SUBMISSSION TO SENATE FOREIGN AFFAIRS DEFENCE AND TRADE REFERENCES COMMITTEE

Inquiry into the ADF use of Mefloquine and Tafenoquine

Associate Professor Harin Karunajeewa

MBBS, FRACP PhD

Table of contents

1. Academic background and experience relevant to this enquiry 2

2. Summary 4

3. Response to Term of Reference 5

b) Nature and extent of any adverse health effects of those who have taken Mefloquine/Tafenoquine on serving and former ADF personnel 5

c) Comparison of international evidence/literature available on the impact of Quinoline anti-malarials 5

I. What was known about the risks of mefloquine at the time the ADF clinical trials in Timor Leste and Bougainville were conducted? 6

II. What do the terms “acquired brain injury” (ABI), “chronic mefloquine toxicity” and the “quinoline toxidrome” refer to and what is the scientific evidence supporting them? 6

III. What is the current evidence regarding long-term clinically significant sequelae from mefloquine use in humans? 8

IV. What is the evidence that tafenoquine causes significant neurotoxicity? 10

d) Other related matters 10

I. A poorly thought out response could cause additional and unnecessary suffering to ADF veterans and might actually further compromise their health. 10

II. It could also undermine measures being applied more broadly to address the mental health of veterans. 11

III. It could seriously undermine public health efforts to combat malaria in our Indo-Pacific neighbors and throughout the world. 11

IV. It could undermine an important Australian institution that has a historic legacy of having contributed very substantively to national safety and security. 12

V. It could undermine Government initiatives that recognize the importance of clinical trials to improving the health and well-being of Australians. 12

4. References 14

1. Academic background and experience relevant to this enquiry

I write as a practicing medical doctor (MBBS, University of Melbourne, 1992) with post-graduate qualifications as a specialist in infectious diseases (Fellow of the Royal Australasian College of Physicians) and as a medical researcher (Australian National Health and Medical Research Council fellow) currently employed by both the Walter and Eliza Hall Institute of Medical Research (Melbourne) and Western Health, a public hospital health service in Melbourne.

My primary research interest is malaria and I have 18 years of experience in clinical research evaluating various malaria drug treatments, including at least 10 clinical trials conducted throughout the Asia-Pacific on which I was a lead investigator. My research has been published in leading international medical journals, presented at numerous international scientific meetings and been used to formulate public health policy at national (Papua New Guinea), regional (other South Pacific countries) and international (World Health Organization) levels. I have previously sat on a technical review panel at the World Health Organization (WHO) evaluating evidence and formulating international guidelines for the use of malaria treatments.

To summarize my work and expertise in the broadest way possible, what I do is use scientific methods to generate and assess evidence as a way to figure out the best way to use malaria drugs in a range of situations.

None of my studies have involved either mefloquine or tafenoquine, although most have included drugs from the broad group of “quinoline” drugs to which both mefloquine and tafenoquine belong. I have no personal involvement in any studies involving the Australian Defence Force (ADF) and have no professional relationship to the Army Malaria Institute (AMI). I do not receive funding, nor have any financial relationship with pharmaceutical companies that manufacture mefloquine or tafenoquine. During the last 3 years I have provided invited media commentary on the issue of mefloquine toxicity in the capacity as an “independent expert”. This has included interviews for The Guardian, ABC radio, Channel 10’s The Project and The Conversation.

Views expressed here are personal and do not necessarily represent those of my employers.

2. Summary

1. Mefloquine has long been recognized as a potential cause of a number of neurological, neuropsychological and neuropsychiatric side effects. Like virtually all medicines, these encompass a spectrum that ranges from none at all (most individuals), through to those who in the rarest cases experience very severe ill-effects. A significant proportion (approximately 5-10%) will experience side effects that are intermediate between these extremes. Data from numerous clinical studies (including many thousands of individuals) have consistently found that these side effects usually (1) develop early on in the drug's use, (2) are more likely to occur in those with pre-existing psychiatric illness, (3) are dose-related (therefore more likely to occur or be more severe if higher doses are used), and (4) generally resolve following cessation of the drug. These findings have been reinforced by the clinical experience in many millions of people treated with mefloquine (currently >30 million per year) throughout the world.

2. In recent years some authors have proposed an alternative theory that mefloquine (and tafenoquine) cause significant neurological toxicity that results in neurological or psychiatric symptoms that can persist for many years after the drugs are ceased or even be permanent. This has variously been described using terms such as "chronic mefloquine toxicity", "mefloquine induced chronic CNS syndrome", "acquired brain injury", and "mefloquine (or quinoline) toxidrome". This theory relies heavily on numerous assumptions, especially in extrapolating findings from older, more toxic quinoline drugs to mefloquine/ tafenoquine and from animal and laboratory studies to humans. **It therefore should be regarded as a speculative hypothesis unless it can be supported by evidence from human subjects treated with mefloquine (see point 3 below).**

3. Based especially on evidence from a recent large and well-conducted study (of over 360,000 US military personnel) comparing users of mefloquine with those who have used alternative drugs for malaria prophylaxis, **if long-term mefloquine toxicity does exist, it seems very unlikely that it causes a significant number of additional neurological and psychiatric problems over and above that which ordinarily occurs.**

4. This means that in any given individual who is experiencing a common psychiatric complaint (such as anxiety, depression or symptoms of post-traumatic stress disorder), it is overwhelmingly more likely that this exists due to factors other than previous mefloquine exposure.

5. **Although tafenoquine can cause significant haematological (blood) problems in susceptible individuals, there is no evidence that it causes increased rates of significant neurological or neuropsychiatric problems, whether acute or chronic, when used at conventional doses in humans.**

6. The manner of the response to this issue could have important implications for the health of ADF veterans and there are risks that that it could seriously undermine current Australian Government initiatives that aim to (1) address the mental health crisis in ADF veterans, (2) improve health security in the Indo-Pacific and (3) improve participation and activity in clinical trials throughout the Australian health system.

3. Response to Term of Reference

b) Nature and extent of any adverse health effects of those who have taken Mefloquine/Tafenoquine on serving and former ADF personnel

The health effects that many have claimed are due to previous mefloquine or tafenoquine use have been widely reported and include a range of psychiatric, psychological and neurological problems. The point of controversy lies not in whether or not individuals are suffering from these symptoms, but in whether or not they are causally related to prior antimalarial drug use. Addressing this controversy regarding causality, therefore, first requires an appreciation of the usual prevalence of these sort of issues in the general community.

Beyond Blue estimates that 3 million Australians are living with anxiety or depression (1) and suicide is now the leading cause of death in Australian adults under 45. Of course, the vast majority of those represented by these figures have never been exposed to drugs for malaria. A recent study of mental health and wellbeing in the ADF found that 1 in 5 met criteria for a significant mental health problem, including approximately 1 in 7 with an anxiety disorder and 1 in 10 with features of depression. (2) So based on these figures, for a group of 2000 ADF veterans (ie similar to the number prescribed mefloquine during ADF deployments) we might expect around 400 to be suffering some sort of mental health issue, including around 300 with anxiety disorder and 200 with depression. So, leaving aside mefloquine, mental health problems are very common, especially in those with military backgrounds and of course the underlying causes may be varied and complex. The question therefore becomes; in a given ADF veteran who is suffering from an already very common illness like anxiety or depression, how likely is it that their previous exposure to malaria drugs either caused this illness or made their illness worse? In other words how much, if anything, does exposure to these malaria drugs *add* to what is already a huge health problem in this group?

c) Comparison of international evidence/literature available on the impact of Quinoline anti-malarials

There are currently over 3000 scientific papers dealing with the drug mefloquine alone. The following refers either to existing literature reviews (where others have already synthesized the available evidence) or to particular papers that I believe provide the highest quality and levels of evidence and that are most relevant to this enquiry. Although we often take into account data from laboratory work and animal studies, generally, we regard the highest level of evidence as that coming from well-designed studies conducted in human populations representative of those in which these malaria treatments are actually used. This is the sort of evidence that is needed to inform good public health policy and addresses the real practical issues we, as doctors face when we make prescribing decisions that we hope will be in the best interests of our patients. Fundamental to this decision making is an acknowledgement that all medications have potential to cause side effects of some type or another. Even commonly used drugs like paracetamol, asprin or penicillin can be lethal under certain circumstances. What becomes critical, therefore is the *frequency* (ie how commonly they occur) and *severity* of those side effects, considered relative to the therapeutic benefits of the drug. In other words we must scrutinize a "*risk-benefit" equation*.

I. What was known about the risks of mefloquine at the time the ADF clinical trials in Timor Leste and Bougainville were conducted?

I draw the committee's attention to the first edition of the book "Manual of Travel Medicine: A guide for practitioners at pre-travel clinics", by Allen P Yung and Tillman Ruff, published in 1999. (3) Although this edition is now almost 20 years old it provides the committee with a snapshot of

conventional, mainstream medical opinion regarding the perceived risks of mefloquine *at a time around which the Timor Leste and Bougainville trials were conducted.* Secondly, it represents a careful, thorough, methodical and considered review of the large body of literature that was already available at this time. Thirdly, its two authors, Allen Yung (now deceased) and Tillman Ruff are very highly regarded throughout both the medical profession and the broader Australian community (both have subsequently been awarded the OAM). Their book could be regarded as something of a "bible" for Australian practitioners of "travel medicine" and contains chapters on the use of prophylactic drugs for preventing malaria in travelers to malaria-endemic parts of the world. These were intended to guide practicing doctors through the difficult risk-benefit decision making that is required when they must choose whether to prescribe drugs to prevent malaria in travelers and if so which drug to choose. Yung and Ruff highlight the complexity involved in this decision making and acknowledge that even at this time the issue of mefloquine's side-effects and potential toxicity was highly controversial. Nonetheless, they do their best to balance these competing opinions and try to actually *quantify* these risks based on the available evidence. I believe that most of their conclusions essentially still hold true today. To summarize, these included the following:

1. In practical terms for travelers exposed to malaria in most parts of the world where there is malaria, given resistance of malaria parasites to many other malaria drugs, at that time (1999) there were *only two* effective drugs available for malaria prevention: Doxycycline and mefloquine.
2. Doxycycline and mefloquine were considered to have similar effectiveness for preventing malaria and that "cost, side effects, patient preference and contraindications of these 2 drugs determine which drug is used".
3. Yung and Ruff quantified the risks of neurological side-effects from mefloquine according to severity as follows:
    a. Risk of severe neuropsychiatric adverse events (such as "psychosis, encephalopathy and convulsions") was estimated at "1 in every 10,000 users" – a figure similar to that seen in the general population. This figure was based on a study of 140,000 European travelers (Steffen et al, Lancet, 1993; 341-1299-1303).
    b. Risk of less serious, but "still sometimes disabling and distressing effects" (such as "confusion, mental clouding, headache, anxiety, agitation, depression, abnormal thinking, dizziness, ataxia and sleep disorders such as insomnia, vivid dreams or nightmares"): as a "rough guide" these were estimated at occurring in "0.5%" (1 in 200) of mefloquine users.
    c. Risk of milder reactions still, but that were "sufficiently severe to interfere with daily activities" (and that might lead to the drug being ceased) was estimated at "5-10%" of mefloquine users.
4. Importantly, Yung and Ruff note that side effects, when they do happen, usually occur "early on in its use" and that "if side effects have not occurred in the first month they are unlikely to develop".
5. They say, "despite all the concerns written about mefloquine, the vast majority of travelers on mefloquine prophylaxis have tolerated the drug and only approximately 5% have had to change to an alternative regimen."

II. What do the terms "acquired brain injury" (ABI), "chronic mefloquine toxicity" and the "quinoline toxidrome" refer to and what is the scientific evidence supporting them?

In recent years, a number of new terms have been used to describe what are considered in some quarters to represent long-term or permanent effects of mefloquine exposure. Some of these terms include "acquired brain injury", "chronic mefloquine toxicity", "mefloquine induced chronic CNS syndrome" and "mefloquine (or quinoline) toxidrome". (4, 5) These terminologies are not currently widely used throughout the mainstream medical community, having until now been restricted to a fairly small core of authors with a particular interest and viewpoint on this matter. However, the

concepts alluded to by these terms are crucial to many of the arguments currently being put forward, so it is essential that they be subject to critical analysis.

The first point to make here is that these new terms that suggest lasting *chronic* or *permanent* neurological damage from mefloquine represent *a conceptual paradigm shift in thinking about mefloquine toxicity.* Before addressing this new, what I will call, "chronic toxicity" paradigm, we should consider the existing paradigm (which I will refer to as the "acute toxicity" paradigm). Nobody disputes that mefloquine neurotoxicity occurs in a subset of individuals – however this has predominantly been considered as acute (arising within a matter of weeks), dose-dependent (so severity is dependent on how much drug body tissues are exposed to) and self-limiting (toxicity will resolve and the subject will recover some time after the drug is stopped). At the heart of this "acute toxicity paradigm" are conventional pharmacological concepts that relate the relationship between the amount of drug body tissue (such as the brain) is exposed to on the one hand, to the severity of effects (including adverse or toxic effects) on that tissue on the other. These concepts (described as "pharmacokinetic-pharmacodynamic relationships") are pretty universal in pharmacology ie they apply very well to just about all drugs we use in medicine and are supported by very good evidence across a range of different drugs. They can in many ways be summarized in the pharmacologist's adage "the dose makes the poison" – meaning that all medicines are toxic in some way, what matters is how much drug reaches body tissues, and that this can vary from person to person and from drug to drug.

By contrast, the "chronic toxicity" paradigm could be thought of as seeing toxicity as chronic (lasting for years), not necessarily dose-dependent (so may occur as an "idiosyncratic event") and permanent (toxicity does not resolve once the drug is ceased). From a biological perspective, this theory relies on assumptions that drug exposure causes permanent tissue damage (such as cell death) which prevents recovery and therefore has lasting effects even well-after the drug is ceased. Although controversial, this is not, in itself an unreasonable hypothesis. Idiosyncratic, non-dose related drug toxicities are well-described for a wide range of drugs (though as a general comment, they usually occur much less commonly than predictably dose-related acute toxicity and often as "allergic" phenomena). However, the committee should make a clear distinction between what remains in the realm of *hypothesis*, conjecture and theory on the one hand, and what is supported by scientific *evidence* on the other.

So what is the evidence supporting the acquired brain injury/ chronic mefloquine toxicity hypothesis? The scientific literature relating to these terms seems to reside in articles authored by a relatively small quorum of prolific individuals. Most take the form of narrative reviews, opinion pieces, commentary and letters to the editor, rather than original evidence-generating research *per se*. Examples include articles by Remington Nevin who seems to be the leading protagonist of the chronic mefloquine toxicity theory in the academic world. A search of literature authored by Nevin on the subject of mefloquine reveals 29 articles of which 17 appear to be letters to the editor, 5 are opinion pieces and 2 case reports. His opinion piece "Idiosyncratic quinoline central nervous system toxicity: Historical insights into the chronic neurological sequelae of mefloquine" (4) seems as good a place as any to start. Nevin draws on a number of sources to support his hypothesis regarding a distinct syndrome (or what he calls a "toxidrome") of chronic or permanent neurological damage from mefloquine: Firstly, he examines various historical reports (including many from the 1930's, 40's and 50's) where toxicity was documented as being caused by earlier versions of quinoline antimalarial drugs in clinical descriptions and autopsy studies of animals and humans, including following overdoses with these drugs. The drugs in question, that included "pamaquine", "plasmocid" and "clioquinol" were all abandoned over 50 years ago largely because they were widely acknowledged to be too toxic. However Nevin seems to argue that because these drugs share similarities in chemical structure to mefloquine and other modern drugs for malaria that their toxic effects are likely to be common to the entire class of drugs, and that therefore drugs like mefloquine become "guilty by association". Secondly, he cites studies in which animals such as rats (or laboratory cultures of neurological tissues) were exposed either to "high doses" or "neurophysiological concentrations of drugs" and then shown to exhibit cellular damage when these tissues were examined microscopically. Thirdly he notes case reports (isolated clinical descriptions of observations from a single person)

where long-lasting neurological effects such as vertigo (a sensation of dizziness and the world spinning), disequilibrium (problems with balance) and parasthesias (pins and needles or abnormal sensations in the hands and feet) have been documented. I don't dispute the legitimacy of each piece of evidence he cites. However, I do very much disagree with the manner in which he has interpreted them collectively. He draws these pieces together to form what he terms a "parsimonious" hypothesis. I would personally prefer to use the term "simplistic" to "parsimonious". Most especially, he effectively draws on a set of assumptions (especially when extrapolating findings from other quinoline drugs to mefloquine and from animal and laboratory studies to humans) that are very questionable and mean that it should remain in the realm of a highly speculative hypothesis. Nonetheless, I think we would both agree that mefloquine, like virtually all drugs, can cause toxicity that encompasses a spectrum from none at all on one side, to very severe on the other. The key question then becomes, in practice, how many people taking the drug fall into the "very severe" category with lasting or permanent significant side effects. Is this likely to be very rare or quite common? To answer this question, our best available approach is to draw on the results of carefully constructed studies that apply the best statistical methods to compare the prevalence of these symptoms in humans who have taken these drugs, with a suitable group for comparison (often referred to as a control group).

III. What is the current evidence regarding long-term clinically significant sequelae from mefloquine use in humans?

Relatively few studies have specifically examined the incidence of long-term neurological and psychiatric symptoms following mefloquine. However, in 2017 a large and well-designed study of 367,840 US military personnel was published by Eick-Cost *et al* that compared the incidence of neuropsychiatric diagnoses occurring up to a year following drug exposure in 36,568 persons who took mefloquine, with 331,272 persons who took an alternative malaria drug (doxycycline or Malarone™). (6) Although an evaluation of this type can never be "perfect" from a methodological standpoint, my assessment of this study is that it used appropriate methods and was analytically very sound. By nature of this and its very large size, it effectively constitutes the best evidence on this subject we currently have, and probably the best evidence we are ever likely to have. Therefore, I would suggest that if the committee were to scrutinize just one piece of scientific evidence this should be it. The study was conducted by a group affiliated with the US Military, but I maintain that its methods are sound and transparent and I see no evidence of bias in the way its results are presented and interpreted by the authors. I note that it has also actually been cited by proponents of the mefloquine chronic toxicity hypothesis as supporting their own arguments. So what were this study's findings? The authors compared the incidence of a long list of diagnoses (including "adjustment disorder", insomnia, anxiety disorder, tinnitus (ringing in the ears), depressive disorder, vertigo, PTSD, suicidal thoughts, convulsions, psychoses, hallucinations, paranoia, actual suicide and confusion) in mefloquine users, firstly in comparison with doxycycline users and then separately with Malarone™ (Atovoquone-proguanil) users. They also did the analyses separately in both "deployed" and "non-deployed" military personnel. This all results in a total of over 50 separate individual comparisons. This creates something of a problem in that the more comparisons you do the more chance you have of finding significant differences purely due to chance. In other words for a study like this, if there was absolutely no real difference between any of the groups, it is likely that we would still come up with 2 or 3 "significant" differences between some groups, purely due to random variability. Indeed a number of "significant" differences between treatment groups emerged from this study – but importantly these were fairly evenly balanced between those that showed a significantly *higher* incidence in mefloquine users, and those that actually showed a significantly *lower* incidence of some diagnoses in mefloquine users. The "statistically significant" findings were as follows:

1. The risk of tinnitus (ringing in the ears) in mefloquine users (occurred in 0.9% of all those who took the drug) was higher than that seen in Malarone™ users. The effect was seen in both deployed and non-deployed groups but was not seen at all when comparing mefloquine with the very large group who took doxycycline.

2. The incidence of PTSD in mefloquine users (0.4% of all those who took the drug) was higher than in Malarone™ users when looking specifically at non-deployed users. Importantly, the effect was not seen in deployed personnel and was not seen compared with doxycycline users (0.8% of all doxycycline users had PTSD), of whom non-deployed personnel actually had a significantly *higher* risk of PTSD than mefloquine users.
3. The risk of anxiety disorders was slightly higher (by 10%) in the mefloquine group than the doxycycline group. This effect was seen only in deployed personnel (not in non-deployed personnel) and was not seen when comparing mefloquine with Malarone™ users.
4. The risks of a further 6 diagnoses (including adjustment disorder, insomnia, anxiety disorder, depressive disorder, vertigo and PTSD) were actually significantly *lower* in non-deployed mefloquine users when compared with non-deployed doxycycline users. The effect was not seen in deployed personnel or when comparing mefloquine and Malarone™ users.

In summary a few possible differences were found but the significance of these in terms of the likelihood of "real" long-term mefloquine toxicity were diminished by the following factors:

1. An expectation that for statistical reasons, we would expect to see some "significant differences" purely due to chance alone.
2. Differences seen were not shown consistently when comparing mefloquine with doxycycline and then mefloquine with Malarone™ or when looking at both deployed and non-deployed groups. We would expect a significant "real" effect to be replicated consistently across multiple comparisons.
3. "Higher" risks of some (total of 3) diagnoses in mefloquine users were effectively balanced by "lower" risks of other (total of 6) diagnoses. This suggests that the differences seen were due to chance and arose due to random variability.

Based on these findings, we cannot absolutely with 100% certainly disprove the theory that mefloquine causes long-term toxicity in humans. In fact we can never do this - that's just not how science works. However, based on the study's findings, we can say, that if mefloquine did cause long-term toxicity (and that is still a very big "if"), then this is likely to occur as a fairly uncommon event and would only contribute to a very small proportion of the background rates of psychiatric disease in the population.

One other study examining the long-term effects of mefloquine (7) is also worth noting. This study, conducted by the United States Centers for Disease Control (CDC) in 2016 invited former Peace Corps volunteers (in the years 1995-2014) to take an internet-based survey relating to malaria prophylaxis and medical diagnosis (up to 21 years following possible malaria prophylaxis during their peace corps deployments). Unfortunately, this study was prone to a number of unavoidable but important methodological problems, including especially potential for "selection bias" (only 11% of those invited participated) and "recall bias" (questioning regarding malaria drugs could have influenced how participants responded to questions regarding those medical diagnoses). Nonetheless its findings are worth noting. These included their overall conclusions that (1) "Malaria prophylaxis use by Peace Corps Volunteers is safe"), (2) "When excluding those with prior psychiatric illness there were no difference in psychiatric diagnosis rates" in mefloquine users and (3) In those with pre-existing psychiatric diagnoses, "certain psychiatric diagnoses were more likely among mefloquine users". This last point is consistent with existing knowledge regarding risk factors for neuropsychiatric effects of mefloquine and emphasizes the importance of good screening for these contraindications prior to prescribing. Overall I think their findings were consistent with and supported by the larger and more rigorous subsequent study by Eick *et al*.

The results of these studies are also borne out by the now very extensive clinical experience with mefloquine. Until as recently as 2011, up to 17,000 Australian travelers were being prescribed mefloquine by GPs and travel clinics. (8) As many as 35 million people a year receive the drug (mostly in much higher treatment doses than are used for prophylaxis). (9) This represents the very

large “denominator” of total mefloquine use in the community and suggests that the isolated reports of serious side effects represent an extremely small fraction of the total users.

IV. What is the evidence that tafenoquine causes significant neurotoxicity?

Whilst I accept that we can legitimately debate the possibility of significant long-term neurotoxicity with mefloquine, I do not believe that we can say the same in the case of tafenoquine. Whilst it is more or less universally accepted that mefloquine can cause at least acute serious neurotoxicity in a small proportion of people, there is no evidence that I am aware of that suggests this exists for tafenoquine. From my reading, much of the rationale for claims that tafenoquine causes significant neurotoxicity stem from the “quinoline toxidrome” hypothesis as propounded by Nevin and others ie that tafenoquine, by belonging to the quinoline class of drugs is “guilty by association” due to its chemical similarities to previous malaria drugs with known neurotoxic properties. (4) Again, this is in the realm of hypothesis that I don’t believe is supported by the literature either from studies of animals (10) or humans (11). In particular, comprehensive reviews of multiple clinical trials suggest that the incidence of “neurological” side effects was no higher in those receiving tafenoquine compared with placebo. Somewhat higher rates of “psychiatric disorders” with tafenoquine, on closer inspection can be explained as higher rates of sleep disturbance (insomnia, abnormal dreams and nightmares). I would contend that, whilst annoying and unpleasant, these issues don’t constitute significant psychiatric diagnoses and I think it was probably a mistake to have classified them as such. By contrast, it is universally accepted that there are indeed, very important issues of toxicity with tafenoquine, particularly in regard to haematological (blood-related) problems. These issues are currently causing those of us in the malaria community a great deal of angst.

d) Other related matters

I would like to raise a number of additional points relevant to this issue, that whilst not specified in the committee’s terms of reference, have very important broader implications for the public interest. In particular, I am concerned that an ill-considered response to this issue has potential to cause great societal harm and could undermine a great deal of good work that is being done both by Government and throughout the broader Australian community. I would like to draw the Committee’s attention to these potential dangers:

I. A poorly thought out response could cause additional and unnecessary suffering to ADF veterans and might actually further compromise their health.

There have been calls for an “active outreach program” for ADF veterans affected by mefloquine. (5) It is not entirely clear what this would involve, but the word “active” suggests that the intention would be a program that would endeavour to find and contact ADF personnel who had received mefloquine or tafenoquine in the past, presumably so that they could be assessed for evidence of the “quinoline toxidrome” and then receive “appropriate medical treatment”. Aside from the fact that I’m not aware of any specific medical treatment that is available for the “quinoline toxidrome” I think this would achieve little and have potential to cause significant additional suffering. Given the high prevalence of mental illness throughout the Australian community and especially in ADF veterans, such a program would of course unearth a great many (possibly many hundreds) of individuals who are suffering or have suffered from mental illness, psychological problems or a variety of neurological symptoms. As I’ve explained, the sum total evidence available suggests that in most if not all of these people, their symptoms are statistically very unlikely to have been caused by previous malaria drug exposure. However, its hard to see how such a program could be implemented without implicitly suggesting to recipients of the outreach that their symptoms are indeed related to previous drug exposure. This approach is therefore highly susceptible to an important and very well characterised phenomenon known as “recall bias”. It effectively becomes a “self-fulfilling prophecy” and one which I believe would contribute significantly to anxiety and other psychological morbidity in these veterans. It

would likely create significant momentum of its own and serve as a way of amplifying the quinoline toxicity movement which I believe is based on some very flawed science and misleading information.

II. It could also undermine measures being applied more broadly to address the mental health of veterans.

I strongly support the Government's existing approach including recent initiatives to address the mental health crisis as part of a broad and inclusive framework as set out in the Veterans Mental Health Package. I worry in particular, that anything that provides legitimacy to the quinoline toxicity lobby reinforces a simplistic explanation of what is in reality a complex multi-factorial problem. It enables people to "blame" a single external factor for their plight, at the expense of a more difficult and possibly confronting process of enquiry into root causes (that may be complex, myriad and include both external and internal factors) but that is likely to be far more useful when it comes to actually getting people better. The risk therefore is that this could undermine efforts to improve mental health, not only in those who have taken malaria medications, but also more broadly throughout the ADF. Because there is no specific treatment for quinoline toxicity, a generic approach is not only medically appropriate, but also ethically desirable, as it implicitly assumes that all veterans with mental or other health problems, regardless of their experiences are equally valued and have equal access to help.

III. It could seriously undermine public health efforts to combat malaria in our Indo-Pacific neighbors and throughout the world.

There are disturbing parallels between the quinoline toxicity lobby and the "anti-vaccination" movement. The latter has already undermined important public health initiatives throughout the world and therefore can effectively be held responsible for a great deal of sickness and death. A pertinent example was when, just as global polio eradication was looking achievable, a conspiracy theory relating to polio vaccination took hold in Nigeria and lead to a resurgent epidemic of that disease that spread throughout the world. Unfortunately, as with vaccinations, there is significant potential for misinformation regarding antimalarial drugs to leak beyond the current sphere and into populations of malaria-endemic countries. This could have disastrous consequences for global health. Mefloquine and other quinoline drugs are now the mainstay of life-saving treatment recommended by WHO (when used in drug combinations known as artemisinin combination therapies: ACTs) for the more than 200 million people who suffer from malarial illness each year. (12) The development of these artemisinin-quinoline drug combinations has been one of the great global public health successes of our time. They have been a significant factor in recent gains in malaria control that have seen global malaria mortality decline by 60% in the last 15 years and that have therefore saved an estimated 6 million lives. The Australian government deserves a great deal of credit for recognizing the importance of malaria to health security and to economic growth and stability, especially in our own Indo-Pacific region. (13) Its support has been instrumental to the development of new, more effective drugs (including many based on quinoline drugs), massive improvements in malaria control in neighbouring countries and commitments to permanently eliminate malaria from our region within the next 15 years. An especially good example of these successes is Timor Leste, which since independence has achieved >99% reductions in its national malaria burden. Last year it had fewer than 30 malaria cases throughout the entire country. Somewhat ironically, were ADF personnel to be deployed in Timor Leste today, they would probably not require any malaria prophylaxis, thanks to these improvements in malaria control.

A particular problem with the "quinoline toxidrome" hypothesis is that all quinoline drugs, new and old, safe and unsafe, are effectively tarred with the same brush by its proponents. Misleading information that overstates the risks of quinoline-containing ACTs and results in people avoiding life-saving malaria treatments could therefore have catastrophic implications that could seriously undermine the efforts of the Australian government and wider global community to control malaria.

IV. It could undermine an important Australian institution that has a historic legacy of having contributed very substantively to national safety and security.

A number of serious accusations have been directed at the Army Malaria Institute (AMI). These include allegations of "medical negligence" and of being subject to corrupting pecuniary interests through relationships to pharmaceutical companies. (5) Some have even called for the AMI to be disbanded. To ensure proper contextual understanding, it is important that the committee has a broad and balanced understanding of the AMI's current and previous work, the achievements of it and its predecessor organizations and its international standing.

The importance of malaria to the ADF, both as a threat to the lives of its personnel, and to the success of its military operations, stretches right back to World War 1- including not only Gallipoli but also Palestinian campaigns (where malaria incapacitated half of the Desert Mounted Corps and resulted in deaths of 100 ADF personnel). In World War 2 malaria was a critical strategic factor, especially in the Pacific theatre. The Australian Army's malaria experimental group that was led by Neil Hamilton Fairley pioneered the development and testing of some of the first synthetic quinoline drugs that, whilst plagued by problems of toxicity, were at least outstandingly successful in preventing death and sickness from malaria in Australian troops. Meanwhile, at some periods during WW2, deaths from malaria in Japanese forces in the Pacific were thought to have outnumbered those due to combat injuries by a factor of 6 to 1 and therefore seriously compromised the enemy's military effectiveness. Australia's very superior expertise in preventing malaria is therefore rightly considered to have been a decisive factor in allied forces having prevailed in this theatre. Fairley and his team are quite justifiably regarded by many as "war heroes". By inheriting this legacy, the AMI's "reason for being" therefore relates to the profound strategic importance that malaria has had in previous military conflicts and could possibly have again in future operations.

The Australian malaria research community is relatively small. I am therefore well aware of the work AMI has done and their contribution to knowledge of how to best fight this disease. My general impressions are that the AMI and its members are very well-respected as scientists and academics and their contributions to this effort are genuinely very highly valued throughout our small community. We all do our best to co-operatively draw on a wide variety of resources including government, academia, public-private partnerships, non-government organizations and industry with a common purpose of alleviating suffering from a disease that has been one of the most important causes of death in the history of mankind. I am not aware of any evidence to support suggestions that clinical trials in Bougainville and Timor Leste were ethically compromised by pecuniary interests or collusion with the pharamaceutical industry. To make accusations of base motives against people who have made significant contributions to what is effectively a collaborative global humanitarian effort, seems to me pretty unfair, to say the least. Many of the accusations levelled seem to belong firmly in the realm of baseless conspiracy theories.

V. It could undermine Government initiatives that recognize the importance of clinical trials to improving the health and well-being of Australians.

There have been strong criticisms levelled at the AMI relating to whether their clinical trials in Bougainville and Timor Leste were conducted within an appropriate ethical framework. (5) Not having been directly involved in these studies, I can't really comment on this, but acknowledge that issues of "informed consent" and "autonomy" of decision making can be subject to complexities and ambiguities when research is conducted in military settings. These criticisms have extended to calls for future clinical research to be banned in the ADF in future. Were this to occur, I honestly don't think it would be the in the best interests of the health and welfare of ADF personnel. It runs counter to evidence that recognizes that clinical trial participants are likely to receive better medical care and have better outcomes to patients receiving routine care. For example there is good evidence that in the UK, hospitals with the highest rates of clinical trials activity have the lowest death rates, and conversely, those with lowest clinical trials activity have the highest death rates (14) My own

experience in conducting clinical trials throughout the world has reinforced this notion. Governments throughout the world, including in Australia are therefore now regarding rates of clinical trial participation as a key quality/ performance indicator for their health systems. The Australian government is currently doing a lot of work to support the development of clinical trials networks to help drive much-needed improvements in healthcare quality in this country. The manner in which the current debate is being conducted (eg frequent use of the term “guinea pig”) has significant potential to undermine these efforts.

The ADF has both a duty of care to protect and maintain the health of its personnel, and a strategic imperative to maintain the fitness and battle-readiness of its troops. It is therefore perfectly logical and ethically appropriate that the ADF should endeavour to understand what the most effective and safest ways are to protect its troops from the high risks of a potentially debilitating and lethal disease. Information of this kind cannot be readily sourced elsewhere – the best way to find out what works best is to actually perform a test in the population for which the treatment is intended. Clinical trials in the military have done a great deal to improve the health, safety and effectiveness of soldiers throughout modern history. It is in the best interest of all soldiers that they continue.

4. References

1. Beyond Blue: https://www.beyondblue.org.au
2. Van Hoof M *et al*. The Australian Defence Force Mental Health Prevalence and Wellbeing Study: design and methods. European Journal of Psychotraumatology. 2014;5:23950
3. Yung AP and Ruff T. Manual of Travel Medicine: A guide for practitioners at pre-travel clinics. Eds Hutchins A. 1st Edition. 1999.
4. Nevin R. Idioscyncratic quinoline central nervous system toxicity: historical insights into the chronic neurological sequelae of mefloquine. International Journal for Parasitology: Drugs and Drug Resistance. 2014;4:118-125
5. International Mefloquine Veterans Alliance: https://imvalliance.org
6. Eick-Cost AA *et al*. Neuropsychiatric Outcomes after Mefloquine Exposure among U.S. Military Service Members. Am J Trop. Med Hyg. 2017;96(1):150-166.
7. Tan KR et al. Long term health outcomes among Returned Peace Corps Volunteers after malraia prophylaxis, 1995-2014. 2017:17:50-55.
8. Australian Statistics on Medicines 2011, Table 1 - Antiparasitic Products Insecticides and Repellents: http://www.pbs.gov.au/info/statistics/asm/2011/table-1-antiparasitic-products-insecticides-and-repellents
9. Karunajeewa H. Mefloquine, an Antimalarial Drug Made to Win Wars. The conversation. Available at: https://theconversation.com/weekly-dose-mefloquine-an-antimalarial-drug-made-to-win-wars-55566 Published April 27, 2016
10. Dow GS *et al.* Tafenoquine is not toxic following supratherapeutic dosing in rats. Travel Med Infect Dis. 2017;17:28-34.
11. Novitt-Moreno A *et al*. Tafenoquine for malaria prophylaxis in adults: An integrated safety analysis. Travel Med Infect Dis. 2017;17:19-27
12. World Health Organization. Guidelines for the treatment of malaria. 3rd Edition. Geneva 2015. Available at: http://apps.who.int/medicinedocs/en/d/Js21839en/
13. Bishop J. Keynote address at the Malaria World Congress. July 2 2018. Available at: https://foreignminister.gov.au/speeches/Pages/2018/jb_sp_180702.aspx
14. Ozdemir RV *et al*. Research Activity and the Association with Mortality. PLoS ONE. Feb 26, 2015.