

Inadequate chemoprophylaxis and the risk of malaria

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BACKGROUND

Malaria is an important disease for Australian travellers, particularly to Papua New Guinea. Travellers often seek health advice from their general practitioner before travel or if they develop illness after travel.

METHOD

A retrospective cohort investigation into malaria risk in a group of adult Australians that trekked the Kokoda trail in Papua New Guinea.

RESULTS

Six of 38 group members were diagnosed with malaria on return from Papua New Guinea. None of the 12 individuals who took chemoprophylaxis for the recommended period post-travel developed malaria compared to 4/24 travellers who terminated prophylaxis prematurely or 2/2 who took no chemoprophylaxis.

DISCUSSION

Chemoprophylaxis is effective if taken for the full recommended period following travel to a malaria endemic area; 4 weeks for doxycycline and mefloquine, and 7 days for atovaquone-proguanil. Malaria is a likely cause of illness in recently returned travellers from Papua New Guinea who develop a febrile illness.

Malaria is the most important parasitic disease affecting people living in and travelling to malaria endemic areas.¹ Due to large scale global travel some people infected with malaria may develop symptoms in countries where malaria is not endemic. The risk of malaria for travellers varies substantially depending on the area visited, intensity of transmission, season and exposure factors, including type of accommodation and itinerary.²

Malaria in humans is caused by four parasite species: *Plasmodium falciparum*, *P. vivax*, *P. ovale* and *P. malariae*. Transmission is through the bite of an infected female Anopheles mosquito. The incubation period varies from 7–30 days but chemoprophylaxis can prevent malaria or delay the onset of illness by weeks or months. Delays characterise *P. vivax* and *P. ovale* infections that produce dormant liver stage parasites. The diagnosis of malaria depends on the demonstration of parasites on a blood smear or a positive blood antigen test. Commonly the clinical picture includes: fever, chills, sweats, headaches, nausea and vomiting, and malaise. Serious complications may accompany *P. falciparum* infections, particularly cerebral malaria, severe anaemia and multi-organ failure. Malaria can be a fatal disease. However, illness and death from malaria can be prevented.³

In Australia there were 799 notifications of malaria in

2004–2005 and none were reported as locally acquired.⁴ Papua New Guinea (PNG) is often implicated as the source of infection among Australian travellers who are diagnosed with malaria after overseas travel.⁵ The contribution of PNG to imported malaria in Australia has ranged from 18–74% depending on the year studied and region of study.^{5–7} Malaria is endemic in areas below 1800 m altitude in PNG, but can also occur in the highlands.⁸ All four malaria species are present in PNG with the potentially life threatening *P. falciparum* being present throughout the malaria affected area at levels rarely found outside sub-Saharan Africa.⁹ The major malaria vectors *Anopheles farauti*, *A. koliensis* and *A. punctulatus* are found in coastal, low lying and highland areas of PNG. These species have different biting activity, but peak activity is between sunset and dawn.¹⁰

Unfortunately no effective vaccine against malaria is currently commercially available.¹¹ Travellers to malaria endemic areas are advised to use effective personal protection measures (PPM) and chemoprophylaxis. The predominant site of action of many antimalarial chemoprophylactic drugs is the blood stage rather than the liver stage of the plasmodium parasite. These antimalarials must be taken for 4 weeks after the last possible exposure to malaria infection to enable action against blood stage

parasites as they emerge from the liver.^{1,12}

Personal protection measures include bed nets and other materials impregnated with insecticides, window and door screens, knockdown insecticides indoors, covering exposed areas with light coloured clothing and shoes and socks, regularly applying an insect repellent that contains N-diethyl-metotoluamide, using mosquito repellent coils and vapourising mats, and avoiding exposure during peak biting times.¹³ Where PPM is combined with appropriate chemoprophylaxis, the risk of malaria infection can be reduced.¹⁴ Australian travellers rely on their general practitioner, or on a GP specialising in travel medicine, for advice on malaria prevention measures and for prescribing malaria prophylaxis before travelling.

We report on the malaria risk experience of a group of 38 Australians who travelled in three teams to PNG at the end of August 2006 and were involved in trekking and volunteer work. After visiting PNG, four adult residents of rural northern New South Wales were notified by an alert GP with a diagnosis of malaria to the local population health unit. The teams spent 15–17 nights in PNG, starting in Port Moresby, trekking the Kokoda trail and finishing in the coastal area near Gona. The groups participated in community work in villages along the way.

The aims of the public health investigation were to ensure that all members were aware of the risks of developing malaria postexposure, to detect and manage cases appropriately, and to analyse contributing risk factors.

Method

A retrospective cohort investigation was conducted. Contact details were obtained and all members of the travel group were included in the investigation. As this was a high priority public health investigation under the auspices of the New South Wales *Public Health Act 1991*, ethics approval for the investigation was not required.

A standard questionnaire was used to investigate signs and symptoms of malaria, itinerary, types of accommodation, nature of activities, use of PPMs, travel advice sought, type of chemoprophylaxis prescribed, doses of chemoprophylaxis taken, post-travel febrile illness and medical advice given.

The use of six recommended PPM during

the high risk mosquito biting period between dusk and dawn were investigated, namely restricting outdoor activities, use of bed nets, indoor knockdown insecticide, mosquito coils, long clothing and topical repellent.

The duration of the investigation extended over 3 months after the group's return from PNG. Group members who had not experienced any illness were advised to immediately seek medical advice should they develop malaria symptoms during the subsequent 3 months and contact the population health unit. Two additional group members were subsequently diagnosed with malaria.

Diagnosis of malaria was made by demonstrating malaria parasites in specifically stained thick or thin blood films or by an immunochromatographic rapid diagnostic test (RDT) when blood films were not available. These tests were conducted by an accredited reference laboratory in Sydney, New South Wales.

Data were analysed using SPSS® for Windows® (version 13 SPSS Inc, Chicago, Ill, USA) for descriptive analysis of proportions, and Fisher's exact test or likelihood ratios were used for comparing proportions as appropriate.

Results

All 38 (100%) members of the travel group participated in the investigation, and there were no missing data. The median age of group members was 45 years with a range 18–70 years. Of seven travellers who reported developing a febrile illness on return to Australia, six (86%, $p < 0.001$) were subsequently diagnosed with malaria. The onset of illness for malaria cases ranged from 1–16 weeks after return. Hospital treatment was required for five of the malaria cases.

P. vivax was identified in blood smears in 4/6 cases. One patient was positive for *P. vivax* using a RDT and included as a case. The remaining case was presumptively diagnosed and treated for malaria based on clinical grounds. This patient had partially self treated during the trip and had no other cause identified for this febrile illness. The pathology for this patient remained negative despite repeated testing.

Malaria was diagnosed in members of each team: 1/21 of team one, 2/12 of team two and 3/4 of team three (likelihood ratio = 4.624,

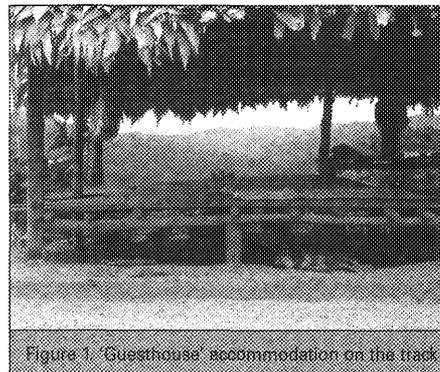


Figure 1. 'Guesthouse' accommodation on the track.

$p = 0.10$). Overnight accommodation included staying briefly in a hotel, open air 'guesthouses' (Figure 1), tents with or without screens, or sleeping in the open. The duration in different accommodation types did not differ significantly between cases and noncases.

Twenty-five (65%) group members always wore long sleeved shirts and trousers and 19 (50%) always used insect repellent during the highest risk period. No members used all six PPMs always or often (Table 1). Only one traveller took their own bed net. There was no significant difference in PPM use between malaria cases and noncases in this group.

All but one of the group consulted a GP before travel. Malaria infection occurred in 2/2 (100%) of the group members who did not take chemoprophylaxis and 4/36 (11%) people who did take chemoprophylaxis ($p = 0.021$). Three types of chemoprophylaxis were used; doxycycline by 28 (78%), mefloquine by 6 (17%), and atovaquone+proguanil by 2 (6%). Malaria occurred in those using doxycycline (3/28) or mefloquine (1/6) but there was no statistical association with type of chemoprophylaxis used.

Five of the individuals using chemoprophylaxis (14%) missed doses and only 12 (33%) continued use for the recommended period after leaving the malarious area (4 weeks for doxycycline and mefloquine, and 7 days for atovaquone+proguanil).¹⁵ None of the 12 individuals who took chemoprophylaxis for the recommended period developed malaria compared to 4/24 (17%) of those who terminated chemoprophylaxis prematurely, either by choice or by following the schedule prescribed by their GP (likelihood ratio = 3.489, $p = 0.062$).

Most (30/38) members of the travel group reported not seeing any mosquitoes during their journey through PNG.

Table 1. Reported number of PPMs always or often used, by malaria diagnosis

Number of PPMs always/ often used	Malaria	No malaria	Total
0	1	2	3
1	1	9	10
2	2	18	20
3	1	3	4
4	1	0	1
>5	0	0	0
Total	6	32	38

Discussion

Chemoprophylaxis and PPMs remain integral to malaria prevention. This investigation documented infrequent use of multiple PPMs even though travel occurred in an area known to have malaria. Pretravel consultations should emphasise the importance of combining chemoprophylaxis with multiple effective PPMs that limit mosquito exposure.¹⁶

The 100% attack rate among people who did not take any chemoprophylaxis is a compelling argument for taking effective chemoprophylaxis when visiting high risk malaria areas. This is particularly important in rural locations in PNG where available accommodation, as in the current case, may not provide an adequate barrier to *Anopheles* mosquitos feeding during peak biting periods.

For travellers returning from a malaria endemic area, including PNG, it is recommended that chemoprophylaxis be continued for the recommended period after travel to cover infection acquired up to the final day of stay. Irregular use has previously been linked with malaria infection in Australian travellers.⁷ Our investigation supports the importance of counselling travellers that chemoprophylaxis should be continued for the recommended period post-travel. Each case of malaria in this investigation occurred in a group member who had taken either no chemoprophylaxis or terminated their chemoprophylaxis earlier than the recommended period.

Malaria risk varies over time, between and within countries and is dependent on a range of factors including climate, the presence of *Anopheles* mosquitoes, malaria parasites being able to complete their growth cycle in the mosquitoes ('extrinsic incubation

period'), nature of accommodation and human behavioural factors.³ It would be useful for GPs who provide pre-travel advice or post-travel assessment to have ongoing access to up-to-date and reliable information on malaria risk and prevention strategies.

This investigation was limited by the small number of travellers in the cohort and the delayed and self reported nature of risk and protective factors.

Malaria infection usually presents as a febrile illness. In patients with inadequate chemoprophylaxis use, disease onset may be delayed for weeks or months. Our investigation demonstrates the importance of maintaining a high index of suspicion for malaria in travellers returning from malaria endemic countries, with 6/7 travellers in this cohort that developed fever post-travel being diagnosed with clinical or confirmed malaria. Being alert for possible clusters of infection and timely notification can ensure optimal clinical and public health management.

Implication for general practice

- Malaria is the most important parasitic disease affecting people living in and travelling to malaria endemic areas.
- Pretravel consultations should emphasise meticulous use of effective chemoprophylaxis for the full recommended period after return coupled with multiple effective PPMs to reduce the risk of infection and disease.
- Malaria infection usually presents as a febrile illness. In patients with inadequate chemoprophylaxis use, disease onset may be delayed for weeks or months.

Conflict of interest: none declared.

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