



Defence Committee

Oral evidence: [An acceptable risk? The use of Lariam for military personnel, HC 567](#)

Tuesday 8 December 2015

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Written evidence from witnesses:

- [Lieutenant Colonel \(retd\) A G Marriott MBE](#)
- [Mrs Trixie Foster](#)
- [Dr Remington Nevin](#)

Watch the meeting – [An acceptable risk? The use of Lariam for military forces](#)

Members present: Dr Julian Lewis (Chair); Douglas Chapman; Johnny Mercer; Jim Shannon; Ruth Smeeth; Mr John Spellar; Phil Wilson

Questions 92–144

Witness[es]: **Dr Ashley Croft**, **Mrs Trixie Foster**, **Lieutenant Colonel (retd) A G Marriott MBE**, and **Dr Remington Nevin** gave evidence.

Q92 Chair: Welcome to the second session of our inquiry entitled, “An acceptable risk? The use of Lariam for military personnel.” May I ask our four witnesses to identify themselves for the record?

Dr Croft: Good morning. My name is Dr Ashley Croft. I am a consultant public health physician and medical epidemiologist. I am registered with the GMC. I have a special interest in infectious diseases and tropical medicine. I served in the Army from 1986 until 2013 as a medical officer. During that time I carried out research into mefloquine, also known as Lariam, and other drugs as well.

Trixie Foster: Good morning. My name is Trixie Foster. I have been helping with research with a group for the past two and a half years.

Dr Nevin: Good morning. My name is Dr Remington Nevin. I am a former US Army preventive medicine officer, and currently a consulting physician epidemiologist and a doctoral candidate at Johns Hopkins University, where I have studied the mental health effects of anti-malarial toxicity.

Q93 Chair: Thank you. I understand you have flown in especially from the United States today. Is that correct?

Dr Nevin: Yes, I did, and unfortunately I have to fly home immediately after this Committee meeting. If I may, I would like to thank the Sullivan family for helping to sponsor some of the costs of my attendance today. They did that in memory of their late son, Sergeant Thomas Sullivan, a US marine who served in Iraq from 2004 to 2005, and later died of what are thought to be deployment-related toxic exposures. I thank the Sullivan family and also the Committee for making my attendance possible, and also very comfortable at short notice.

Chair: You are very welcome today and we will ensure that you have an adequate opportunity to get your point of view across.

Lieutenant Colonel Marriott: Good morning. My name is Andrew Marriott. I am a retired Army officer. I served in the infantry for almost 35 years. I took Lariam for one year for a deployment to Sierra Leone in 2003 and I have some residual problems arising from the toxicity of the drug.

Chair: Thank you. John Spellar will start our questions.

Q94 Mr Spellar: We could start by looking at the Lariam guidelines. As we all know, Roche issued guidelines with Lariam. Do you think those guidelines accurately describe the risks that are attached to taking Lariam?

Lieutenant Colonel Marriott: Perhaps I will begin with a comment. If you are referring to the most up-to-date guidelines, I guess that they probably do. My experience is that, in the UK and the Ministry of Defence, there has been knowledge of toxicity related to Lariam for a number of years. Indeed, many of the common side effects were well known when I started taking the drug in 2003.

Over the next three or four years of my service, I became aware of a number of issues related to problems with Lariam—what would be described as both psychiatric and physiological—that were impairing individuals and operational effectiveness.

I think that, over the years, there has probably been an incremental and steady improvement and recognition formally as to what is put into things like the patient information leaflet, but I am not sure that that has been transcribed into effective briefing of soldiers collectively, never mind individually, over the past 10 to 12 years of my experience with the drug.

Dr Nevin: My concern with the product insert, both here and internationally, is that it tends not to emphasise as much as it should the important nature of prodromal symptoms. These are symptoms that have been known to occur with use of this class of drug for more than 70 years. They were first recognised with the use of the related anti-malarial drug Quinacrine, which was marketed as Mepacrine here and as Atabrine in the US.

It was noted during the early use of this synthetic anti-malarial drug that more serious reactions were often preceded by sometimes very subtle psychiatric symptoms, things such as vivid dreaming, insomnia and slight changes in mood. These were the earliest warning signs that an individual was not tolerating the drug and, for whatever reason, was susceptible to its toxicity.

So we have known for 70 years that these prodromal symptoms should be taken seriously—should mandate the immediate discontinuation of the drug—and even though this guidance is written in the product inserts, it is not adequately emphasised. Even when given the opportunity to clarify and emphasise these points, representatives from Roche tend not to emphasise them. So that is what I find troubling. We could have prevented much of the trouble with this drug had the significance of prodromal symptoms been better understood.

Dr Croft: I agree with my colleague, Dr Nevin. The guidelines can be summarised in one sentence, which is that mefloquine is the least safe of the available anti-malarial regimens currently used, and the Roche representatives came out with that statement when they gave evidence here four weeks ago. Whether that statement is in the guidelines, I do not know. I think that the guidelines give a lot of information about side effects, but do they actually spell it out as simply as that, that this is the least safe drug you can take to prevent malaria?

Q95 Chair: How widely recognised would you say that statement is?

Dr Croft: It is documented from a randomised control trial carried out in international travellers and reported in 2001—the Overbosch study. It was a very late study because the drug had already been used on travellers for more than 20 years, and the study proved without doubt that mefloquine is the least safe of the drugs, and causes neuro-psychiatric effects in travellers at a greater level than equivalent medication—in that case they were comparing it to Malarone.

Q96 Chair: You were professionally in the military in this capacity, so is this a point that you ever raised with the Ministry of Defence?

Dr Croft: I raised it constantly, and the response was a mixture of incomprehension, indifference and sometimes hostility.

Q97 Chair: Why do you think there is that determination or, if you like, denial of what you say is a widely recognised assessment of the risks of the drug?

Dr Croft: As you said yourself, Mr Chairman, four weeks ago, this position seems to be contrary to reason. It is not a position that anyone in a reasonable world would take, to be giving soldiers the least safe drug to prevent malaria. So that is a question you would have to put to those who have adopted this illogical and irrational position.

Q98 Mr Spellar: That brings us neatly on to the next question, which is: should it be the MOD that has the prime responsibility to ensure widespread knowledge of, and to enforce, the guidelines, or should it be Roche? Roche told this Committee that it supplies exclusively through wholesalers, who would therefore be the intermediary, so is it the intermediary? Is there a problem with this fractured chain of communication? Where should the responsibility lie for ensuring the enforcement of the guidelines?

Dr Croft: The knowledge is evolving all the time and it is up to the practitioners to use all the knowledge available to them when prescribing a drug to recipients. The knowledge can come from the manufacturers, from science and from their own experience. It is a combination of sources that needs to be applied. I think that that answers the question. It is partly the manufacturers that have to be responsible and partly the practitioners.

Lieutenant Colonel Marriott: Might I add something? From a service point of view, I believe categorically that the responsibility lies with the Ministry of Defence and the Surgeon-General's Department. The reason why I say that is that when we are dealing with this sort of health issue, there is a command responsibility laid on the military chain of command as well as the medical chain of command to ensure compliance with every possible health and safety regime in the theatre of operations.

The Surgeon-General's Department and the local medics, for example, told me in 2003 that they had conducted a risk assessment and that there was no alternative to Lariam. Therefore, as a commander, I had a responsibility to ensure compliance among the team that I was deployed with. I did my duty in ensuring that they complied with all aspects of health, whether by using mosquito nets and mosquito cream, drinking clean water and so on, including the weekly regime of taking Lariam.

We have very specific conditions under which we conduct military operations, and I believe that that has to be recognised. The advice that is given by organisations such as Public Health England and the Advisory Committee on Malaria Prevention can give very general guidance, but I do not think that it is at all appropriate for the specific conditions under which military forces are required to deploy. Indeed, I would say that there is a great deal in the ACMP guidelines that would be quite incompatible with the product of military operations.

Q99 Phil Wilson: What military representation is there on the Advisory Committee on Malaria Prevention, and how effective do you think it is?

Trixie Foster: That is Surgeon Commander Andrew Green, who is on the ACMP. He is going to feed back the information on their advice. The MOD says that "the MOD reviews its policy on the use of anti-malarials in line with advice from the ACMP." However, I queried an aspect of that, and I had an email from Dr Hilary Kirkbride, a consultant epidemiologist and Public Health England representative. She said, "However, the ACMP is not responsible for providing advice on malaria prevention to the military, and therefore I regret that we are unable to make specific comments in relation to the use of mefloquine in troops."

With that, I wrote to the Surgeon-General to ask what was going on. On Friday, I got a response. It says, "The ACMP issues generic guidance for all UK travellers to areas of malaria risk, but it does not give specific advice to anybody, including the armed forces. The MOD uses ACMP guidance to make a risk assessment for the different areas of the world. You mention the 2015 guidance of the ACMP stating that each individual must have a stringent risk assessment prior to mefloquine being prescribed. Since 2004-05, defence policy has endorsed mefloquine to be prescribed, with an implied accompanying risk assessment." I don't quite see what that actually means. It sounds quite ambiguous.

Q100 Chair: Can the medically qualified members enlighten us as to what an implied assessment might be, as a substitute for an individual assessment? Does it mean that attention is drawn to a leaflet, perhaps, that comes with the drug?

Dr Croft: As ever, this is a letter from the Surgeon-General. It is not signed. No one knows who has written it. It is a meaningless statement.

Q101 Chair: But presumably, an implied assessment must mean that they are not getting an individual assessment, which is recommended for civilians, who do not have to undertake the super-stressful engagements and experiences of the military. So it would appear to be an admission that there are no individual assessments.

Dr Croft: Exactly.

Trixie Foster: May I just say that in the summer 300 servicemen from 1 Scots were sent out to Somalia and Sudan? Would they have had individual risk assessments? Were they given Lariam?

Q102 Chair: Lieutenant Colonel Marriott, can you tell us? You had to be part of the machine that distributed this drug. What sort of individual assessments did anybody get and what sort of warnings did they get about the contra-indications that, if they knew of them, should make them decline taking the drug?

Lieutenant Colonel Marriott: In 2003, my own experience was that the drug wasn't prescribed; it was issued. So, if you were deployed to somewhere like sub-Saharan Africa, you would be given Lariam and not assessed for which was the appropriate anti-malarial.

As part of my pre-deployment in September 2002, I saw a doctor who simply told me that he had to have an interview with me because apparently it was then believed that between one in 20,000 people and one in 25,000 people would have a bad psychiatric reaction to the drug. Therefore I needed to take it for three weeks before deployment, but I should expect to have various other side effects, such as vivid dreams, loss of balance, dizziness and so on.

In a subsequent experience, two years later, when I had to redeploy back to Sierra Leone, despite the fact of having been processed through a number of consultants at a tropical diseases clinic in Birmingham, part of my routine deployment was simply to be given Lariam again, just by a practice nurse. I actually wrote to the practice saying that they should have been aware that I had an issue with Lariam and that I had learned, in the background and from medical civilian friends, that there was an alternative called doxycycline, and that if I was deployed to Sierra Leone I would only go if I had doxycycline given to me.

Otherwise, I guess that most of what I can offer is what I have heard anecdotally, which includes comments from serving personnel who are not permitted to approach this Committee at all. The anecdotal evidence is very much that, at least until two years ago, the drug was routinely handed out by people such as Company Sergeant Majors who would not be medically qualified at all. The recipients were unaware what the drug was, whether it could have been Malarone, mefloquine or Lariam. Indeed, I had a conversation with a civilian doctor in August 2014 who was working for the Army in a very large garrison in the north of England and when I mentioned Lariam he told me, "Yes. I issue that all the time." And the fact that he said "issue" is really very telling.

I was very concerned in 2003 about the problems with Lariam, because after I had arrived in theatre I took over an in situ team of about eight people. I was commanding a couple of Majors, Captains and Warrant Officers. After I had been there a few days, my medic, who was a corporal from the Royal Army Medical Corps, had to be casevaced back to the UK

with malaria. My first question to the team was, “How on earth can the medic be going back with malaria?” The team then advised me that at least half of them—I think that is right—were throwing away their anti-malarials, because they preferred the risk of catching malaria to suffering the adverse side effects of the drug.

That is what I then took up with the medical commander at our base in Freetown and that was when I was told—I learned later that it was incorrect, shall we say, rather than untruthful—that there was no alternative to Lariam for that theatre and that the Surgeon-General had conducted a full risk assessment. On the basis of that risk assessment, we would have Lariam or nothing else. I have actually tried to get details of that risk assessment from the Ministry of Defence, but they have not been forthcoming.

Q103 Chair: Perhaps the Ministry of Defence will furnish that information to this Committee—you never know.

Lieutenant Colonel Marriott: I hope so.

Q104 Phil Wilson: This question is for Dr Croft. The MOD has stated that it cannot confirm whether individual risk assessments were carried out in every case, even after the creation of the defence primary healthcare organisation, because of the time and resources required. In your professional experience, were individual risk assessments recorded centrally or only on individuals’ medical records?

Dr Croft: I have not been involved in prescribing mefloquine at a clinical level, because I have tended to work in headquarters. I cannot say that I have actually seen risk assessments carried out. As we have been saying, it does seem to be wholly implausible that such individual risk assessments could be carried out, because the scale of the operation would be enormous. It would take at least half an hour to conduct a detailed risk assessment, and we are talking about hundreds of troops deploying at short notice. There just would not be the time before a major deployment for such an exercise to occur.

Trixie Foster: In the United States, they rely on the “Yellow Book”. On the differences with the recommendations for the US military’s use of malaria chemoprophylaxis, US military policy states: “Individualizing advice and recommendations for large military deployments is rarely logistically possible or feasible.” They recognise that. The policy states: “Recognizing this reality, in April 2013, the US military adopted a new policy on the use of malaria chemoprophylaxis in the US military. Atovaquone-proguanil”—or Malarone—“and doxycycline are now the first-line drugs of choice to prevent malaria in deployed US military forces...Atovaquone-proguanil is the drug of choice for short-term travel...and for people who travel frequently, to minimize long postexposure...mefloquine is not recommended as a primary option. It should be reserved for people with intolerance or contraindications to atovaquone-proguanil and doxycycline. Before using mefloquine for prophylaxis, care should be taken to identify any contraindications on an individual basis and ensure the required FDA mefloquine medication guide is given to people prescribed mefloquine.” It is completely recognised in the US.

Q105 Phil Wilson: Did you want to add something?

Trixie Foster: Just to ask why the MOD does not recognise that. It is extraordinary.

Q106 Phil Wilson: Dr Nevin, would you like to add to that from the US experience?

Dr Nevin: Certainly. Thank you. I can speak to the US experience and some of my research in this area. The US military does notionally provide for a face-to-face clinical assessment of all service members prior to deployment. There is a requirement for a clinician to evaluate the service member and identify pertinent aspects of their medical history and, if necessary, prescribe malaria chemoprophylaxis. Unfortunately, even that fairly stringent process has proven inadequate to prevent the inappropriate prescribing of mefloquine to service members with contra-indicating medical conditions.

The reason for that should make sense to the Committee: many service members will mask or not fully disclose a history of mental illness for fear of stigma or fear that it may threaten their deployability or career. Many service members want to deploy, even in the presence of contra-indicating medical conditions. Research I conducted showed that service members with a documented mental health history were more likely than not to answer “No” to the question, “Do you have a history of mental health problems prior to deployment?” Even stringent risk assessments conducted in military populations, in private and prior to deployment, will likely not identify those with contra-indications to the use of the drug.

For that reason, research that I conducted showed the one in seven US service members with contra-indications to mefloquine were none the less prescribed the drug. That was back in 2007, when awareness of these concerns was not as high. The US military experience in subsequent years, following the further restriction of mefloquine, has been odd, in that as we have restricted the drug’s use more and more, our use of the drug seems to be increasing in risk. This is a graph taken from a 2014 military publication that shows the rate of inappropriate prescribing of mefloquine had actually gone up threefold since the restrictions were first put in place, so the more we restrict the drug, the more high-risk these prescriptions seemingly become. It is very difficult to prescribe this drug safely in military settings.

Q107 Chair: Before I ask Jim Shannon to continue with the questioning, may we have a copy of that graph in due course?

Dr Nevin: Yes, certainly, Mr Chairman.

Q108 Jim Shannon: Every one of you this morning has highlighted the fact that Lariam has been dispensed rather than prescribed. You spoke of your personal experience of that, Colonel Marriott, and others have recalled experiences that people have told them about. Public Health England has said that Lariam may increase the risk of psychosis and anxiety reactions, and that it is under continual review. When I hear Public Health England saying those things, I wonder how that can be.

Dr Croft, in your comments to us, you referred to Lariam being handed out in the parade ground along with your tropical kit—“Here’s your net, here’s your cream and here’s your Lariam”—without any real understanding of what that means. That concerns me. Colonel Marriott, in your introduction you described the MOD policy as one of dispensing a stock drug rather than one of prescription—in other words, “There you have it. You take it,” without any knowledge of what is going to happen. My question is this: apart from the evidence from personnel that you presented this morning, what other concrete evidence have you of such widespread dispensation rather than prescription?

Dr Croft: We keep hearing from soldiers—there have been some written submissions to this effect—who say, “I turned up for my pre-deployment equipment, which would include the tropical uniform, the mosquito net, the sunscreen and the packet of malaria tablets,” and that was it; I think that is pretty much standard, even now.

Lieutenant Colonel Marriott: There are probably two orbits in this problem. One relates to the internal mechanisms of the MOD and the Surgeon-General’s department in the Armed Forces, and then there is the wider nexus described by Dr Nichol a couple of weeks ago with Roche, the producers, the various UK regulatory authorities—Public Health England, the MHRA and so on—and the prescribers or dispensers, be they civil or military. Personally, I think that that process is quite dysfunctional. I can give you an immediate example of that.

Dr Nichol said that Lariam is a prescription-only medicine that is not available from pharmacists; you cannot get it over the counter, and you can only get it after a one-on-one session with a physician. That is actually not true. We were able a couple of weeks ago to get Lariam dispensed over the counter from Boots, without a one-on-one with a physician. It may be that they are working within the Public Health England guidelines, but I think if you go to those guidelines, you will not see it mandated that there has to be the Roche expectation of a one-on-one with a physician. What is put in Public Health England’s ACMP guidelines is very loose and open to a variety of interpretations, which then causes a breakdown within the military structures.

You then have the military orbit of these problems, where you have to deploy quickly. It may be that the Army needs a go-to drug for emergency deployments, but it should be one that is understood and can be safely managed. If not, there needs to be a range of safety and observational protocols for the people who are taking a very risky drug, and that is certainly not in place—certainly not during my own service experience, and from what I have learned from people who have recently left the forces and, indeed, people who are still currently serving.

Q109 Jim Shannon: The soldiers tell me exactly what both yourself and Dr Croft have said—the drugs are handed out in the line a number of hours before they engage. I have made this comment before, but it has to be said: at a time of emotional stress, you leave your family behind and maybe you want to spend the last few hours with your friends—these are all things that happen—and then you have, “By the way, take this”, and how that is done really concerns me.

Dr Nevin, I want to thank you. It is not every day that someone comes all the way from America to address us. It is quite a journey, but thank you for coming. In your evidence, you stated that “numerous challenges are encountered by military physicians in prescribing Lariam in a manner that is fully compliant”. When you look at the background information as well, in 2013 the US Army declared it a drug of last resort. It is banned by special forces, which gives you an indication of how potent it is. The US FDA issues a black box warning. All the markers of the psychiatric side effects are there. Can you detail more fully what the challenges are?

Dr Nevin: Thank you very much. I have discussed some of the challenges. There are two main components to the safer use of this medication. The first component is ensuring it is prescribed only to those individuals without contra-indications. I have alluded to how this

is very difficult in military settings owing to concerns of stigma and under-reporting of mental health problems. Service members simply do not want to report or admit that they may have one of the conditions listed in the product insert that is a contra-indication to the use of the drug.

In the United States, research that we conducted showed that despite the contra-indications in the product insert, and despite every effort being made to minimise the inappropriate prescribing, still one in seven service members with a mental health contra-indication were none the less prescribed the drug. In recent years, with the graph I showed, the trend is towards more risky prescribing. More and more service members with contra-indications are being prescribed the drug. So that is the first component, and the US military has experienced great challenges in that.

The second component is more important, because it is often erroneously claimed or believed that only individuals with mental health histories can suffer the adverse effects of this drug. This is simply not true. Anyone is seemingly at risk. We do not know precisely what it is that causes some people to experience these idiosyncratic effects and others not to. There is some research being conducted. It is speculated there may be some genetic risk factors or environmental risk factors. Now the only warning we have that somebody may be susceptible is these early prodromal symptoms. It is critically important therefore that service members are educated and informed about the meaning of these symptoms and are told to discontinue the drug and seek medical care if they occur.

In this regard, the MOD's statistics are a cause for concern. I have before me their most recent release on the use of anti-malarial medication in the military, dated 20 August. The MOD describes experience with personnel prescribed Lariam during Operation Herrick. I believe a total of 536 service members were prescribed Lariam between April 2007 and December 2014; 536 individuals were prescribed mefloquin. Of those 536, only 11 personnel, according to the MOD, experienced side effects that were subsequently reported. This works out to approximately 2% of users.

Yet from the MOD's own research, we know that over a third of service members prescribed Lariam will experience such prodromal symptoms as vivid dreams, nightmares and insomnia, which the current Lariam SPC indicates are cause to immediately discontinue the medication. So the question that should be asked is: why weren't more service members reporting these side effects and why were more service members not immediately discontinuing the drug and being switched to another drug? I believe this second component of safe and ethical prescribing is more important than the first.

Q110 Johnny Mercer: I understand that this will be difficult for you to answer—we will ask it of the MOD in due course, but we want to understand the two sides of the same coin, as it were—but, in your collective view, why has this drug not been used properly in line with the very clear user guidelines that have been set out by the manufacturer? Dr Croft, you said that the MOD had been hostile in dealing with the effects associated with this drug; why do you think that was? We will obviously ask this of the MOD and try to understand why it was like that, but what is your view? What is the underlying reason? There must be a reason why this drug continues to be used even though the clear empirical evidence that you have presented this morning would indicate otherwise. Can you start, Dr Croft?

Dr Croft: A simple answer is that for a while there have been legal actions against the MOD, and it will dig in its heels when there is a legal challenge. That is one reason why it might take that position. One has to ask what kind of advice the MOD has been taking. It has been advised by the Surgeon-General, of course, but the Surgeon-General is advised by external advisers, and they may be influenced improperly by Roche. I know of one particular adviser who has links with that company. I wrote about that in the *British Medical Journal* on 24 April 1999.

Q111 Johnny Mercer: Sorry, to be clear, you are saying that the Surgeon-General is advised at times by an individual who also advises the drug manufacturer in this case?

Dr Croft: Yes. The Surgeon-General obviously cannot be knowledgeable about all areas of medicine.

Q112 Johnny Mercer: So he relies on advisers.

Dr Croft: Yes, although he has never actually said that. But the reality is that he must take advice.

Q113 Johnny Mercer: And one of his advisers works for the drug company?

Dr Croft: One of the advisers to the military over a long period of time doesn't work for the drug company, but it is known that he has, or has had in the past, strong financial links with Roche. That is documented, and I have in fact reported that in the *British Medical Journal*. He still says he's an adviser—

Q114 Johnny Mercer: That is quite a serious allegation. What was the reaction to it in the *British Medical Journal*? Was there any reaction from the MOD?

Dr Croft: He didn't respond. In fact, I was quoting his own words, where in a previous paper he had said, "I've received research funds from Roche." I was commenting on an article he had written that was advocating the use of mefloquine. I said, "The problem with this article is that some of the authors have conflicts of interest that they are not declaring." That adviser—there may be others—has links to Roche, which is a big company with all sorts of research interests and the ability to confer patronage, direct and indirect. That could be a problem. This could be partly why the Ministry of Defence has this entrenched position, because of the advice they have been given.

Q115 Johnny Mercer: You don't think it relies on any science.

Dr Croft: Certainly their position is to some extent based on science, but it may be based on, shall we say, biased interpretations of science.

Trixie Foster: It could be cost. Over, say, a six-week period, in a calculation on retail prices, Lariam is about £25, doxycycline is about £30 to £54, and Malarone is £288.

Q116 Johnny Mercer: Okay, so you think cost is a factor. What about you, Dr Nevin?

Dr Nevin: I can speak about the US experience. Of course, the US military developed mefloquine and then recruited Roche as its commercial partner to market the drug. It really is of some note that the US military has declared the drug it developed to now be a drug of last resort. US Army Special Operations Command, which arguably has the most

experience with this drug, going back even before it was licensed, has taken the very wise step of banning it altogether.

I think the US military took those steps based on the totality of evidence before it. It was presented with unequivocal evidence that it could not prescribe the drug safely in accordance with the product documentation, but there was also, for example, the guidance of a number of military authors writing in the CDC's yellow book—a travel guide—stating that the psychiatric side effects of mefloquine can confound or complicate the diagnosis of post-traumatic stress disorder and traumatic brain injury, which makes the continued routine use of mefloquine less desirable. I think that that, the box warning, the continued media attention and the fact that service members simply were not taking the drug, all together led to the US military's wise decision to de-prioritise its use.

Q117 Johnny Mercer: What about you, Colonel Marriott?

Lieutenant Colonel Marriott: This is a multifaceted problem. It is one of the issues that I have been trying to extract from the MOD for many years. I tried internally while I was serving, and then after I retired, to go through what I thought would be internal processes that could help people identify the problem and then address it. I have had a great deal of difficulty in pursuing all those routes. To give the MOD credit, the drug was initially introduced in the 1990s for very good reasons to overcome the problem of malaria, but as we progressed through the next decade, and certainly during the time when I was serving, it was clear that there were problems with the drug. The way in which the drug was being administered was a problem.

It is partly hubris that there has been difficulty in recognising a problem and grasping the nettle at an early stage. A series of vested interests among the people who had been advising the Surgeon-General, and the Surgeon-General then saying that he is simply taking advice from Public Health England, has created a situation whereby there is no end of problems and no one—either in the formal chain of command from the Chief of the Defence Staff downwards or from the Surgeon-General downwards—has been prepared to recognise that there is a problem. I suspect that they are persisting with it in the hope that they will be able to quietly stop dispensing this drug over the next year or so and that, if they do so, they can perhaps avoid a massive bow wave of litigation because of the individual and institutional neglect and incompetence that, in my experience, has surrounded this issue for eight to 10 years.

Q118 Chair: Before we leave that point, can I ask a question of Dr Nevin? When the US changed its policy and said that this will now be used only as a last resort, was there a bow wave of litigation in America?

Dr Nevin: The US military may be somewhat unique in that the US Government is protected from civil claims by something called the Feres doctrine. A Supreme Court decision from many decades ago bars service members from suing the US Government for injuries sustained during military service, even if due to gross negligence or incompetence, so service members are not able to seek damages for injuries due to mefloquine. I believe that the reasoning of the Supreme Court in making that decision many decades ago was that there is a system in place, the veterans administration and the military disability system, to provide for care of individuals who may have been injured in this manner. It is

possible that the US military was free to make decisions about the use of mefloquine unconstrained, or unconcerned, about possible legal ramifications.

Chair: That is very helpful.

Q119 Johnny Mercer: That is really interesting. And the overall wraparound care perhaps forces individuals to look out for themselves and go after some sort of civil case.

Finally, all drugs clearly have side effects, and they are mentioned time and again by both the manufacturer and the MOD, and it is totally accepted. My worry, which interestingly none of you has mentioned, is that, because these are mental health side effects, they are not taken anywhere near as seriously as physical health side effects—for some reason we still have a problem with destigmatising in this country not only across society but in the military—and that those mental health side effects have built up. The body of evidence has stacked up, and a study last year indicated that in the Royal Navy, of those who took it, 54% were affected by mefloquine, but because it is mental health those side effects are not being picked up. Is that a fair assessment, or do you think it goes beyond that?

Dr Nevin: It is a very fair assessment. It is unfortunate that psychiatric side effects of anti-malarial drugs are not studied as carefully in a prospective manner as physical side effects. Psychiatric side effects, by definition, cannot be detected, observed or measured; they require the subject, the patient, to report the presence of symptoms. We know, time and again, that in the populations that these drugs are tested on and used in there are many disincentives or barriers to reporting the symptoms. So there is a systematic bias against properly assessing the incidence and prevalence of psychiatric side effects from anti-malarial drugs, particularly in military settings, but also when used in developing nations, for example. Treatment of malaria is a very serious problem and I hope that the attention given to the issue among veterans will help to inform improvements in anti-malarial drug development in future.

Q120 Johnny Mercer: It is worth saying at this stage that the Committee absolutely accepts that some people have had their lives decimated by this. The fact that it is a mental health problem for us is irrelevant; it is a physical problem—that is why we are spending so much time on it. Thank you.

Lieutenant Colonel Marriott: May I add something that is important regarding the data available to the Ministry of Defence? I refer to the situation of Major Cameron Quinn, who committed suicide, as you all probably know. His widow, Dr Quinn, at the behest of the Chief of the General Staff, received a reassurance in one of the various protocols that is supposed to be monitoring the use of this drug. This states that all military medical practitioners are required to report adverse reactions to Lariam to the MHRA. This also appears in various military policy documents, so it is not discretionary. In fact, when Dr Nichol was presenting her evidence she said that, in the civilian world yes, it is discretionary, and that it is something between the patient and the doctor.

I read that in around 2007 or 2008 with a degree of surprise, because I had passed through at least five military medical practitioners and not one of them had mentioned the yellow card reporting system. I checked with the MHRA to see whether a yellow card had been raised on my behalf, but the MHRA was unable to find one. I then followed up then with another query to ask, “Can you give me an indication over the past decade of how many

adverse reactions have been reported by the Ministry of Defence?” I think over the period of about a decade it was something like 10.

Personally, however, I have come across multiples of them within one year. This is part of the issue, that for various reasons these things are not being picked up and reported. There have been other incidences of medical personnel in Sierra Leone who have seen people who have got what appear to be very bad reactions to Lariam, but for various reasons have not been reporting them. That happened not just in my tour, but in a subsequent tour, when an incident destroyed the marriage and life of the family who are sitting behind me.

These all relate to the issues that you are addressing. Why is the MOD not addressing them? The more we look at this, unfortunately the darker it becomes. I am sorry to have to expose these things in public; it is inimical to me. I have had 35 years of what I believe to be loyal service and I do not like to have to expose these problems in the Ministry of Defence, but they need to be gripped, because soldiers’ lives are at risk, as are the lives and welfare of many of the families who are subsequently affected.

Johnny Mercer: Yes, absolutely. That is precisely why the Committee is doing this.

Chair: I mention in passing that Dr Jane Quinn has sent in a substantial piece of written evidence. I assure all people who supply written evidence that, as well as the oral evidence, it is all very much taken into account in the reports that we draft.

Ruth Smeeth, I know you are under time pressure, so I am bringing you in as quickly as I can.

Q121 Ruth Smeeth: Apologies—I need to be in the Chamber at 12.30. Trying to get more detail on the side effects, can Colonel Marriott and Trixie Foster in particular give us some information on how big a problem this genuinely is in terms of numbers?

Lieutenant Colonel Marriott: My experience is that probably somewhere between 25% and 35% of personnel who deploy using Lariam are experiencing side effects that we would not accept in any other operational condition. I will put it to you this way. Never mind deployments, we conduct a lot of very sophisticated live-firing exercises, requiring co-ordination, balance and clear vision. This drug causes problems of dizziness, loss of co-ordination, poor decision making, and issues of anger management practically as a routine element within about 25% of the population. Now, that is one of the reasons why we don’t allow soldiers to appear on parade having had alcohol inside them, yet we accept it with a drug.

Concerning the longer-term residual issues, I am not in a position to say. I have a long-term condition of nightmare disorder, which I guess I am going to have to endure for the rest of my life. I am sure that there are other people who are experiencing similar conditions. I am not medically qualified enough to be able to say so, but I am very confident that many of the issues that affect our service personnel in terms of violence among retired veterans and so on and things that might be PTSD may be indeed be Lariam related. I think that it is really important for the Ministry of Defence to understand such issues, because unless we understand the drug and those other issues, we will have no idea how many people are being misdiagnosed and perhaps even mistreated for psychiatric problems and then perhaps administered inappropriate medications when Lariam may be a player behind it that physicians have not recognised.

Indeed, in the case that I was citing—I won't name the name—an individual was casevaced" back from Sierra Leone with a number of conditions, but his behaviours had not actually been reported to the receiving physician back in the UK. Until we get openness and find out, I don't know, but I would be surprised if the figure is less than 25% in an operational situation. I have no idea how many are then disguised in terms of longer-term toxicity.

Trixie Foster: The statistics that I have are that, as of last Friday, there are 85,895 prisoners, and of that figure 6% to 8% are veterans. We know that they are now being asked by people in our group if they have taken Lariam, and it is very evident that a lot of them were given Lariam. I think that it is a great concern that they might have been condemned because of effects that could be from Lariam.

Dr Nevin: The prevalence or incidence of long-term side effects requires study. I hope that this is something that militaries around the world will commit to studying, because military populations are the best populations in which to study this question.

The Danes—the Scandinavians actually—have done some work on this. They looked at the long-term follow-up of travellers who had reported side effects from mefloquine. Of a small case series of 42 who had reported cognitive dysfunction initially, 14 were still reporting that over three years after taking the drug. Forty-three people had reported nightmares, and nine were still reporting nightmares over three years after use of the drug. That makes sense, because mefloquine is a neuro-toxicant. Unlike the other anti-malarials that we have been discussing that have side effects, only mefloquine is neurotoxic. Neurotoxicity is very, very different and requires us to examine these side effects in a different light. The US military did research, as early as 2006, on the neurotoxicity of mefloquine in animals, administering high doses, admittedly, of mefloquine to animals. It showed these remarkable areas of damage to the brain stems of animals given the drug. There is no reason to believe that the same effect is not occurring in some people suffering from the side effects of mefloquine. We are dealing with long-term neurotoxic injury in many cases. The question that remains is: is mefloquine neurotoxic only to some or is it like lead—an exposure for which there is no safe lower limit? Is every military service member who took mefloquine potentially at some increased risk of psychiatric and neuro-degenerative problems in the coming years? That question will require much research to settle.

Dr Croft: Ruth Smeeth has now left, but her question was: what, roughly, is the prevalence of neuro-psychiatric disorders in military users of mefloquine? I conducted two successive randomised control trials—double blinded trials—of mefloquine in British soldiers in Kenya 20 years ago in 1995. We looked at this exact question. We compared mefloquine with the pre-existing standard regimen of chloroquine and proguanil. The mefloquine users did not know that they were taking mefloquine; they were just taking Drug A. In those trials, we found that about a third of the mefloquine users reported no side effects at all. They were quite happy with it. About a third had very minor side effects that might or might not have been related to the trial, and about a third had very severe side effects, which interfered with their daily life and were intolerable.

What was especially worrying was that in the second trial, which I conducted in a very rigorous way to try to ensure that soldiers were actually taking the drugs, there were two extreme, unpredictable events. One soldier became psychotic and had to be flown back to

the UK. We reported that in *The Lancet* on 3 February 1996. Another soldier committed suicide as the trial was ending. By that time, I had been taken off the trial and sent to Bosnia. I did not find out about it until quite a long time afterwards. That seemed to be related to mefloquine because he was also taking it. That is a really worrying aspect. This drug has a level of background traffic noise, as all drugs have, but it has the potential to cause extreme, unpredictable, completely out-of-character events such as psychoses, violence and disciplinary offences in soldiers who often have unblemished records. As that cannot be predicted in any way, it is especially inappropriate for the military.

Q122 Chair: Just as a matter of fact, what would happen if a member of the armed forces, having heard this hearing and the descriptions of the possible dangers, were to turn around and say, when issued with Lariam, “Sorry sir, I don’t wish to take this. I think it’s too dangerous”? Can anyone throw any light on what would happen to a serving soldier under those circumstances?

Lieutenant Colonel Marriott: A lot would depend on the unit. It would also depend on the rank of the individual. The further down the ranks you go, the less likely it is that he is will protest.

Q123 Chair: No, but let’s assume that he does.

Lieutenant Colonel Marriott: Assuming that he does, I think that peer pressure, NCO pressure and officer pressure will be far too great and he will be told, “You will take it.” It is very unlikely that he would have any right of appeal. Indeed, as you go further up the chain, it is unlikely that a leader will not take it. He will say, “Look, watch me. I’ll take it—no side effects. The rest of you follow on.” There will be all sorts of pressures to prevent him from doing it. I suspect that, were he to put his head above the parapet, he would probably be seen as a troublemaker and an irritant, and would be perhaps discarded from the operation or pressured into taking the drug.

Q124 Chair: I just wondered about what would happen if somebody were sufficiently obstreperous or, one might say, courageous to simply say, “No sir, I’m not going to take this. I’ve heard too much about it.” Would that be a chargeable offence in military terms?

Johnny Mercer: You can be charged with a self-inflicted injury.

Dr Croft: Yes, but in reality they just throw it into the bushes. If they find it, they throw it away and they risk getting malaria.

Q125 Douglas Chapman: Thank you for giving evidence today. We have talked about the side effects of Lariam and that is well documented, but in what way are the side effects exacerbated by the fact that it has been taken by people who are in a military setting? What is so special about that that makes it a much more dangerous drug to administer?

Dr Nevin: This is in reference to the prodromal symptoms that I discussed earlier. The SPC, the product documentation that Roche discussed, makes it very clear that the drug must be discontinued at the onset of any psychiatric symptom. So, with the onset of insomnia, vivid dreams, mild anxiety or mild depression the drug must be discontinued because these symptoms could be the only warning of the developing intoxication—the developing neuro-toxic reaction.

Of course, in military settings there are many reasons why someone may develop insomnia, nightmares, anxiety, so it is very tempting for military clinicians who are individual service members to misattribute potentially these symptoms to the situation, to their deployment, to the stresses of traveller combat and not to the drug. The danger is that if a service member misattributes their symptoms of insomnia, for example, to travel and not to the drug, they may continue taking mefloquine, contrary to the product insert guidance. And if they have a personal susceptibility, the drug may accumulate to what we think are neuro-toxic levels and they risk the more serious event that is alluded to in the product insert, which we think is neuro-toxicity and the risk of permanent disability. The risk is confounding. The particular use of mefloquine in military settings risks confounding the prodromal symptoms for situational stresses.

Lieutenant Colonel Marriott: I would endorse that. Perhaps I could also say that I have deployed to practically all parts of the world on operations and exercises. Sierra Leone is the only area where I have served personally and in among a population that has been taking Lariam. The behaviours that I witnessed within that group—I would not say they were unique, things like confusion, acts of violence, loss of temper and so on—the prevalence among what was quite a small team, only about 100 to 120, was quite remarkable. While you may have had things like interrupted sleep, confusion and so on in other operational theatres in the Middle East, the Balkans and Northern Ireland, they were tiny in comparison with the prevalence that I saw in Sierra Leone. So they are partly the stresses that will cause these sorts of events, but they are in all military deployments and I guess they are exacerbated by Lariam, but that is something that I would cede to the medical experts. But there is a clear coincidence between the use of the drug and a significant peak in these sorts of activities among military personnel.

Dr Croft: I have an observation on that. My own research suggests that in the Army it is the use of alcohol and certain other medications that could precipitate severe Lariam reactions in some users. I published this suggestion and the rationale for it in 2002 with a clinical pharmacologist colleague. After that, the Army very helpfully in 2005 put out an instruction that soldiers taking Lariam were not to drink alcohol at the same time. The same applied to women taking the oral contraceptive pill and other medications that could cause an interaction with mefloquine. After that, it was my impression there were fewer of these extreme reactions such as we have seen frequently in the military. So that is my own suggestion. It is alcohol and other agents like that. Also, soldiers take a lot of anabolic steroids, which, in conjunction with Lariam, tend to cause a bit of difficulty.

Q126 Douglas Chapman: Part of the evidence we received fairly early on was about the alcohol that you mentioned, and we discussed earlier today the advice that is given to serving personnel taking Lariam. Maybe there is a weakness in that advice as it is being prescribed or dispensed. In your experience, at the end of a tour of duty, what advice would be given to serving personnel at that stage? Obviously, if someone is coming back from a tour of duty and they are still taking Lariam in the weeks that follow, are there instructions saying, “Do not go for a beer with the boys, because any Lariam that you are taking may exacerbate your symptoms”? In terms of a duty of care, do you think such instructions might be given?

Dr Croft: You are quite right. When you come back from the tropics, you have to carry on taking Lariam for four weeks. During that time, you are de-kitting, handing in your equipment and going to a few parties. There is a temptation to take alcohol then, even

though you are still taking mefloquine, and I am sure that has caused some problems. In fact, the suicide I mentioned in 2005 seemed to occur at exactly that stage. When he came back from Kenya, it was just before Christmas. He was disordered—more than depressed. By then he was on his 11th tablet of mefloquine and he killed himself. So that could well have been the factor that tipped him over the edge. At that time, we did not know about the possible link to alcohol.

Q127 Douglas Chapman: We have seen the letter from Bolt Burdon Kemp solicitors as part of the evidence. It says that people who were involved in, for example, flight crews and so on, or who may be involved in diving at depth, were almost exempted from using Lariam because of the nature of these drugs. What is specific about these drugs that says you should not be using Lariam at all in these circumstances? Is there any correlation between being a member of service personnel in quite a difficult, stressful situation and the fact that you are diving to a great depth or being in a flight crew?

Lieutenant Colonel Marriott: This is one of the serious anomalies with the Ministry of Defence position. It has long been recognised that Lariam should not be taken by air crew and deep sea divers, but there is a real muddle within the Ministry of Defence as to the various restrictions. There was an answer to a question in the House of Lords about a year ago from the Ministry of Defence, which said that it always follows the safety protocol suggested by the manufacturer. For that reason, Lariam was not used by people piloting aircraft, deep sea divers and also drivers. That is quite astonishing. If you were to say that drivers could not take Lariam—it is contra-indicated—again, it is incompatible with military deployments. Certainly to my knowledge, in 2003 and 2005, everybody in Sierra Leone had to be able to drive. The World Health Organisation—I think for at least 20 years—has been saying that Lariam is contra-indicated in people who operate heavy and dangerous machinery, and yet the MOD says that there is nothing in world knowledge about this drug that suggests it should not be used by people who handle weapons.

Heavy and dangerous machinery—to me—includes weaponry. I cannot understand why all of these various restrictions that apply to the drug have only focused in on air crew and deep sea divers. Deep sea divers are perhaps very irregular users of anti-malarials. In the case of air crew, it is probably a reflection of the very high and stringent safety regulations that exist in the Royal Air Force. They are second to none and they will not take any risks, so maybe that is how it got into the SOPs for the use of these drugs. However, to suggest that the MOD is following the manufacturer's advice regarding the use of the drug is quite incorrect.

Q128 Jim Shannon: Dr Croft, this question is for you. We have been told that if a soldier is told that they are going to Afghanistan or Iraq, they have time beforehand. Most soldiers tell me that they say, "Look, boys. Let's have a wee drink before we go. This is the last time we'll have a beer. We will not get a beer in Afghanistan or Iraq." That is the reality of life for soldiers. When you hand them the Lariam pills to take, who checks to see that the boys do not have a beer before they go or a last blowout with their friends? How realistic is it to say, "Take your Lariam, but do not drink"?

Dr Croft: It is not realistic, not for the military. That is why the drug should not be given to troops, or kept as a last resort or as a third or fourth line. Alcohol is part of life in the military.

Jim Shannon: That is exactly the answer that I thought you would give.

Q129 Douglas Chapman: One final question from me. The MOD has asserted that “there is no evidence that mefloquine causes Post Traumatic Stress Disorder per se.” Is any member of the panel aware of evidence that challenges that view?

Dr Nevin: I have written a few chapters on this with a colleague of mine who is a forensic psychiatrist and was the Army’s former top psychiatrist in the United States. There have been a few well-reported cases of US soldiers developing a reaction to mefloquine that was misdiagnosed as an acute stress reaction or a combat operational stress reaction and who were subsequently assigned a diagnosis of post-traumatic stress disorder.

The symptoms caused by mefloquine intoxication are very similar to those we attribute to post-traumatic stress disorder, so it is plausible that some service members suffering from acute, sub-acute or even lasting chronic effects of mefloquine toxicity might be considered for a diagnosis of post-traumatic stress disorder. In the United States, we have the DSM—the “Diagnostic and Statistical Manual of Mental Disorders”, which is the guidebook for diagnosing mental disorders. The previous edition did not exclude the diagnosis of PTSD if it was due to a drug, but the latest edition—the DSM-5—for some reason specifically excludes assigning the diagnosis if the symptoms could be caused by a drug.

I suspect that that change was made in recognition of the fact that some US service members had been diagnosed with PTSD when what they were suffering from was the chronic effects of mefloquine toxicity. As a reminder, those effects can include nightmares, sleep disturbances, dissociative symptoms, irritability, aggression and many of the other criteria listed in the DSM for a diagnosis of PTSD. I discussed that in two recent chapters, which I would be happy to share with the Committee.

Q130 Chair: Thank you very much. Time is beginning to run on, so I will try to abbreviate some of the remaining questions and will not necessarily request an answer from every member of the panel. Although we have covered a lot of ground, there are a number of things further to discuss. Doctors Croft and Nevin, you have both highlighted instances of murders by military personnel who were taking Lariam, but the MOD states that any link between Lariam and these cases was “discredited at the time” and that the US Department of Defense “found no links” between Lariam use and suicide. How do each of you respond to that?

Dr Croft: There have been a number of extreme violent events going back as far as 1992, when Canadian soldiers in Somalia tortured some local civilians who had broken into their camp. At the time they were taking Lariam, and they were also drinking beer. There was a parliamentary inquiry that decided that Lariam was not a factor. I think that parliamentary inquiry might come to a different conclusion now. There were events in Fort Bragg, where four American servicemen had come back. Three of them had been in Afghanistan taking Lariam. All four of them killed their wives and three of them killed themselves. There was an inquiry as to whether Lariam was involved. The inquiry was conducted by two US Army medical colonels, at least one of whom had been involved in developing Lariam, so naturally they also found that Lariam was not the implicating factor.

More recently there was a major act of homicide in Afghanistan by Staff Sergeant Robert Bales—which you mentioned, Mr Mercer—in February 2012, where he went out at night and killed 16 Afghan civilians. It seems that he may have been taking mefloquine, because

subsequently a report was filed with FDA to say that this individual—or an individual—US serviceman went out and killed 17 people, they said, though in fact it was 16. I have that report here; it is an official report.

Q131 Chair: For the record, that is what—a single paragraph?

Dr Croft: No, it's called "FDA Adverse Event Reporting System: Case ID 8504150". American healthcare providers can write in to the FDA giving examples of adverse reactions to particular drugs. In this case they call the reaction "multiple homicide". The FDA files it and discusses it with the manufacturer and comes out with a recommendation.

This particular notification clearly refers to Staff Sergeant Bales, and it has not been denied by the US military as far as I know. So there is evidence.

Q132 Chair: Dr Nevin, do you have a short comment on that?

Dr Nevin: We know, from post-marketing surveillance studies of reported adverse events, that mefloquine is strongly associated with acts of violence. The same safety signals that led the FDA to issue the boxed warning of permanent neurological effects have identified a strong risk of violence—homicide and other acts of violence directed towards others and the self. That should not be surprising. Roche notes in its product insert that the drug is associated with aggression and the drug is associated with a particular risk of very disturbing, dissociative, manic, confusional psychosis, which may underlie some of the more disturbing acts of violence that we see during acute intoxication.

As well, populations administered the drug—large groups of persons administered the drug—tend to score higher on measures of tension and anger. That is thought to shift the distribution of behaviour so there are more outliers who may commit these extreme events.

From the US experience in particular, with regard to the two events that were discussed, the Fort Bragg investigation of many years ago should be looked at again. The conclusions of that investigation had already been drawn, I think, prior to the team investigating. My co-author Colonel Ritchie was a member of that taskforce. Not to put words in her mouth, but I believe that she would today testify that there was indeed an association, at least in one case, between mefloquine use and homicide.

As for the Bales case, that is very interesting. We do know that Sergeant Bales had taken mefloquine on prior deployments. Bales is an example of a service member who had a documented mental health history and may have been deployed and at risk of being prescribed Methloquine. On his most recent deployment, during which he committed the terrible murders, he was prescribed the safer daily drug doxycycline. Yet at the time of his arrest, US military documents show that that bottle of doxycycline was in his possession unopened. That raises the question, if he was not taking his doxycycline, what medication was he taking? It is known that Sergeant Bales was issued a number of prescription medications by his special forces teammates. So it is entirely within the realm of plausibility that he may have been taking Lariam, but the US military has not confirmed or denied that either way, so it remains speculative.

Q133 Johnny Mercer: Dr Croft, I know you want to speak on this. Regarding your 1997 study in defence of the MOD's policy on Lariam, can you explain the findings of that study and say what persuaded you to come to your current position?

Dr Croft: The study was carried out in 1995. In fact, there were two successive trials. The first one was from January to March, and that was in the 1st Battalion of the Grenadier Guards. The second one was from October to December, and that was in the 1st Battalion of the Princess of Wales's Royal Regiment.

Then, we were really looking at what I call the background noise—the intolerable side effects—that we really didn't know existed. The official line was that this was a really well tolerated drug that had no side effects at all; believe it or not, that's what the experts were saying.

In the first study we were comparing the new regimen with the existing regimen, and we found that they were about the same in terms of intolerability. That was the main finding, although in the mefloquine group three people reported extreme or very severe neuro-psychiatric reactions, compared with only one in the other group. That was of some interest; it was really the headline finding of that study. But a lot of the soldiers were just not taking the drug at all and were not responding to the questionnaire, so it looked as though there was a problem, which wasn't being declared.

That was why I then set up the second study, which was much more rigorously controlled, where we got a 100% response rate to the questionnaires—until I got taken off the study and sent to Bosnia. There, we were trying to really pin down the numbers more succinctly. Indirectly and unexpectedly, we got these two terrible events that occurred really without our knowledge. But the central finding remained the same—that Chloroquine and Proguanil is about as generally intolerable as mefloquine. There is no such thing as a well-tolerated anti-malarial drug; they are all poorly tolerated. But mefloquine has a particular problem of being poorly tolerated in a neuro-psychiatric sense.

Q134 Johnny Mercer: Colonel Marriott and Ms Foster, you have both been collating research on the risks of Lariam. How much of that research has been focused on the military? We hear a lot about how all drugs have side effects; how this is suitable to be used as a last resort; how, in the general civilian arena, travellers going with the FCO, or for leisure, or wherever it may be—we receive advice on that. How much of your work has been specifically focused on the military and the very specific stresses that they will come under, having perhaps been on multiple tours before or conducted operations at that time?

Trixie Foster: Most of the research has been on the military and overall on the different times, such as, from Iraq, 1991—upwards from that. I have also been contacting civilian GPs and you would be amazed how many do not prescribe Lariam. My own GP's surgery has not prescribed Lariam for four years because of the side effects, and if that is known in the civilian world, why are they issuing it when there is stress in the MOD? It just seems ridiculous when, as Andrew has said, they are dealing with tanks, machinery and other things. In the US, they put people under stress with special forces and using night goggles, apparently, is a problem with that. Why are they doing it? That's the main reason I've been doing the research on it.

Lieutenant Colonel Marriott: I think it is probably best to say that my research, as such, is initially based on my own military experience and what I have been able to observe in others and collect anecdotally. It has been informed by military information, but that has largely been from the experience of other nations, because the MOD won't answer any of my questions, and that has been part of the problem since I began to address the issue after retirement. There had been a range of—

Q135 Johnny Mercer: Why does the MOD not answer your questions?

Lieutenant Colonel Marriott: I think it is because no one has actually got the moral courage to recognise that there is a problem. This is something that you will have to elicit from the Ministry of Defence, but you should be aware that the Ministry of Defence has been found to be in breach of the Freedom of Information Act in refusing to answer questions. They have lost letters that I have sent. Letters that had been sent by my MP from the Palace of Westminster to Main Building have been lost. The last letter that I sent to the Ministry of Defence languished for five weeks before it was addressed, and then I got another of these standard Surgeon-General letters—cut and paste, with no signature at the bottom—stating policy. Most of the information that I have garnered has actually been from overseas research, very much from the work that Dr Nevin and his colleagues have been doing, and, more latterly, informed by what has been going on in Australia, because they have a very similar situation unfolding there. Access to data here has been extremely limited.

Chair: Dr Nevin, I know you have to leave us on the dot of 1 o'clock, and we are only going to go a few minutes over, so I am going to ask Douglas Chapman to ask our final questions to you in one go. I would like to take the opportunity, because I know you have to slip away while we wind up with the remaining three witnesses, to thank you once again for the extraordinary trouble you have taken to come along and give evidence today on this important matter. Thank you very much indeed.

Q136 Douglas Chapman: Dr Nevin, you have outlined the position in the United States of America very well indeed, and the change of direction. For yourself and Dr Croft, in your opinion, is there any medical reason why the MOD has come to a different conclusion on the use of Lariam by military personnel? Why are we in this position at the moment? Are there solid medical reasons why Lariam should be used?

Dr Nevin: Thank you. Mr Chairman, I actually can stay a little longer. My flight is a little later this afternoon, so I am happy to stay with the rest of the panel.

Chair: That is appreciated. Thank you.

Dr Nevin: I suppose it is often said that everyone is entitled to their own opinions, but not to their own facts. My sense is that the MOD, in some of its responses, has either misconstrued some of the science or misstated some of the facts. For example, MOD has stated that it is the opinion of the Centers for Disease Control in the United States that all drugs are considered equally suitable. This is not correct; this is a misinterpretation of CDC's position.

In the United States, the Centers for Disease Control publishes the Yellow Book, which contains a chapter describing military personnel as travellers with specific needs. It

includes a section stating very clearly that there should be special considerations for US military deployments. This chapter, in contrast to claims that CDC believes all drugs are equal, states that the “continued routine use of mefloquine” is “less desirable” in military personnel, for the reasons I have described and also, specifically, because “Neuropsychiatric side effects” of mefloquine “may confound the diagnosis and management of post-traumatic stress disorder and traumatic brain injury”. That is a fairly unique consideration in the military.

The Australian military and the US military, on reviewing the evidence, have declared Lariam a drug of last resort, and the most recent statistics show that fewer than 1% of all anti-malarial users in both countries now use mefloquine.

Q137 Chair: What is their drug of first resort?

Dr Nevin: The United States some years ago initially declared doxycycline to be the drug of choice, possibly out of concerns for the high cost of the better-tolerated drug Atovaquone/Proguanil—Malarone. But by 2013, the US military had declared Malarone the drug of choice for all deployments. One reason for that, despite its high cost, might be that to send a US service member overseas is very expensive. It costs between £500,000 and £1 million. So even the cost of the most expensive anti-malarial is just a few thousand dollars—a small fraction of that. It is a false economy, I think, for the US military to have selected the cheaper drug, which is less well tolerated.

Q138 Douglas Chapman: Looking at other international examples as well, is it your belief that, in the way they support their military personnel, other nations are moving more towards the US or the UK approach?

Dr Nevin: The UK military is increasingly isolated among Western militaries in its continued preferential use of Lariam. Many of our Western allies have all but abandoned the use of the drug. The US was not the first to do this—the French were many years ahead of us in forgoing the use of mefloquine—but it is telling, and it is a fact that should not be ignored, that the US military, the military that initially developed mefloquine, has now declared it a drug of last resort, or, in the case of special forces, banned it completely. These decisions were made after reviewing all available evidence, reviewing, particularly, unique military circumstances, which apply, I think, fairly equally among all militaries. So why the UK MOD is continuing to use mefloquine preferentially in certain deployment settings is something of a mystery.

Dr Croft: Yes, I concur with that entirely. We have already touched on some of the other reasons why the Ministry of Defence might be adopting this seemingly wholly irrational, illogical and unethical position. There is another consideration we have not really gone into, which is that in the British Army, this is a problem in primary care. mefloquine does not feature in hospitals; it is primary care doctors who are giving it out, Many regiments do not have their own regimental medical officers now; they rely on sessional civilian general practitioners who come and go and there is not the continuity of care. They do not know the soldiers like the RMOs used to; like I did when I was an RMO.

Furthermore, Army primary care has been organised since 2000—it used not to be—into a district-wide service. In each district there is a regional clinical director who is a senior RAMC officer, but usually they are not doctors but medical administrators—occasionally

a nurse or maybe a pharmacist, but not doctors. They have never prescribed; they do not really understand this issue, because it is complex. I had experience of this when I was in a district and this issue was raised with the regional clinical director. He just said, “Well, the Surgeon-General says the troops have got to take Lariam, so—”. That was his answer. The problem is that the service is being administered by people who do not understand science in the complex manner in which this topic needs to be understood.

Chair: I have one question each from Jim Shannon, Johnny Mercer and myself and then I will invite our witnesses to have the final word if there is anything else they feel they would like to add.

Q139 Jim Shannon: This is more of a statement than a question, because you have all answered our questions very well this morning. Our inquiry is to do with the Ministry of Defence and its use of Lariam within the forces. A Member of Parliament, a good friend of all of us here, Jeremy Lefroy, the hon. Member for Stafford, gave an example in Parliament just two weeks ago in an answer to a question from me to the Minister of Defence. In a very personal contribution, he said he had used Lariam—when he was in Tanzania—and it had a very profound side effect upon him. Knowing him as I do, he would have used it exactly to the lines that were agreed and it had an effect upon him. If it had that effect upon someone in civilian life who used it right, it would have an effect all the more so upon our service personnel.

Dr Croft: Yes.

Q140 Johnny Mercer: May I ask briefly about the science? People like me cannot really argue with science; we are not clever enough. I was a soldier until 18 months ago, but you are very much specialists in this field. People come and give us evidence and we then take that evidence and draw conclusions. One of the key strands of evidence is that there are some areas in the world where only mefloquine will work to provide defence. Is that true?

Dr Croft: No.

Dr Nevin: Oh, no. This is an unfortunate occurrence that seems to have emerged from these hearings. Some of the documents I have reviewed from MOD allude to this idea that there are certain drugs, not naming the drug, that are more or less effective in certain areas. We should be perfectly clear that Lariam, or mefloquine, is not the most effective drug. There is no area of the world where mefloquine is, or should be, the preferred drug. There are vast areas of the globe where there is resistance to Lariam. Contrast that with the other two medications that are commonly used—doxycycline and Malarone. There is no resistance anywhere to doxycycline, and that drug can be administered for deployments worldwide, beginning a few days prior to deployment. The drug is fairly well tolerated. Similarly, there is no reliable, widespread report of resistance to Malarone anywhere. For many reasons, Malarone is the preferred drug for short-notice deployments, particularly to highly endemic areas such as Africa. The US military has considered this issue very carefully and, beginning in 2011, issued a series of escalating policy documents describing the rationale for the preferred use of Malarone over mefloquine. We have good, empiric evidence of it being a better drug.

You may recall the disastrous US military mission to Liberia over a decade ago—I believe it was in 2003—where just a few hundred marines deployed ashore on short notice. Within

a few days, many dozens became ill with malaria. The reason was that they were simply not taking their mefloquine, as they should not have been, because many had been experiencing the prodromal symptoms, which require the drug's discontinuation. They didn't feel comfortable admitting that to their officers so, when asked, they claimed that they had simply forgotten. Having spoken to a few of those marines retrospectively, we know that they just didn't take it because they knew it made them ill. Contrast that disastrous experience with the recent, very successful mission to Liberia, where many thousands of our forces deployed to the exact same location and stayed many months. At the latest count, there were only five cases of malaria among US forces, which I believe is in part because we were using the safer and better tolerated drug, Malarone, over mefloquine.

Q141 Chair: Thank you very much. Mine is the last question, and it is to Dr Croft. In responding to that, you may add any final remarks. I will then move along the panel.

Dr Croft, you drew our attention to an article that you had published in *The Pharmaceutical Journal* on 12 November, and I propose to have a link to that article put on the bottom of the transcript of this session on our website. A section in that article refers to three “specious arguments,” as you describe them. I want to concentrate on argument 2. You say that the Ministry of Defence use this argument, and I have seen for myself that they do use it. You quote them as saying: “Malaria is a life-threatening disease and strong drugs are needed to prevent it; inevitably, these have side effects”. You then comment on the fact that, as we have heard today, “mefloquine causes neuro-psychiatric illness, and doxycycline and Malarone, on the whole, do not. The British National Formulary lists 27 neuro-psychiatric side effects linked with mefloquine, seven linked with Malarone, and two linked with doxycycline.”

You then make this comment, upon which I would like you to expand: “Malaria, in any event, is easily diagnosed and treated, and its risk to soldiers has been overstated by successive Surgeons-Generals. No soldier has died of malaria recently. Even before mefloquine's adoption, no British soldier had died from malaria for at least 20 years.” I want to be quite clear about that. For 20 years before the Ministry of Defence was prescribing this controversial drug, no British soldier had died from malaria.

Dr Croft: Yes, I think that is the case. I wrote an article with two military colleagues about 12 or 15 years ago, and we looked back at deaths due to cases of malaria, which were very rigorously recorded at one time on a special database—they are not recorded very well at all now, because we are dispersed into the NHS—but we could not find a case of death in a soldier. There had been two deaths in Air Force personnel round about that time—one was on holiday and one had been in Cambodia where his regime had changed—but no soldier had died. For the Ministry of Defence to keep saying that it is a life-threatening risk to soldiers seems to be overstating the risk and this Committee is all about the balance of risk, isn't? It is life threatening if the diagnosis is missed for any reason, but the diagnosis is not going to be missed in the Army, because as an Army doctor, you are always thinking about malaria. Nowadays, there are very simple bedside kits that can be used to detect malaria very quickly. It is a test you would do immediately on a soldier presenting with a fever who is ill in the tropics and you immediately give them the treatment that will cure them.

Q142 Chair: Thank you. Any other final comments?

Dr Croft: Yes, I have a final comment, and it might be of interest to Mr Mercer. The Army and the military generally are relying on reservists more and more—I'm sure you all know that. Let's say there is a deployment in a few weeks' time and Mr Mercer was called out and told to report to the reservists mobilisation centre in Chilwell in Nottinghamshire. You would have a two-week quick re-induction and you would be told that in two weeks' time you were going to east Africa where there is a training base for Middle East operations.

They would ask you there, maybe, "We are going to give you Lariam. Have you got any mental illnesses?" but they would not have access to your medical records—your civilian GP record—because it takes ages for civilian GPs to produce that. Lariam is potentially going to be given to reservists where there is no possibility that a proper assessment, as is required, can be carried out. Even if that assessment was a guarantee that the individual would not get a neuro-psychiatric reaction—and there is never a guarantee—it is just not going to be possible for reservists. So again, it is not a drug for the military, because the military includes both Regulars, where they do have the record and the disciplinary record, and reservists, for whom the medical record is a great unknown.

Trixie Foster: The MOD relies a lot on the King's Centre for Military Health Research to submit papers on PTSD and alcohol. Since 1998 to 2015, over 425 publications have been done and 85% have been either written or co-authored by Professor Neil Greenberg and Professor Sir Simon Wessely. Only two, as far as I could see, by Dominic Murphy, have mentioned mefloquine—nothing. I have been in contact with Professor Neil Greenberg and had an email back to say that pharmaceutical research is not on their to-do list. So they are not even considering the idea that mefloquine or any other vaccinations have anything to do with this.

Q143 Chair: I think that, out of courtesy to that centre, we will alert them to your comments and invite them to write in if they wish to respond.

Trixie Foster: Yes.

Dr Nevin: I would like to make one comment. I know much has been made by the Surgeon-General of the recent paper published in the Journal of Travel Medicine. I will merely point out that I recently submitted a letter describing some methodological scientific concerns with how this study was conducted. The editors have accepted my letter for publication and I will be happy to share it with the Committee, outlining the reasons why I think some of the recommendations of this paper should be taken with a grain of salt, given the poor quality evidence on which they are based.

I am also somewhat concerned from an ethical perspective that the UK MOD intends, apparently, to conduct a large tolerability study, seemingly intentionally enrolling, possibly, hundreds or even thousands more UK service members to take mefloquine in a head-to-head comparison with Malarone. I would argue that many more studies of mefloquine need to be done, but not these types of studies. We know very well how mefloquine is tolerated in comparison to Malarone and to other drugs. We have all the information we need in that regard. I don't think it is ethical to expose many hundreds of servicemen, or more, to the risks of mefloquine to conduct what might be, judging by this most recent paper, a poor-quality study. I hope that the Committee will pay some attention to that and also possibly work to encourage proper scientific research into this field.

Q144 Chair: Thank you very much indeed. Finally, Lieutenant Colonel Marriott.

Lieutenant Colonel Marriott: Thank you. I want to address a few issues, if I may. First, I want to reinforce the point that Dr Croft was making about the overstating of the malaria threat. I mentioned earlier that after I arrived in Sierra Leone my team medic was casevaced home with malaria. In fact, when he got home it was actually diagnosed as Lassa fever and not malaria at all.

I have also had a very similar experience to Trixie Foster. I have looked through a lot of the recent investigations from organisations such as King's College London, where there have been examinations of veterans' behaviour and violence, and the absence of Lariam as a causative effect is outstanding. It strikes me as odd that there is a lack of institutional curiosity about Lariam as a causative factor in these sorts of behaviours.

Finally, as well as the issues of Lariam, I would hope that an outcome of this investigation will be a realisation that if people inside the Ministry of Defence, or serving soldiers, or medical officers, recognise that there is a problem, it should be addressed at the earliest opportunity. I think we have had something like 10 or 12 years-worth of opportunities to address this. Significant numbers of personnel need not have been put at risk. That process, if you like—this idea of the duty of care—should not be dismissed. Too much of the MOD response has been to regard people like us as a bit of a nuisance. I find that a little disappointing, given my own background, but also given the background of other people who have presented. Otherwise, thank you very much.

Chair: Speaking for the Committee, I think the MOD probably regards us as a bit of a nuisance as well, but we certainly don't regard witnesses as a nuisance at all. On the contrary, it would be impossible to proceed without such comprehensive testimony. I thank you all once again. I wish you a safe journey home, Dr Nevin; it was tremendous of you to cross the Atlantic for this session. With that, I close the meeting.