# Malaria in the Australian Defence Force: the Bougainville experience

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THE ISLAND OF BOUGAINVILLE lies about 600 km north-east of mainland Papua New Guinea (PNG) and geographically is in the northernmost part of the Solomon Islands chain. The island itself is 200 km long and 65 km across at its widest part. Formerly a dependency of Australia, it has been administered as a province of PNG since that country achieved independence in 1975. Widespread civil unrest has been present since then, focusing mainly on dissatisfaction by native islanders with the presence of a large copper mine. This led to open conflict erupting in 1988. The main instigators of unrest were a loose coalition of parties named the Bougainville Revolutionary Army (BRA). Despite several years of intervention by the PNG Defence Force, ongoing guerrilla warfare continued unabated, with the BRA seeking full independence for the island.

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## Abstract

- During a 5-year period, almost 4000 Australian personnel served in the Papua New Guinean province of Bougainville.
- The first randomised, double-blind trial comparing Malarone (a combination of atovaquone and proguanil) with doxycycline was conducted during the deployment. Malarone was as effective as doxycycline and better tolerated.
- Another trial compared a 3-day course of tafenoquine with the course of primaquine that was standard at that time for post-exposure prophylaxis. There was no statistical difference in rates of malaria following either regimen.
- There were 64 episodes of malaria affecting 50 individuals. This gave an attack rate of 41.6 malarious episodes per 1000 man years. Most attacks occurred after the person had returned to Australia.
- The dosage of primaquine was increased partway through the deployment, from 22.5 mg to 30 mg per day. The attack rate fell from 67.1 to 13.2 per 1000 man years. The attack rate following tafenoquine post-exposure prophylaxis was 63.5 per 1000 man years.

*ADF Health 2004; 5: 69-72*

In late 1997, a fragile truce was negotiated between several parties to restore order to the troubled PNG province. As part of the truce, teams of both military and civilian international observers were deployed to Bougainville, along with associated support staff, to facilitate the peace process. Personnel from New Zealand, Fiji, Vanuatu and a large contingent from the Australian Defence Force (ADF) were among the first to commence monitoring operations from December 1997.

During the following five and a half years, until the official winding-down of the operation on 30 June 2003, Australia committed more than 3500 military personnel and 300 civilian monitors to the Truce Monitoring Group (TMG) and later the Peace Monitoring Group (PMG), as part of Operation Bel Isi.[1] This article is a brief summary of the experience of these personnel with malaria during and following their deployment to Bougainville.

Bougainville was known to be hyperendemic for *Plasmodium vivax* and *P. falciparum* malaria before the deployment of the TMG. In accordance with ADF policy on malaria prophylaxis at the time,[2] all personnel commenced taking doxycycline (100 mg daily) 2 days before leaving for Bougainville, continuing for 2 weeks after return to Australia. In addition, they received primaquine (7.5 mg three times daily for 14 days) after leaving the endemic area to eliminate potential *P. vivax* hypnozoites, the liver stages of the parasite that cause clinical relapses of malaria. In September 2000, the dose of primaquine was increased to 15 mg twice daily in response to higher than expected rates of *P. vivax* malaria in members returning to Australia.


## Research activities

Two major clinical trials were conducted by the Army Malaria Institute (AMI) during the course of Operation Bel Isi. These resulted in significant variations to the standard ADF antimalarial protocol. There were also activities for sampling malaria vectors on Bougainville and for assessing the effectiveness of the bednetting currently used in the ADF.

### *Malarone*

The first trial was a randomised, double-blind study assessing the tolerability and effectiveness of Malarone compared with doxycycline.[3] Malarone, a combination of atovaquone 250 mg and proguanil 100 mg, was a relatively new antimalarial agent for the treatment of *P. falciparum* malaria. This trial was the first double-blind comparative prophylaxis trial of Malarone. The study was sponsored by the ADF, and blinded treatment drugs were supplied by Glaxo Welcome.

One hundred and fifty personnel were recruited from the February and April rotations and randomised to either Malarone or doxycycline 100 mg once daily throughout their deployments.

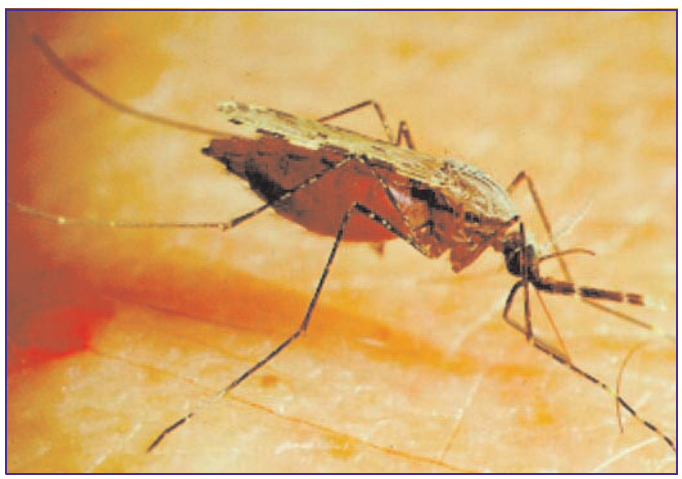
Preliminary analysis of the findings indicates that Malarone is as effective as doxycycline in preventing malaria infection, and is better tolerated. It appears to be a safer alternative, with no changes observed in clinical chemistry or full blood counts. Although it appears to produce gastrointestinal effects of its own, these tend to be less troublesome or severe than those experienced with doxycycline. There were no reports of photosensitivity in the Malarone group; however, headaches were more frequent.

Malarone appears to be an effective alternative to doxycycline for use by ADF personnel. The current price of $58 (US$45) per 12 tablets militates against its general introduction at this time, given that for most recipients of doxycycline there were few significant adverse effects to justify the much higher cost of Malarone. In 2002, Malarone was registered for prophylaxis of falciparum malaria.

### *Tafenoquine*

The second clinical trial conducted during the operation was of a new 8-aminoquinolone drug, tafenoquine, for post-exposure prophylaxis.[4] Five hundred and ninety-two personnel were randomised into either the standard 14-day primaquine regimen or the 3-day tafenoquine regimen. Six of the 214 personnel given primaquine developed *P. vivax* malaria, compared with eight of the 378 personnel given tafenoquine. These figures were not significantly different. Both drugs induced symptoms of mostly gastrointestinal intolerance, with tafenoquine producing statistically significant slightly higher rates. Despite this, most people preferred the shorter course of tafenoquine over primaquine.

This was the first trial conducted on the use of tafenoquine to be conducted for the indication of post-exposure prophylaxis. The trial was sponsored by the ADF, with treatment courses of tafenoquine provided by SmithKline Beecham under their



Anopheles farauti *is the main malaria vector on Bougainville*

collaborative development program with the United States Army Medical Materiel Development Activity.

### Vector sampling

In addition to the clinical pharmacological trials, there were malaria vector sampling activities conducted by AMI. These found that the main malaria vector on Bougainville is *Anopheles farauti.*[5]

### Bednet protection

A further study conducted during the deployment to Bougainville assessed the protection provided by the standard ADF bednet compared with a new self-supporting bednet developed by the Walter Reed Army Institute of Research in the United States. The newer US bednet did provide greater protection than the ADF model. However, both provided > 97.8% protection compared with no protection.[6]

## Malaria statistics

Notwithstanding the positive findings of these trials, a significant number of cases of malaria occurred as a result of the deployment of ADF personnel on Operation Bel Isi.

The first case of malaria reported from Operation Bel Isi was diagnosed on 11 Mar 1998, about 4 months after the operation commenced. This was a case of *P. vivax* diagnosed 2 months after the person had returned to Australia. This pattern — of the first clinical episode of malaria occurring on return to Australia — was common for most cases of malaria recorded by the AMI. At 15 June 2004, the last case had been diagnosed on 12 December 2003, about 3 months after return from Bougainville.

Examination of the AMI Central Malaria Register data reveals that there were 59 cases of *P. vivax*, three cases of *P.* falciparum and two cases in which the species was not identified.

When examining where these cases occurred, there were:

- 5 cases in Bougainville (three *P. falciparum* and two *P. vivax*)
- 58 cases after return to Australia, and
- 1 case that occurred overseas as a relapse of an unknown/ unidentifiable species.

Of the cases that occurred on return to Australia:

- 45 were primary presentations (44 *P. vivax* and one unknown/unidentifiable species),
- 8 were a first relapse,
- 3 were a second relapse, and
- 2 were a third relapse.

Overall, there were 64 episodes of malaria affecting 50 individuals. Nine individuals went on to have one further relapse; three of these had a second relapse, and two a third relapse. One member had true recrudescence: a recurrence of parasitaemia within 28 days after primary treatment with 1500 mg chloroquine; this was counted as one episode in total. This member was not given primaquine with the primary treatment. One other member had a recurrence more than 1 month after treatment with chloroquine but not primaquine. This has been included as two episodes. Of the total number of patients, one had three clinical relapses, which responded to chloroquine on each occasion; however, no parasites were found on slides when reviewed at AMI or on polymerase chain reaction (PCR) testing performed at AMI. These events were included in the statistics above.

*Some of the village children in Bougainville*

The overall attack rate for primary presentations was 41.6 malarious episodes per 1000 man years of exposure. For context, before the ADF deployment to East Timor in 1999, the rate had been exceeded in the ADF only twice since the Second World War: in 1962, during the Malayan – Campaign (85 per 1000 man years), and in 1968, during an outbreak in the Vietnam War (127/1000 man years).[7] Nevertheless, the attack rate seen in Bougainville is lower than the attack rates seen in the battalions deployed to East Timor (52–135 per 1000 man years).[8] East Timor lies in the Indonesian archipelago and is endemic for similar strains of malaria as those found in Bougainville, and thus provides a valid comparator.

After the dosage of primaquine was increased from 22.5 mg to 30 mg per day for post-exposure prophylaxis, the rate of primary presentation of vivax malaria fell from 67.1 to 13.2 per 1000 man years. The rate of primary presentation for those receiving tafenoquine post-exposure prophylaxis was 63.5 per 1000 man years.

## Comments

These figures highlight the fact that most cases of malaria in personnel who have been deployed to an endemic area occur after the member has left the area of operations and has

returned to Australia. The major burden of disease in the ADF is caused by the relapsing *P. vivax* strain. The fact that 90% of cases occurred after return to Australia indicates that doxycycline is effective in suppressing *P. vivax* while it is being taken. It also implies that compliance with doxycycline while on deployment was good.

Continued emphasis on personal protective measures to prevent initial inoculation with the parasite, and further refinement of and compliance with post-exposure prophylaxis, are required to help rectify the problem of large numbers of malaria cases on return to Australia.

Of significant note is the large decrease in attack rate for malaria presentations when the dose of primaquine was increased from 22.5 mg to 30 mg per day. This increased the total dose from 315 mg to 420 mg. In 1977, Clyde and McCarthy demonstrated that it is the total dose of primaquine that determines the successful treatment of *P. vivax* malaria. They found 6 mg/kg was the recommended optimum dose for the Chesson strain of *P. vivax*, the strain typically present in the South-West Pacific region.[9]

Although tafenoquine post-exposure prophylaxis gave protection similar to a daily dose of 22.5 mg primaquine, it compared poorly with the 30 mg daily dose. It must be noted that this is not a direct comparison and confounders may exist, such as improvement of facilities and preventive medicine vigilance over time.

Furthermore, many individuals performed multiple tours of duty in Bougainville and thus received multiple eradication courses of primaquine, which may further bias the results towards finding no difference between treatments. Multiple repeated primaquine prophylaxis would reduce the likelihood of primary presentation, as hypnozoites not cleared with the first course might be cleared with subsequent courses before sufficient time had elapsed for clinical illness to develop.

A major limitation in collating these statistics is that the reporting of malaria in the ADF is wholly reliant on the initial treating medical practitioner or health facility notifying AMI of a malaria case. There have been many examples when, long after the initial clinical episode, advice has been sought from AMI regarding the treatment of a relapse in an individual who was never notified to AMI at the first instance. This is particularly the case with ADF reserves, who constituted a significant proportion of the Bougainville personnel. On return to Australia, reservists usually present to their local civilian medical practitioner for treatment of any health problems. Quite understandably, the civilian medical practitioner is unaware of the ADF's treatment and reporting protocols. Given the inherent limitations in the reporting process, these figures may underestimate the true incidence of malaria occurring in service personnel returning from operational duties.

## Acknowledgements

Ethical approval for the trials described in the article was obtained from the Australian Defence Human Research Ethics Committee. The trials described within were wholly conducted using the resources and personnel of the ADF, except where specified above. This article is published with the approval of the Director General Defence Health Services (Australia). The opinions expressed are those of the authors and do not necessarily reflect those of the Defence Health Service or any extant ADF policy

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*(Received 17 Jun 2004, accepted 27 Jul 2004)* ❑