QIMR Berghofer
Medical Research Institute

Committee Secretary
Senate Foreign Affairs, Defence and Trade References Committee
PO Box 6100
Parliament House
Canberra ACT 2600

Re: Senate Enquiry in the Australian Defence Force use of Mefloquine and Tafenoquine

Dear Chairman,

I write regarding this enquiry. I believe that I am well qualified to provide a view to this committee based upon my qualifications and previous experience. I am a registered medical practitioner with specialist training in Internal Medicine, Infectious Diseases and Tropical Medicine. I undertook training in infectious diseases and tropical medicine in Australia, The London School of Hygiene and Tropical Medicine, The University of Maryland, USA and the National Institutes of Health, Bethesda, MD, USA before returning to Australia in 2002. I now hold a position of Professor of Tropical Medicine and Infectious Diseases at the University of Queensland, Senior Scientist, QIMR Berghofer Medical Research Institute and Senior Consultant Infectious Disease Physician at the Royal Brisbane and Women's Hospital.

My specialist area of research relates to development of antimalarial drugs; I have prescribed antimalarial chemoprophylaxis for patients attending my clinic, and have treated patients with mild, moderate and severe malaria in the Hospital and in the Intensive Care Unit at the Royal Brisbane and Women's Hospital. I have undertaken field work in Papua New Guinea, the Solomon Islands, the Cook Islands and Ecuador, and have personally taken Mefloquine chemoprophylaxis for a number of weeks while on assignment in Papua New Guinea. Further, I have undertaken two clinical trials that have entailed the use of Mefloquine and Tafenoquine respectively.

I have undertaken clinical trials of 11 investigational antimalarials in healthy human volunteers in Brisbane, Australia. These studies have involved experimentally infecting human volunteers with malaria, followed by test of drug activity in these volunteers using highly sensitive molecular techniques to monitor for drug activity before the parasite reached a level where the human volunteers become symptomatic. These clinical trials systems are supported by a $10 million dollar grant from the Bill and Melinda Gates Foundation, as well as support from pharmaceutical companies to test their drugs, from the so-called Product Development Partnership "Medicines for Malaria Venture" (MMV). MMV is in part funded by DFAT under the Minister's Health Security Initiative. As well my work has been supported by the National Health and Medical Research Council (NHMRC). A I regularly review research proposals for the NHMRC, and for international bodies including the Wellcome Trust and the United Kingdom Medical Research Council. I sit on the editorial board of three journals and regularly review and manage research papers submitted to these journals.

I should state that I have a potential conflict of interest in that I have worked for some time with researchers at the Australian Army Malaria Research Institute (AAMRI) based at Enoggera in Brisbane. This has entailed work on malaria diagnostics and collaboration on testing of antimalarial drugs.

300 Herston Road, Herston Qld 4006 Australia | QIMR Berghofer Locked Bag 2000, Royal Brisbane Hospital, Qld 4029
T +61 (7) 3362 0222 F +61 (7) 3362 0111 W www.qimrberghofer.edu.au
ABN 31 411 813 344

Regarding the terms of reference of this enquiry, I would like to make the following points:

Firstly, it is extremely important to differentiate Mefloquine and Tafenoquine from each other. They are entirely different chemicals with very different chemical structures; they have different mechanisms of action and are metabolised differently in the human body. From a point of view of toxicology, there is insignificant overlap in their toxicological profiles and therefore it is important not to conflate the two drugs because they all have the suffix '-quine' at the end of their name.

Secondly, with respect to Mefloquine, It has been known since the drug was developed that it has neuropsychiatric side effects, and it is absolutely without question that Mefloquine routinely causes these problems when administered in full treatment doses where the patient has acute malaria, and I myself observed this in clinical practice. However, the potential for long term toxicity of the drug has never been unequivocally established in randomised clinical trials. In fact, in studies conducted in US Peace Corp volunteers showed that the longer that Peace Corps volunteers took Mefloquine, the less likely they were to experience neuropsychiatric side effects1-2.

As I noted above, a small proportion of individuals taking Mefloquine weekly for malaria prophylaxis experience neuropsychiatric side effects. These side effects are more likely to occur in people with predisposing causes, such as a pre-existing mental health condition, epilepsy or other neurologic problems. These side effects usually begin soon after they begin taking the weekly prophylactic medication; such side effects can typically be readily identified, and the patient changed to an alternate drug for antimalarial chemoprophylaxis. In addition, it is very frequent for people taking Mefloquine to have vivid dreams on the evening they take their weekly medication, and all people taking the medication should be advised that they are likely to experience these side effects.

The issue of long term Mefloquine use and neuropsychiatric side effects are obviously well publicised, and this committee will no doubt receive submissions on this matter. From my perspective as a clinical researcher and a scientist, it is extremely important to ensure that cause and effect of a drug's side effect is well established. This is typically done in randomised controlled trials where a control group would be expected to have a background incidence of whatever side effect is under study, and it is only when the incidence in the people taking the drug on the study exceeds that of background, and does so at a statistically significant level than can this association be confirmed.

I myself have great respect for our Defence Force personnel and the work that they do, particularly in stressful and dangerous work environments overseas, and particularly in areas where they need protection against malaria which can be a lethal disease if contracted in an area where health care is relatively difficult to obtain. It is also fair to say that the incidence of Post-Traumatic Stress Disorder and mental health problems in returning veterans is one that the veterans community, the medical profession and the wider Australian community all are very well aware of. The issue for me as a clinician and scientist is to determine whether or not Mefloquine increases the risk of this problem, ie has a statistically significant increased frequency in service men and women taking this medication versus another.

As you would understand, undertaking these studies with sufficient numbers of people to prove or disprove this assertion is extremely difficult, and large scale epidemiologic studies particularly undertaken in the United States have indicated that there is some increase in risk of neuropsychiatric side effects in military populations3. However, this was specifically a problem in individuals who have a pre-existing condition who in normal circumstances should not be prescribed Mefloquine.

In summary, I believe with hindsight and in accordance with current military medical practices around the world, Mefloquine should be used with caution for antimalarial chemoprophylaxis both in our Defence Forces as well as for travellers going on holiday. However, in my mind there is no proof that there is a definitive cause and effect relationship between administration of weekly Mefloquine chemoprophylaxis and long term irreversible mental health outcomes.

With respect to Tafenoquine, as I note above Tafenoquine has a completely different chemical class. It has never been associated with neuropsychiatric side effects at a level that is statistically significant above background in any of the clinical trials undertaken with this drug. It is true to say that such side effects have been observed in studies with TQ, but they were not statistically significantly higher than would be expected under normal circumstances, and furthermore, there have been no confirmed instances of acute neurologic toxicities in human subjects taking Tafenoquine in the doses proposed and tested in clinical trials.

It is important also to recognise that Tafenoquine is an extremely promising antimalarial drug whose development has been supported by Glaxo Smith Kline, the Bill and Melinda Gates Foundation, Medicines for Malaria Venture, and the US Military. This is because of its high safety profile, its convenient dosage regime and its lack of association with any of the side effects associated with Mefloquine.

I would like to note that in the clinical trials I conducted, a number of subjects who were administered treatment doses of Mefloquine developed dizziness, but when a similar group of subjects were treated with Tafenoquine, that no such side effects were reported. Tafenoquine has been given to thousands of people in clinical trials without confirmed evidence of acute or chronic neuropsychiatric side effects. The dossier on its safety has been recently reviewed by the US FDA and I am confident that it will be approved for Registration in the US by the FDA, based on the accrued safety data.

With respect to the care of veterans who have had a perceived adverse health outcome after taking antimalarial chemoprophylaxis or participating in clinical trials, I am not an expert in this area and would expect that it is handled under standard DVA guidelines. With regard to the response of Government to the concerns raised with respect to this matter, again I am not completely across the details but am aware of the Inspector General's report and the detailed investigation that was conducted by the Australian Defence Force.

In conclusion, I believe that it is extremely important that a safe antimalarial is available for use by our military personnel serving in areas where they are at risk of potentially lethal malaria. It is therefore extremely important that these drugs are investigated in this very population. Without clinical trials in the target population, it is very difficult to extrapolate results from trials in other settings to ones where defence force personnel are working and need to take antimalarial chemoprophylaxis. If this whole issue results in our defence forces being unable to test drugs to protect our service personnel in such areas that would be a detrimental outcome indeed.

I would be available to answer specific technical questions related to Mefloquine and Tafenoquine if the committee so desires.

Yours sincerely,

Professor James S. McCarthy *MD FRACP DH&TM*

Professor, Tropical Infectious Diseases, University of Queensland
Senior Consultant, Infectious Diseases Physician, Royal Brisbane and Women's Hospital
Senior Scientist, QIMR Berghofer Medical Research Institute

1. Travel Med Infect Dis. 2017 May - Jun;17:50-55.
Long term health outcomes among Returned Peace Corps Volunteers after malaria prophylaxis, 1995-2014.
Tan KR, Henderson SJ, Williamson, Ferguson RW, Wilkinson TM, Jung P, Arguin PM.
Author information: Malaria Branch, Centers for Disease Control and Prevention, Atlanta, GA, USA. Peace Corps, Washington D.C., USA.
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.

2. Lancet. 1993 Apr 3;341(8849):848-51.
Long-term malaria prophylaxis with weekly mefloquine.
Lobel HO, Miani M, Eng T, Bernard KW, Hightower AW, Campbell CC.
Authors: Malaria Branch, Centers for Disease Control, Atlanta, Georgia 30333.
The spread of chloroquine-resistant Plasmodium falciparum malaria has led to increased use of mefloquine prophylaxis by US Peace Corps volunteers in sub-Saharan Africa. We compared long-term mefloquine with other drug regimens for effectiveness and tolerance. The incidence of Plasmodium falciparum infections and of adverse reactions was compared in Peace Corps volunteers who took chloroquine weekly, mefloquine weekly, mefloquine every other week, or weekly chloroquine plus daily proguanil. Weekly mefloquine was 94% more effective than chloroquine (95% CI 86% to 97%), 86% more effective than chloroquine plus proguanil (95% CI 67% to 94%), and 82% more effective than prophylaxis with mefloquine when taken every other week (95% CI 68% to 90%). No serious adverse reactions were observed. Mild adverse events were equally frequent in mefloquine users and chloroquine users, and the frequency of these events declined with increasing duration of prophylaxis. Mefloquine is an effective and well-tolerated drug for prophylaxis of malaria by short-term and long-term travellers.

3. Am J Trop Med Hyg. 2017 Jan 11;96(1):159-166.
Neuropsychiatric Outcomes After Mefloquine Exposure Among U.S. Military Service Members.
Eick-Cost AA, Hu Z, Rohrbeck P, Clark LL.
Epidemiology and Analysis Section, Armed Forces Health Surveillance Branch, Defense Health Agency, Silver Spring, Maryland ;Epidemiology and Analysis Section, Armed Forces Health Surveillance Branch, Defense Health Agency, Silver Spring, Maryland.
Mefloquine was widely prescribed to U.S. military service members until 2009 when use was limited to personnel with contraindications to doxycycline and no contraindications to mefloquine. The need to estimate the occurrence of neuropsychiatric outcomes (NPOs) in service members prescribed mefloquine warranted a comprehensive evaluation of this issue. Active component service members filling a prescription for mefloquine, doxycycline, or atovaquone/proguanil (A/P) between January 1, 2008 and June 30, 2013, were included in the analysis. The risk of developing incident NPOs and the risk of subsequent NPOs among subjects with a history of the condition were assessed. A total of 367,840 individuals were evaluated (36,538 received mefloquine, 318,421 received doxycycline, and 12,881 received A/P). Among deployed individuals prescribed mefloquine, an increased risk of incident anxiety was seen when compared with doxycycline recipients (incidence rate ratio [IRR] = 1.12 [1.01-1.24]). Among nondeployed mefloquine recipients, an increased risk of posttraumatic stress disorder (PTSD) was seen when compared with A/P recipients (IRR = 1.83 [1.07-3.14]). An increased risk of tinnitus was seen for both deployed and nondeployed mefloquine recipients compared with A/P recipients (IRR = 1.81 [1.18-2.79]), 1.51 (1.13-2.03), respectively). Six percent of the mefloquine cohort had an NPO in the year before receiving mefloquine. When comparing individuals with a prior neuropsychiatric history to those without, the ratio of relative risks for adjustment disorder, anxiety, insomnia, and PTSD were higher (not statistically significant) for mefloquine compared with doxycycline. These findings emphasize the continued need for physicians prescribing mefloquine to conduct contraindication screening.