Chloroquine/proguanil</td>
<td>1</td>
<td>a</td>
</tr>
</tbody>
</table>

a The recommended time prophylaxis should be taken after leaving a malarious zone.

Time to presentation and diagnosis of malaria species

Recognition, time to diagnosis and treatment of malaria varied dependent on where the subject presented.

Two presented prior to three months, one with \( P. \) falciparum and the other having been unwell with an unrelated illness necessitating intensive care treatment in the month prior to his development of malaria. The time taken to diagnose the type of malaria varied considerably. Three people reported being initially declined malaria testing by local doctors and accident and emergency departments in the UK. Mistakenly these health professionals believed that malaria would not present over three months from exposure. Fortunately they persisted and all three tested positive for malaria. Those presenting to hospitals with an interest in tropical diseases were diagnosed on the same day of presentation. Delay in type identification occurred in some of the patients presenting to local district hospitals in which samples are sent to tertiary referral centres for typing.

Discussion

This is one of the very few ‘clusters’ of \( P. \) vivax malaria reported and uniquely concerns a group with identical exposure to malaria both temporally and geographically. Although it relies on self reporting, adherence to prophylaxis was closely monitored by one of us (AM) who was responsible for malaria compliance; the early case of \( P. \) falciparum in the subject not on conventional prophylaxis contributed to the high degree of compliance observed and reported. In this group 50% of those on Mefloquine and 66% on Doxycycline developed \( P. \) vivax malaria. Nobody on Atovaquone/Proguanil developed either \( P. \) falciparum or \( P. \) vivax infection.

Apart from good adherence to prophylaxis the group had a plentiful supply of N,N-diethyl-3-methylbenzamide
Atovaquone/proguanil prevents *Plasmodium vivax* relapse

(DEET), mosquito nets, or tents with mesh liners were used, and care was taken to cover up at dusk. During the trip nightly reminders were given. Missed doses did not correlate with subsequent *P. vivax* relapse and the long half life of Mefloquine (21 days) makes it unlikely that a single missed dose would have led to susceptibility to infection. Despite good compliance 32% developed malaria in the 2 year follow up period.

Atovaquone/Proguanil differs from Mefloquine and Doxycycline in its action on stages of the life cycle of malarial plasmodia. All three agents act on the blood stage as schizonticides. In addition Atovaquone/Proguanil acts on the replication of hepatic trophozoites, thus it is advised to be continued for one week after leaving the endemic area whereas the others have to be continued for four weeks to act on any mature schizonts released from the liver into the bloodstream. None of the recommended antimalarial drugs are reported to act against the hypnozoite form of *P. vivax* and *ovale*. Primaquine is currently the only effective agent against the reservoir of the latent hypnozoite form although cases of Primaquine resistance are reported. None of these subjects took Primaquine and no current guidelines advise it to be taken as a follow on from any conventional anti-falciparum prophylaxis. One previous report from an analogous survey of expedition travellers to Ethiopia17 comments on the success of Primaquine as prophylaxis against *P. vivax* and reports its use as single agent prophylaxis. In this report, of 106 subjects on Primaquine alone 4 developed *P. falciparum*, one *P. vivax* and one dual infection. Despite suggestions that Primaquine alone is potentially adequate protection this would be considered as an unacceptable risk of *P. falciparum*. The efficacy of Atovaquone/Proguanil we report would obviate such a risk. Interestingly short course treatment with Atovaquone/Proguanil followed by Primaquine has been shown to be almost 100% effective in acute treatment of *P. vivax*.18 Atovaquone/Proguanil has also been reported as 85% efficacious for prophylaxis against *P. vivax* in a randomised placebo controlled study,19 however isolated case reports exist of its failure20 however it appears that none of the subjects in these publications have been as scrupulously monitored as in the study reported here. The relative efficacy of Atovaquone/Proguanil in preventing relapse without Primaquine treatment suggests that the parasite is in a drug sensitive phase within the liver prior to developing into a hypnozoite.

In this study all recommended prophylactic agents prevented *P. falciparum* malaria. Atovaquone/Proguanil prophylaxis appears to be very effective at preventing all types of malaria. Travellers to areas where *P. vivax* is a risk might be advised to use Atovaquone/Proguanil prophylaxis. This is licensed for only 28 days continuous usage so if travelling for longer or, if they choose Mefloquine or Doxycycline, Primaquine could be administered after G6PD testing to eliminate hypnozoites. Further research on the efficacy of Atovaquone/Proguanil on hepatic forms of *P. vivax* is warranted.

**Summary**

A survey of compliance, efficacy and side effects of malaria prophylaxis identified a cluster of infection in a cohort of 33 travellers to Ethiopia 32% of whom developed *P. vivax* malaria. Of those taking Mefloquine and Doxycycline as prophylaxis 50% and 66% respectively subsequently developed *P. vivax*, compared to none taking Atovaquone/Proguanil. Failure to use Primaquine led to second relapses. Although prophylaxis against *P. falciparum* was successful *P. vivax* malaria infection was common despite the use of recommended regimes of known efficacy against the parasite. Atovaquone/Proguanil may provide previously unrecognised protection against liver stages of *P. vivax*.

**Conflict of interest**

None.

**Acknowledgements**

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**References**


