QUINOLINE VETERANS AND FAMILIES ASSOCIATION

SUPPLEMENTARY SUBMISSION TO THE FOREIGN AFFAIRS, DEFENCE AND TRADE REFERENCES COMMITTEE INQUIRY INTO THE USE OF THE QUINOLINE ANTI-MALARIAL DRUGS MEFLOQUINE AND TAFENOQUINE IN THE AUSTRALIAN DEFENCE FORCE

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Introduction

QVFA thanks the Committee for their continued efforts with this inquiry. The purpose of this supplementary submission is to provide a more detailed, factual explanation of the use of quinoline and other antimalarial drugs in the Australian Defence Force (ADF), including the (AMI) clinical trials in Bougainville and East Timor. We trust that this information will assist the Committee in questioning future witnesses, assessing the evidence and preparing its report. This submission also identifies additional witnesses who may assist the inquiry.

Malaria Species

Malaria is caused by protozoan parasites of the genus Plasmodium – single-celled organisms that cannot survive outside of their host(s). Different species of malaria are endemic to different geographic areas.

P. falciparum is responsible for the majority of malaria deaths globally and is the most prevalent species in sub-Saharan Africa.

The remaining species are not typically as life threatening as *P. falciparum*.

P. vivax is the second most significant species and is prevalent in Southeast Asia and Latin America.

P. vivax and *P. ovale* have the added complication of a *dormant liver stage*, which can be reactivated in the absence of a mosquito bite, leading to clinical symptoms.

P. ovale and *P. malariae* represent only a small percentage of infections.

A fifth species *P. knowlesi* – a species that infects primates – has led to cases of human malaria, but the exact mode of transmission remains unclear.

Antimalarial Drug Treatments in General

The malaria life cycle is complex, with different antimalarial drugs being used to target different species at different stages of the life cycle, typically the erythrocytic stage (blood stage) or the dormant liver stage.

Antimalarial drugs are used to both prevent malaria ("chemoprophylaxis") by suppressing or killing the parasite, and to treat or cure malaria in patients when they become sick after infection.

The two different methods of malaria chemoprophylaxis are *suppressive* prophylaxis and *causal* prophylaxis.

Chloroquine, atovaquone/proguanil (Malarone), mefloquine, and doxycycline are suppressive prophylactics. They are only effective at killing the malaria parasite once it has entered the erythrocytic stage (blood stage) of its life cycle, and therefore have no effect until the liver stage is complete. This is why these prophylactics must continue to be taken for some time after leaving the area of risk.

Causal prophylactics target not only the blood stages of malaria, but the initial liver stage as well. This means that the individual can cease taking the drug soon after leaving the area of risk. Malarone and primaquine are the only causal prophylactics in current use. The terms "post exposure prophylaxis"

(PEP) or "eradication" are used to describe causal prophylactics which are used at the end of a period of exposure, for example the ADF's use of primaquine for *P. vivax* PEP.

Many of the prophylactic drugs are also used for malaria treatment, usually at higher doses. Combination drug treatments are often used to target different stages of the life cycle and prevent relapse. The term "radical cure" describes a drug which can be used for a short duration, both treatment and PEP.

Risk vs Benefit

The decision to use any medical treatment ultimately comes down to a consideration of risk vs benefit. A person who is already seriously ill, suffering from a life-threatening disease, would naturally be prepared to accept a higher risk of drug side effects than a healthy person wanting to prevent being infected with a less severe illness.

Submissions from Defence and other organisations have highlighted the number of infections and deaths from various species of malaria. There is no denying that malaria is a serious, life threatening disease, however it is important for the Committee to note that the vast majority of malaria deaths occur in malaria endemic countries in the developing world, as a result of:

- Infections among infants, children and the elderly.
- Poor access to basic vector control measures such as mosquito nets and insecticides.
- Poor access to basic health services.
- Poor access to malaria diagnostics and treatments.

By contrast, the last recorded malaria death in the ADF occurred 50 years ago. Some of the reasons for this include:

- ADF personnel are not infants, children or elderly.
- Ready access to basic vector control measures such as mosquito nets and insecticides.
- Ready access to world class health services, both on deployment and on return to Australia.
- Ready access to malaria diagnostics and treatments, both on deployment and on return to Australia.

Malaria infections from different species present different risks. *P. falciparum* is a high risk, life threatening type of malaria, however there are already numerous safe, effective prevention and treatment drugs approved by drug regulators. *P. vivax* is also a serious illness, however it presents a lower risk than *P. falciparum*, particularly in the ADF context where effective diagnosis and treatment is readily available.

QVFA emphasises the risk of *neuropsychiatric side effects* presented by the quinolines. ADF policy in fact prohibits the use of mefloquine by aircrew, divers and some other occupations specifically because of the risk of cognitive and balance problems, while the manufacturer warns that the drug should not be used while driving or operating heavy equipment. As several witnesses have already highlighted, for this reason alone the drug is unsuitable for military use.

We do not suggest that antimalarial medications are unnecessary. This is a question of which drugs are used in the ADF and how they are used. The Committee is inquiring into the use of antimalarial drugs *in the ADF, not by civilians in the developing world*. The risks and benefits of antimalarial medications are completely different in those two contexts. Emphasising the number of malaria deaths that occur each year in the developing world is not only irrelevant to the ADF context, it is a distraction.

ADF Malaria Chemoprophylaxis

Since the late 1980s, subject to some geographic variations, the standard ADF Malaria chemoprophylaxis regimens have been:

- **1st Line**. Doxycycline as prophylaxis against *P. falciparum* and other species *during* the deployment, followed by primaquine at the end of the deployment for *P. vivax* PEP.

- **2nd Line**. Mefloquine as prophylaxis against *P. falciparum* and other species *during* the deployment, followed by primaquine at the end of the deployment for *P. vivax* PEP.

- **3rd Line**. Malarone as prophylaxis against *P. falciparum* and other species *during* the deployment, followed by primaquine at the end of the deployment for *P. vivax* PEP.

Malarone replaced mefloquine as the 2nd line agent in 2006, specifically due to the risk of neuropsychiatric side effects from mefloquine.

In considering the safety and efficacy of this overall regimen we ask the Committee to make particular note of the following:

- There are numerous *registered* drugs for the prevention of *P. falciparum* and other malaria species. Numerous drugs from other classes are under development for the prevention of *P. falciparum*, to counter the problem of drug resistance.

- The *only reason* primaquine is needed is for *P. vivax* PEP and treatment.

- Unlike the other malaria species, there is *no direct scientific proof* of genetic mutation in the *P. vivax* parasite as a mechanism of "drug resistance".

- *Both primaquine and tafenoquine* require activation by CYP2D6 to be effective against the malaria parasite.

- Approximately 12-23% of caucasians are CYP2D6 poor or intermediate metabolisers, for whom *primaquine and tafenoquine do not work* in preventing malaria.

- Tafenoquine is not currently required for *P. falciparum* prevention because other safe, effective, registered drugs are available.

Antimalarial Drug Compliance, Resistance and Metabolism

The term "drug resistance" is commonly used to justify the continued development of antimalarial drugs. Unfortunately this term has various definitions depending on context, which may cloud the Committee's understanding of the issues under consideration during this inquiry.

Broadly speaking, there are a number of reasons that a given antimalarial drug may fail to prevent or treat a given malaria infection:

- **Poor compliance**, i.e. an individual not taking the directed dose regimen.

- **Insufficient dose**, i.e. the individual does take the directed dose but the dose is insufficient to prevent or treat the infection.

- **Drug metabolism**, i.e. the individual does take the directed regimen at a dose normally sufficient to prevent or treat an infection, but is incapable of metabolising the drug for it to be effective.

- **Drug resistance**, i.e. the Plasmodium strain in a given region has *genetically mutated* over time in such a way that the directed dose regimen is no longer effective in preventing or treating that given strain.

The Defence submission highlights the issue of poor compliance in justifying the use of mefloquine (which requires a weekly rather than daily dose) and the development of tafenoquine (which also requires only a weekly dose for prophylaxis). We do not dispute that some of the malaria infections experienced by ADF personnel are likely have been the result of poor compliance. However, as the Committee has heard from numerous witnesses, the ADF chain of command goes to extraordinary lengths to ensure compliance, including direct supervision of individual personnel as they take their antimalarial medications.

What QVFA does dispute is that "poor compliance" or "drug resistance" plausibly explain the overall high rate of *P. vivax* infections among ADF personnel after returning to Australia and undergoing PEP (Table 1). The relatively low rate of infections *during* these deployments indicates that the vast majority of personnel do actually comply with the directed antimalarial drug regimen.

	Timor Leste	Bougain-ville	Solomon Islands	Other Countries[a]	Total by species	
					n	%
Plasmodium vivax (Pv)	433	57	19	38	547	85.9
P. falciparum (Pf)	49	3	2	11	65	10.2
P. ovale (Po)	1	0	0	1	2	0.3
P. malariae (Pm)	1	0	0	0	1	0.2
Mixed Pf/Pm	2	0	0	0	2	0.3
Mixed Pf/Pv	9	0	1	1	11	1.7
Identification unknown	6	1	0	2	9	1.4
Total by country (%)	501 (78.6)	61 (9.6)	22 (3.4)	53 (8.3)	637	

[a] Indonesia, Malaysia, Sudan, Thailand, Papua New Guinea and one case with exposures in multiple countries throughout Africa

Table 1. Number of malaria notifications to the Australian Defence Force Central Malaria Register by country and species from 1998 to 2007.[1]

During my recent testimony I highlighted the fact that there is no direct scientific proof of true primaquine drug resistance in the *P. vivax* parasite, i.e. particular strains of *P. vivax* genetically mutating to resist standard dose regimens then reproducing in a geographic area in such a way that primaquine is no longer effective in that area. This broad *assumption* of primaquine "drug resistance" to *P. vivax* has not been substantiated by Defence or other organisations in their evidence to the Committee. Although it *may occur in future*, there is insufficient evidence to prove that it has already occurred. This contrasts with *P. falciparum* and other species, which have definitely mutated become resistant to various drugs over time, indeed mefloquine was developed in response to direct evidence of *P. falciparum* resistance to chloroquine in Southeast Asia in the 1970s.

As I also explain in my original submission, the most plausible explanation for the high rate of primaquine failure in the ADF is the fact that primaquine and tafenoquine both require CYP2D6 metabolism for activation against *P. vivax*. This is substantiated by scientific discoveries by WRAIR and further research by other research institutions. The significance of these findings is that CYP2D6 screening allows antimalarial drugs to be used more *safely and effectively*. Marcsisin et al. wrote in 2016:

> *The CYP 2D6/primaquine discovery also provides clinicians an additional avenue to address possible causes of relapse despite primaquine/8-aminoquinoline therapy. CYP 2D6 genotyping is readily available through multiple diagnostic vendors in addition to purchasable kits. Determining an individual's CYP 2D6 genotype in relation to relapse could inform clinicians to opt for alternative treatment options to manage relapses and better inform patients. Additionally, the CYP 2D6/primaquine link allows physicians and pharmacists to be more conscientious and aware of possible CYP 2D6 mediated drug–drug interaction as possible causes for primaquine therapy failures. Furthermore, awareness of the CYP 2D6/primaquine link is important to consider when primaquine failures are observed clinically. Often clinical failures with malaria treatment are commonly attributed to the emergence of drug resistance, however, in the case of primaquine, it is important to investigate the phenotype of individuals failing primaquine treatment to determine if the drug failure is the result of poor metabolic activation rather than the emergence of resistance to primaquine.*[2]

A recent case report of apparent primaquine treatment failure highlights the utility of CYP2D6 screening in improving antimalarial safety and efficacy. This report describes how a patient who was seriously ill with *P. falciparum* and *P. vivax* malaria underwent seven rounds of unsuccessful primaquine treatment within a year, before he was eventually screened for his CYP2D6 status. When he did undergo CYP2D6 screening, his doctors used the results to successfully treat his malaria without further relapse:

> *Primaquine (an 8-aminoquinoline malarial therapy) is the only FDA-approved therapy to treat the hypnozoite stage of P. vivax. We think of relapse occurring because of parasitic resistance or poor compliance secondary to drug toxicities. However, in patients with repeated treatment failure, we must consider CYP-450 mutations affecting drug metabolism as an important*

> *cause of relapse. A 47-year-old man who travelled to a jungle in Venezuela was diagnosed with P. falciparum and P. vivax in July 2015. He was treated with seven rounds of primaquine-based therapy in the following year, all resulted in relapse without further exposure to endemic areas. On his eighth presentation, he was found to have CYP-4502D6 mutation that affected the metabolism and activation of primaquine. Thereafter, he was treated without relapse. Primaquine efficacy depends on many factors. Understanding the mechanism responsible for malaria relapse is paramount for successful treatment and reduction in morbidity and mortality. This case illustrates the importance of considering cytochrome mutations that affect drug efficacy in cases of relapsing malaria.*[3]

QVFA requests that the Committee be particularly careful in asking for substantiating evidence whenever witnesses use the term "drug resistance" or "primaquine resistance" in relation to *P. vivax* or malaria more generally. We also request that witnesses from Defence, health agencies and malaria research institutions be challenged about their reluctance to act upon the evidence of CYP2D6 metabolism of primaquine and tafenoquine, not only as a more plausible explanation for 8-aminoquinoline treatment failures in the ADF but also as an avenue to improve the safety and effectiveness of antimalarial medications including tafenoquine.

Army Malaria Institute Quinoline Clinical Trials in Bougainville and East Timor 1999-2002

The AMI clinical trials in Bougainville and East Timor involving the use of mefloquine and/or tafenoquine were conducted as follows:

- **Tafenoquine vs Primaquine PEP Study, Bougainville, 1999**. This trial administered tafenoquine PEP to personnel from the Peace Monitoring Group as they were returning from Bougainville to Australia in small groups throughout 1999. The tafenoquine study group of 374 personnel were given doses of 200 or 400 mg per day for three consecutive days, totalling 600 or 1,200 mg. The comparator group of 210 personnel were given standard doses of primaquine for 14 days.[4-6]

- **3 RAR and 5/7 RAR, Tafenoquine vs Primaquine PEP Study, East Timor, 2000**. This trial administered tafenoquine PEP to personnel from the 3 RAR battalion group as they were returning from East Timor to Australia in February 2000 then the 5/7 RAR battalion group as they were returning from East Timor to Australia in April 2000. The tafenoquine study group of 639 personnel were given doses of 400 mg per day for three consecutive days, totalling 1,200 mg. The comparator group of 210 personnel were given standard doses of primaquine for 14 days.[4-6]

- **1 RAR, Tafenoquine vs Mefloquine Prophylaxis Study, East Timor, 2000-01**. This trial administered tafenoquine and mefloquine prophylaxis to personnel from the 1 RAR battalion group for the duration of their deployment to East Timor in 2000-01. The tafenoquine study group of 492 personnel were given an initial loading dose of 200 mg per day for three days, then 200 mg weekly. The mefloquine control group of 162 personnel were given an initial loading dose of 250 mg per day for three days, then 250 mg weekly.[7]

- **4 RAR and 2 RAR, Mefloquine vs Doxycycline Prophylaxis Study, East Timor, 2000-01**. This trial administered mefloquine and doxycycline prophylaxis to personnel from the 4 RAR and 2 RAR battalion groups for the duration of their deployment to East Timor in 2001-02. The mefloquine study group of 1,157 personnel were given an initial loading dose of 250 mg per day for three days, then 250 mg weekly. The doxycycline control group of 388 personnel were given standard doses of 100 mg per day.[8]

- **Tafenoquine Relapse Prevention Study, Australia 2000-02**. This trial involved personnel at numerous locations in Australia who had contracted vivax malaria which had not successfully been treated with primaquine and continued relapsing. 31 individuals were initially given 200 mg per day for three days then 200 mg weekly.[9]

The dates, locations, drugs, dosages and units involved in each of these trials are summarised at Attachment 1.

In considering the justification and conduct of the AMI clinical trials, as well as the adverse health impacts on the trial subjects, we ask the committee to make particular note of the following facts:

- Tafenoquine was not required for *P. falciparum* prevention because other safe, effective, registered drugs were available and in use.

- Prior to the 1999-2001 tafenoquine clinical trials, AMI had trialled Malarone in 1998, finding it to be as effective against malaria (less *P. vivax* PEP) and better tolerated than doxycycline.

- The mefloquine loading doses used in the AMI clinical trials were several times higher than the doses recommended by the manufacturer and approved by the TGA.

- The tafenoquine dosages used in the AMI clinical trials were many times higher than the primaquine dosages. Primaquine had been the standard *P. vivax* PEP drug for many decades.

- The tafenoquine dosages used in the AMI clinical trials, including the PEP doses of up to 1,200 mg over three days or "loading doses" of 600 mg over three days were several times higher than those recently approved by the U.S. FDA. The fact that the FDA approved tafenoquine does not prove that tafenoquine was used safely in these trials.

The Committee has now received considerable evidence relating to the conduct of the AMI quinoline clinical trials which we believe supports our position that the trials were conducted unethically. For the last several years Defence has countered this position simply by stating that the trials were approved by the Australian Defence Medical Ethics Committee (ADMEC), which later became the Australian Defence Human Research Ethics Committee (ADHREC). QVFA will make a separate submission addressing the ADMEC/ADHREC approvals and subsequent oversight of these trials.

One key question which we believe the Committee should now address is: who in the ADF *operational* chain of command gave the *operational* approvals for these trials to be conducted in an *operational* military setting?

When this controversy first came to light in the media in the years following the AMI clinical trials, public statements by senior ADF officials suggest that the operational chain of command may not have been fully informed about the conduct of the trials or the numbers of personnel involved. For example in late 2004 when ADF Surgeon General Air Commodore Tony Austin responded publicly to a legal class action by a number of the trial subjects he stated that the number of ADF personnel given mefloquine was “in the dozens rather than hundreds.” Soon afterwards, Chief of Army Lieutenant General Peter Leahy stated publicly that the actual figure was 1351.[10]

We believe that the following individuals would best be able to answer questions relating to the operational approvals for the AMI trials should they appear as witnesses:

- **General (ret) Peter Cosgrove**. General Cosgrove was Chief of Army during the period of the trials and is now the Governor General of Australia.

- **Lieutenant General Peter Leahy**. Lieutenant General Leahy was Chief of Army during the period of the trials and is now the Chairman of Soldier On Australia.

- **Major General (ret) John Pearn**. Major General Pearn was SGADF during the period of the trials and is now a Director of the Gallipoli Medical Research Foundation. In his capacity as SGADF at that time he will have been the chair of ADHREC and played a key role in approving the AMI clinical trials.

Additional Witnesses

During the recent hearing in Townsville, the Committee heard testimony from Lieutenant General (ret) Caligari, the Commanding Officer of 1 RAR during one of the AMI quinoline clinical trials in East Timor. This testimony provided crucial insights into the practical application of "informed consent" and the overall conduct of clinical trials in the military operational setting. We believe that the Committee would find it equally useful to hear from other Commanding Officers, AMI staff and medical officers who were involved in these trials to establish a better understanding of how command decisions, health policies and ethical principles were applied during the period of these trials. We recommend that the following individuals be called as witnesses:

- **Major General (ret) Mark Kelly**. Major General Kelly was Commander 3rd Brigade during this period, the higher commander of many of the units involved in the clinical trials. Since 2010 Major General Kelly has also served as the DVA Repatriation Commissioner, an appointment in which he is responsible for representing the interests of veterans.

- **Brigadier Leonard Brennan**. Brigadier Brennan was the 3rd Brigade Senior Medical Officer during the period of the clinical trials and is named as a co-author on the AMI tafenoquine-mefloquine trial involving 1 RAR.[7] Brennan is currently serving in a strategic role in Joint Health Command, answering directly to the ADF Surgeon General for a variety of responsibilities including oversight of AMI.

- **Colonel Peter Nasveld**. Colonel Nasveld was the lead AMI researcher responsible for the conduct of the AMI tafenoquine trials in Bougainville and East Timor.[4] He is now serving at Headquarters Joint Operations Command.

- **Colonel (ret) Peter Singh**. Colonel Singh was the Commanding Officer of 3 RAR during the February 1999 AMI tafenoquine-primaquine PEP clinical trial at the end of their East Timor deployment.[5-6]

- **Brigadier (ret) Simon Gould**. Brigadier Gould was the Commanding Officer of 5/7 RAR during the April 1999 AMI tafenoquine-primaquine PEP clinical trial at the end of their East Timor deployment.[5-6]

- **Major General (ret) Jeff Sengleman**. Major General Sengleman was the Commanding Officer of 4 RAR during the 2001 AMI mefloquine-doxycycline clinical trial in East Timor[8] and recently retired as the Commander of Special Operations Command.

- **General Angus Campbell**. General Campbell was the Commanding Officer of 2 RAR during the 2001-02 AMI mefloquine-doxycycline clinical trial in East Timor[8] and is now serving as the Chief of the Defence Force.

Conclusion

QVFA completely accepts that antimalarial drugs are an important part of ADF preventative health measures. However, we emphasise that the risks and benefits relevant to ADF personnel in military operational settings fundamentally differ from those relevant to civilian populations in developing, malaria-endemic countries. We also completely accept the need for continued antimalarial drug development, however we are seriously concerned that scientific discoveries such as CYP2D6 metabolism of the 8-aminoquinolines are not being acted upon because commercial considerations are taking primacy over drug safety and efficacy. Tafenoquine may indeed be able to be used safely and effectively by a majority of the population in future, however widespread use of this drug without first acting upon the evidence of CYP2D6 metabolism and neurotoxicity presents an unacceptable public safety risk. We trust that this information will be useful to the Committee's ongoing inquiry.

Attachments

1. Summary of ADF mefloquine and tafenoquine clinical trials, 1998-2002

References

1. N. Elmes, “Malaria notifications to the Australian Defence Force Central Malaria Register by country and species from 1998 to 2007,” *International Health*, vol 2, no 2, 2010, pp. 130-135. http://doi.org/10.1016/j.inhe.2010.03.001
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Summary of ADF Mefloquine and Tafenoquine Clinical Trials, 1998-2002

Year	Refs	Location	Purpose	Population	Study Cohort			Comparator Cohort		
					Drug	Dose	Subjects	Drug	Dose	Subjects
1998-1999	1-4	Bougainville, PNG	PEP	Peace Monitoring Group	Tafenoquine	400mg od[a] or 200mg bid[b] for 3d	374[d]	Primaquine, doxycycline	7.5mg tid[c] for 14d	210[d]
2000	1-4	East Timor	PEP	3 RAR, 5/7 RAR	Tafenoquine	400mg od[a] or 200mg bid[b] or 200mg od[a] for 3d	639[d]	Primaquine, doxycycline	7.5mg tid[c] for 14d	289[d]
2000-2001	1, 2, 5	East Timor	Prophylaxis	1 RAR	Tafenoquine	200mg daily for 3d, then 200mg weekly	492	Mefloquine	250mg daily for 3d, then 250mg weekly	162
2001-2002	6	Australia	Relapse prevention	Australian military	Tafenoquine	200mg daily for 3d, then 200mg weekly	31	Nil	Nil	Nil
2001-2002	1, 7	East Timor	Prophylaxis	4 RAR, 2 RAR	Mefloquine	250mg daily for 3d, then 250mg weekly	1,157	Doxycycline	100mg daily	388

[a] Once daily.

[b] Twice daily.

[c] Thrice daily for primaquine plus 100mg doxycycline daily.

[d] These figures are the totals of enrolled subjects administered each drug. A total of 239 of the enrolled subjects who were co-administered other drugs were excluded from the reported findings.

References

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6. Kitchener et al., Tafenoquine for the treatment of recurrent Plasmodium vivax malaria, 2007.
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