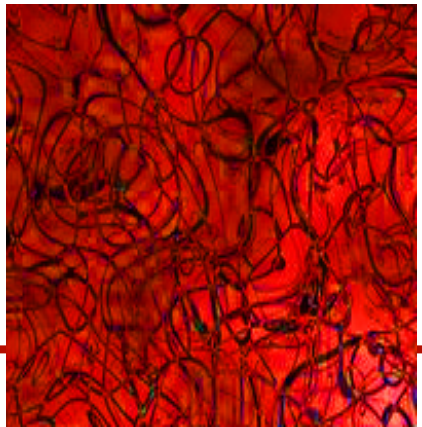
SANITAS

Surgeon General Report On Mefloquine



CHAPTER 1 Introduction to the Report

1.1 Background

Malaria is a potentially life-threatening parasitic disease that occurs in many tropical and sub-tropical areas of the world. It presents a risk to Canadian Armed Forces (CAF) personnel who travel to endemic areas, whether for operational or leisure travel. Prevention of malaria relies on multiple tactics, including avoiding the bites of its mosquito vectors, and using malaria medication (called malaria chemoprophylaxis (MCP)) to eliminate parasites that are inoculated through bites.

The CAF approach to malaria prevention, including use of MCP, is consistent with the Canadian clinical practice guidelines (CPG) on malaria prevention and treatment (reference 1.1). In most areas where the most dangerous form of malaria occurs (*Plasmodium falciparum*), the Canadian CPG and the CAF recommend that travelers use one of three options for MCP: mefloquine, atovaquone-proguanil (AP) (brand name Malarone®), or doxycycline. Within the CAF and with respect to these options, the current policy is that the individual member, after suitable discussion with their health care provider, can choose his/her preferred agent from among those that are deemed medically suitable.

The continued use of mefloquine as a MCP option in the CAF has recently received significant scrutiny. This has included inquiries from the Standing Committee on Veteran Affairs (reference 1.2), media commentary and concerns raised by veterans. Similar criticisms have been raised in other jurisdictions, e.g., the United States, the United Kingdom and Australia. Although the specifics have varied between jurisdictions, the core concern has centered on the suitability of mefloquine as a MCP agent for military personnel. This usually has been expressed in the sense of military personnel being a unique population with specific risk factors that might predispose them to adverse effects potentially associated with mefloquine, e.g., neuropsychiatric harms (reference 1.1).

Some of the recent focus on mefloquine in Canada may potentially be associated with the August, 2016 change in the product monograph (reference 1.3) to include a “Serious Warnings and Precautions” box. This box is placed near to the beginning of the monograph and highlights contraindications and potential neuropsychiatric adverse reactions that may occur with use. These include:

- “*Mefloquine should not be prescribed for prophylaxis in patients with major psychiatric disorders”;*
- *“Mefloquine may cause neuropsychiatric adverse reactions than can persist after mefloquine has been discontinued”; and,*
- *“During prophylactic use, if psychiatric or neurologic symptoms occur, mefloquine should be discontinued and an alternative medication should be substituted”.*

These warnings were included in previous versions of the product monograph. However, Health Canada has changed the way it produces monographs. It now includes a boxed warning to make information on serious warnings and precautions more prominent. The decision to include a boxed warning is based on the potential for clinically significant or life-threatening adverse events in association with the drug. Hence, many products (including mefloquine) now carry box warnings.

1.2 Purpose of the Report

Given the concerns that have been raised about mefloquine, the Canadian Armed Forces Chief of Defence Staff (CDS) instructed the Surgeon General (SG) to critically analyze the body of knowledge regarding mefloquine, and to undertake a review of the CAF experience with the medication. This report is the SG response to this tasking.

1.3 Structure of the Report

The report is divided into several chapters, each of which addresses one to several key questions:

- What has been the CAF experience with mefloquine? (chapter 2)
- Is the CAF following recommended practices for prescribing mefloquine, e.g., does the process include an individual level encounter with a clinician? (chapter 3)
- Are the Canadian practice guidelines for malaria prevention (and by extension the CAF approach) consistent with the approaches employed by other national and international jurisdictions? (chapter 4)
- Compared to alternatives, are military personnel using mefloquine at relatively increased risk for potentially associated adverse effects? (chapter 5)
- Compared to alternatives, does mefloquine result in reduced ability to execute occupational duties? (chapter 5)
- Is there evidence of adverse long term effects potentially associated with use of mefloquine in military personnel? (chapter 5)

The final chapter of the report, chapter 6, summarizes findings and makes recommendations.

1.4 Development of the Report

This report was developed by the Surgeon General's Task Force (TF) on Mefloquine. The TF was comprised of personnel from the CAF and civilians from the Department of National Defence (DND). All members have been involved in developing CAF policy related to malaria prevention, including recommendations for MCP. As well, a single member of the TF also serves as a departmental representative on the committee responsible for, among other things, developing the Canadian CPG on malaria prevention.

Each research chapter (chapters 2-5) outlines its own methods. Where possible, emphasis is placed on developing objective evidence-based analyses. In some circumstances, stringent criteria were applied (e.g., chapter 5) so as to only include the most relevant and highest quality data. Throughout the report, we place an emphasis on transparency to allow the reader to understand why analytic decisions were made and conclusions reached.

References

1.1 Committee to Advise on Tropical Medicine and Travel. 2014. Canadian Recommendations for the Prevention and Treatment of Malaria.

1.2 Standing Committee on Veterans Affairs. Mental Health and Suicide Prevention Among Veterans. 42nd Parliament, 1st Session.

http://www.parl.gc.ca/Committees/en/ACVA/StudyActivity?studyActivityId=9153634 (accessed December 22, 2016)

1.3 Product Monograph – mefloquine. https://www.aapharma.ca/downloads/en/PIL/2016/Mefloquine-PM.pdf (accessed 20/03/2017)

CHAPTER 2 The Mefloquine Experience

Key question(s)

What has been the CAF experience with mefloquine?

Summary

- *The CAF policy on malaria prevention including its approach to use of MCP is consistent with the Canadian CPG on malaria prevention.*
- *As described in the Canadian CPG, mefloquine continues to be a useful MCP agent. In some cases it is the preferred MCP option, for example because it is specifically recommended for certain populations (e.g., first trimester of pregnancy), other agents are contraindicated, or individuals prefer the drug.*
- *Over the last 15 years, prescription patterns for MCP have changed dramatically. In the early 2000's, most prescriptions were for mefloquine. However, starting in 2004 (coinciding with the availability AP), this pattern changed with relative rates of use of mefloquine decreasing and relative more people receiving prescriptions for AP.*

Conclusion(s)

The CAF has used mefloquine as an antimalarial for more than twenty years. It remains an option, along with doxycycline and AP in areas where the most dangerous form of malaria (Plasmodium falciparum) occurs. In the past 15 years, the pattern of MCP use in the CAF has changed, with mefloquine now accounting for a small minority of prescriptions.

2.1 Introduction

From 1991 to July 1992, ninety-six National Defence officials travelling to Cambodia and Africa were given mefloquine under the provisions of the Lariam Safety Monitoring Study (SMS), an ''open label, compassionate access" clinical trial held under the sponsorship of the drug's manufacturer (reference 2.1). Several months later, in the fall and winter of 1992-1993, CAF members deployed to Somalia. The Advance Party arrived in theatre (along with the Medical Officer) on 13 December 1992, with the main body deploying 1 Jan 1993. Based on an estimated potential malaria attack rate of 2-3% per month, it was calculated that there could be 18-27 cases of malaria per month if personnel were deployed without protection. This would potentially result in 1-3 malaria-associated deaths during the six month long deployment. Since the region was known as an area of chloroquine resistance, mefloquine was recommended as the malaria chemoprophylactic of choice. While most of the 1400 CAF personnel (land, sea and air) would go on to be prescribed mefloquine, some would use doxycycline as an alternative due to contraindications or intolerance.

The CAF members deploying to Somalia did not participate in the SMS study, since the guidelines of the study were not compatible with the operational requirement to deploy to Somalia (reference 2.2). Within weeks of the start of the Somalia deployment, the medication was licenced for use in Canada, receiving

notice of compliance on 22 January 1993, chronologically following the footsteps of many countries that had already approved the medication, and agencies that had already recommended its use (including the World Health Organization and Centers for Disease Control). So began the CAF experience with mefloquine.

2.2 A brief history of the challenge to prevent malaria

While the cause of "marsh fever", later called malaria after the Italian term for "bad air" (mal'aria), was shrouded in mystery for thousands of years, it did not stop attempts to treat sufferers of the disease (reference 2.3). After all, malaria was, and is, the most important parasitic disease in the world. It is a potentially deadly illness that is spread by the bite of certain mosquitoes. Throughout history, it has stopped armies in their tracks, and shifted the political will of empires as key leaders succumbed to the fever. Even today, more than one-half of the world's population remains at risk of contracting malaria, and nearly 500,000 deaths worldwide are attributed to malaria infections (reference 2.4).

The search for the cure for malaria has been a long road. Although the parasite that causes malaria was not identified until 1880, for nearly two millennia, Chinese healers boiled the leaves of a fern-like weed to make a tea to cure conditions like marsh fever and other ailments. The active ingredient was extracted from the herb and developed in the 1970s as an antimalarial medication now known as artemisinin. In South America, Jesuit missionaries living in Peru in the 1600s used boiled and crushed bark from the cinchona tree for treatment. In 1820, quinine was extracted from the bark, and the purified chemical then replaced the bark as the standard treatment for malaria (reference 2.5).

Quinine remained the mainstay of malaria treatment until the 1920s, when more effective synthetic anti-malarials, including pamaquine and mepacrine, became available. In 1945, following research by German scientists to discover a substitute for quinine seven years earlier, the most important of these new drugs, chloroquine, was synthesized by US scientists. After the war, chloroquine and the ill-fated DDT emerged as the two principal weapons in WHO's global eradication malaria campaign. Unfortunately, resistance to chloroquine began to be reported in 1959, and with rising numbers of malaria cases and deaths during the US-led war in Vietnam, a push to discover new antimalarial medications began.

In 1963, the newly created US Army Antimalarial Drug Development Program was invested with the task of developing drugs for the prevention or treatment of malaria, specifically the chloroquine-resistant strains of P. falciparum (reference 2.6). The program was designed as an inclusive research platform, screening available chemicals from a variety of sources, as well as synthesizing new compounds following successful leads.

The program looked at more than 200 000 compounds over a 10-year period, but few compounds made it past the rigorous screening procedures. Tolerance and efficacy in a variety of primary and secondary animal test systems were major hurdles to clear, long before clinical testing was done. By 1974, only 26 compounds or combinations were selected for clinical trials, representing 14 broad classes of compounds. Many hundreds more showed varying degrees of activity in one or more test systems, but only the most active within each class of drugs were selected. Some belonged to families of compounds already known as antimalarials. Within this group of 26 was the compound labelled as WR 142 490, which would eventually be called mefloquine, an abbreviation of its chemical name a-(2- piperidyl)-2,8-bis(tri**fl**u**o**ro**me**thyl)-4-***quin***olinemethanol hydrochloride. This drug was effective both as a treatment and, when taken as a weekly dose, as a prevention against malaria.

2.3 Use of antimalarials within the CAF

Malaria is a potentially life-threatening parasitic disease to which CAF personnel can be exposed in the performance of their duties during deployment or travel in the regions of the world where malaria is present. The use of medication to prevent malaria is a critical component of the protection provided to CAF members, along with insect bite avoidance through use of DEET-containing topical repellents, bed nets, and in some circumstances uniforms with permethrin applied to the fabric.

The CAF uses all malaria chemoprophylaxis (MCP) agents in accordance with the Canadian malaria clinical practice guidelines developed by the Committee to Advise on Tropical and Travel Medicine (CATMAT). Before an individual is prescribed MCP, they are screened by a health care provider for, among other things, contraindications to the recommended options for MCP, as outlined in the current product monograph. If contraindications, or other concerns, are identified for a given agent, the individual is recommended to take one of the alternatives.

Large deployments present their own unique challenges. Authorized prescribers of MCP include Medical Officers, Nurse Practitioners, Physician Assistants, and more recently pharmacists. To address the challenges of large deployments, “Collective Prescriptions” for MCP have been used. This process refers to a delegation from a physician to specific pharmacist(s) authorizing the pharmacist(s) to dispense MCP for a group of individuals in accordance with D FHP (Directorate of Force Health Protection) operational guidance. Patient screening tools, questionnaires and checklists, are used to identify patients that require referral to a physician.

For deployments or travel to chloroquine-resistant regions, there are three options currently recommended as first-line agents: mefloquine, atovaquone-proguanil (AP), and doxycycline. Members have the option to choose – after discussion with their health care provider – from among the agents that are deemed medically suitable for their use. Even for chloroquine sensitive areas, there is a choice (e.g., any of chloroquine, AP, doxycycline or mefloquine could be chosen for Haiti).

All recommended primary MCP regimens involve taking a medicine before, during and after deployment to an area with malaria. Beginning the drug before travel allows the MCP agent to be in the blood before the deployed personnel is exposed to malaria parasites. It also has the additional benefit of ascertaining if there will be any adverse reaction to the medication prior to deployment, as adverse reactions typically occur within the first few doses.

Mefloquine is typically started 3 weeks before entering a malaria endemic area, following an oral dosing schedule of 250 mg once weekly (for adults). Doxycycline and AP are both once daily medications to be started 3 days prior to entering a malaria endemic area. The adult oral dose for doxycycline is 100 mg, and the adult oral dose for AP is 250/100 mg (combined as a single tablet). The following table summarizes the current CAF policy on MCP timings (Table 2.1; reference 2.7).

Table 2.1: D FHP Standard #CDCP/2011/27 excerpt "MCP timings" (Ref. 2.7)

Prophylactic Regimes Against Malaria			
Medication	**Frequency**	**Before entering area**	**After leaving area**
In Chloroquine Resistant Areas			
Mefloquine (Not in chloroquine/mefloquine resistant areas)	weekly	3 weeks	4 weeks
Doxycycline	daily	3 days	4 weeks
Atovaquone-proguanil	daily	3 days	7 days
Additional Option in Chloroquine Sensitive areas			
Chloroquine	weekly	3 weeks	4 weeks

Mefloquine is highly effective at preventing malaria infection. As one of the few choices of antimalarial chemoprophylaxis agents, the dosing regimen of the drug, as well as use in specific populations, may be seen as advantageous over the others. The once per week dosing schedule both has the capacity to improve compliance and to provide better protection – in a sense, more forgiving of late or "missed" doses – than the daily dosed medications. It can also be used in pediatric patients and in all trimesters of pregnancy.

Prior to 2002, mefloquine was the preferred medication for malaria chemoprophylaxis in CAF in many scenarios where chloroquine-resistance occurred, and from its initial use in 1992 through to 2002, it has been used in a number of deployments, including:

- Op DELIVERANCE (Somalia)
- Op MARQUIS/Cambodia Mine Action Centre (Cambodia)
- Op CONSONANCE (Mozambique)
- Op PANDA (Papau New Guinea)
- Op PRUDENCE (Central African Republic)
- Op TANGO (Western Sahara)
- Op LANCE/Op PASSAGE (Rwanda)
- Op PASTEL (Angola)
- Op PRESERVE (Ethiopia)
- Op ADDITION/Op ECLIPSE (Ethiopia/Eritrea)
- Op SCULPTURE/Op REPTILE (Sierra Leone)
- Op ASSURANCE/Op CROCODILE (Democratic Republic of the Congo/Zaire)
- Op TOUCAN (East Timor)
- Op APOLLO (Afghanistan)

In 2004, recommendations from DFHP gave preference to either mefloquine or doxycycline for exposures (in personnel deployed to malaria endemic areas) of greater than four weeks, and to AP or doxycycline for exposures of less than 28 days[1]. Since 2008, these recommended preferences were removed and, when malaria chemoprophylaxis is required, an informed choice from among all possible options is allowed. Throughout the entire CAF experience with mefloquine, there have been approximately 18,000 personnel

[1]Experience with the daily dosed AP was limited to shorter durations, and it requires a shorter run-in period. The weekly dosed mefloquine was successfully being used for longer deployments, and requires a longer run-in period.

prescribed mefloquine (since Somalia and up to the most recent data of 2016). Of note, mefloquine has never been approved for use by aircrew[2].

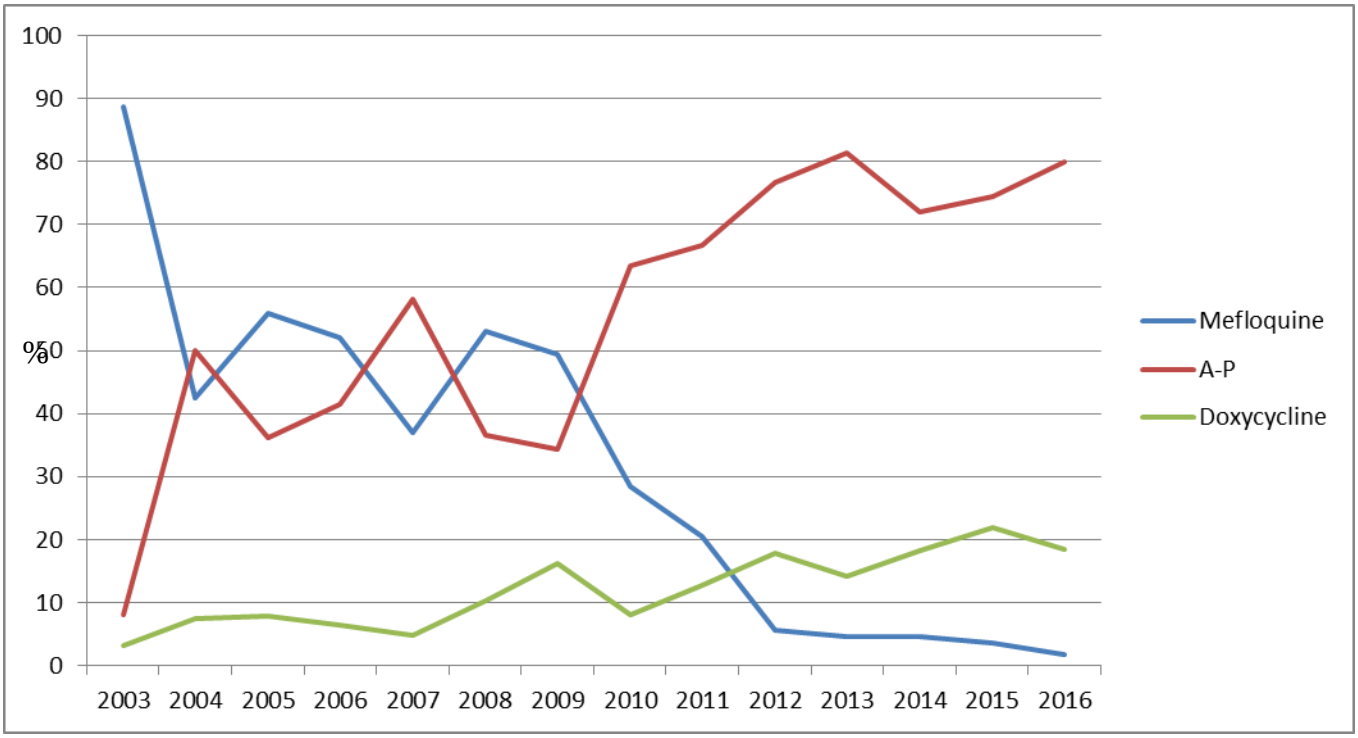
In choosing MCP, there are a number of factors that must be considered, both intrinsic to the mission and intrinsic to the individual. To that end, before final health protection recommendations are made, a thorough analysis of the malaria transmission in the deployed region is completed. This capability has grown since the creation of the Directorate of Force Health Protection within the Canadian Forces Health Services Group Headquarters following the Rx2000 initiative (reference 2.8).

Choice of MCP can now be influenced by the detailed risk assessments of the locations and possible activities of CAF personnel, an improvement in force health protection approach that has grown since 2003. For example, in Kabul during 2005 and Kandahar Airfield during 2006, it was recommended that no MCP was required at these locations. However, if personnel traveled and remained overnight outside of Kabul or outside Kandahar Airfield, then AP or doxycycline was recommended for these short duration excursions.

Looking over the entire experience with MCP use in the CAF, the recommendations and choice offered to personnel is reflected somewhat in the trends of medication usage for malaria chemoprophylaxis (over the past fourteen years) (Table 2.2). In 2003, almost 89% of CAF personnel who required MCP were prescribed mefloquine, with both AP and doxycycline distant alternatives. From 2004 through 2009, the proportion taking mefloquine ranged between 37% and 56%, at times equally used along with AP; in 2010, the proportion fell to 28.5%, in 2011 to 20.4%, and in 2012 only 5.6% of individuals who required MCP were prescribed mefloquine. For the most recent time period, only 20 prescriptions (or 1.7% of total malaria chemoprophylaxis prescriptions) were written in 2016.

[2]The RCAF has not carried out primary research on mefloquine, nor has it systematically analysed evidence related to mefloquine. Rather, non-use of mefloquine is based on acceptance of generally accepted positions articulated by non-CAF aviation medicine authorities.

Table 2.2: Proportion (%) of prescriptions from 2003 to 2016



2.4 Past CAF responses to mefloquine-based concerns

Following the events that occurred in Somalia in 1993, the CAF (specifically the Surgeon General and the directorates responsible for force health protection) responded to inquiries about the adverse effect profile of mefloquine. Starting in 1994, various questions were fielded from the House of Commons and the Senate. Expert responses were provided both from within the CAF as well as from Canadian leaders in Tropical Medicine. The lines of inquiry continued up to and became part of the Somalia Inquiry Report in 1997, the release of the Report of the Auditor General of Canada in April 1999, and the Standing Committee on Public Accounts deposition in November 1999.

Meanwhile, in 1997, the DND announced that a clinical study would be conducted, intended to investigate possible side effects related to mefloquine use. The DND-specific research study would seek to determine whether there was any objectively measurable "neuro-psychological" effects associated with mefloquine. The study design, previously approved by the Medical Services Research Board in 1995, would consist of a double blinded, randomized, placebo controlled trial. Subjects for the study would be volunteer military personnel scheduled for deployment to a malaria endemic region and who would have been prescribed mefloquine as part of their usual pre-deployment preparation. The study would run for several weeks prior to the actual deployment. The suggested sample size required 280 persons per active and placebo groups respectively. By 1998, the study had not been conducted because CAF personnel were not deploying in sufficient numbers to a region where the use of mefloquine was required, and by early 1999 the proposal was dropped.

In 1998, as part of a series of Parliamentary questions regarding mefloquine use in the CAF, the following question, labelled as Q-138, was asked:

Of those members of the Canadian Forces who were administered mefloquine since 1992, how many have attempted suicide or committed suicide; in what year; in Canada or abroad; and if abroad, name the country.

In preparation to answer the Parliamentary question Q-138, an informal review was completed by the DPM Police (reference 2.9). The methodology consisted of a crude listing of the attempted and completed suicides reported to the military police. This was cross-referenced to locations of the suicide and if those locations would have mandated malaria chemoprophylaxis. None of the files were individually reviewed, therefore potential associations or causality were not assessed. The caveat was also made that prior exposure to mefloquine was not determined, again because the data was being used from a central spreadsheet, which lacked that granularity of information.

This appears to be the first instance of data being used to ascertain an increased risk of suicide while deployed on a CAF operation and while taking mefloquine for malaria chemoprophylaxis. The inherent limitations of this process are readily apparent, and many potential study questions remain unanswered by this exercise. However it serves to illustrate some of the requirements should a more robust study be undertaken.

2.4.1 Additional studies

As mentioned above, there is limited existing research analyzing either short or long term possible adverse effects of MCP use *within the CAF*. Unfortunately, any study conducted within the CAF attempting to achieve such an analysis will be severely constrained by its statistical power. Statistical power is the likelihood that a study will detect an effect when there is an effect to be detected. As there have only been a total of approximately 18,000 CAF personnel ever prescribed mefloquine in the CAF, a study of possible adverse effects could only detect a very large effect. As will be discussed in Chapter 5 of this report, large effects are not seen and therefore studies require several hundreds of thousands of participants in order to detect statistically significant effects.

2.5 Controversy with mefloquine

Despite early reports that mefloquine was well tolerated with limited adverse effects (reference 2.10), once the drug began to be used as a regular antimalarial (specifically at the higher doses for treatment), reports of both common and uncommon adverse effects possibly linked to the use of mefloquine began to be published (reference 2.11). Of most interest, both academically and within the public interest, were adverse effects labelled neuropsychiatric disorders, which include 2 broad categories of symptoms: central and peripheral nervous system disorders (headache, dizziness, vertigo, seizures) and psychiatric disorders (major psychiatric disorders, affective disorders, anxiety, and sleep disturbances)(reference 2.12). Unfortunately, experts disagreed (and continue to disagree) over the tolerability of mefloquine prophylaxis versus alternatives, mainly with regard to neuropsychiatric events.

In 1989, the WHO convened an informal consultation on the subject of central nervous system reactions related to the use of mefloquine (reference 2.13). Although data was considered too preliminary to warrant wholesale changes in international guidelines, interim guidelines regarding exclusion of certain populations (airline pilots, for example) were promulgated. This was considered a precautionary measure based on the potential for vestibular effects. In 1991, the WHO went further to draft a project to assess

central nervous system disorders associated with mefloquine in terms of the type of adverse events experienced, their frequency, and their outcome. Using a crude estimate of the number of users of MCP and treatment in Europe, it was estimated that 5 per 100 000 (1:20 000) prophylactic users experienced severe adverse events. With a conversion factor – taking into account a maximum of 50% underreporting – the frequency became 1:10 000. This figure continues to be used as a rough estimate of the risk of severe neuropsychiatric adverse effects during or following use of mefloquine as a chemoprophylactic. Rates of adverse effects when mefloquine is used as a treatment have been reported as high as ten-fold greater.

Still, many studies from the early 1990s did not identify any significant excess of neuropsychiatric adverse events in mefloquine users. Peace Corps volunteers using mefloquine prophylaxis for more than 2 years experienced strange dreams (25%), insomnia (9%), and dizziness (8.4%), similar to those using chloroquine (corresponding incidence 26%, 6.5%, and 10%); no severe neuropsychiatric reactions were causally associated with mefloquine (reference 2.14). However, as research continued to accumulate on the tolerability of mefloquine, more reviewers began to suggest that adverse effects actually occurred at higher rates than was being reported.

Much of the research regarding use of mefloquine explores one or more characteristics of mefloquine regarding effectiveness (as MCP or treatment), tolerability (with emphasis on compliance), and adverse reaction profile. There are many reasons for this disparity in observational findings, analysis and, ultimately, conclusions. The literature supporting an association of drugs with neuropsychiatric adverse effects is largely comprised of case reports, postmarketing surveillance and retrospective observational studies, making the case for causality difficult. There are few quality prospective, controlled trials with objective assessments of these types of symptoms or diagnostic criteria. Later in this report, we look at studies that specifically concern military personnel, as one of the key considerations and concerns with mefloquine use is the possibility of degradation of performance within a combat or military environment.

2.6 Exploring adverse reactions

When deciding on the most appropriate malaria chemoprophylaxis, both the risks and the benefits of the drug must be considered. Hence, the development of adverse effects while on medications is a common challenge for prescribers. Side effects, adverse drug reactions, adverse drug effects, adverse drug events and adverse drug experiences all describe unintended and (usually) undesired signs and symptoms during or following exposure to a medication. Adverse drug reactions have been classified into a number of different classification schemes, however for brevity, the simplest is according to severity and frequency.

Mild adverse drug reactions can be described as not requiring an antidote or treatment, and if the patient is already hospitalized, no prolonging of the stay is required. A moderate adverse drug reaction may see a change in treatment (for example, modified dosage or addition of another drug), but not necessarily discontinuation of the drug. A severe adverse drug reaction is potentially life threatening and requires discontinuation of the drug with possible specific and focused treatment of the reaction.

The Council of International Organizations of Medical Sciences (reference 2.15) lists the frequency of adverse drug reactions as follows:

Very common	≥ 1/10
Common (frequent)	≥ 1/100 and < 1/10
Uncommon (infrequent)	≥ 1/1000 and < 1/100
Rare	≥ 1/10000 and < 1/1000

Very rare	<1/10000

Some of the most commonly reported adverse reactions – associated with the use of the top 200 most commonly prescribed medications – have been reported as follows: nausea (most common), dizziness (2nd most common), headache (3), fatigue (12), depression (15), tremor (18), somnolence (19), paresthesia (23), anxiety (24), myalgia (25) and nervousness (27) (reference 2.16). Some of these adverse effects are also reported with mefloquine use (incidentally, not one of the top 200 most commonly prescribed medications), with a wide disparity of reported rates (from 25% to >90%)(reference 2.17). There are a number of possible reasons for the lack of consensus on adverse reaction rates.

When reporting possible adverse reactions to a medication, one must be cognizant of the potential confounders, like pre-existing symptoms. Some researchers have mentioned that there is an indeterminate background rate of some of these symptoms. Indeed, an interesting 2012 study found a background rate of dizziness (an oft reported adverse reaction of medications) in the city of Sau Palo at 42% in the general population (study criteria excluded those on medications)(reference 2.18). In another study focusing on 3500 malaria patients treated along the Thai Burmese border, dizziness occurred in 83% of adults and 59% of children (under 15 years) in the first three days after treatment with mefloquine (reference 2.19). Dizziness just prior to treatment, however, was found to occur in 63% of adults.

A corollary of the above is simply response bias. Since most possible adverse reactions are self-reported, mild to moderate symptoms may not drive the patient to a health care practitioner to seek another MCP or treatment for symptoms. The event may then go unreported. Or the symptoms may not be recognized as having an association with the medication.

2.6.1 Neuropsychiatric adverse effects and causality

The term “neuropsychiatric” has historically been linked to mental health disorders with an organic component. The universal examples of neuropsychiatric symptoms (NPS) are delusions, hallucinations, anxiety and irritability. In literature regarding mefloquine, the list of possible neuropsychiatric adverse effects (sometimes called neuropsychiatric outcomes) related to mefloquine use has expanded from the above list to include neurologic signs and symptoms (like vertigo and paresthesias) and common mental health issues (like depression)(reference 2.20).

The assessment of causality and the explanation of mechanisms of psychiatric and neurologic disorders reported with mefloquine use are difficult for biological and epidemiological reasons. Certain criteria need to be met to establish a relationship between a drug and a particular side effect (reference 2.21). The usual criteria for a definite reaction would be that the reaction follows a temporal sequence from administration of the drug or from when the drug level has been established in body fluids or tissues, the reaction follows a known pattern of response to the drug, the reaction improves on stopping the drug (dechallenge), and the reaction reappears on repeated exposure to the drug (rechallenge). Less likely relationships are considered if underlying conditions could contribute, or if the reaction does not follow a known pattern of response to the drug.

A substantial body of knowledge has grown with regards to understanding what role mefloquine might have in causing neuropsychiatric adverse effects. However, it remains a difficult challenge to quantify and qualify within a framework of risk management: the benefit of the drug preventing the clinical manifestation of malaria, and the risk of an adverse effect related to its use. The issues revolve around

understanding the patterns of self-reported adverse effects, analyzing the disparity in rates of adverse events reported in different studies, and ratifying differing expert opinion.

Some researchers have looked outside of observational studies (case studies, retrospective and prospective studies) to explain reported adverse effects in a pathophysiologic context (the biological model supporting a neurotoxicity syndrome). This is also a difficult challenge because even the therapeutic action of mefloquine is still not completely understood. Two of the prominent issues with researching adverse effects associated with mefloquine have been: the original observation that no significant levels of mefloquine were found in the cerebral spinal fluid of patients; and, aside from animal models and cadaveric/autopsy studies, the difficulty in assessing what accumulation occurs in the human brain.

Early researchers, referring to reports of abnormal hepatic enzymes, theorized that adverse effects were as a result of liver damage ("post-hepatic syndrome") as well as "disturbed thyroid function" (reference 2.22). Although the theory remains as such, a similar idea was resurrected in a study from 2013. In this case, the author stated that evidence supported "the hypothesis that mefloquine neurotoxicity and other adverse effects reflect an endogenous form of hypervitaminosis A due to a process involving: mefloquine-induced dehydrogenase inhibition; the accumulation of retinoids in the liver; retinoid-induced hepatocellular damage; the spillage of stored retinoids into the circulation; and the transport of these compounds to the gut and brain in toxic concentrations" (reference 2.23).

Over the last decade, a number of animal models have been used to propose hypotheses that seek to explain the neuropsychiatric profile of adverse effects reported with mefloquine use. In some circumstances, hypotheses were built upon other studies that were not directly looking at mefloquine as a therapeutic agent, but rather as a chemical catalyst, in effect searching for chemical compounds that would assist in the focus of the study. For example, the neuronal gap junction proteins (termed "connexins") have been implicated in seizures. Developing a mouse model to use for seizure research required either modifying the mouse brain or just "blocking" the connexins. Mefloquine was one of many substances that were trialed successfully as a blocker (reference 2.24). This led to a number of "connexin blockade" theories explaining the neuropsychiatric symptoms attributed to mefloquine use.

A number of other neurologic targets have been added to the list of hypotheses. These include disruption of calcium homeostasis of neuronal cells (and oxidative stress), inhibition of enzymes such as acetylcholinesterase or butylcholinesterase, inhibition of cellular transport systems (APT-sensitive potassium channel, P-glycoprotein), and blockage of receptors (adenosine A2A, p2x7, receptor-mediated spontaneous inhibitory postsynaptic currents) (reference 2.25). It must be pointed out that, since many of the studies were not looking specifically at mefloquine "toxicity", concentrations were often relatively high, and involved rodent brain slices as well as tissue and cell cultures. This makes the extrapolation of this knowledge to human pharmacokinetics a daunting task.

2.8 References

2.1 Other Audit Observations: National Defence and Health Canada, Report of the Auditor General of Canada – April 1999

2.2 Inquiry of Ministry Q-91 27 March 1998: Reply by the Minister of National Defence

2.3 E. Hempelmann and K. Krafts. 2013. Bad air, amulets and mosquitoes: 2,000 years of changing perspectives on malaria. Malaria Journal. 12:232

2.4 WHO World Malaria Report 2016 http://apps.who.int/iris/bitstream/10665/252038/1/9789241511711-eng.pdf?ua=1

2.5 Achan J. et al. 2011. Quinine, an old anti-malarial drug in a modern world: role in the treatment of malaria. Malaria Journal. 10: 144.

2.6 C.J. Canfield and R.S. Rozman. 1974. Clinical testing of new antimalarial compounds. Bull. Wld Hlth Org. 50, 203-212

2.7 D FHP Standard #CDCP/2011/27: Malaria Chemoprophylaxis in the Canadian Forces

2.8 Synopsis Sheet (Effective Project Approval) 00000297 Rx2000 - Force Health Protection Initiative, March 2001

2.9 Email 09/10/1998 DPM Police 3 to D Med Svcs

2.10 P. Magnussen and I.C. Bygbjerg. 1990. Treatment of Plasmodium falciparum malaria with mefloquine alone or in combination with IV quinine at the Department of Communicable and Tropical Diseases, Righospitalet, Copenhagen 1982-1988. Danish Medical Bulletin 37, 563-564.

2.11 J. Bernard, J Le Camus, J Sarrouy. 1987. Encephalopathie toxique à la mefloquine. Press Médicale 16, 1654-1655.

2.12 P. Schlagenhauf. “Mefloquine for Malaria Chemoprophylaxis 1992-1998: A review”. J Travel Med 1999. 6:122-133.

2.13 WHO 1989 Central Nervous System Reactions related to the antimalarial drug Mefloquine. 1054

2.14 H.O. Lobel, M. Miani, T. Eng, K.W. Bernard, A.W. Hightower, C.C. Campbell. 1993. Longterm malaria prophylaxis with weekly mefloquine. Lancet 341:848-851.

2.15 Council for International Organisations of Medical Sciences. 1987. International reporting of adverse drug reactions. CIOMS working group report. Geneva: World Health Organisation, 1987.

2.16 M.J.Roswarski, K.R.Villa, M.Kiersma, A.Hess, B.M.Shepler, M.Murawski. “Prevalence of Adverse Drugs Effects and Adverse Drug Reactions in the 200 Most Commonly Prescribed Drugs Corrected for Prescription Volume”. Poster. Purdue University, School of Pharmacy and Pharmaceutical Sciences

2.17 Patricia Schlagenhauf. Mefloquine for Malaria Chemoprophylaxis 1992-1998: A Review. J Travel Med 1999; 6: 122-133.

2.18 R.S. Bittar, J. Oiticica, M.A. Bottino, F.F. Ganança, R. Dimitrov. 2013. Population epidemiological study on the prevalence of dizziness in the city of São Paulo. Braz J Otorhinolaryngol. 79(6):688-698.

2.19 F. Nosten, F. ter Kuile, T. Chongsuphajaisiddhi, C. Luxemburger, H.K. Webster, M. Edstein, L. Phaipun, K.L. Thew, N.J. White. 1991. Mefloquine-resistant falciparum malaria on the Thai-Burmese border. Lancet. 337(8750):1140-1143.

2.20 AAPharma. Mefloquine drug monograph. August 2016

2.21 F.E. Karch and L. Lasagna. “Adverse drug reactions: A critical review”. JAMA. 1975. 234, 1236–1241

2.22 A.M.Croft and A. Herxheimer. 2002. Adverse effects of the antimalaria drug, mefloquine: due to primary liver damage with secondary thyroid involvement? BMC Public Health. 25;2:6.

2.23 A.R. Mawson. 2013. Mefloquine use, psychosis, and violence: A retinoid toxicity hypothesis. Med Sci Monit. 19: 579–583.

2.24 S.J. Cruikshank, M. Hopperstad, M. Younger, B. W. Connors, D. C. Spray, M. Srinivas. 2004. Potent block of Cx36 and Cx50 gap junction channels by mefloquine. PNAS. 101(33):12364-12369

2.25 P. Schlagenhauf, M. Adamcova,L. Regep, M.T. Schaerer, H.G. Rhein. 2010. The position of mefloquine as a 21st century malaria chemoprophylaxis. Malar J. Dec 9;9:357

CHAPTER 3 Chart Audit to Review Mefloquine Prescribing Practices in the CAF

Key question(s)

Is the CAF following recommended practices for prescribing mefloquine?

Summary

- *To evaluate prescription practices for mefloquine in the CAF, a chart audit was undertaken for personnel (n=111) prescribed this drug from 1 Dec 2013 to 1 Dec 2016, inclusive.*
- *Of the 111 patients who were prescribed mefloquine, more than 95% (106) had documentation indicating that the prescription process included a face to face encounter with a clinician.*
- *Among the reviewed charts, 42/111 (38%) included documentation that patients were screened for contraindications and precautions; and 13 of 111 (12%) patients who were prescribed mefloquine had a potential contraindication or precaution in their chart.*

Conclusion(s)

The CAF malaria policy is generally being followed, i.e. personnel receiving prescriptions have a face to face encounter with a clinician. However, there is insufficient documentation of screening for contraindications and, in some cases, personnel have received a prescription for mefloquine despite evidence of potential contraindications or precautions in their medical records. These latter occurrences, i.e. patients who received a mefloquine prescription despite a potential contraindication, represent patient safety incidents that should be investigated.

3.1 Introduction

MCP is a key measure for preventing malaria. It is universally recommended by national (reference 3.1) and international public health authorities for travel to relatively higher risk areas for malaria (see Chapter 4).

Like therapeutic interventions generally, use of MCP is, for some users, associated with unwanted side effects. Usually, adverse effects (AE) are mild, though more rarely they can be serious. Moreover, some patients should avoid drugs (if they are contraindicated) based on pre-existing medical conditions or other factors. For example, the drug AP is, when used as MCP, contraindicated for patients with a known hypersensitivity to its constituents or for persons suffering from severe renal impairment (reference 3.2).

Guideline panels, when making recommendations for MCP, consider both the benefits (improved health through malaria prevention) and harms (negative impacts, e.g., adverse effects) of the drug (see reference 3.1). Further, they generally stress the importance of taking a medical history and considering the patient's personal preferences when prescribing MCP. For example, the Canadian CPG for malaria prevention indicate:

> *"A health care provider should prescribe drugs for the prevention of malaria after an individual risk assessment to ensure that only those travellers truly at risk of malaria infection receive chemoprophylaxis…Careful adherence to dosing guidelines, precautions and contraindications can minimize any adverse effects"*

and,

> *"Present all the options to travellers and, unless there is a contraindication, give them a choice of which chemoprophylaxis they prefer; all recommended first-line malaria chemoprophylactic regimens are equally effective"*

The CAF approach to malaria prevention (reference 3.3) is based on the Canadian CPG (reference 3.1) and requires careful medical screening of the patient:

> "*The prescription for a specific MCP for an individual must be based on an assessment of the individual's travel itinerary, malaria drug resistance in the region being visited, his/her underlying health status, other medications being taken, and the risk of adverse drug reactions… After suitable information transfer, the individual can make a personal decision on which of the MCP drug options he/she wishes to be prescribed. This is a clinical process.*"

For mefloquine, which is one of the three primary MCP options[3] recommended in the Canadian CPG (the others are AP and doxycycline), neuropsychiatric outcomes are included as a potential adverse effect (references 3.1 and 3.4) and the drug is contraindicated in patients with active or a history of psychiatric illness:

> "*Patients with active depression or a history of psychiatric disturbances (including depression, generalized anxiety disorder, psychosis, schizophrenia or other major psychiatric disorders) or a history of convulsions should not be prescribed MEFLOQUINE prophylactically since MEFLOQUINE may precipitate these conditions.*" (excerpted from the product monograph, reference 3.4)

Thus, if mefloquine is being considered as MCP, patients are to be screened for current or past neurologic disorders and mental illness.

To assess whether such screening is taking place in the CAF, a medical chart review was carried out for patients prescribed mefloquine from 2013 to 2016. Three aspects of the prescription process were specifically sought:

- was there documentation of a medical encounter with a clinician related to the prescription;
- were there annotations in the medical file that were indicative of contraindication and precaution-based screening; and,
- was there evidence in the medical file to indicate whether potential contraindications were present at the time of prescribing, e.g., current or history of mental illness?

[3] In areas where there is chloroquine resistance.

3.2 Methods

3.2.1 General

For this chapter, the TF was responsible for: identifying relevant medical records; carrying out the chart review; reviewing and analyzing data extracted from the charts; and, chapter writing. As outlined in chapter 1, members of the TF are employees of the DND or members of the CAF. The chart review was authorized by the SG.

3.2.2 Research Questions

- Over the review period, was there documentation in the medical record to indicate that the patient had received a face to face encounter with a clinician related to MCP?
- Over the review period, was there documentation in the medical record to indicate that the patient had been screened for contraindications and other precautions related to mefloquine?
- Over the review period, was there documentation in the medical record to indicate that the patient had potential contraindications to mefloquine?
- Over the review period, was there documentation in the medical record to indicate that the patient had discontinued mefloquine due to potentially associated adverse effects?

3.2.3 Chart review

A list of CAF members who received mefloquine from 1 Dec 2013 to 1 Dec 2016 was obtained from the Canadian Forces Health Services (CFHS) Pharmacy Database. This list was kept as protected B information and was used to generate a spreadsheet (Microsoft Excel) onto which information from the chart review could be extracted. The spreadsheet did not contain personal identifiers so as to protect the privacy of the included individuals. All information collected and stored as part of this study will be maintained in accordance with established DND procedures.

Two physicians on the TF with the required permissions for the Canadian Forces Health Information System (CFHIS) access carried out the review. A given patients' record was reviewed by one of these physicians. In the event of uncertainty, e.g., a diagnosis that was unclear, both physicians discussed the information and reached a consensus. The extracted dataframe included: anonymized demographic information; purpose and location of travel; presence of potential contraindications in the medical record (see Table 3.1 for a listing); documentation of any information to indicate that a medical encounter with a clinician (related to the prescription) had occurred; documentation of other medical encounters potentially related to the prescription; documentation that individuals who were prescribed mefloquine were screened for contraindications (including use of a questionnaire); and documentation related to discontinuation of mefloquine due to possible associated adverse effects.

Table 3.1 – List of contraindications (extracted from product monograph, reference 3.4)

Contraindications to mefloquine

• **known hypersensitivity or past severe reaction to mefloquine**
• **active depression**
• **history of psychiatric disturbances**
  o **depression**
  o **generalized anxiety disorder**
  o **psychosis**
  o **schizophrenia**
  o **other major psychiatric disorders**
• **history of seizures**
• **cardiac conduction delays**

3.3 Results

Over the review period, 111 patients were identified as being prescribed mefloquine. The average age of patients was 37.8 years (range = 23-59 yrs). Most were male (88%), 55% were officers, and the majority (61%) were travelling to a malaria endemic area as part of a deployment. The most common destination was Africa (56%). Among deployed personnel, the most common operations were Op Crocodile in the Democratic Republic of Congo (15 prescriptions), Op Sirona in Sierra Leone (7 prescriptions), and Op Soprano in South Sudan (19 prescriptions).

More than 95% (106) of patients had documentation in their medical chart of a face to face encounter with a clinician related to the mefloquine prescription. There was evidence of screening for contraindications and precautions in 38% (42/111) of charts. Among the remaining patients, 14/69 (20%) had chart notations indicating that they had previously taken and tolerated mefloquine.

Thirteen (12%) of the medical charts included diagnoses and/or other information that suggested a mefloquine contraindication. The most common contraindication was current or past neuropsychiatric illness (depression and/or anxiety and/or PTSD, n= 13). One of these 13 individuals also had a cardiac arrhythmia (atrial fibrillation).

The medical records indicated that four patients discontinued mefloquine due to associated adverse effects: one member had difficulty sleeping; one member had diarrhea; one member had mood changes and fatigue; and, one member discontinued the medication before deployment due to flu-like illness.

3.4 Discussion and Conclusions

The primary purpose of the chart review was to assess adherence to recommended MCP prescription practices. In this respect, and given the research questions (see above) that were identified, we found:

- The large majority (>95%) of mefloquine prescriptions involved a face-to-face consultation between the patient and clinician. This is consistent with best practices, and differs from the situation for some other militaries where individual-level consultation and individual-specific advice has sometimes been identified as a potential challenge[4] (references 3.5 and 3.6).
- A minority (38%) of the reviewed charts included clear annotation(s) to indicate that the patient was screened for contraindications. A further 13% indicated that the patient had previously received and tolerated mefloquine. Among the approximately 50% remaining charts, there was no documentation of contraindication screening (although such might have occurred without being recorded).
- Mefloquine was provided to 13 persons (12%) with potential contraindications. Similar results have been identified in previous studies with military populations (references 3.7 and 3.8).
- Four patients (4%) had annotation in their chart to indicate that mefloquine was discontinued owing to potentially associated adverse effects. This rate is similar to estimates for other military populations (references 3.9 and 3.10; see chapter 5).

3.5 Strengths and Limitations

Our chart review had a number of strengths. First, it included the entire cohort of CAF personnel prescribed mefloquine over a three year period. Further, it involved a thorough search for entries (e.g., primary care notes, periodic health examinations, deployment related forms, immunization and Preventive Medicine ancillary notes, and scanned documents) for relevant information. As a result, we were able to construct a detailed patient profile for each mefloquine prescription given over a three year period.

The chart review also had limitations. In particular, screening for contraindications by the prescribing clinicians or other health care providers might have occurred without being annotated in the medical record. If true, this would result in an underestimation of the rate of screening for contraindications.

3.6 References

3.1 Committee to Advise on Tropical Medicine and Travel. 2014. Canadian Recommendations for the Prevention and Treatment of Malaria.

3.2 Product Monograph – Malarone. 2015. http://ca.gsk.com/media/591413/malarone.pdf (accessed 21/01/2017).

3.3 D FHP Standard #CDCP/2011/27: Malaria Chemoprophylaxis in the Canadian Forces.

[4]Reference 3.5 (referring to the US military MCP recommendations) states: "*individualizing advice and recommendations for large military deployments is rarely logistically possible or feasible*".

3.4 Product Monograph – mefloquine. https://www.aapharma.ca/downloads/en/PIL/2016/Mefloquine-PM.pdf (accessed 21/01/2017).

3.5 US CDC Yellow Book. 2016. Chapter 8. Special Considerations for US Military Deployments. https://wwwnc.cdc.gov/travel/yellowbook/2016/table-of-contents (accesses 26/01/2017)

3.6 UK Parliament. 2016. An acceptable risk? The use of Lariam for military personnel: Government Response to the Committee's Fourth Report of Session 2015–16 (accessed 26/01/2017) http://www.publications.parliament.uk/pa/cm201617/cmselect/cmdfence/648/648.pdf

3.7 Nevin RL. 2010. Mefloquine prescriptions in the presence of contraindications: prevalence among US military personnel deployed to Afghanistan, 2007. Pharmacoepidemiol Drug Saf. 19:206-10.

3.8 Eick-Cost et al. 2016. Neuropsychiatric Outcomes after Mefloquine Exposure among U.S. Military Service Members. ASTMH. doi:10.4269/ajtmh.16-0390

3.9 Saunders et al. 2015. Safety, Tolerability, and Compliance with Long-Term Antimalarial Chemoprophylaxis in American Soldiers in Afghanistan. Am J Trop Med Hyg. 93: 584-90.

3.10 Sonmez el al. 2005. The efficacy and tolerability of doxycycline and mefloquine in malaria prophylaxis of the ISAF troops in Afghanistan. J Infect. 51: 253-8.

CHAPTER 4 Comparison of Civilian and Military Recommendations for the Prevention of Malaria

Key question(s)

Are the Canadian guidelines for malaria prevention (and by extension the CAF approach) consistent with the approaches employed by other national and international jurisdictions?

Summary

- *Two international (World Health Organization (WHO), International Association for Medical Assistance to Travellers (IAMAT)) and eight national (Canada, United States, United Kingdom, Australia, France, Germany, Switzerland and Netherlands) civilian sources were reviewed (Annex 3). For military guidelines, six sources (Canada, United States, United Kingdom, Australia, France, Germany) were reviewed (Annex 3[5]).*

- *International and national civilian guidelines include atovaquone-proguanil (AP), mefloquine or doxycycline (excluding Netherlands) as MCP options for malaria prevention in relatively higher risk areas. They differ in their approach for relative lower risk areas where some guidelines (e.g., Switzerland, Germany) indicate MCP need not be used.*

- *Guidelines stress the importance of appropriate medical screening to match travellers with suitable MCP agents.*

- *Military guidelines are more varied than international and national guidelines. All of those reviewed included mefloquine as an option, however the majority (US, France, Australia, Germany[5]) include it as a less preferred drug (after doxycycline and/or AP). The US and French guidelines do not specifically address why mefloquine is not a first-line option. The Australian military (ADF) prefers doxycycline, as it might confer protection against other diseases; the ADF acknowledges that public perception affected its approach to MCP, in contrast to national civilian CPG.*

- *The two military guidelines (Canadian and UK) that include mefloquine as an option, also explicitly link their approaches to national clinical practice guidelines.*

Conclusion(s)

The Canadian guidelines for malaria prevention (and by extension the CAF approach) are consistent with the guidelines of other civilian national and international health authorities. In particular, mefloquine along with AP and doxycycline are generally considered as suitable options for protection in areas where the most dangerous type of malaria (Plasmodium falciparum) occurs. However, some militaries consider mefloquine as a less preferred MCP option. Where military and national civilian approaches differ, operational (e.g., US) or societal (e.g., Australia) justifications have been used to explain the difference.

[5]The approach of the German military was identified after evidence was collated for the report. Hence, a summary of the German approach is not included in Annex 3.

4.1 Introduction

As discussed in Chapters 2 and 3, malaria is a serious and potentially fatal disease caused by parasites transmitted by mosquitoes. It can affect military personnel and missions. Prevention of malaria is therefore a military health priority.

The CAF approach (reference 4.1) to malaria prevention is based on the Canadian CPG (reference 4.2). For MCP, the Canadian CPG recommends that, in most areas where there is resistance to chloroquine, one of three agents be used: mefloquine; doxycycline; or, AP. When prescribing a MCP agent, the CPG recommends:

> *"Present all the options to travellers and, unless there is a contraindication, give them a choice of which chemoprophylaxis they prefer; all recommended first-line malaria chemoprophylactic regimens are equally effective"*

In line with this, the CAF approach to use of MCP (reference 4.1) is summarized as:

> *"The prescription for a specific MCP for an individual must be based on an assessment of the individual's travel itinerary, malaria drug resistance in the region being visited, his/her underlying health status, other medications being taken, and the risk of adverse drug reactions. CATMAT Guidelines provides guidance on: risk assessment (chapter 2); selection of a MCP regimen for individuals in general (chapter 4); malaria prevention for women who are pregnant or breast-feeding (chapter5); malaria prevention for individuals with co-morbidities (chapter5); and the indications/ efficacy/ adverse effects/ contraindications/ precautions of the specific drugs (chapter 8). After suitable information transfer, the individual can make a personal decision on which of the MCP drug options he/she wishes to be prescribed".*

The purpose of this chapter is to compare the Canadian CPG on malaria prevention to other international and national guidelines, and to compare the CAF policy on MCP to these CPG as well as to the guidelines of other militaries.

4.2 Methods

4.2.1 General

For this chapter, the TF was responsible for: identifying relevant international, national and military guidelines; evidence synthesis and analysis; and, writing. As outlined in chapter 1, members of the TF are employees of the DND or members of the CAF.

A systematic review for evidence was not carried out. Rather, a convenience sample of CPGs from international/national/military jurisdictions was reviewed.

4.2.2 Research Questions

- Are MCP recommendations different between civilian international and national guideline panels? If so, why?
- Are MCP recommendations different between militaries? If so, why?
- Are MCP recommendations different between military and civilian authorities? If so, why?

- What evidence was used to develop the included guidelines, and how was it assessed?

4.3 Results

4.3.1 Included guidelines

Our review included two international civilian, eight national civilian and six[5] military guidelines (references 4.1-4.14 and 4.19).

International (WHO and IAMAT) and national (Canada, USA, UK, Australia, France, Germany, Switzerland, Netherlands) civilian sources (see Annex 3) were consistent in that they indicated that mefloquine, AP and doxycycline[6] were suitable MCP agents. They also specifically identified neuropsychiatric adverse effects as a potential harm associated with use of mefloquine; and a variety of AE as being potentially associated with use of AP and doxycycline. Finally, civilian guidelines emphasized the need to medically screen patients to maximize the likelihood that the traveller would be prescribed the most suitable MCP agent.

In contrast to civilian CPG, there is substantial heterogeneity in military approaches to use of MCP (see Annex 3). The CAF follows the respective national civilian CPG, as does the United Kingdom Ministry of Defence[7]. The approach of the Australian Defence Force (ADF) differs from the Australian national guideline in that it recommends doxycycline as the first-line MCP, followed by AP. Mefloquine is considered a third-line agent. In explaining their approach, the ADF explicitly states:

> "*…antibiotic properties* [of doxycycline] *also prevent typhus, leptospirosis, and some gastro-intestinal, urinary tract and skin infections*"
>
> "*Due to the wide-spread public perception of severe mefloquine adverse events, mefloquine is best used only by those who have previously tolerated the medication*"

In 2009 (reference 4.15), the US DoD specifically identified doxycycline as its first-line MCP agent followed by, in terms of preference, AP and mefloquine. This approach was subsequently updated in 2013 (reference 4.11) when AP and doxycycline were identified as first-line agents, and mefloquine as an option if these were not suitable. In its guidance (references 4.11 and 4.15), the US DoD does not specifically articulate why its approach differs from the US national guidelines, though the earlier guidance does discuss neuropsychiatric outcomes that are potentially associated with use of mefloquine (also see reference 4.17). The French military has, for some time, used doxycycline as its first-line agent, though apparently will use mefloquine as an alternative MCP if doxycycline is not suitable. We were not able to find information that explains why the approach of the French military differs from the French national CPG. The German military has just recently changed its approach and mefloquine is no longer used as MCP.

[6] The exception is the Netherlands, where AP and mefloquine are listed as first line agents, and doxycycline (which is not registered for this use in the Netherlands) is included as a second line agent.

[7] The UK MoD is currently reviewing its malaria prevention policy.

4.3.2 Guideline Development - Use of Evidence

The Canadian national CPG (reference 4.2), and by extension the CAF policy[8] for malaria prevention (which are based on the Canadian CPG), is the only guideline that indicates recommendations were developed using Evidence-based Medicine (EBM)[9]. Other civilian guidelines, including from the US, Switzerland and the UK, indicate recommendations are based on risk of malaria to travellers, but do not include a description of the process used to develop their guidance. The Swiss CPG is the only civilian doctrine that explicitly links recommendations to estimates of malaria risk, whereas the US DoD doctrine is the only military policy that does this. In this regard, the approaches are somewhat different, the US military indicates MCP need not be used if risk to the military traveller is estimated to be <1/1,000 per month of exposure (in the absence of countermeasures) whereas the Swiss guidelines indicate a threshold of 1/100,000 for non-use of MCP (and 1/10,000 for use of emergency standby treatment).

4.4. Discussion and conclusions

Despite different approaches to elaborating recommendations, e.g., use of EBM vs. expert opinion, and presumably different societal normatives, the reviewed international and national CPG for malaria prevention are consistent, i.e. mefloquine along with doxycycline (excepting the Netherlands, see footnote 1) and AP are considered suitable MCP agents. These guidelines are also similar in that they stress the importance of medical screening when selecting MCP. We believe that such consistency, despite different guideline contexts, supports the appropriateness of the overall approach. Applied to the Canadian context, the reviewed international and national guidelines are similar to those espoused in Canada – whether at a general level (reference 4.2), or applied at the level of CAF personnel (reference 4.1).

Military guidelines are not always consistent with national guidelines. Where differences occur, they are not always well explained, or are based on operational (e.g., US) or societal (e.g., Australia) considerations. None of the reviewed military guidelines explicitly explain whether or how scientific and or medical evidence was weighed in policy decision-making.

4.5 Limitations

The analyses undertaken in this chapter is subject to several limitations. Most importantly, analyses and conclusions are based on a convenience sample of international, national and military guidelines. We do not know if these are representative of the broader population of malaria CPG. However, we did intentionally select the three western jurisdictions reporting the most travel-associated cases of malaria annually (France, UK and the US, cumulatively, ca. 6,000 cases annually and approximately 60% of all cases reported, reference 4.18).

Second, current guidelines are generally based on expert opinion, without application of modern EBM methods. This reduces confidence in the quality of the evidence underpinning the recommendations.

[8] In 2013, after the black box warning for mefloquine had been added to the US product monograph, the CAF asked the Canadian Committee to Advise on Tropical Medicine and Travel (CATMAT) to review the revised US safety information. The committee, which is responsible for the Canadian CPG, did so and concluded that its guidance on use of MCP remained appropriate.

[9] CATMAT has since updated its approach to use of EBM (reference 4.16). It is currently reviewing the Canadian malaria guidelines with the revised methodology.

Nevertheless, the consistency among international and national guidelines is striking, and supports the conclusion that MCP recommendations (including for use of mefloquine) are appropriate.

Finally, several guidelines are under active review (e.g., Canadian and UK) and MCP recommendations might change in future CPG.

4.6 References

4.1 D FHP Standard #CDCP/2011/27: Malaria Chemoprophylaxis in the Canadian Forces.

4.2 Committee to Advise on Tropical Medicine and Travel. 2014. Canadian Recommendations for the Prevention and Treatment of Malaria.

4.3 World Health Organization. 2012. International Travel and Health. http://www.who.int/ith/en/ (accessed 12/01/2017).

4.4 International Association for Medical Assistance to Travellers (IAMAT). 2016. World Malaria Risk Chart. https://www.iamat.org/elibrary/view/id/1376 (accessed 12/01/2017).

4.5 United States Centers for Disease Control and Prevention. 2016. Yellow Book. http://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-travel/malaria (accessed 12/01/2017).

4.6 Public Health England. 2016. Malaria Prevention Guidelines for Travellers from the UK. https://www.gov.uk/government/publications/malaria-prevention-guidelines-for-travellers-from-the-uk (accessed 12/01/2017).

4.7 Northern Territory Government. 2012. Guidelines for Malaria. http://digitallibrary.health.nt.gov.au/prodjspui/bitstream/10137/555/1/Guidelines%20for%20Malaria%202012.pdf (accessed 12/01/2017).

4.8 Sante Public France. 2016. Recommandations sanitaires pour les voyageurs. http://invs.santepubliquefrance.fr/fr/Publications-et-outils/BEH-Bulletin-epidemiologique-hebdomadaire/Archives/2016/BEH-hors-serie-Recommandations-sanitaires-pour-les-voyageurs-2016 (accessed 12/01/2017).

4.9 DeutscheGesellschaft für Tropenmedizin und Internationale Gesundheit (DTG). 2016. Empfehlungen zur Malariavorbeugung https://www.klinikum.uni-heidelberg.de/fileadmin/inst_hygiene/tropenhygiene/Tropenambulanz/PDF/DTG_Malaria_2016.pdf (accessed 12/01/2017).

4.10 Office federal de la sante publique OFSP. 2016. Prophylaxie antipaludique pour les sejours a l'etranger de courte duree (sejours jusqu'a 3 mois). https://www.bag.admin.ch/dam/bag/fr/dokumente/mt/i-und-b/richtlinien-empfehlungen/empfehlungen-risikogruppen-risikosituationen/malariaschutz-kurzzeitaufenthalter-bis-3-monate.pdf.download.pdf/malaria-2016-prophylaxie.pdf (accessed 12/01/2017).

4.11 United States DoD. 2013. Guidance on Medications for Prophylaxis of Malaria. Office of the Assistant Secretary of Defense – Health Affairs (April 2013). http://www.health.mil/~/media/MHS/Policy%20Files/Import/13-002.ashx (accessed 12/01/2017).

4.12 Australian Defence Force. 2017. ADF Health Portal – Mefloquine. http://www.defence.gov.au/Health/HealthPortal/Malaria/Anti-malarial_medications/Mefloquine/default.asp (accessed 12/01/2017).

4.13 United Kingdom Ministry of Defence. 2017. Ad Hoc Statistical Bulletin Mefloquine Hydrochloride prescribing in the UK Armed Forces, 1 April 2007 – 31 March 2015 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/491134/20160112_Adhoc_Statistical_Bulletin_Mefloquine_prescribing_in_the_UK_Armed_Forces_-O.pdf (accessed 12/01/2017).

4.14 Migliani et al. 2008. Paludisme chez les militaires français en Côte-d'Ivoire de 1998 à 2006. BEH thématique 23-24 (accessed 12/01/2017).

4.15 United States DoD. Policy Memorandum on the Use of Mefloquine (Lariam®) Malaria Prophylaxis. Office of the Assistant Secretary of Defense – Health Affairs (Sept. 2009). http://www.lariaminfo.org/pdfs/policy-memo-secy-defense%20malaria-prophylaxis.pdf (accessed 12/01/2017)

4.16 Neumann et al. 2014. CATMAT Statement on International Travellers and Typhoid – A welcome development. CCDR. Volume 40-4. http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/14vol40/dr-rm40-04/dr-rm40-04-edit-eng.php (accessed 12/01/2017).

4.17 Eick-Cost et al. 2016. Neuropsychiatric Outcomes after Mefloquine Exposure among U.S. Military Service Members. ASTMH. doi:10.4269/ajtmh.16-0390.

4.18 Tatem et al. 2017. The geography of imported malaria to non-endemic countries: a meta-analysis of nationally reported statistics. Lanet ID. 17: 98-107.

4.19 Het Landelijk Coördinatiecentrum Reizigersadvisering. 2015. Malariaprofylaxe Bulletin 2015. http://www.mmmig.nl/static/filebank/aa7250d5010c1cf84eaaaa68fa39f17a/2015-feb-lcr-malaria-profylaxe-bulletin.pdf (accessed 15/01/2017).

CHAPTER 5 Tolerability of Mefloquine compared to Other Antimalarials for Military Personnel

Key question(s)

Compared to alternatives, are military personnel using mefloquine at relatively increased risk for potentially associated adverse effects?

Compared to alternatives, does mefloquine result in reduced ability to execute occupational duties?

Are there adverse long term effects of using mefloquine evident in Canadian soldiers?

Summary

- *To further evaluate tolerability of mefloquine for military personnel, we sought and assessed evidence specific to this population. Emphasis was placed on studies that included doxycycline and/or AP as comparators.*
- *To identify relevant literature, a search of Ovid Medline was performed. After screening the title and abstracts of the 113 identified studies, 7 were retained. An additional two studies identified after the initial literature search were also included.*
- *Mefloquine, used as MCP in (primarily deployed) military populations, was most often compared to doxycycline (8 studies, ca. 400,000 participants). It was usually associated with similar or lower rates of AE than doxycycline.*
- *Self-reported rates of compliance with mefloquine MCP were usually similar or higher than for doxycycline.*
- *Self-reported rates of impact on day-to-day activities [and/or discontinuation of MCP due to potentially associated AE] for mefloquine were generally similar to or lower than rates for doxycycline.*
- *Compared to doxycycline, mefloquine was not associated with increased risk of post-traumatic stress disorder (PTSD), depression or suicide.*
- *Although fewer studies incorporated an AP cohort, evidence suggests that rates of adverse events potentially associated with this drug are generally similar or lower than for mefloquine.*
- *In the aggregate, the evidence suggest mefloquine is as well or better tolerated than doxycycline among military personnel, though it might be associated with a modest increase in potentially associated AE compared to AP.*
- *Evidence included safety data for up to one year after use of MCP.*

- *At the study level, the quality of the evidence for the included studies was very low to low. Specific concerns included: risk of bias indirectness (evidence derived from non-Canadian militaries) and imprecision.*

Conclusion(s)

Compared to currently recommended alternatives (doxycycline and AP), mefloquine is not consistently associated with an excess overall risk of adverse effects (low to very low quality evidence). This includes neuropsychiatric outcomes.

Compared to currently recommended alternatives (doxycycline and AP), mefloquine is not associated with an excess risk of not being able to perform occupational duties (low to very low quality evidence).

Evidence addressing potential long term adverse effects of mefloquine or other MCP agents on health was not identified.

5.1 Introduction

Military personnel, whether travelling for occupational or leisure reasons, are at personal risk of malaria. Like other travellers (references 5.1 and 5.2), this is affected by where they are going, what they are doing, whether they are immunologically naïve, and a variety of other health and travel-related factors. Added to this, malaria can, in certain circumstances, affect the mission. This is particularly applicable in areas where malaria transmission is intense and personnel do not use preventive measures (e.g., repellents and malaria chemoprophylaxis). Examples of malaria-associated mission impact include historic conflicts (e.g., Pacific theatre during World War II) and more recent deployments such as an outbreak among US Marines deployed to Liberia in 2003 (up to a 40% attack rate; reference 5.3).

The potential for malaria to affect individuals and missions has prompted significant effort on the part of Western militaries to prevent this disease. Commonly employed measures include products that prevent mosquitoes from biting (e.g., topical repellents) and medications (MCP agents) that prevent development of clinical disease once infected. While used by the military, these approaches are not specific to this population, rather they are recommended for prevention of malaria by national [e.g., the Public Health Agency of Canada (reference 5.1), the US Centers for Disease Control and Prevention (reference 5.4)] and international [e.g., the World Health Organization (reference 5.5)] public health organizations.

As outlined in Chapter 3, the CAF follows the Canadian CPG on malaria prevention (reference 5.1). This includes recommendations related to use of MCP. In this respect, the Canadian CPG (as well as other national and international authorities) recommend that, in most areas where there is resistance to chloroquine, one of three agents (presuming medical suitability) be used: mefloquine; doxycycline; or, AP. The Canadian CPG do not distinguish between military personnel[10] and other travellers as respects use of MCP. Rather, the CPG emphasizes decision-making based on the circumstances of the individual, for example, is the person travelling for an extended period, do they have contraindications to any of the MCP agents, etc. This approach is suitable to the military context to the extent that it is relatively inclusive.

[10] The exception is Presumptive Anti-relapse Therapy (PART), where military personnel (as well as long term travellers and expatriates) are identified as a population for whom the intervention might be apt.

However, it is true that military personnel can operate in contexts not experienced by most leisure travellers, e.g., long-term deployment in a stressful environment. This has led some to question strict application of the Canadian (and other) CPG to the military environment. For example, it has been suggested that mefloquine ought not to be used by military personnel (see Chapter 1, also see reference 5.6). Reasons cited for this view include: concern that mefloquine is relatively poorly tolerated by military personnel; concern that mefloquine is potentially associated with long term neurologic or other sequelae; concern that AE potentially associated with mefloquine could complicate the diagnosis of mental health conditions like PTSD; and, concern that deploying personnel recommended to take MCP might not be fully screened for contraindications or other precautions that might impact upon the decision to prescribe mefloquine.

The perspective of the CFHS has been that the Canadian CPG for malaria prevention is suitable for guiding its approach to protecting CAF personnel against malaria. However, it also is important that we consider new information and, as necessary, update our approach to use of MCP. To this end, this chapter appraises the military-specific scientific evidence related to the tolerability of mefloquine as MCP. It also was intended to evaluate evidence related to potential long-term negative impacts of mefloquine use on military personnel.

5.2 Methods

5.2.1 General

For this chapter, the TF was responsible for: identifying key research questions; literature retrieval, synthesis and analysis; and, writing. As outlined in chapter 1, members of the TF are employees of the DND or members of the CAF.

Evidence appraisal was done through a narrative approach. We did not, for example, undertake a meta-analysis of identified literature, nor did we subject the identified evidence to a formal outcome-based evidence-based medicine (EBM) process to yield recommendations. We did, however, apply a qualitative approach based on an EBM methodology (GRADE, see reference 5.7) to characterize the quality of the evidence (see below).

5.2.2 Research Questions

- Is mefloquine used as antimalarial chemoprophylaxis by military personnel associated with an increased likelihood of harm (i.e., tolerability, rates of AE) compared to alternatives (doxycycline or AP)?

- Is mefloquine used as antimalarial chemoprophylaxis by military personnel associated with long-term mental health or other neurologic harms compared to alternatives (doxycycline or AP)?

- Is mefloquine used as antimalarial chemoprophylaxis by military personnel associated with an increased likelihood of not being able to perform occupational tasks compared to alternatives (doxycycline or AP). For this question, we considered discontinuation of MCP due to potentially associated AE as a surrogate for impact on ability to perform occupational tasks. While recognized as a poor surrogate, alternative evidence does not exist.

We did not search for or evaluate evidence related to the clinical efficacy of the currently recommended MCP (mefloquine, doxycycline or AP)[11]. This decision was taken because: current interest is focused on the potential harms associated with MCP; and, there is agreement among national and international advisory panels that these agents, if used appropriately, provide high levels of protection against malaria (particularly *Plasmodium falciparum*).

5.2.3 Literature search and inclusion criteria

We carried out a literature search using Ovid Medline. The search terms were "mefloquine" and "military", i.e. a study would have to include both terms to be included in the results. We did not limit our search by date excepting that it could only include studies listed in Medline up to and including the date of the search (November 19, 2016). We also identified potentially relevant evidence by reviewing the reference lists of the retrieved studies.

Titles, abstracts and (as necessary) the full text of identified studies were reviewed by a single assessor to determine if they met the following inclusion criteria:

- English language publications;
- A population that included, as an assessable entity, military personnel;
- Mefloquine (intervention) compared against doxycycline and/or AP;
- Relevant outcomes, e.g., adverse effects (AE), impact on occupation duties; and,

With these inclusion criteria, case series or case reports are excluded from the analysis. This is appropriate for at least three reasons. First, in the absence of a relevant comparator, the role (if any) of the intervention in the reported outcome(s) usually cannot be ascribed with confidence. Second, and as a natural consequence of the previous point, these studies generally provide the lowest quality level of evidence. Third, and specific to this report, we identified multiple observational studies with comparators that were specific to military personnel. Such studies are, *a priori*, considered to provide a higher quality of evidence than case reports or case series. In this situation, it is preferable to limit analyses to the higher quality evidence.

5.2.4 Evidence summary and quality assessment

We did not undertake quantitative assessments of the body of evidence, e.g., by performing a meta-analysis. This reflected, *inter alia*, the disparate study designs, outcomes and comparisons made in the included studies. Instead, qualitative assessments were done. For example, at the level of the individual study, we compared outcomes to determine if mefloquine was associated with relatively fewer, similar or more events than comparator. These were then tabulated across studies (see Annex 2, Tables 1 and 2) to yield trends in effect.

We considered quality of the evidence on a per study basis. We used the same domains as are used in GRADE to assess the quality of the evidence across studies: risk of bias, indirectness, imprecision and inconsistency[12] (see reference 5.7 for more detail). To be clear, GRADE is not specifically designed to

[11] We did consider evidence related to compliance with MCP.

[12] For inconsistency specifically, we considered the body of evidence. If there was serious inconsistency across studies (for example because of widely divergent results for a given outcome), we would apply a downgrade across the body of evidence. We judged that such inconsistency was not apparent among the included studies.

undertake qualitative assessments of individual studies. Nevertheless, its assessment domains are apt for a general characterization of quality. In this respect and as is done in formal GRADE reviews, for intervention-associated outcomes (e.g., adverse effects associated with MCP) we assumed randomized studies start out as high quality and observational studies as low quality. In terms of the meaning, high quality indicates we have greater confidence that the result represents the true state of affairs, whereas low or very low quality indicates we have less confidence that the result reflects reality.

5.3 Results

5.3.1 Literature search

Our literature search identified 113 studies (Annex 1). After screening titles and abstracts for relevance, 34 studies were retained for full text review. Of these, seven were considered to have met the inclusion criteria (references 5.8-5.14). Two additional studies (references 5.15-5.16), identified through supplementary search methods, were also included. The nine included studies are described in Annex 2, Tables 1 and 2.

The nine studies included evidence related to safety/tolerability endpoints and/or effects on ability to perform occupational tasks. They did not include evidence of potential associations between use of MCP and long-term mental health or other neurologic harms [one study (reference 5.15) included data up to one year after MCP use].

5.3.2 Safety/tolerability of mefloquine compared to doxycycline and/or AP

Nearly 400,000 military personnel were involved in the included studies. Approximately 40,000 were prescribed mefloquine, 320,000 were prescribed doxycycline and 12,000 were prescribed AP.

In all but one (reference 5.15) of the studies, safety/tolerability of MCP was based on self-reporting of symptoms assessed through questionnaires and/or interviews. In these studies, AE possibly associated with MCP use were commonly reported, i.e. per study rates ranged from about 20% to 60%, but also were usually self-limited (see Annex 2, Table 1).

The largest included study (reference 5.15) involved more than 350,000 US military personnel. Rather than self-reporting methods, it used retrospective analyses of medical records for personnel prescribed MCP (mefloquine, doxycycline and AP) to identify neuropsychiatric outcomes (NPO). The assessment period included the prescription period plus the subsequent 12 months. Expressed as incidence per 1,000 person years, overall rates of identified NPO[13] (ca. 1 event per 10 person years) were similar for all three MCP cohorts (mefloquine, doxycycline and AP). For individual NPO (e.g., adjustment disorder, anxiety disorder, depressive disorder, PTSD, suicide ideation, psychoses) the mefloquine cohort generally had similar or lower rates[14] than the doxycycline cohort. The exception was anxiety disorder (deployed personnel) where the mefloquine cohort had a relatively elevated rate (Incidence Rate Ratio (IRR) =1.12, 95% CI 1.01, 1.24). Compared to the AP cohort, rates for most of the individual NPO in the mefloquine cohort were similar, although rates of tinnitus (IRR 1.81 and 1.51 for deployed and nondeployed cohorts,

[13] The finding of an NPO does not mean that it is linked to use of MCP; though if there was a clear excess of NPO in certain cohorts it could indicate an association.

[14] For the non-deployed cohort, this included: adjustment disorder, insomnia, anxiety disorder, depressive disorder, vertigo, and PTSD (IRR ranged from 0.52 to 0.70)

respectively) and PTSD in the non-deployed cohort (IRR=1.83, 95% CI 1.07, 3.14) were relatively elevated. Although the doxycycline cohort was not compared directly to AP cohort, it is likely that rates of some of the individual NPO in this group were relatively elevated (given they were relatively elevated compared to mefloquine).

Similar trends as described above were also evident in the other included studies (summarized in Annex 2, Table 2). Specifically, mefloquine was as well or better tolerated (based on rates of potentially associated AE) than doxycycline (6/7 studies), the exception being a RCT (reference 5.16) where AE rates were relatively elevated in a mefloquine compared to a doxycycline treatment group, but paradoxically were relatively reduced compared to a placebo group. Further, and in line with reference 5.15, mefloquine was associated with similar (reference 5.8) or relatively elevated (reference 5.11) self-reported rates (e.g., sleep disturbance, nightmares) of potentially associated AE compared to AP.

5.3.3 Previous history of NPO

A single included study (reference 5.15) considered previous history of NPO as a predictor for future NPO. Described above (and in Annex 2, Table 1), it used medical records of US servicepersons to extract NPO information. For this assessment, only servicepersons who had a NPO in the year preceding MCP prescription were considered (n=2,164 for mefloquine and n=29,405 for doxycycline). Previous likelihood of NPO was higher in the doxycycline cohort (9.2%) than the mefloquine cohort (5.9%). For both cohorts, a NPO diagnosis in the year preceding prescription was associated with elevated risk of subsequent diagnosis (IRR ranged from 4.32 to 134.80). For individual NPO, there were no differences in estimates of future risk based on MCP prescription, i.e. mefloquine compared to doxycycline.

5.3.4 Long term effects of MCP

We did not identify any evidence (that met our inclusion criteria) for potentially associated long term mental health or neurologic effects of mefloquine compared to doxycycline or AP.

5.3.5 Impacts on occupational tasks: mefloquine compared to doxycycline and/or AP

We did not identify evidence to suggest that military personnel prescribed mefloquine were at increased risk (relative to comparators) for not being able to perform occupation duties. Indeed, the evidence suggests the opposite, i.e. mefloquine was similar to or protective relative to comparators. For example, compared to military personnel who received doxycycline as chemoprophylaxis, personnel receiving mefloquine were about 50% less likely to report impact on duties (22.2% vs. 12.6%, reference 5.9) or to discontinue MCP due to AE (references 5.10 and 5.12, estimates 10% vs 4% and 27.6% vs. 11.4%, respectively). In the single study where it was considered, potentially associated impacts on work activities were higher for AP (6%) than for mefloquine (2%) (reference 5.11).

5.3.6 Quality of the evidence

Annex 2 (Table 1) includes an assessment of the quality of the evidence on a per study basis. Excepting reference 5.15 (low quality), quality was assessed as very low for all studies. This is because all but one of the studies (reference 5.16) were observational (which increases risk of bias) and hence “start out” as low quality evidence. Additionally, each study (excepting reference 5.15) suffered at least one additional methodologic limitation that was judged to reduce quality, for example imprecision owing to low sample

size. The included randomized trial also was assessed as very low quality evidence reflecting our assessment that it was at a high risk of bias (residual confounding, self-reporting, see Annex 2, Table 1) and suffered from imprecision (small sample size). An important limitation for some of the studies was user adherence to MCP: it was sometimes unknown (e.g., reference 5.15), and other times mefloquine was self-reported as being more likely to be taken than comparator (references 5.8, 5.10, 5.14). This could lead to underestimation (if AE were truly associated with use of MCP) of effect estimates in the first instance or, with relatively higher rates of adherence to mefloquine, overestimation of the relative risks associated with this drug.

5.4 Discussion and Conclusions

The purpose of this chapter was to assess military-specific evidence related to the tolerability and impact on occupational duties of mefloquine as MCP (against comparators). We searched for, but did not find evidence (within the confines of our inclusion criteria) related to long-term mental health or other neurologic impacts of mefloquine or other MCP agents (doxycycline and AP) on military personnel.

After performing a literature search and applying inclusion criteria, we identified nine relevant references (5.8-5.16). Bases on qualitative analyses of this evidence, we concluded:

- Compared to doxycycline, mefloquine is generally as well or better tolerated and is associated with similar or reduced relative impact on ability to perform occupational duties.

- Compared to AP, mefloquine is generally as well or less well (e.g., tinnitus) tolerated.

- Rates of adherence are generally similar to or higher for mefloquine compared to doxycycline.

- In the largest included study (approximately 320,000 subjects), patients receiving a prescription for mefloquine were not at increased risk for NPO compared to alternatives. Mefloquine compared to doxycycline was not associated with an increased relative risk for future NPO in patients who had a previously documented NPO.

- There was overall consistency in the evidence, i.e., there were no clear outliers in terms of reported outcomes.

- At the study level (and hence also in the aggregate), the quality of the evidence was low (1 study) to very low (8 studies) (see Annex 2, Table 1). The important implication of low or very low quality evidence is that we have lower confidence in effect estimates. Put another way, new evidence is relatively more likely (compared to higher quality data) to result in meaningful changes in aggregated measures of outcome.

Our analysis was intentionally limited to military personnel and experimental designs with an appropriate comparator (doxycycline or AP). Case reports, studies involving only mefloquine, studies with comparators other than those listed above, and evidence from civilian populations were not included. This censoring was intentional and appropriate, i.e. the purpose of this chapter was to assess comparative tolerability of MCP in military personnel. Our findings, however, should be considered against the wider evidentiary context of harms and benefits of MCP. These are well laid out in the Canadian CPG for malaria prevention (reference 5.1). Reference 5.15 also provides a brief but useful overview of current evidence

related to mefloquine as MCP. Summarizing from this study, and consistent with our findings, military-specific evidence suggests that mefloquine often is not associated with an excess risk of NPO, though an exception might be personnel with a previous diagnosis. In contrast, evidence for civilian travellers indicates mefloquine has sometimes been associated with a relative excess of NPO (reference 5.1). This difference, if real, is noteworthy as it suggests mefloquine might be relatively better tolerated by military personnel.

5.4.1 Limitations

The analyses undertaken in this chapter has several limitations. First, we applied strict exclusion criteria. This allowed a focused assessment, but resulted in the exclusion of many studies. Second, we did not identify evidence (that met our inclusion criteria) specific to Canadian military personnel. It could therefore be argued that indirectness (see reference 5.7 for definition) reduces confidence in our conclusions. However, we argue against this for at least two reasons. We included large recent studies involving US military personnel. While not a perfect surrogate, there is no *a priori* reason to believe that results derived from US personnel would not be generalizable to Canadian military personnel. Moreover, evidence was generally consistent across disparate military populations (US, UK, Italian, Indonesian, Australian, Swedish and Turkish) and it seems unlikely that this would not also be the case for Canadian personnel.

The third and perhaps most important limitation of our analyses (implications discussed above) is the low to very low quality of the included studies. All studies had potential biases (e.g., residual confounding, lack of blinding, uncertainty about adherence or different rates of adherence to MCP, under ascertainment, self-reporting, low response rates) and most were limited by small sample size (see Annex 2, Table 1).

5.5 References

5.1 Committee to Advise on Tropical Medicine and Travel. 2014. Canadian Recommendations for the Prevention and Treatment of Malaria.

5.2. Checkley et al. 2012. Risk factors for mortality from imported falciparum malaria in the United Kingdom over 20 years: an observational study. British Medical Journal. 344: e2116

5.3 Whitman et al. 2010. An outbreak of Plasmodium falciparum malaria in US Marines deployed to Liberia. Am J Trop Med Hyg. 83:258-65

5.4 US CDC Yellow Book. 2016. https://wwwnc.cdc.gov/travel/yellowbook/2016/table-of-contents (accessed December 22, 2016)

5.5 World Health Organization. 2016. International Travel and Health. http://www.who.int/ith/en/ (accessed December 22, 2016)

5.6 Standing Committee on Veterans Affairs. Mental Health and Suicide Prevention Among Veterans. 42nd Parliament, 1st Session. http://www.parl.gc.ca/Committees/en/ACVA/StudyActivity?studyActivityId=9153634 (accessed December 22, 2016)

5.7 GRADE working group. http://www.gradeworkinggroup.org/ (accessed January 4, 2017)

5.8 Tuck et al. 2016. Malaria protection in Sierra Leone during the Ebola outbreak 2014/15; The UK military experience with malaria chemoprophylaxis. Travel Med Infect Dis. 14: 471-474

5.9 Terrell et al. 2015. Malaria Chemoprophylaxis and Self-Reported Impact on Ability to Work: Mefloquine Versus Doxycycline. J Travel Med. 22: 383-8

5.10 Saunders et al. 2015. Safety, Tolerability, and Compliance with Long-Term Antimalarial Chemoprophylaxis in American Soldiers in Afghanistan. Am J Trop Med Hyg. 93: 584-90.

5.11 Andersson et al. 2008. Well-tolerated chemoprophylaxis uniformly prevented Swedish soldiers from Plasmodium falciparum malaria in Liberia, 2004-2006. Mil Med. 173: 1194-8.

5.12 Sonmez el al. 2005. The efficacy and tolerability of doxycycline and mefloquine in malaria prophylaxis of the ISAF troops in Afghanistan. J Infect. 51: 253-8.

5.13 Kitchener el al. 2005. Mefloquine and doxycycline malaria prophylaxis in Australian soldiers in East Timor. Med J Aust. 182: 168-71.

5.14 Sánchez el al. 1993. Mefloquine or doxycycline prophylaxis in US troops in Somalia. Lancet. 341: 1021-2.

5.15 Eick-Cost et al. 2016. Neuropsychiatric Outcomes after Mefloquine Exposure among U.S. Military Service Members. ASTMH. doi:10.4269/ajtmh.16-0390

5.16 Ohrt et al. 1997.Mefloquine compared with doxycycline for the prophylaxis of malaria in Indonesian soldiers. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 126:963-72.

CHAPTER 6 Summary and Recommendations

6.1 General

This Surgeon General's Task Force Report on Mefloquine provides a detailed overview of the Canadian Armed Forces' history and experience with using mefloquine for MCP, an analysis of mefloquine prescribing practices in the CAF, a detailed analysis of international/national/military guidelines for malaria prevention through MCP recommendations, and an evidence review of the tolerability/safety of mefloquine for military personnel compared to alternatives (doxycycline and/or AP).

6.2 Chapter summaries

6.2.1 Summary of chapter 2

The CAF has previously and currently adheres to the Canadian CPG on malaria prevention (reference 6.1). For areas where the most dangerous form of malaria (*Plasmodium falciparum*) occurs, the CPG and the CAF (reference 6.2) generally recommend mefloquine, doxycycline or AP as equally suitable MCP options. Moreover, and also consistent with the Canadian CPG, the choice of which medication to use is up to the individual. Such choice, however, is only to be made after careful discussion with a health care provider and is to include screening for contraindications.

Conclusion #1. The CAF policy on malaria prevention including its approach to use of MCP is consistent with the Canadian CPG on malaria prevention.

Conclusion #2. As described in the Canadian CPG, mefloquine continues to be a useful MCP agent. In some cases it is the preferred MCP option, for example because it is specifically recommended for certain populations (e.g., first trimester of pregnancy), other agents are contraindicated, or individuals prefer the drug.

The CAF records and analyzes MCP prescriptions. Over the last 15 years, prescription patterns for MCP have changed dramatically. In the early 2000's, most prescriptions were for mefloquine. However, starting in 2004 (coinciding with the availability of AP), this pattern changed with relative rates of use of mefloquine decreasing and relatively more people receiving prescriptions for AP. Currently, relatively few CAF personnel receive mefloquine prescriptions, e.g., 1.5% (17 members) of the total prescriptions in 2016. We do not have clear evidence to explain this shift though it likely reflects factors such as: availability of AP as an option; increasing knowledge of MCP options within the CAF; negative publicity related to mefloquine; perceived advantages of AP vs comparators (doxycycline and mefloquine), e.g., shorter run in and post-return dosing; and, the impact of these factors on personal choice.

Conclusion #3. The pattern of MCP prescribing in the CAF has undergone a dramatic shift. Mefloquine now accounts for a small minority of prescriptions.

6.2.2 Summary of chapter 3

Our evaluation of the prescribing practices showed that more than 95% of patients prescribed mefloquine from 1 Dec 2013 to 1 Dec 2016 had medical record documentation indicating that the

prescription process included a face to face encounter with a clinician. However, only 38% of the records specifically mentioned that patients were screened for contraindications and precautions. Further, 12% of patients who were prescribed mefloquine had a potential contraindication or precaution noted in their chart.

Conclusion #4. The CAF malaria policy is generally being followed, i.e. personnel receiving prescriptions have a face to face encounter with a clinician. However, there is insufficient documentation of screening for contraindications and, in some cases, personnel have received a prescription for mefloquine despite evidence of potential contraindications or precautions in their medical records. These occurrences represent patient safety incidents that should be investigated.

Recommendation #1. The CAF will develop policies and procedures to enhance screening for contraindications and precautions related to mefloquine and other MCP agents. This will include a requirement to improve documentation of these procedures in medical records.

Recommendation #2. A malaria training package should be developed and provided to all authorized prescribers of malarial chemoprophylactic medications to improve knowledge about malaria in general, how to prevent it and how to safely prescribe MCP.

Recommendation #3. A formal audit process should be developed and implemented to allow required patient screening and prescription practices to be monitored for all MCP agents (e.g., mefloquine, doxycycline and AP).

6.2.3 Summary of chapter 4

We did not identify, through our review of national and international malaria CPG, substantial deviations from the Canadian clinical CPG on malaria prevention. We did identify differences among militaries in their approach to malaria prevention. In particular, some militaries do not adhere to their national CPG in that mefloquine is not included as a co-option with doxycycline and AP. Explanations for differences in approach for militaries from national CPG were lacking or were based on reasons other than direct and evidence-based comparisons of harms and benefits, e.g., operational and/or societal considerations.

Conclusion #5. The Canadian CPG for malaria prevention is consistent with other national and other international guidelines in that mefloquine is considered a suitable MCP option in most endemic areas where doxycycline and AP are also considered as suitable choices. However, some militaries consider mefloquine as a less preferred MCP option.

6.2.4 Summary of chapter 5

We carried out a literature search and evidence review to evaluate tolerability/safety of mefloquine for military personnel compared to currently recommended alternatives (doxycycline and AP). We also sought evidence related to impact of MCP on job duties, as well as evidence related to potential long-term impacts of currently recommended MCP agents on health. Our final analyses were based on nine studies and approximately 400,000 military personnel. The reviewed body of evidence does not support that mefloquine is, among military personnel, more poorly tolerated or associated with increased rates of adverse effects including neuropsychiatric outcomes compared to alternatives. Mefloquine when compared against doxycycline was usually associated with similar or lower rates of adverse events (and

similar or relatively higher rates compared to AP). Self-reported rates of compliance with mefloquine MCP were usually similar or higher than for doxycycline, whereas self-reported rates of impact on day-to-day activities (and/or discontinuation of MCP due to potentially associated adverse events) were generally similar or lower for mefloquine than for doxycycline. Compared to doxycycline, mefloquine was not associated with increased risk of post-traumatic stress disorder (PTSD), depression or suicide. Compared to AP, there was evidence that mefloquine was associated with increased risk of tinnitus, and for PTSD among non-deployed personnel. We searched for, but did not find any studies that evaluated long-term mental health or other neurologic impacts of mefloquine or other MCP agents (doxycycline and AP) on military personnel; the maximum follow-up time in the reviewed studies was two years after mefloquine was prescribed. The quality of the included studies was low or very low, meaning that we have relatively less confidence in the study-specific estimates of effect.

Conclusion #6. Compared to currently recommended alternatives (doxycycline and AP), the body of evidence suggests mefloquine is not consistently associated with an excess overall risk of adverse effects, nor is it associated with an excess risk of not being able to perform occupational duties (low to very low quality evidence). However, for individual adverse effects and within individual studies (see chapter 5), mefloquine was sometimes associated with a relative excess or relative deficit of AE compared to AP and doxycycline.

Conclusion #7. We did not identify any evidence (that met our inclusion criteria) addressing potential long term adverse effects of mefloquine or other MCP agents on health.

Conclusion #8. We did not identify any evidence (that met our inclusion criteria) specific to CAF personnel. However, we believe the available evidence (comprising approximately 400,000 military personnel)[15] is sufficient to support our conclusions.

Conclusion #9. The currently available data linking MCP to potentially associated adverse effects extends to approximately two years post-MCP initiation. While this evidence supports our conclusion that mefloquine is as well tolerated as alternatives by military personnel in the shorter term, it would be useful to have evidence that addresses potentially associated impacts over the long term. Novel research, in which appropriate comparators are included, could address this evidence gap.

6.3 General discussion and recommendations

The current CAF approach to use of MCP is consistent with international and national clinical practice guidelines for malaria prevention. The included scientific evidence (for military populations) does not support the notion that mefloquine is less safe or less well tolerated than alternatives; or that it has a relatively greater impact on ability to perform occupational duties. These findings, however, need to be interpreted in the context of the quality of the evidence, which was assessed as low to very low (on a per study basis). In this respect, at least two points should be considered. First, lower quality evidence means that we have less confidence in our findings. Second, there is increased possibility that biases, in particular residual confounding, might have obscured intervention-based effects.

[15] Case reports of series were not included as they represent the lowest level of evidence for observational trials.

By itself, the reviewed scientific evidence (military populations) does not provide compelling evidence for or against a change in policy related to use of mefloquine. However, there are other important considerations in this regard.

- The chart audit indicated that 12% of mefloquine prescriptions were to CAF members with potential contraindications. These represent patient safety incidents. If this deficiency cannot be corrected, then maintaining the current approach to use of MCP might result in a relative increase in harms for use of mefloquine against comparators;
- The large majority of CAF members prescribed MCP are choosing an agent other than mefloquine. This suggests that the values and preferences of CAF members are for use of MCP agents other than mefloquine;
- In addition to the above noted limitations related to the quality of the evidence, there is a lack of research evaluating the long term effects of mefloquine (or other MCP agents) on health. As a result, we could not address this specific concern through "scientific" assessment;
- The current CAF approach differs from that of many other western militaries;
- There is significant societal and media concern related to mefloquine. If we maintain the status quo, this attention, whether or not based on science, could erode the confidence that CAF personnel have in their medical services; and,
- There currently are two alternatives to mefloquine for areas where it is recommended, i.e. AP and doxycycline. Given that the majority of personnel are choosing to receive these agents, maintaining mefloquine as a co-option is not considered an operational necessity. In other words, and presuming adherence to the alternate MCP regimens, we do not believe that increased reliance on the alternative MCP regimes will result in a meaningful increase in risk of malaria to CAF personnel.

Recommendation #4. Based on the above-discussed considerations, the Surgeon General's Task Force on Mefloquine recommends a change to the CAF policy on malaria prevention. Specifically, we recommend that AP and doxycycline (and, depending on resistance patterns, chloroquine) be used as the preferred MCP agents. Further, we recommend that mefloquine be viewed as a less preferred agent that may be considered:

- **When alternatives are considered unsuitable, e.g., due to contraindications to or intolerance of alternatives.**
- **For persons who have previously tolerated, indicate a preference for and do not have contraindications to use of mefloquine as MCP.**

Recommendation #5. If Recommendation #4 is accepted by the Surgeon General, the CFHS should immediately update its policy on malaria prevention to reflect the revised approach to use of mefloquine.

Annex 1. Studies identified through literature search of Ovid Medline. Search terms were mefloquine AND military

1: Tuck J, Williams J. Malaria protection in Sierra Leone during the Ebola outbreak 2014/15; The UK military experience with malaria chemoprophylaxis Sep 14-Feb 15. Travel Med Infect Dis. 2016 Sep - Oct;14(5):471-474. doi: 10.1016/j.tmaid.2016.07.005. PubMed PMID: 27474994.

2: Livezey J, Oliver T, Cantilena L. Prolonged Neuropsychiatric Symptoms in a Military Service Member Exposed to Mefloquine. Drug Saf Case Rep. 2016 Dec;3(1):7. PubMed PMID: 27747687; PubMed Central PMCID: PMC5005770.

3: Fernando SD, Dharmawardana P, Semege S, Epasinghe G, Senanayake N, Rodrigo C, Premaratne R. The risk of imported malaria in security forces personnel returning from overseas missions in the context of prevention of re-introduction of malaria to Sri Lanka. Malar J. 2016 Mar 8;15:144. doi: 10.1186/s12936-016-1204-y. PubMed PMID: 26955813; PubMed Central PMCID: PMC4784464.

4: Cullen KA, Mace KE, Arguin PM; Centers for Disease Control and Prevention (CDC).. Malaria Surveillance - United States, 2013. MMWR Surveill Summ. 2016 Mar 4;65(2):1-22. doi: 10.15585/mmwr.ss6502a1. PubMed PMID: 26938139.

5: Quinn JC. Better approach needed to detect and treat military personnel with adverse effects from mefloquine. BMJ. 2016 Feb 10;352:i838. doi: 10.1136/bmj.i838. PubMed PMID: 26865279.

6: Nevin RL. Bias in military studies of mefloquine. J Travel Med. 2016 Feb 1;23(2):tav028. doi: 10.1093/jtm/tav028. PubMed PMID: 26849885.

7: Ferner RE, Gogtay NJ. Authors' reply to Green and colleagues. BMJ. 2015 Dec 9;351:h6588. doi: 10.1136/bmj.h6588. PubMed PMID: 26655828.

8: Green AD, Hodgetts TJ, Ross DA, Connor P. Value of mefloquine chemoprophylaxis in military personnel. BMJ. 2015 Dec 9;351:h6584. doi: 10.1136/bmj.h6584. PubMed PMID: 26655347.

9: Nevin RL. Rational Risk-Benefit Decision-Making in the Setting of Military Mefloquine Policy. J Parasitol Res. 2015;2015:260106. doi: 10.1155/2015/260106. Review. PubMed PMID: 26579231; PubMed Central PMCID: PMC4633683.

10: Gogtay NJ, Ferner RE. Mefloquine for malarial prophylaxis in military personnel. BMJ. 2015 Nov 3;351:h5797. doi: 10.1136/bmj.h5797. PubMed PMID: 26534919.

11: Terrell AG, Forde ME, Firth R, Ross DA. Malaria Chemoprophylaxis and Self-Reported Impact on Ability to Work: Mefloquine Versus Doxycycline. J Travel Med. 2015 Nov-Dec;22(6):383-8. doi: 10.1111/jtm.12232. PubMed PMID: 26424621.

12: O'Dowd A. MPs may hold inquiry into safety of using antimalarial mefloquine in military. BMJ. 2015 Sep 11;351:h4868. doi: 10.1136/bmj.h4868. PubMed PMID: 26361783.

13: Saunders DL, Garges E, Manning JE, Bennett K, Schaffer S, Kosmowski AJ, Magill AJ. Safety, Tolerability, and Compliance with Long-Term Antimalarial Chemoprophylaxis in American Soldiers in Afghanistan. Am J Trop Med Hyg. 2015 Sep;93(3):584-90. doi: 10.4269/ajtmh.15-0245. PubMed PMID: 26123954; PubMed Central PMCID: PMC4559701.

14: Cullen KA, Arguin PM; Centers for Disease Control and Prevention (CDC).. Malaria surveillance--United States, 2012. MMWR Surveill Summ. 2014 Dec 5;63(12):1-22. PubMed PMID: 25474160.

15: Kanani K, Amr ZS, Shadfan B, Al-Rashadan M, Bani Hani R. A retrospective study on imported malaria in Jordan. 1. Malaria among Jordanian UN peacekeeping forces. Bull Soc Pathol Exot. 2014 May;107(2):110-4. doi: 10.1007/s13149-014-0356-7. PubMed PMID: 24639137.

16: Dow GS, McCarthy WF, Reid M, Smith B, Tang D, Shanks GD. A retrospective analysis of the protective efficacy of tafenoquine and mefloquine as prophylactic anti-malarials in non-immune individuals during deployment to a malaria-endemic area. Malar J. 2014 Feb 6;13:49. doi: 10.1186/1475-2875-13-49. PubMed PMID: 24502679; PubMed Central PMCID: PMC3942710.

17: Peragallo MS, Sarnicola G, Boccolini D, Romi R, Mammana G. Risk assessment and prevention of malaria among Italian troops in Afghanistan, 2002 to 2011. J Travel Med. 2014 Jan-Feb;21(1):24-32. doi: 10.1111/jtm.12046. PubMed PMID: 24383651.

18: Adshead S. The adverse effects of mefloquine in deployed military personnel. J R Nav Med Serv. 2014;100(3):232-7. PubMed PMID: 25895400.

19: McGuire JM, Wilson JT. Reply: possible confounding by mefloquine in the association of emergence delirium with PTSD and TBI among combat veterans. J Perianesth Nurs. 2013 Dec;28(6):335-6. doi: 10.1016/j.jopan.2013.09.007. PubMed PMID: 24267620.

20: Kersgard CM, Hickey PW. Adult malaria chemoprophylaxis prescribing patterns in the military health system from 2007-2011. Am J Trop Med Hyg. 2013 Aug;89(2):317-25. doi: 10.4269/ajtmh.13-0013. PubMed PMID: 23817331; PubMed Central PMCID: PMC3741255.

21: Nevin RL. Mass administration of the antimalarial drug mefloquine to Guantánamo detainees: a critical analysis. Trop Med Int Health. 2012 Oct;17(10):1281-8. doi: 10.1111/j.1365-3156.2012.03063.x. PubMed PMID: 22882560.

22: Keene DD, Tong JL, Roughton S, Fadden SJ. Anti-malarial chemoprophylaxis following evacuation from Afghanistan. J R Army Med Corps. 2012 Mar;158(1):38-40; discussion 40. PubMed PMID: 22545372.

23: Fall B, Diawara S, Sow K, Baret E, Diatta B, Fall KB, Mbaye PS, Fall F, Diémé Y, Rogier C, Wade B, Bercion R, Pradines B. Ex vivo susceptibility of Plasmodium falciparum isolates from Dakar, Senegal, to seven standard anti-malarial drugs. Malar J. 2011 Oct 20;10:310. doi: 10.1186/1475-2875-10-310. PubMed PMID: 22014157; PubMed Central PMCID: PMC3210113.

24: El-Bahnasawy MM, Dabbous HKh, Morsy TA. Imported malaria as a threat to Egypt. J Egypt Soc Parasitol. 2010 Dec;40(3):773-88. PubMed PMID: 21268544.

25: Peterson AL, Seegmiller RA, Schindler LS. Severe neuropsychiatric reaction in a deployed military member after prophylactic mefloquine. Case Rep Psychiatry. 2011;2011:350417. doi: 10.1155/2011/350417. PubMed PMID: 22937403; PubMed Central PMCID: PMC3420400.

26: El Jaoudi R, Benziane H, Khabbal Y, Elomri N, Lamsaouri J, Cherrah Y. [Long-term malaria prophylaxis with mefloquine: a study of adverse drug reactions]. Therapie. 2010 Sep-Oct;65(5):439-45. doi: 10.2515/therapie/2010049. French. PubMed PMID: 21144479.

27: Whitman TJ, Coyne PE, Magill AJ, Blazes DL, Green MD, Milhous WK, Burgess TH, Freilich D, Tasker SA, Azar RG, Endy TP, Clagett CD, Deye GA, Shanks GD, Martin GJ. An outbreak of Plasmodium falciparum malaria in U.S. Marines deployed to Liberia. Am J Trop Med Hyg. 2010 Aug;83(2):258-65. doi: 10.4269/ajtmh.2010.09-0774. PubMed PMID: 20682864; PubMed Central PMCID: PMC2911167.

28: Nevin RL. Mefloquine prescriptions in the presence of contraindications: prevalence among US military personnel deployed to Afghanistan, 2007. Pharmacoepidemiol Drug Saf. 2010 Feb;19(2):206-10. doi: 10.1002/pds.1879. PubMed PMID: 19998269.

29: Nasveld PE, Edstein MD, Reid M, Brennan L, Harris IE, Kitchener SJ, Leggat PA, Pickford P, Kerr C, Ohrt C, Prescott W; Tafenoquine Study Team.. Randomized, double-blind study of the safety, tolerability, and efficacy of tafenoquine versus mefloquine for malaria prophylaxis in nonimmune subjects. Antimicrob Agents Chemother. 2010 Feb;54(2):792-8. doi: 10.1128/AAC.00354-09. PubMed PMID: 19995933; PubMed Central PMCID: PMC2812156.

30: Andersson H, Askling HH, Falck B, Rombo L. Well-tolerated chemoprophylaxis uniformly prevented Swedish soldiers from Plasmodium falciparum malaria in Liberia, 2004-2006. Mil Med. 2008 Dec;173(12):1194-8. PubMed PMID: 19149338.

31: Touze JE, Debonne JM, Boutin JP. [Current situation and future perspectives for malaria prophylaxis among travellers and military personnel]. Bull Acad Natl Med. 2007 Oct;191(7):1293-302; discussion 1302-3. Review. French. PubMed PMID: 18447051.

32: Zaher T, Ahmadi M, Ibrahim A, El-Bahnasawy M, Gouda H, Shahat SA. Malaria in Egypt, Saudi Arabia and Yemen: a clinical pilot study. J Egypt Soc Parasitol. 2007 Dec;37(3):969-76. PubMed PMID: 18383796.

33: Nevin RL, Pietrusiak PP, Caci JB. Prevalence of contraindications to mefloquine use among USA military personnel deployed to Afghanistan. Malar J. 2008 Feb 11;7:30. doi: 10.1186/1475-2875-7-30. PubMed PMID: 18267019; PubMed Central PMCID: PMC2259366.

34: Maguire JD, Llewellyn DM. Relapsing vivax malaria after 6 months of daily atovaquone/proguanil in Afghanistan: the case for expanded use of primaquine as a causal prophylactic. J Travel Med. 2007 Nov-Dec;14(6):411-4. PubMed PMID: 17995538.

35: Fujii T, Kaku K, Jelinek T, Kimura M. Malaria and mefloquine prophylaxis use among Japan Ground Self-Defense Force personnel deployed in East Timor. J Travel Med. 2007 Jul-Aug;14(4):226-32. PubMed PMID: 17617844.

36: Moudden MK, Boukhira A, Zyani M, Boughalem M, Hda A. [Severe imported malaria: the experience of the Avicenna military hospital of Marrakech]. Sante. 2006 Oct-Dec;16(4):259-62. French. PubMed PMID: 17446159.

37: Croft AM. A lesson learnt: the rise and fall of Lariam and Halfan. J R Soc Med. 2007 Apr;100(4):170-4. Review. PubMed PMID: 17404338; PubMed Central PMCID: PMC1847738.

38: Charles BG, Blomgren A, Nasveld PE, Kitchener SJ, Jensen A, Gregory RM, Robertson B, Harris IE, Reid MP, Edstein MD. Population pharmacokinetics of mefloquine in military personnel for prophylaxis against malaria infection during field deployment. Eur J Clin Pharmacol. 2007 Mar;63(3):271-8. PubMed PMID: 17216435.

39: Moudden MK, Boukhira A, Zyani M, Boughalem M, Hda A. [Severe imported malaria. The experience of the military hospital of Marrakech]. Ann Biol Clin (Paris). 2006 Sep-Oct;64(5):501-5. French. PubMed PMID: 17040884.

40: Rafiev KhK, Chalyĭ VF, Abdullaeva ZIa. [Improvement of epidemiological surveillance of malaria among frontier guards in Tadjukistan]. Med Parazitol (Mosk). 2006 Apr-Jun;(2):42-5. Russian. PubMed PMID: 16813251.

41: Kitchen LW, Vaughn DW, Skillman DR. Role of US military research programs in the development of US Food and Drug Administration--approved antimalarial drugs.

Clin Infect Dis. 2006 Jul 1;43(1):67-71. Review. PubMed PMID: 16758420.

42: Wells TS, Smith TC, Smith B, Wang LZ, Hansen CJ, Reed RJ, Goldfinger WE, Corbeil TE, Spooner CN, Ryan MA. Mefloquine use and hospitalizations among US service members, 2002-2004. Am J Trop Med Hyg. 2006 May;74(5):744-9. PubMed PMID: 16687673.

43: Milhous W. Development of new drugs for chemoprophylaxis of malaria. Bull Soc Pathol Exot. 2001 Jul;94(2 Pt 2):149-51. PubMed PMID: 16579068.

44: Sonmez A, Harlak A, Kilic S, Polat Z, Hayat L, Keskin O, Dogru T, Yilmaz MI, Acikel CH, Kocar IH. The efficacy and tolerability of doxycycline and mefloquine in malaria prophylaxis of the ISAF troops in Afghanistan. J Infect. 2005 Oct;51(3):253-8. PubMed PMID: 16230223.

45: Dao NV, Quoc NP, Ngoa ND, Thuy le T, The ND, Dai B, Binh VQ, Rieckmann KH, Edstein MD. Fatty food does not alter blood mefloquine concentrations in the treatment of falciparum malaria. Trans R Soc Trop Med Hyg. 2005 Dec;99(12):927-31. PubMed PMID: 16143357.

46: Kitchener SJ, Nasveld PE, Gregory RM, Edstein MD. Mefloquine and doxycycline malaria prophylaxis in Australian soldiers in East Timor. Med J Aust. 2005 Feb 21;182(4):168-71. PubMed PMID: 15720172.

47: Tuck JJ, Green AD, Roberts KI. A malaria outbreak following a British military deployment to Sierra Leone. J Infect. 2005 Feb;50(2):171-2. PubMed PMID: 15667923.

48: Picot S, Brega S, Gérôme P, Velut G, de Monbrison F, Cheminel V, Peyron F. Absence of nucleotide polymorphism in a Plasmodium vivax multidrug resistance gene after failure of mefloquine prophylaxis in French Guyana. Trans R Soc Trop Med Hyg. 2005 Mar;99(3):234-7. PubMed PMID: 15653127.

49: Burton B. Australian army faces legal action over mefloquine. BMJ. 2004 Nov 6;329(7474):1062. PubMed PMID: 15528599; PubMed Central PMCID: PMC526142.

50: Ollivier L, Tifratene K, Josse R, Keundjian A, Boutin JP. The relationship between body weight and tolerance to mefloquine prophylaxis in non-immune adults: results of a questionnaire-based study. Ann Trop Med Parasitol. 2004 Sep;98(6):639-41. PubMed PMID: 15324471.

51: Cayley WE Jr. Mefloquine for preventing malaria in nonimmune adult travelers. Am Fam Physician. 2004 Feb 1;69(3):521-2. Review. PubMed PMID: 14971832.

52: Lessells R, Jones ME, Welsby PD. A malaria outbreak following a British military deployment to Sierra Leone. J Infect. 2004 Feb;48(2):209-10. PubMed PMID: 14720499.

53: Chambers JA. Military aviators, special operations forces, and causal malaria prophylaxis. Mil Med. 2003 Dec;168(12):1001-6. Review. PubMed PMID: 14719625.

54: Hussain SM, Rahman MM, Ahmed Z, Siddique MM. The recent malaria situation in Chittagong, Bangladesh. Southeast Asian J Trop Med Public Health. 2003;34 Suppl 2:1-5. PubMed PMID: 19238662.

55: Kitchener S. Epidemiology of malaria from East Timor among Australian Defence Force personnel. Trans R Soc Trop Med Hyg. 2002 Jul-Aug;96(4):376-7. PubMed PMID: 12497972.

56: Peragallo MS, Croft AM, Kitchener SJ. Malaria during a multinational military deployment: the comparative experience of the Italian, British and Australian Armed Forces in East Timor. Trans R Soc Trop Med Hyg. 2002 Sep-Oct;96(5):481-2. PubMed PMID: 12474471.

57: Ohrt C, Purnomo, Sutamihardja MA, Tang D, Kain KC. Impact of microscopy error on estimates of protective efficacy in malaria-prevention trials. J Infect Dis. 2002 Aug 15;186(4):540-6. PubMed PMID: 12195382.

58: Coker WJ. Malaria remains a military medical problem--MJ World. Published in Vol 147, Number 3, October 2001. J R Army Med Corps. 2002 Mar;148(1):101-2; author reply 102. PubMed PMID: 12024882.

59: Silveira FT, Ishikawa EA, De Souza AA, Lainson R. An outbreak of cutaneous leishmaniasis among soldiers in Belém, Pará State, Brazil, caused by Leishmania (Viannia) lindenbergi n. sp. A new leishmanial parasite of man in the Amazon region. Parasite. 2002 Mar;9(1):43-50. PubMed PMID: 11938695.

60: World MJ. Malaria remains a military medical problem. J R Army Med Corps. 2001 Oct;147(3):274-80. PubMed PMID: 11766209.

61: Fall IS, Ba-Fall KM, Gning SB, N'doye S, Diop I, Wade B. [Malaria prevention in the army: experience in senegal]. Med Trop (Mars). 2001;61(1):83-6. Review. French. PubMed PMID: 11584663.

62: Touze JE, Paule P, Baudon D, Boutin JP. Malaria prophylaxis in the French armed forces: evolution of concepts. Med Trop (Mars). 2001;61(1):79-82. Review. PubMed PMID: 11584662.

63: Buma AH, van Thiel P. Experiences with malaria chemoprophylaxis in Dutch troops. Med Trop (Mars). 2001;61(1):77-8. Review. PubMed PMID: 11584661.

64: Croft AM, Geary KG. The malaria threat. Med Trop (Mars). 2001;61(1):63-6. Review. PubMed PMID: 11584659.

65: Peragallo MS. The Italian army standpoint on malaria chemoprophylaxis. Med Trop (Mars). 2001;61(1):59-62. Review. PubMed PMID: 11584658.

66: Edstein MD, Walsh DS, Eamsila C, Sasiprapha T, Nasveld PE, Kitchener S, Rieckmann KH. Malaria prophylaxis/radical cure: recent experiences of the Australian Defence Force. Med Trop (Mars). 2001;61(1):56-8. Review. PubMed PMID: 11584657.

67: Baudon D, Michel R, Meynard JB, Keundjian A, Boutin JP. [Antimalarial chemoprophylaxis in the French army: development from 1986 to 2001]. Med Trop (Mars). 2001;61(1):51-5. Review. French. PubMed PMID: 11584656.

68: Milhous WK. Development of new drugs for chemoprophylaxis of malaria. Med Trop (Mars). 2001;61(1):48-50. Review. PubMed PMID: 11584654.

69: Schwartz E, Paul F, Pener H, Almog S, Rotenberg M, Golenser J. Malaria antibodies and mefloquine levels among United Nations troops in Angola. J Travel Med. 2001 May-Jun;8(3):113-6. PubMed PMID: 11468111.

70: Sanchez JL, Bendet I, Grogl M, Lima JB, Pang LW, Guimaraes MF, Guedes CM, Milhous WK, Green MD, Todd GD. Malaria in Brazilian military personnel deployed to Angola. J Travel Med. 2000 Sep-Oct;7(5):275-82. PubMed PMID: 11231212.

71: Croft AM, Garner P. Mefloquine for preventing malaria in non-immune adult travellers. Cochrane Database Syst Rev. 2000;(3):CD000138. Review. Update in: Cochrane Database Syst Rev. 2000;(4):CD000138. PubMed PMID: 10908460.

72: de Vries M, Soetekouw PM, Van Der Meer JW, Bleijenberg G. Fatigue in Cambodia veterans. QJM. 2000 May;93(5):283-9. PubMed PMID: 10825404.

73: Trouiller P, Rey JL, Bouscharain P. [Pharmaceutical development concerning diseases predominating in tropical regions: the concept of indigent drugs]. Ann Pharm Fr. 2000 Jan;58(1):43-6. Review. French. PubMed PMID: 10669812.

74: Peragallo MS, Sabatinelli G, Sarnicola G. Compliance and tolerability of mefloquine and chloroquine plus proguanil for long-term malaria chemoprophylaxis in groups at particular risk (the military). Trans R Soc Trop Med Hyg. 1999 Jan-Feb;93(1):73-7. PubMed PMID: 10492796.

75: Miller SA, Bergman BP, Croft AM. Epidemiology of malaria in the British Army from 1982-1996. J R Army Med Corps. 1999 Feb;145(1):20-2. PubMed PMID: 10216843.

76: Weina PJ. From atabrine in World War II to mefloquine in Somalia: the role of education in preventive medicine. Mil Med. 1998 Sep;163(9):635-9. PubMed PMID: 9753993.

77: Bwire R, Slootman EJ, Verhave JP, Bruins J, Docters van Leeuwen WM. Malaria

anticircumsporozoite antibodies in Dutch soldiers returning from sub-Saharan Africa. Trop Med Int Health. 1998 Jan;3(1):66-9. PubMed PMID: 9484972.

78: Todd GD, Hopperus Buma AP, Green MD, Jaspers CA, Lobel HO. Comparison of whole blood and serum levels of mefloquine and its carboxylic acid metabolite. Am J Trop Med Hyg. 1997 Oct;57(4):399-402. PubMed PMID: 9347952.

79: Smoak BL, Writer JV, Keep LW, Cowan J, Chantelois JL. The effects of inadvertent exposure of mefloquine chemoprophylaxis on pregnancy outcomes and infants of US Army servicewomen. J Infect Dis. 1997 Sep;176(3):831-3. PubMed PMID: 9291347.

80: Conrad KA, Kiser WR. Response to doxycycline vs. mefloquine. Mil Med. 1997 Jun;162(6):iii. PubMed PMID: 9183154.

81: Peragallo MS, Sabatinelli G, Majori G, Calì G, Sarnicola G. Prevention and morbidity of malaria in non-immune subjects; a case-control study among Italian troops in Somalia and Mozambique, 1992-1994. Trans R Soc Trop Med Hyg. 1997 May-Jun;91(3):343-6. PubMed PMID: 9231213.

82: Bohnker BK. Doxycycline vs mefloquine. Mil Med. 1997 Apr;162(4):i, iv. PubMed PMID: 9110542.

83: Croft AM, Clayton TC, World MJ. Side effects of mefloquine prophylaxis for malaria: an independent randomized controlled trial. Trans R Soc Trop Med Hyg. 1997 Mar-Apr;91(2):199-203. PubMed PMID: 9196769.

84: Smoak BL, DeFraites RF, Magill AJ, Kain KC, Wellde BT. Plasmodium vivax infections in U.S. Army troops: failure of primaquine to prevent relapse in studies from Somalia. Am J Trop Med Hyg. 1997 Feb;56(2):231-4. PubMed PMID: 9080885.

85: Longuet C, Ramiliarisoa O, Thor R, Bouchaud O, Basco LK, Doury JC, Le Bras J. [Drug sensitivity of falciparum malaria imported into France in 1995]. Bull Soc Pathol Exot. 1997;90(4):253-6. French. PubMed PMID: 9479463.

86: Conrad KA, Kiser WR. Doxycycline vs. mefloquine. Mil Med. 1997 Jan;162(1):viii. PubMed PMID: 9002694.

87: Shamiss A, Atar E, Zohar L, Cain Y. Mefloquine versus doxycycline for malaria prophylaxis in intermittent exposure of Israeli Air Force aircrew in Rwanda. Aviat Space Environ Med. 1996 Sep;67(9):872-3. PubMed PMID: 9025805.

88: Trouiller P. [Research and pharmaceutical development on the subject of communicable diseases in the intertropical region]. Sante. 1996 Sep-Oct;6(5):299-307. French. PubMed PMID: 8998593.

89: Jaspers CA, Hopperus Buma AP, van Thiel PP, van Hulst RA, Kager PA. Tolerance of mefloquine chemoprophylaxis in Dutch military personnel. Am J Trop Med Hyg. 1996 Aug;55(2):230-4. PubMed PMID: 8780466.

90: Hopperus Buma AP, van Thiel PP, Lobel HO, Ohrt C, van Ameijden EJ, Veltink RL, Tendeloo DC, van Gool T, Green MD, Todd GD, Kyle DE, Kager PA. Long-term malaria chemoprophylaxis with mefloquine in Dutch marines in Cambodia. J Infect Dis. 1996 Jun;173(6):1506-9. PubMed PMID: 8648231.

91: Croft AM, World MJ. Neuropsychiatric reactions with mefloquine chemoprophylaxis. Lancet. 1996 Feb 3;347(8997):326. PubMed PMID: 8569381.

92: Calì G. The Italian Army Medical Corps in the United Nations "peace-keeping" operations: Somalia and Mozambique, December 1992-December 1994. Med Trop (Mars). 1996;56(4):400-3. PubMed PMID: 9112621.

93: Wallace MR, Sharp TW, Smoak B, Iriye C, Rozmajzl P, Thornton SA, Batchelor R, Magill AJ, Lobel HO, Longer CF, Burans JP. Malaria among United States troops in Somalia. Am J Med. 1996 Jan;100(1):49-55. PubMed PMID: 8579087.

94: Shanks GD, Roessler P, Edstein MD, Rieckmann KH. Doxycycline for malaria prophylaxis in Australian soldiers deployed to United Nations missions in Somalia and Cambodia. Mil Med. 1995 Sep;160(9):443-5. PubMed PMID: 7478027.

95: Peragallo MS, Sabatinelli G, Majori G, Calí G, Sarnicola G. Prevention of malaria among Italian troops in Somalia and Mozambique (1993-1994). Trans R Soc Trop Med Hyg. 1995 May-Jun;89(3):302. PubMed PMID: 7660442.

96: Shanks GD, Barnett A, Edstein MD, Rieckmann KH. Effectiveness of doxycycline combined with primaquine for malaria prophylaxis. Med J Aust. 1995 Mar 20;162(6):306-7, 309-10. PubMed PMID: 7715493.

97: Miller JH, Byers M, Whiteoak R, Warrell DA. Imported falciparum malaria in British troops returning from Kenya. J R Army Med Corps. 1994 Oct;140(3):119-23. PubMed PMID: 8822063.

98: Jones R, Kunsman G, Levine B, Smith M, Stahl C. Mefloquine distribution in postmortem cases. Forensic Sci Int. 1994 Sep 6;68(1):29-32. PubMed PMID: 7959478.

99: Newton JA Jr, Schnepf GA, Wallace MR, Lobel HO, Kennedy CA, Oldfield EC 3rd. Malaria in US Marines returning from Somalia. JAMA. 1994 Aug 3;272(5):397-9. PubMed PMID: 8028173.

100: Shanks GD. 1993 Sir Henry Wellcome Medal and Prize recipient. The rise and fall of mefloquine as an antimalarial drug in South East Asia. Mil Med. 1994 Apr;159(4):275-81. PubMed PMID: 20058419.

101: Eamsila C, Singharaj P, Yooyen P, Chatnugrob P, Nopavong Na Ayuthya A, Webster HK, Lasserre R, Mittelholzer ML, Stürchler D. Prevention of Plasmodium falciparum malaria by Fansimef and Lariam in the northeastern part of Thailand. Southeast Asian J Trop Med Public Health. 1993 Dec;24(4):672-6. PubMed PMID: 7939938.

102: Magill AJ, Smoak BL. Failure of mefloquine chemoprophylaxis for malaria in Somalia. N Engl J Med. 1993 Oct 14;329(16):1206. PubMed PMID: 8377800.

103: Boudreau E, Schuster B, Sanchez J, Novakowski W, Johnson R, Redmond D, Hanson R, Dausel L. Tolerability of prophylactic Lariam regimens. Trop Med Parasitol. 1993 Sep;44(3):257-65. PubMed PMID: 8256107.

104: Sánchez JL, DeFraites RF, Sharp TW, Hanson RK. Mefloquine or doxycycline prophylaxis in US troops in Somalia. Lancet. 1993 Apr 17;341(8851):1021-2. PubMed PMID: 8096898.

105: Rieckmann KH, Yeo AE, Davis DR, Hutton DC, Wheatley PF, Simpson R. Recent military experience with malaria chemoprophylaxis. Med J Aust. 1993 Apr 5;158(7):446-9. PubMed PMID: 8469191.

106: Gullahorn GM, Bohman HR, Wallace MR. Anaesthesia emergence delirium after mefloquine prophylaxis. Lancet. 1993 Mar 6;341(8845):632. PubMed PMID: 8094856.

107: Suriyamongkol V, Timsaad S, Shanks GD. Mefloquine chemoprophylaxis of soldiers on the Thai-Cambodian border. Southeast Asian J Trop Med Public Health. 1991 Dec;22(4):515-8. PubMed PMID: 1820636.

108: Shanks GD, Watt G, Edstein MD, Webster HK, Suriyamongkol V, Watanasook C, Panpunnung S, Kowinwiphat W. Halofantrine for the treatment of mefloquine chemoprophylaxis failures in Plasmodium falciparum infections. Am J Trop Med Hyg. 1991 Oct;45(4):488-91. PubMed PMID: 1951857.

109: Arthur JD, Echeverria P, Shanks GD, Karwacki J, Bodhidatta L, Brown JE. A comparative study of gastrointestinal infections in United States soldiers receiving doxycycline or mefloquine for malaria prophylaxis. Am J Trop Med Hyg. 1990 Dec;43(6):608-13. PubMed PMID: 2267964.

110: Arthur JD, Shanks GD, Echeverria P. Mefloquine prophylaxis. Lancet. 1990 Apr 21;335(8695):972. PubMed PMID: 1970042.

111: Shanks GD, Karwacki JJ, Singharaj P. Malaria prophylaxis during military operations in Thailand. Mil Med. 1989 Oct;154(10):500-2. Review. PubMed PMID: 2515474.

112: Reams GG. Review of malaria prophylactic drugs for performance effects in naval aviators. Aviat Space Environ Med. 1989 Jul;60(7 Pt 2):A77-9. Review.

PubMed PMID: 2673202.

113: Myint Lwin, Kyaw Win, Ye Htut, Ye Thwe, Tin Thein Lwin, Khin Win. The use of immunofluorescence to evaluate the efficacy of malarial chemoprophylaxis. Trans R Soc Trop Med Hyg. 1987;81(6):896-8. PubMed PMID: 3332506.

Annex 2. Chapter 5 Tables.

Table 1 Description and quality assessment of included studies for assessment of mefloquine, as a malarial chemoprophylaxis, against doxycycline and/or AP.

Description	Sample size	Summary	Conclusion	Strengths, Limitations and Quality Assessment
Eick-Cost et al. 2016. Retrospective cohort study (US military personnel 2008-2013). Data extracted from US military healthcare databases. Outcomes were neuro-psychiatric outcomes (NPOs). Analyses with Poisson regression models with adjustment: denominator was person years accrued during each risk period. Evidence expressed as incidence rate ratio (IRR). IRR of 1 suggests equivalent rates for the outcome of interest, whereas IRR significantly less than or greater than 1 suggests lower and higher relative risks, respectively.	Mefloquine - 36,538 Doxycycline - 318,421 AP - 12,881	For most NPOs (including suicide and suicide ideation), adjusted rate estimates among mefloquine recipients were not significantly different from estimates for comparators (doxycycline or AP). Where there were differences, at least for the mefloquine against doxycycline comparison, adjusted rates were more often relatively lower in the mefloquine cohort. For example, while the IRR for anxiety was significantly elevated for mefloquine compared to doxycycline (1.12; 95% CI = 1.01–1.24) among deployed personnel; it was lower among nondeployed personnel for adjustment disorder, insomnia, anxiety disorder, depressive disorder, vertigo, and PTSD. Compared to AP, persons receiving mefloquine had a relatively elevated IRR for tinnitus and, among the nondeployed cohort, for PTSD (IRR = 1.83; 95% CI = 1.07–3.14). Among individuals with a prior history of an NPO, the study did not identify a statistically significant increased risk for subsequent diagnoses of the same condition among mefloquine subjects compared with doxycycline subjects.	Overall risk of NPOs in year following use of mefloquine is similar to comparators (doxycycline and AP). For individual NPO where there is a difference, mefloquine was generally associated with lower rates than doxycycline, and higher rates than AP.	Strengths: Very large cohort of military personnel increases power to detect differences. Based on clinically relevant diagnoses. Limitations: Possibility of under-ascertainment (of NPO). Uncertainty that personnel used MCP. Possibility of miscoding of data. Potential for residual confounding. Not randomized, nor blinded. Unblinded clinicians, e.g., there might have been a NPO attribution bias in persons receiving certain agents.

Included deployed and non-deployed groups. Follow-up for one year (after cessation of malaria chemoprophylaxis (MCP)).				Different baseline NPO rates in cohorts (potential for bias for baseline future risk of NPO). **Overall quality of the evidence**: Low quality evidence (risk of bias)
Tuck et al. 2016. Retrospective cohort study (UK military personnel deployed to Sierra Leonne 2014-2015). Questionnaire based self-report survey on MCP tolerability. 337 personnel were eligible, of whom 151 (46.3%) returned questionnaires.	Mefloquine - 13 Doxycycline - 20 AP - 118	No differences in self-reported rates of AE between different MCP regimes (range: 23.1%-28%). Self-reported compliance rates highest for mefloquine (100%); rates were 79% for AP and 75% for doxycycline. No significant NPOs reported.	In this small cohort study, mefloquine was as well tolerated as comparators, with better self-reported rates of compliance.	Strengths: Recent experience with a deployed military population. High rates of self-reported adherence. Limitations: Low response rate. Small sample size; power to detect differences is poor. Generalizability. Not randomized, nor blinded. Self-reporting. **Overall assessment**: Very low quality evidence (serious risk of bias, serious risk of imprecision).
Terrell et al. 2015. Prospective cohort study (UK military personnel deployed to Kenya during 2012 and 2014).	Mefloquine - 938 Doxycycline - 752 AP - 122	Self-reported rates of AE were common, though usually did not affect job functions. Nearly twice as many respondents indicated that they believed doxycycline interfered with their job functions	Compared to doxycycline, personnel in the mefloquine were less likely to self-report impact on ability to perform job functions.	Strengths: Recent experience with a deployed military population.

Questionnaire based self-report survey on MCP tolerability (mefloquine against doxycycline). The survey was administered while personnel were returning from a training exercise. Response rate was low. Emphasis was placed on impact on job functions.		compared to those receiving mefloquine (22.2% vs 12.6%). There were high levels of compliance with MCP in both arms (>90%).		High rates of self-reported adherence. Limitations: Low response rate. Generalizability. Not randomized, nor blinded. Self-reporting. **Overall assessment**: Very low quality evidence (serious risk of bias, risk of imprecision).
Saunders et al. 2015. Retrospective cohort study (US military personnel returning from Afghanistan to Fort Drum 2006 to 2007). Questionnaire based self-report survey on MCP tolerability (primarily mefloquine against doxycycline). Surveys provided during redeployment medical screening. Response rate was ca. 90% (2,351/2,601) and large majority of respondents (>90%) had not previously	Mefloquine - 596 Doxycycline - 2011 AP - 78	Self-reported AE were common (ca. 33%) in personnel receiving doxycycline or mefloquine. For mefloquine, the most often reported AE were NPOs, e.g., vivid dreams, whereas for doxycycline it was GI effects, e.g., nausea and diarrhea. Self-reported rate of discontinuation due to potentially associated AE was higher for doxycycline (10%) than mefloquine (4%). Self-reported rate of compliance was lower for doxycycline (60%) than for mefloquine (80%).	While rates of AE were similar for mefloquine and doxycycline, impact of AE (as indicated by discontinuation) was higher for doxycycline.	Strengths: Deployed military population. High response rate. Limitations: Not randomized, nor blinded. Mefloquine was generally used as a second line treatment, i.e. for those who had initially received doxycycline (bias). Generalizability. Self-reporting. **Overall assessment**: Very low quality evidence (serious risk of bias, risk of imprecision).

taken chemoprophylaxis.				
Andersson et al. 2008. Retrospective cohort study (Swedish military personnel returning from Liberia to Sweden 2004 to 2006). Questionnaire based self-report survey on MCP tolerability (mefloquine against AP). Surveys provided during redeployment medical screening. Response rate >80%. High rates of adherence to MCP regimes (>90%). No soldiers reported giving up MCP altogether.	Mefloquine - 488 AP - 121	Self-reported AE were relative more frequent for mefloquine compared to AP, e.g., 57% reported at least one adverse event (most commonly reported were nightmares and sleep disturbance) for mefloquine compared to 34% for AP (most commonly reported was sleep disturbance, followed by stomach pain). 2% of persons in the mefloquine cohort and 6% of persons in the AP cohort reported potentially associated impacts on work activities. Of those taking mefloquine, 79% stated that they would take it again, 7% would not, 13% might, and 1% did not know. In the atovaquone/proguanil group, the corresponding figures were 93%, 1%, 4%, and 1%, respectively. No serious associated adverse events, defined as need of hospitalization or medical treatment, were recorded. No association was found with mefloquine use and medical evacuation for NPOs.	Self-reported rates of AE were more frequent from mefloquine compared to AP. However, impact on work duties were, if anything, more frequent for AP.	Strengths: Deployed military population. High response rate. High rates of self-reported adherence. Limitations: Not randomized, nor blinded. Self-reporting. Estimates not adjusted for lack of contemporaneity, e.g., AP only used in the latter rotos. Small sample size. Generalizability. **Overall assessment**: Very low quality evidence (serious risk of bias, risk of imprecision).
Sonmez et al. 2005. Cohort study (Turkish military personnel deployed to Afghanistan in 2002). Questionnaire based self-report survey on MCP tolerability (mefloquine against doxycycline).	Mefloquine - 226 Doxycycline - 506	Self-reported AE were relatively more often reported in personnel taking doxycycline (59%) compared to mefloquine (41.2%). Potentially associated GI AE were more commonly reported in the doxycycline cohort, as were NPOs (at week 2, but not week 6). Among soldiers who did not take MCP, 27.6% in the doxycycline group compared	Mefloquine, compared to doxycycline, was associated with lower self-reported rates of potentially associated AE. Doxycycline was associated with a higher rate of MCP discontinuation.	Strengths: Deployed military population. High rates of self-reported adherence. Limitations: Not randomized, nor blinded.

Administered during deployment. Response rate 52% (734/1400).		to 11. 4% in the mefloquine group, did so because of (self-reported) potentially associated AE. High rates of self-reported compliance (ca. 80% for both drugs). No reports of drug related severe AE.		Use of doxycycline and mefloquine were not contemporaneous. Relatively low response rate (ca. 50%). Self-reporting. Generalizability. Small sample size. **Overall assessment**: Very low quality evidence (serious risk of bias, risk of imprecision, serious indirectness).
Kitchener et al. 2005. Prospective cohort study (Australian military personnel deployed to East Timor 2001 to 2002). After 6 months of deployment, personnel received a medical questionnaire and structured interview (mefloquine against doxycycline).	Mefloquine - 1157 Doxycycline - 388	The proportion of deployed personnel reporting at least one potentially associated AE was similar for mefloquine and doxycycline (ca. 56%). The most commonly reported adverse effects for both drugs were: sleep disturbance; headache; tiredness and nausea. 94% of respondents using mefloquine indicated they would do so again, compared 89% for doxycycline.	Mefloquine, compared to doxycycline, was associated with similar self-reported rates of potentially associated AE and, based on willingness to use again, might have been associated with higher user acceptability.	Strengths: Deployed military population. Limitations: Not randomized, nor blinded. Adherence unknown. Self-reporting. Generalizability. Unbalanced design, e.g., evidence for doxycycline only reported for second part of trial. Small sample size.

				Overall assessment: Very low quality evidence (serious risk of bias, risk of imprecision).
Ohrt et al. 1997. Randomized, double-blind, placebo-controlled field trial of chemoprophylaxis of malaria (Indonesian military personnel 1994). Tolerability assessed through self-report AE, a self-report questionnaire and in-depth investigation of individuals who discontinued drug (mefloquine against doxycycline).	Mefloquine - 68 Doxycycline - 67 Placebo - 69	Mefloquine and doxycycline were significantly better tolerated than placebo (based on potentially associated AE). Doxycycline, compared to mefloquine, was associated with relatively fewer potentially associated AE. Overall attack rate in placebo group was high, e.g., 77% by conclusion of study. Both MCP agents were highly efficacious.	Doxycycline, compared to mefloquine, was associated with a lower (overall) self-reported rate of AE.	Strengths: Deployed military population. Randomized and blinded. Directly observed therapy. Limitations: Self-reporting. Generalizability. Small sample size. Residual confounding, explanation for reduced tolerability of placebo (e.g., authors posit protective effect of doxycycline against other pathogens; possibility that high attack in placebo resulting in confounding of malaria associated effects with placebo-associated AE, placebo group had shorter follow-up, analysis did not adjust estimates for potential confounding). **Overall assessment**: Very low quality evidence (serious risk of bias, risk of imprecision).
Sanchez et al. 1993. Retrospective cohort study (US military	Mefloquine - 344 Doxycycline -	Doxycycline associated with higher incidence of self-reported photosensitivity	Mefloquine, compared to doxycycline, was associated with a lower	Strengths: Deployed military population.

personnel in Somalia 1992-1993). Questionnaire based self-report survey on MCP tolerability (mefloquine against doxycycline). Surveys provided before redeployment.	52	(21.2% vs 5.2%) and gastrointestinal (34.6% vs. 12.8%) AE than mefloquine. Lightheadedness was relatively more frequently associated with doxycycline (19.2% vs 10.5%) without differences in the self-reported prevalence of nightmares or bad dreams (7.8% in both groups). Self-reported adherence with mefloquine was higher than for doxycycline (98% compared to 81%). No AE requiring hospitalization were reported.	(overall) self-reported rate of AE.	High self-reported rate of adherence. Contemporaneous with Canadian deployment to Somalia. Limitations: Not randomized or blinded (bias). Small sample size. Self-reporting. Generalizability. **Overall assessment**: Very low quality evidence (serious risk of bias, risk of imprecision).

Table 2 Summary of outcomes, mefloquine (MQ) against doxycycline (doxy) and/or atovaquone-proguanil (AP). Assessment based on a qualitative review of overall study results. In some cases, a specific outcome(s) might have deviated from the overall tendency for a study. For example, in Eick-Cost et al., rate estimates for most neuropsychiatric outcomes (NPO) associated with MQ were similar to or less than for doxy, though a single outcome, anxiety, was relatively elevated for MQ. This type of finding is indicated by a "*" appended to the overall study result. The other symbols mean the following: >, MQ associated with relatively fewer AE than comparator; <, MQ associated with relatively more AE than comparator; =, MQ and comparator associated with similar rates of AE; symbols can be combined where consideration is of multiple outcomes. **, there were relatively more potentially associated NPO AE with mefloquine and relatively more potentially associated GI AE with doxycycline. N/A, not applicable as comparator not included or comparison not made. ***, MQ and doxy associated with relatively fewer self-reported AE than placebo.

Study	Population	Safety MQ vs Doxy	Safety MQ vs AP	Work function MQ vs Doxy	Work function MQ vs AP
Eick-Cost et al. 2016.	US military	MQ ≥ Doxy*	MQ ≤ AP	N/A	N/A
Tuck et al. 2016.	UK military	MQ = Doxy	MQ = AP	MQ > Doxy	N/A
Terrell et al. 2015.	UK military	MQ = Doxy**	N/A	MQ > Doxy	N/A
Saunders et al. 2015.	US military	MQ = Doxy**	N/A	MQ > Doxy	N/A
Andersson et al. 2008.	Swedish military	N/A	MQ < AP	N/A	MQ > AP
Sonmez et al. 2005.	Turkish military	MQ > Doxy	N/A	MQ > Doxy	N/A
Kitchener et al. 2005.	Australian military	MQ = Doxy	N/A	N/A	N/A
Ohrt et al. 1997.	Indonesian military	MQ ≤ Doxy***	N/A	N/A	N/A
Sanchez et al. 1993.	US military	MQ > Doxy	N/A	N/A	N/A

Annex 3. Recommendations for use of chemoprophylaxis – selected international, national and military guidelines.

Jurisdiction	Authority (and reference)	Recommendations
International		
World Health Organization	World Health Organization http://www.who.int/ith/2016-ith-county-list.pdf?ua=1 (reference 4.3) (accessed 11/01/2017)	Areas with chloroquine resistant *P. falciparum*: mefloquine, doxycycline or atovaquone-proguanil (AP).[16] Process for developing recommendations not described.
International Association for Medical Assistance to Travellers (IAMAT)	IAMAT https://www.iamat.org/elibrary/view/id/1376 (reference 4.4) (accessed 11/01/2017)	Areas with chloroquine resistant *P. falciparum*: mefloquine, doxycycline or AP. Process for developing recommendations not described.
National		
Canada	Public Health Agency of Canada (Committee to Advise on Tropical Medicine and Travel) http://www.publications.gc.ca/site/eng/463465/publication.html (reference 4.2)	Areas with chloroquine resistant *P. falciparum*: mefloquine, doxycycline or AP. MCP recommendations developed through a narrative process combined with an evidence-based medicine schema and expert opinion.

[16]For international and national recommendations, medical screening (e.g., for contraindication and precautions) to determine suitability of potential MCP agents is emphasized.

	(accessed 11/01/2017)	
United States	United States Department of Health and Human Services (US Centers for Disease Control and Prevention (US CDC) – Division of Global Migration and Quarantine). http://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-travel/malaria (reference4.5) (accessed 11/01/2017)	Areas with chloroquine resistant *P. falciparum*: mefloquine, doxycycline or AP. US CDC indicates guidance is evidence-based and reflect best practice, but does not provide documentation to describe the process by which MCP recommendations are made.
United Kingdom	Public Health England (Advisory Committee on Malaria Prevention). https://www.gov.uk/government/publications/malaria-prevention-guidelines-for-travellers-from-the-uk (reference 4.6) (accessed 11/01/2017)	Areas with chloroquine resistant *P. falciparum*: mefloquine, doxycycline or AP. MCP recommendations informed by baseline risk to travellers, but ultimately decided based on expert opinion.
Australia	Northern Territory Government http://digitallibrary.health.nt.gov.au/prodjspui/bitstream/10137/555/1/Guidelines%20for%20Malaria%202012.pdf (reference 4.7) (accessed 11/01/2017)	Territorial recommendations used as a surrogate. Areas with chloroquine resistant *P. falciparum*: mefloquine, doxycycline or AP (Follows US CDC and WHO guidelines). Methodologic process as per US CDC and WHO.

France	Avis du Haut Conseil de la santé publique. http://invs.santepubliquefrance.fr//fr/Publications-et-outils/BEH-Bulletin-epidemiologique-hebdomadaire/Archives/2016/BEH-hors-serie-Recommandations-sanitaires-pour-les-voyageurs-2016 (reference 4.8) (accessed 11/01/2017)	Areas of chloroquine-resistant *P. falciparum*: mefloquine (if medically suitable), doxycycline or AP MCP recommendations informed by baseline risk to travellers, but ultimately decided based on expert opinion.
Germany	German Society for Tropical Medicine and International Health http://www.dtg.org/3.html; https://www.klinikum.uni-heidelberg.de/fileadmin/inst_hygiene/tropenhygiene/Tropenambulanz/PDF/DTG_Malaria_2016.pdf (reference 4.9) (accessed 11/01/2017)	Areas of chloroquine-resistant *P. falciparum*: mefloquine (if medically suitable), doxycycline or AP Process for developing recommendations not described.
Switzerland	https://www.bag.admin.ch/dam/bag/fr/dokumente/mt/i-und-b/richtlinien-empfehlungen/empfehlungen-risikogruppen-risikosituationen/malariaschutz-kurzzeitaufenthalter-bis-3-	Areas of chloroquine-resistant *P. falciparum*: mefloquine (if medically suitable), doxycycline or AP. MCP recommendations informed by baseline risk to travellers and explicit thresholds set by guideline panel. No clear indication of how thresholds were set (from discussion in guideline, it can be inferred that it is based on the likelihood of serious AE (estimated at 1/10,000) associated with MCP).

	monate.pdf.download.pdf/malaria-2016-prophylaxie.pdf (reference 4.10) (accessed 11/01/2017)	
Netherlands	http://www.mmmig.nl/static/filebank/aa7250d5010c1cf84eaaaa68fa39f17a/2015-feb-lcr-malaria-profylaxe-bulletin.pdf http://www.rivm.nl/Documenten_en_publicaties/Professioneel_Praktisch/Richtlijnen/Infectieziekten/LCI_richtlijnen/LCI_richtlijn_Malaria (reference 4.19) (accessed 15/01/2017)	Areas of chloroquine-resistant *P. falciparum*: mefloquine (if medically suitable), or AP; doxycycline as a second line agent.
Military		
Canadian Armed Forces	D FHP Standard #CDCP/2011/27: Malaria Chemoprophylaxis in the Canadian Forces (reference 4.1) (accessed 11/01/2017)	Areas of chloroquine-resistant *P. falciparum*: mefloquine, doxycycline or AP. Approach is to follow the national clinical practice guidelines for malaria prevention. *"The prescription for a specific MCP for an individual must be based on an assessment of the individual's travel itinerary, malaria drug resistance in the region being visited, his/her underlying health status, other medications being taken, and the risk of adverse drug reactions. CATMAT Guidelines provides guidance on: risk assessment (chapter 2); selection of a MCP regimen for individuals in general (chapter 4); malaria prevention for women who are pregnant or breast-feeding (chapter5); malaria prevention for individuals with co-morbidities (chapter5); and the indications/ efficacy/ adverse effects/ contraindications/ precautions of the specific drugs (chapter 8). After suitable*

		information transfer, the individual can make a personal decision on which of the MCP drug options he/she wishes to be prescribed". Currently, < 5% of annual MCP prescriptions are for mefloquine (over last several years, generally < 50 prescriptions/annum).
United States DoD	Assistant Secretary of Defense – Health Affairs http://www.health.mil/libraries/HA_Policies_and_Guidelines/13-002.pdf (reference 4.11) (accessed 11/01/2017)	Areas of chloroquine-resistant *P. falciparum*: doxycycline or AP; for individuals with intolerance or contraindications to both of these agents, mefloquine as an alternative. *"Atovaquone-proguanil and doxycycline are considered first line chemoprophylaxis medications in chloroquine-resistant malaria risk areas"*. *"Mefloquine should be reserved for individuals with intolerance or contraindications to both first-line medications. Before using mefloquine for prophylaxis, care should be taken to identify any contraindications on an individual basis and ensure the U.S. Food and Drug Administration (FDA)-required patient information handouts are available for distribution"* Rationale for difference in approach compared to national clinical practice guidelines not explained. Currently, < 1% of annual MCP prescriptions are for mefloquine (in 2015, 164 prescriptions in total).
Australian Defence Force	http://www.defence.gov.au/Health/HealthPortal/Malaria/Antimalarial_medications/Mefloquine/default.asp (reference 4.12) (accessed 11/01/2017) Previously, ADF policy was articulated in the Surgeon	Areas of chloroquine-resistant *P. falciparum*: doxycycline otherwise AP; if doxycycline or AP not suitable, then mefloquine. Before licensing of AP (2006), doxycycline then mefloquine. Currently, < 1% of annual MCP prescriptions are for mefloquine (= 15 prescriptions in 2015 and 4 prescriptions in 2016).

	General Australian Defence Force Health Directive No 215 http://www.navy.gov.au/reserves/e-docs/DATA/ADFPUBS/HPD/HD215.pdf (link is no longer active) (last accessed 30/09/2013)	Rationale for approach to use of MCP in ADF was articulated (last accessed 30/09/2013) in appendix 2 to Annex A of HD 125 as: <u>For deployments < 6 months</u> - doxycycline is first line drug, advantage stated as *"…antibiotic properties also prevent typhus, leptospirosis, and some gastro-intestinal, urinary tract and skin infections"*. - Malarone is the second-line drug for individuals who are intolerant of doxycycline. - "*Mefloquine (Lariam®) has also been used for Defence members who are unable to take doxycycline. Due to the wide-spread public perception of severe mefloquine adverse events, mefloquine is best used only by those who have previously tolerated the medication. Any Defence member starting mefloquine for the first time is to be warned about the possibility of severe central nervous system adverse effects which means mefloquine is contraindicated in many military occupations*".
UK MoD	https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/491134/20160112_Adhoc_Statistical_Bulletin_Mefloquine_prescribing_in_the_UK_Armed_Forces_-O.pdf (reference 4.13) (accessed 12/01/2017)	Areas of chloroquine-resistant *P. falciparum*: chloroquine-proguanil, mefloquine, doxycycline or AP. Approach is to follow the national clinical practice guidelines for malaria prevention. UK MoD has indicated that its recommendations for malaria prevention are under review (http://www.publications.parliament.uk/pa/cm201617/cmselect/cmdfence/648/648.pdf, accesses 12/10/2017). *"The MOD use a range of prevention drugs in line with the guidance provided by Public Health England's Advisory Committee on Malaria Prevention (ACMP) to ensure the treatment provided is going to be the most effective.* *The Ministry of Defence needs to be able to use the most appropriate drug for the areas to where our people deploy to help ensure their protection against this*

		disease. The choice of prescribed treatment depends upon a number of factors including: - *the region to which personnel are being deployed* - *the individual's medical history, for example, past history of side effects or contraindications to the drug.* *Drug options include Chloroquine; Chloroquine plus Proguanil; Mefloquine (Lariam); Doxycycline; and Atovaquone plus Proguanil (Malarone®)"* Between April 2007 and 2015, 16% of annual MCP prescriptions were for mefloquine (17,368 prescriptions in total).
French military	Source: http://opac.invs.sante.fr/doc_num.php?explnum_id=1497 Source : https://jeanyvesnau.com/2015/08/19/lariam-les-militaires-francais-sont-proteges-contre-ses-effets-psychiatriques-quen-est-il-des-civils/	Doxycycline as MCP; mefloquine as an alternative. *"Une prophylaxie médicamenteuse complète ces mesures. Avant 2001, la prophylaxie préconisée était l'association chloroquine-proguanil. De 2001 à octobre 2002 deux schémas étaient utilisés : l'association chloroquine-proguanil pour les militaires en séjour de longue durée (deux ans) et la méfloquine pour les militaires en mission de courte durée (quatre mois). A partir de fin octobre 2002, la prophylaxie a été standardisée avec utilisation pour tous les militaires du monohydrate de doxycycline. Quelle que soit la prophylaxie, elle devait être poursuivie quatre semaines au retour"* *Nous annoncions alors que nous chercherions à savoir ce qu'il en est des militaires et autres agents secrets français. La réponse n'a pas tardé, grâce à l'efficacité du « bureau communication » du Service de Santé des Armées (SSA):* "*Pour tous militaires français partant en opération, le SSA prescrit la doxycycline, nous a-t-on répondu. Et ce depuis une quinzaine d'années. Pour autant le Lariam® n'a pas été abandonné : il peut toujours être utilisé – en deuxième recours, en cas d'intolérance à la doxycycline*"