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Self-reported health of Australian Defence Force personnel after use of anti-malarial drugs on deployment

The University of Queensland | School of Public Health

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Contents

Summary	4
1. Introduction	
1.1 Study overview.....	5
1.2 Research questions	5
1.3 Anti-malarial use on Bougainville, Solomon Islands and East Timor deployments	6
1.4 Reported adverse reactions to anti-malarial drugs	6
1.5 Literature on mefloquine and long-term health outcomes.....	8
1.6 The present study	9
2. Methods	
2.1 Data sources and analyses	10
2.2 Participants	13
3. Results	
3.1 Self-reported reactions to anti-malarial drugs on deployment.....	15
3.2 Associations between use of anti-malarial drugs and mental health outcomes.....	16
Mefloquine.....	16
Primaquine.....	18
3.4 Associations between use of anti-malarial drugs and physical health outcomes	19
Mefloquine.....	19
Primaquine.....	22
3.5 Open-ended question responses about anti-malarial drugs	23
3.6 Descriptive findings from the Solomon Islands Health Study.....	25
4. Discussion	
4.1 Summary of findings	27
4.2 Interpretation of findings.....	28
4.3 Comparison with similar research	29
4.4 Strengths and limitations	29
4.5 Discussion summary.....	30
References	31

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Statement of ethical approval

This study received ethical approval from the Departments of Defence and Veterans' Affairs Human Research Ethics Committee [026-18]

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Summary

- The Department of Defence and the Department of Veterans' Affairs commissioned The University of Queensland to use data from 2007/8 studies of deployment to East Timor, Bougainville and the Solomon Islands to investigate the issue of anti-malarial drugs and long-term health.
- This report presents the results of a descriptive analysis of self-reported anti-malarial drug use on deployment and self-reported physical and mental health. The analysis focused on the East Timor and Bougainville studies.
- Sixty-six military members who deployed to East Timor reported mefloquine use, and 27 members who deployed to Bougainville reported mefloquine use. The self-reported health of these members was compared with members who did not take mefloquine.
- Twenty per cent of these East Timor veterans, and 11% of these Bougainville veterans who used mefloquine reported that they had a significant reaction to this drug. Between 4 and 5% of veterans who used doxycycline reported having a significant reaction.
- East Timor and Bougainville veterans who used mefloquine on deployment reported more symptoms of psychological distress than those who used other drugs. However, the average differences observed were below the threshold of clinical significance and based on a small sample size in the mefloquine group.
- Bougainville veterans who used mefloquine on deployment were more likely to report poorer general health and more general health symptoms than veterans who did not use mefloquine. However, these associations were not observed in the East Timor study.
- Fifty-seven respondents (1.6%) to the East Timor and Bougainville studies mentioned use of anti-malarial drugs as an area of concern in response to open-ended questions.
- There was no clear association between doxycycline or primaquine use and self-reported physical or mental health in the analyses undertaken.
- The results presented in this report should be interpreted with caution due to the small sample size of mefloquine users included in the analysis, and the cross-sectional design of the studies.

1. Introduction

1.1 Study overview

In August 2017, the Repatriation Medical Authority (RMA) released the results of an investigation into chemically acquired brain injury caused by the anti-malarial drugs mefloquine, tafenoquine and primaquine [1]. These drugs have been used by Australian Defence Force (ADF) personnel on deployments and there is concern among some veterans about their long-term health effects. The RMA investigation concluded that there is insufficient sound-medical-scientific evidence that exposure to these drugs can cause chronic brain injury. However, the RMA noted that the clinical trials used to assess the safety of these drugs did not include longer term follow-up of participants.

The present study is the first to investigate associations between different types of anti-malarial drugs used by ADF personnel and health status several years after use. The Department of Defence and Department of Veterans' Affairs (DVA) commissioned The University of Queensland (UQ) to use data from published health studies of ADF deployments to Bougainville, Solomon Islands and East Timor to investigate such associations. These cross-sectional, self-report, survey studies, undertaken in 2007 and 2008, asked respondents to name what anti-malarial drugs they used on deployment and any reactions they had to them, and to complete a number of validated measures of current general and mental health. Respondents could also answer open-ended questions.

This descriptive analysis will present self-reported reactions to anti-malarial drugs and examine associations between the use of mefloquine, primaquine and doxycycline and self-reported physical and mental health. Associations with tafenoquine will not be examined in this study as the number of study respondents who reported that they took this drug was too low to permit proper investigation.

1.2 Research questions

1. Did deployed veterans report a significant reaction to anti-malarial drugs received during their deployment?
2. Did deployed veterans who reported taking mefloquine during their deployment have different rates of mental health outcomes compared to veterans who reported taking doxycycline, or other anti-malarial drugs?
3. Did deployed veterans who reported taking mefloquine during their deployment have different rates of general health outcomes compared to veterans who reported taking doxycycline, or other anti-malarial drugs?
4. Did deployed veterans who reported taking primaquine on return to Australia have different rates of mental health outcomes compared to veterans who reported they did not take primaquine on return to Australia?
5. Did deployed veterans who reported taking primaquine on return to Australia have different rates of general health outcomes compared to veterans who reported they did not take primaquine on return to Australia?
6. Did deployed veterans mention previous use of anti-malarial drugs as an area of concern in response to open-ended questions, and what was the nature of these responses?

1.3 Anti-malarial use on Bougainville, Solomon Islands and East Timor deployments

Deployments to Bougainville commenced in November 1997 and concluded in August 2003. Deployments to East Timor commenced in June 1999 and concluded in March 2013, with the bulk of personnel deployed over 1999 to 2002. Deployments to the Solomon Islands commenced in November 2000 and concluded in August 2013.

Malaria is endemic in each of these locations. Deployed personnel were therefore required to take pre-exposure and post-exposure prophylactic drugs to reduce the chance of infection. Doxycycline was the pre-exposure prophylactic and primaquine the post-exposure prophylactic used by the majority of personnel on these deployments. Personnel who were intolerant to doxycycline were prescribed mefloquine (with a small number prescribed Malarone (atovaquone/proguanil) or chloroquine).

During the Bougainville and East Timor deployments, mefloquine and a then experimental anti-malarial called tafenoquine were tested by the Australian Army Malaria Institute to determine their efficacy, tolerability and safety. Tafenoquine was trialled for both pre-exposure and post exposure prophylaxis (i.e. for both prevention and eradication). Details about the trials of these drugs is shown in Table 1.

Table 1. Details on anti-malarial drug trials with ADF personnel

	Timeframe	Deployment	Trial drug	n	Comparator	n	Reference
1	Nov 1998 – Sept 1999	Bougainville	Tafenoquine	378	Primaquine	214	[2]
2	Feb 1999 – Apr 2000	East Timor	Tafenoquine	636	Primaquine	289	[3]
3	Oct 2000 – Apr 2001	East Timor	Tafenoquine	492	Mefloquine	162	[4]
4	Apr 2001 – May 2002	East Timor	Mefloquine	1157	Doxycycline	388	[5]

As shown in the Table, mefloquine was only examined in the trials that occurred in East Timor. Therefore the only personnel who took mefloquine during the Bougainville or Solomon Islands deployments were likely to be intolerant to doxycycline. The number of personnel who took mefloquine on each deployment location because they were intolerant to doxycycline is unknown. The Department of Defence states that centralised medicines dispensing information has only been available in the ADF since 2000 [6]; records show that, outside of the trials, 94 personnel were prescribed mefloquine in 2001, 77 in 2002, 69 in 2003, 67 in 2004 and 73 in 2005, with the numbers generally falling each year to 20 in 2013 [7].

1.4 Reported adverse reactions to anti-malarial drugs

Reports from clinical trials, survey studies and case studies have detailed adverse reactions to anti-malarial drugs. These reports feed into the product inserts that are produced by the drug's manufacturer to inform consumers about potential side effects and their reported frequency. Details on adverse reactions to anti-malarial drugs are available in a summarised form in the Australian Medicines Handbook and these are shown in Table 2.

Table 2. Adverse reactions associated with Doxycycline, Mefloquine and Primaquine¹

Doxycycline
Common (>1%) Nausea, vomiting, diarrhoea, epigastric burning, tooth discolouration, enamel dysplasia, photosensitivity
Infrequent (0.1-1%) Rash, stomatitis, bone deformity, fungal overgrowth
Mefloquine
Common (>1%) Nausea, vomiting, diarrhoea, abdominal pain, headache, vertigo, dizziness (dose-dependent), somnolence, sleep disorders (insomnia, abnormal dreams)
Infrequent (0.1-1%) Rash, myalgia, dyspnoea, sensory and motor neuropathies, visual disturbances, elevated liver enzyme concentrations, chest pain, tachycardia, asymptomatic bradycardia, neuropsychiatric disorders ² , seizures
Primaquine
Common (>1%) Abdominal pain, nausea and vomiting, dizziness, headache, leucocytosis
Infrequent (0.1-1%) Methaemoglobinaemia

¹ [8-10]² "Disorders such as anxiety, panic attacks, agitation, aggression, acute psychosis, depression, forgetfulness, encephalopathy, can occur and may be prolonged"

Information on adverse reactions to anti-malarial drugs in Australia is also available from the Therapeutic Goods Administration (TGA). The TGA maintain a Database of Adverse Event Notifications for Medicines that contains reports that are voluntarily provided by members of the public and health professionals and mandatory reports of serious adverse events provided by drug manufacturers [11]. The TGA uses this database to identify when a safety issue may be present; however, an adverse event report does not mean that the medicine is the cause of the event. Table 3 shows reported adverse events associated with mefloquine, doxycycline and primaquine.

Table 3. Top 10 adverse events reported to the TGA for doxycycline, mefloquine and primaquine¹

Doxycycline ²		Mefloquine ³		Primaquine ⁴	
Reaction term	Cases	Reaction term	Cases	Reaction term	Cases
Photosensitivity	150	Depression	55	Methaemoglobinaemia	15
Rash	136	Dizziness	53	Headache	5
Pruritus	130	Nausea	52	Diarrhoea	5
Nausea	114	Anxiety	51	Abdominal pain	4
Urticaria	90	Headache	29	Nausea	4
Rash maculo-papular	72	Nightmare	28	Fatigue	4
Rash erythematous	68	Insomnia	24	Pruritus	4
Vomiting	67	Agitation	22	Tinnitus	4
Diarrhoea	60	Abdominal pain	19	Cyanosis	4
Abdominal pain	58	Diarrhoea	17	Rash	3

¹ [12-14]² First report 11/1972, most recent 04/2018 ³ First report 01/1990, most recent 05/2018 ⁴ First report 07/1973, most recent 04/2016

Adverse reactions to the anti-malarial drugs trialled with ADF personnel are reported in the published papers about the trials. Table 4, constructed from a table provided in the paper describing trial 4 (East Timor, refer to Table 1), shows the adverse events self-reported by soldiers who took mefloquine or doxycycline. Adverse event reporting is expected to be higher in studies as adverse events are specifically asked for, whereas reports from general population surveillance rely on individuals making a voluntary report.

Table 4. Most commonly reported adverse events by soldiers who took Mefloquine (n=536) or Doxycycline (n=388) in a clinical trial¹

Adverse event	Mefloquine n (%)	Doxycycline n (%)
Sleep disturbance	161 (30.4)	83 (21.4)
Nausea	112 (20.9)	83 (21.4)
Tiredness	92 (17.5)	95 (24.5)
Headache	71 (13.2)	69 (17.8)

¹ Constructed from [5] Kitchener, S.J., et al 2005

Adverse events to tafenoquine and mefloquine in trial 3 (East Timor, refer to Table 1) that were attributed to use of these drugs (reported adverse events that have been determined by a medical professional to most likely have been caused by the drug used) were presented in a Table in the paper that described this trial – this Table is shown in Figure 1.

Adverse event	No. (%) of patients in treatment group	
	Tafenoquine (n = 492)	Mefloquine (n = 162)
At least one AE	66 (13.4)	19 (11.7)
Nausea	14 (2.8)	4 (2.5)
Vertigo	10 (2.0)	2 (1.2)
Diarrhea	9 (1.8)	3 (1.9)
Abdominal pain	7 (1.4)	2 (1.2)
Abnormal dreaming	6 (1.2)	1 (0.6)
Somnolence	6 (1.2)	1 (0.6)
Headache	3 (0.6)	2 (1.2)
Insomnia	3 (0.6)	2 (1.2)

^a Events occurring in >1% of subjects are shown. AE, adverse event.

Figure 1. Table 5 from [4]. Nasveld, P.E., et al 2010

1.5 Literature on mefloquine and long-term health outcomes

Long-term health is defined here as health outcomes several years after use of mefloquine. Two population studies (published in 2015 and 2018) examined the long-term health of people who have taken mefloquine. The 2015 study [15] examined health in people who had had an adverse reaction to mefloquine and the 2018 study [16] compared the health of a group of people who had taken mefloquine with those who received other anti-malarial drugs.

Ringqvist and colleagues looked at the health of civilians who had reported adverse reactions to mefloquine to a Danish National Register [15]. Seventy-three people who had reported an adverse reaction between January 1996 and August 2000 were followed up in September-November 2000 with a questionnaire. The mean time span from onset of adverse reactions to filling out a questionnaire was 2.7 years. Among other measures, the respondents completed subscales from the Short-Form-36 (SF-36), a self-report measure of current general and mental health [17]. The study found that people who had adverse reactions to mefloquine had worse long-term mental health outcomes, as measured by the SF-36, compared to matched controls.

The subscales that were statistically significantly lower ($p < 0.01$) were 'vitality', 'role emotional' and 'mental health'. The vitality subscale asks questions about energy and fatigue (e.g. Did you feel worn out?) in the past four weeks on a six-item Likert scale that ranges from 'none of the time' to 'all of the time'. The role emotional subscale asks if emotional problems had an impact (yes or no) on work and daily activities in the past four weeks (e.g. accomplished less than you would like). The mental health subscale asks questions about emotional state (e.g. how much of the time have you felt downhearted and blue) in the past four weeks on the same Likert scale as for the vitality subscale.

No difference was found between the mefloquine group and the matched controls on the physical health subscale of the SF-36. In discussing their findings, the authors hypothesised that the adverse reactions to mefloquine may have signified a stressful life event that could have increased the risk of long-term poorer mental health.

Schneiderman and colleagues conducted a survey of US military personnel who deployed to the Middle East between 2001 and 2008 to examine associations between anti-malarial drug use and health outcomes [16]. Survey data was collected from 2009 to 2011—one to ten years after the deployments. From 3,435 respondents who could name the anti-malarial drug they received, 23.3% reported using mefloquine (alone or with other anti-malarial drugs).

The respondents completed the Short-Form-12, the Post-Traumatic Stress Disorder Checklist (both detailed in section 2.1 of this report) and the Patient Health Questionnaire, an instrument that screens for common mental disorders by asking questions about being bothered by problems in the past two weeks (e.g. little interest or pleasure in doing things), scored on a 4-item Likert scale. Having adjusted for combat exposure, no significant associations between the use of mefloquine and adverse mental and physical health outcomes were found.

1.6 The present study

In this report we will undertake a descriptive analysis of anti-malarial drug use and the self-reported physical and mental health of study respondents. Each study asked specific questions about anti-malarial drug use on deployment and also collected free-text information where respondents could highlight health concerns.

This study is a secondary exploratory analysis of data collected in 2007-2008, as opposed to a new study specifically designed and powered to assess the association between anti-malarial drug use and health outcomes. We are limited to the datasets available and have not recruited any new participants or sourced any new survey responses as part of this project. As such, for some of the comparisons presented, the number of respondents who reported taking a specific anti-malarial medication may be small, and the comparisons made may have low statistical power to detect a difference in self-reported health.

The original studies were designed to compare the health of deployed personnel to a comparison group of non-deployed personnel. The analyses presented will focus solely on the deployed groups who responded to questions regarding anti-malarial drug use on deployment.

2. Methods

2.1 Data sources and analyses

This study uses de-identified data from the Bougainville, Solomon Islands and East Timor Deployment Health Studies conducted by the then Centre for Military and Veterans' Health. The original study reports were published in 2009 and are available on the Department of Defence website [18-20]. The analysis presented focusses on the deployed groups in each study who completed questions on anti-malarial drug use. The original survey response rates in the deployed arm of these studies were 46% for East Timor, 49% for Bougainville and 45% for Solomon Islands.

The study surveys were completed in 2007 or 2008, approximately four to ten years after the Bougainville deployments, three to seven years after the Solomon Islands deployments that were investigated in the study, and two to eight years after the investigated East Timor deployments. Questions about anti-malarial drug use, physical and mental health measures and open-ended questions were identical across the three studies.

Reported use of anti-malarial drugs

The questions shown in Figure 2 determined who took which antimalarial drugs for their deployment and whether they changed from one drug to another. The analysis of reported use is detailed in the following section (2.2).

Did you take tablets to protect you against malaria on your deployment to East Timor?

No Yes Don't know

If Yes,

a. Which antimalarial did you use mostly?

Doxycycline (Doxy) Mefloquine (Lariam)

Malarone Other

Don't Know

b. Did you change antimalarial drug?

Yes No

If yes, what to?

Doxycycline (Doxy) Mefloquine (Lariam)

Malarone Other

Don't Know

Did you use primaquine on return to Australia (post exposure antimalarial drug)?

No Yes Don't know

Figure 2. Questions in the Bougainville, Solomon Islands and East Timor Health Studies on use of anti-malarial drugs on deployment

Reactions to anti-malarial drugs

Data were analysed from the participants' responses to the three survey questions shown in Figure 3.

- Q17. Did you have a significant reaction to any vaccinations or medications that you received for your deployment? [Tick boxes No; Yes; Don't know]
- a. Which vaccination(s) or medication(s) did you react to? Please specify [Open-ended text box]
- b. Did you seek medical advice for this reaction? [Tick boxes Yes; No]

Figure 3. Questions in the Bougainville, Solomon Islands and East Timor Health Studies about reactions to health countermeasures

In response to Question 17a, participants either:

- named a specific vaccination or medication;
- named a specific vaccination or medication and detailed the reaction; or
- detailed a reaction but did not name a specific vaccination or medication

Descriptive statistics are presented on the number of respondents who reported a reaction to doxycycline, mefloquine and primaquine and the type of reactions that were reported. In this question, a 'significant reaction' (Figure 3) was not defined in the questionnaire, so respondents decided for themselves which reactions were significant.

Use of anti-malarial drugs and mental health outcomes

Mental health outcomes for this analysis are defined as psychological distress as measured by the Kessler-10 (K10) and symptoms of post-traumatic stress disorder as measured by the Post-Traumatic Stress Disorder Checklist – Civilian Version (PCL-C). The K10 is a 10-item scientifically validated instrument designed to produce a measure of an individual's global level of psychological distress [21]. Individuals rate their level of anxiety and depressive symptoms during the preceding four weeks by reporting the frequency of each experience on a five-point scale ranging from 'all of the time' to 'none of the time'. An example of the questions is 'About how often did you feel depressed?'

The PCL-C is a scientifically validated checklist designed to produce a measure of the symptoms of PTSD that are identified in the Diagnostic and Statistical Manual of Mental Disorders [22]. Individuals rate how much they have been bothered by a problem in the past month by checking a five-point Likert scale ranging from 'not at all' to 'extremely'. An example is 'Trouble falling or staying asleep'. While a military version of the PCL is available, the civilian version is more commonly used in research.

Linear regression models were used to compare the mean scale scores of the K10 and PCL-C between those who took different types of anti-malarial drugs and those who did not, and between the type of anti-malarial drug used 'mostly'. When comparing mean scale score we were interested in whether there was a statistically significant difference and whether the difference was clinically significant. Clinical significance is defined as a change which has a noticeable effect on daily life [23]. In the context of treatment of patients, an improvement of over 6.73 points [24] on the K10 scale, and 10 points on the PCL-C scale [25], have been proposed as clinically significant differences.

Logistic regression models were used to compare the proportion who scored above recommended screening cut-off scores on the K10 (≥ 25) and PCL-C (≥ 29). In the Health and Wellbeing Study of the ADF, a cut-off of 25 on the K10 score corresponded to 30 day ICD-10 affective disorder as measured by the Composite International Diagnostic Interview (CIDI), and using a cut-off of 29 on the PCL-C scale would detect 79% of cases with ICD-10 PTSD [26].

Use of anti-malarial drugs and physical health outcomes

The 12-Item Short Form Health Survey (SF-12) (Ware et al. 2002) is a 12-item scientifically validated survey designed to produce a measure of physical and mental health. The first question, SF-1, is an overview question that asks respondents to rate their health, in general, as either excellent; very good; good; fair or poor. The percentage who reported their health to be 'fair' or 'poor' was compared between groups who used different anti-malarial drugs, using logistic regression.

A 67 item symptom checklist was adapted from the Australian Gulf War Veteran Health Study [27] and the Operation TELIC study of UK Gulf War veterans [28]. Logistic regression was used to compare the prevalence of five individual symptoms known to be adverse effects of mefloquine use (sleeping difficulties, headaches, distressing dreams, nausea and dizziness) [13]. The mean total number of symptoms, reported in the last month, was also compared between exposure groups using negative binomial regression models.

All statistical models were adjusted for rank (enlisted or officer), sex, age (20-29, 30-39, 40+) and Service (Navy, Army, Air Force). The models which assessed self-reported mental health were also adjusted for stressful or combat exposures on deployment. If a respondent answered yes to one of the following events: 'saw dead bodies'; 'handled dead bodies'; 'were witness to human degradation and misery on a large scale'; 'were present when a close friend or co-worker was injured or killed'; or 'were present when a loved one was injured or killed', they were recorded as having a 'stressful or combat exposure' on deployment. These self-reported exposures were collected as part of the Traumatic Exposure Scale Revised (TSES-R) [29].

Open-ended question responses about anti-malarial drugs

Open-ended questions in surveys allow for illustration and understanding of responses to closed-ended questions and an identification of issues of importance to respondents that were not covered in closed-ended questions [30, 31]. Specific open-ended questions about anti-malarial drugs were not asked in the CMVH studies. Open-ended questions were asked about 'reasons for medical care on deployment'; 'positive and negative experiences of deployment'; 'traumatic events on deployment'; 'stressful experiences on deployment'; 'military experiences or exposures on deployment'; 'important health concerns' and 'additional comments'. All responses to the survey open-ended questions were read. Thematic analysis (identifying patterns in content) of the responses was performed. Respondent quotes presented in the findings were edited to correct spelling, with punctuation the respondent's own. A respondent number is provided next to the quote to allow for verification (the row number of the response in an Excel spreadsheet and not the respondent's study identification number).

2.2 Participants

The number of participants who responded to questions about anti-malarial drug use on deployment is given in Table 5. The East Timor and Bougainville deployed study groups (n=1519 and n=1884 respectively) were considerably larger than in the Solomon Islands study (n=205). Approximately 3% in each deployment location reported that they did not use anti-malarial drugs. The percentage of respondents who reported that they changed the anti-malarial drug they were using was approximately 5% in East Timor and Bougainville. In all three deployment locations over 80% reported that they took their anti-malarial drugs ‘all of the time’.

Table 5: Use of anti-malarial drugs on each deployment

	East Timor n (%)	Bougainville n (%)	Solomon Islands n (%)
Used anti-malarial drugs on deployment			
Yes	1435 (94.5)	1767 (93.8)	198 (96.6)
No	50 (3.3)	64 (3.4)	6 (2.9)
Don't know	34 (2.2)	53 (2.8)	1 (0.5)
Changed anti-malarial drug			
Yes	55 (5.5)	65 (4.8)	2 (1.1)
No	946 (94.5)	1282 (95.2)	175 (98.9)
Answer not available	434	420	22
Took anti-malarial drugs			
All of the time	852 (85.7)	1188 (88.2)	147 (83.1)
Most of the time	107 (10.8)	105 (7.8)	20 (11.3)
Some of the time	26 (2.6)	37 (2.7)	3 (1.7)
Rarely or never	9 (0.9)	17 (1.3)	7 (4.0)
Answer not available	441	420	22

Table 6 reports the number of respondents who reported using each of the anti-malarial drugs on the three deployments. These totals included the drug they used ‘mostly’ and drugs respondents used if they had to change their medication. In total, 66 of the respondents reported mefloquine use in East Timor and 27 reported using mefloquine in Bougainville. Of the 27 who used mefloquine in Bougainville, 10 (37.0%) had changed to mefloquine after using doxycycline. Of the 66 who used mefloquine in East Timor, 19 (28.8%) had changed to mefloquine after using doxycycline.

Only descriptive findings will be presented from the Solomon Islands Health Study as the number of members who reported use of mefloquine in this study was too low to permit inferential analysis (n=5).

Table 6: Anti-malarial drugs used on deployment

	East Timor (n=1058)	Bougainville (n=1432)	Solomon Islands ¹ (n=205)
Doxycycline	895 (84.6%)	1257 (87.8%)	163 (79.5%)
Mefloquine	66 (6.2%)	27 (1.9%)	5 (2.4%)
Malarone	7 (0.7%)	12 (0.8%)	0
Others	14 (1.3%)	20 (1.4%)	1 (0.5%)

¹ 32/205 did not provide a response to ‘which anti-malarial drug they used ‘mostly’

Primaquine use was reported by approximately 70% of respondents in each of the three surveys (Table 7). Between 10% and 17% did not know whether or not they had used primaquine. Ninety-one per cent of East Timor and Bougainville veterans reported that they took primaquine as directed.

Table 7: Use of primaquine on each deployment

	East Timor n (%)	Bougainville n (%)	Solomon Islands n (%)
Used primaquine			
Yes	1018 (67.2)	1284 (68.6)	143 (70.4)
No	237 (15.6)	301 (16.1)	39 (19.2)
Don't know	260 (17.2)	288 (15.4)	21 (10.3)
Took primaquine			
As directed	648 (91.0)	876 (91.0)	115 (82.7)
Most of the time	49 (6.9)	67 (7.0)	15 (10.8)
Some of the time	8 (1.1)	11 (1.1)	4 (2.8)
Rarely or never	7 (1.0)	9 (0.9)	5 (3.5)
Answer not available	306	321	64

One of the primary comparisons in this report is between those who used doxycycline and those who used mefloquine on deployment. In Table 8, we compare the demographic characteristics of those who took each medication. The statistical models used adjusted for demographic differences between these group by including age, sex, service and rank as independent predictors.

Table 8: Demographic characteristics of respondents who used mefloquine and doxycycline¹

	East Timor		Bougainville	
	Doxycycline	Mefloquine	Doxycycline	Mefloquine
Age at survey				
20-29	110 (12.3%)	14 (21.2%)	74 (5.9%)	1 (3.7%)
30-39	432 (48.3%)	33 (50.0%)	552 (43.9%)	12 (44.4%)
40+	353 (39.4%)	19 (28.8%)	631 (50.2%)	14 (51.9%)
Sex				
Male	792 (88.5%)	58 (87.9%)	1094 (87.0%)	24 (88.9%)
Female	103 (11.5%)	8 (12.1%)	163 (13.0%)	3 (11.1%)
Service				
Navy	79 (8.8%)	1 (1.5%)	218 (17.3%)	3 (11.1%)
Army	721 (80.6%)	63 (95.5%)	974 (77.5%)	24 (88.9%)
RAAF	95 (10.6%)	2 (3.0%)	65 (5.2%)	0
Rank				
Officer	242 (27.0%)	11 (16.7%)	447 (35.6%)	13 (48.1%)
Enlisted	653 (73.0%)	55 (83.3%)	810 (64.4%)	14 (51.9%)
ADF Employment				
Active	749 (83.7%)	56 (84.8%)	1081 (86.0%)	25 (92.6%)
Terminated	146 (16.3%)	10 (15.2%)	176 (14.0%)	2 (7.4%)
Total	895	66	1257	27

¹ Demographics measured at the time of survey response

3. Results

3.1 Self-reported reactions to anti-malarial drugs on deployment

In both East Timor and Bougainville, 'significant reactions' to mefloquine were more frequently reported than 'significant reactions' to doxycycline (19.7% v 5.0%, p=0.0001 and 11.1% v 4.1%, p=0.11) (Table 9). Among those who reported taking primaquine, fewer than two per cent reported a significant reaction to this drug.

Table 9: Self-reported significant reactions to medications received on deployment

	East Timor	Bougainville
<i>Reported significant reactions to:</i>		
Doxycycline	45/897 (5.0%)	52/1257 (4.1%)
Mefloquine	13/66 (19.7%)	3/27 (11.1%)
Primaquine	19/1020 (1.9%)	20/1284 (1.6%)

The types of reactions that respondents associated with their use of anti-malarial drugs are shown in Table 10. Some respondents reported more than one type of reaction and some detailed the duration of their reaction. The majority of respondents sought medical advice for their reaction (doxycycline 64%; mefloquine 62.5%; primaquine 56.4%).

Table 10: Number of respondents who reported a significant reaction to anti-malarial drugs on Bougainville or East Timor deployments and number of particular reactions

Doxycycline n=97 ¹		Mefloquine n=16		Primaquine n=39	
Reaction term	Cases ²	Reaction term	Cases	Reaction term	Cases ³
<i>No description</i>	50	<i>No description</i>	10	<i>No description</i>	22
Photosensitivity	20	Nightmares	3	Nausea/feeling 'ill'	7
Abdominal pain	7	Disturbed sleep	2	Vomiting	4
Vivid dreams	7	Abdominal pain	1	Diarrhoea	2
Heartburn/reflux	6	Motion sickness	1	Fever	2
Nausea	5	Late-onset overheating	1	Nightmares	2
Diarrhoea	3				
Dizziness	2				
Vision problems	2				
Vomiting	2				

¹ Another 14 respondents reported that they reacted to doxycycline, however they had not answered the questions about anti-malarial use. Reactions these respondents reported were diarrhoea, abdominal pain, nausea, prickly heat, shortness of breath, erratic heart beats. One Bougainville Health Study respondent stated: "Doxycycline. We were taking in excess of the recommended dosage and it caused night sweats, vivid dreams and melancholia, bursting into tears for no reason" (R1894).

² 1 case each of aches, amenorrhoea, cough, fever, hallucinations, lethargy, lowered immunity, sore gums.

³ 1 case each of anger, dizziness, flushes, headaches, mouth ulcers, shingles, ulcer.

Two respondents reported a reaction to other anti-malarial drugs. One respondent who reported that they took chloroquine, doxycycline and primaquine stated that chloroquine gave them an upset stomach. One respondent who conveyed that they were "involved in the Primaquine/Etaquine [an earlier name for tafenoquine] anti-malarial study" (R1773), said that etaquine caused them substantial stomach cramping.

Thirty-six respondents detailed a reaction to an anti-malarial drug but did not name which drug they thought was associated with their reaction. Twenty of these respondents reported use of primaquine, 18 doxycycline, five mefloquine, one Malarone (atovaquone/proguanil) and five unspecified anti-malarial drugs.

Of these thirty-six, 14 respondents reported that they reacted to ‘malarial pills/trial malaria drug’, i.e. they did not name a specific anti-malarial drug. These reactions reported included eight cases of vivid dreams, four of nausea, four of photosensitivity, four of aggression, and one case each of abdominal pain, blurring of peripheral vision, calcium deposits in eyes, diarrhoea, headaches, indigestion, intolerance to shellfish, migraines, lethargy and loss of appetite.

3.2 Associations between use of anti-malarial drugs and mental health outcomes

Mefloquine

East Timor

East Timor veterans who used mefloquine reported a mean K10 score 2.1 points higher than those who did not (Table 11). While this difference was statistically significant ($p=0.04$) a two-point difference in K10 scores is not considered to be clinically significant. Similarly, East Timor veterans who used ‘mostly’ mefloquine had a K10 score 3.3 points higher ($p=0.004$) compared to respondents who ‘mostly’ used doxycycline (Table 12). Assessing the proportion who scored ≥ 25 on the K10 scale, those who used ‘mostly’ mefloquine were more likely to score above this cut-off compared to the ‘mostly’ doxycycline group (OR 1.99 (1.01, 3.95), $p=0.05$) (Table 12).

In contrast, there was no evidence of an association between mefloquine use and PCL-C scores in East Timor veterans (Tables 11 and 12).

Table 11: K10 and PCL-C scores in mefloquine users in East Timor

K10	N	Mean (SD)	Adj. Difference 95% CI	p- value	N	K10 \geq 25 n (%)	Adj. Odds Ratio 95% CI	p- value
Used mefloquine	65	19.6 (9.9)	2.10 (0.10, 4.05)	0.04	65	15 (23.1)	1.60 (0.86, 2.99)	0.14
Did not use mefloquine	964	17.3 (7.5)	0 (Reference)		977	157 (16.1)	1 (Reference)	
PCL-C	N	Mean (SD)	Adj. Difference 95% CI	p- value	N	PCL-C \geq 29 n (%)	Adj. Odds Ratio 95% CI	p- value
Used mefloquine	57	29.4 (13.9)	0.77 (-2.65, 4.20)	0.66	62	23 (37.1)	1.17 (0.67, 2.05)	0.57
Did not use mefloquine	940	27.9 (12.4)	0 (Reference)		963	308 (32.0)	1 (Reference)	

¹ Adjusted for combat exposure, rank (enlisted v officer), sex, age (20-29, 30-39, 40+) and Service.

Table 12: K10 and PCL-C scores and anti-malarial drug used ‘mostly’ in East Timor

K10	N	Mean (SD)	Adj. Difference 95% CI	p- value	N	K10 ≥ 25 n (%)	Adj. Odds Ratio 95% CI	p- value
Doxycycline	868	17.3 (7.5)	0 (Reference)		880	144 (16.4)	1 (Reference)	
Mefloquine	47	20.9 (10.7)	3.30 (1.06, 5.54)	0.004	47	13 (27.7)	1.99 (1.01, 3.95)	0.05
Malarone	3	17.7 (8.1)	0.97 (-7.57, 9.52)	0.82	3	1 (33.3)	3.03 (0.27, 34.48)	0.37
Other	12	21.3 (9.3)	3.21 (-1.09, 7.51)	0.14	12	4 (33.3)	2.17 (0.63, 7.47)	0.22
Don't know	57	14.9 (5.7)	-2.46 (-4.76, -0.16)	0.04	54	3 (5.6)	0.32 (0.09, 1.09)	0.07
PCL-C	N	Mean (SD)	Adj. Difference 95% CI	p- value	N	PCL-C ≥ 29 n (%)	Adj. Odds Ratio 95% CI	p- value
Doxycycline	845	28.0 (12.6)	0 (Reference)		868	279 (32.1)	1 (Reference)	
Mefloquine	41	30.0 (13.4)	1.10 (-2.85, 5.05)	0.58	44	18 (40.9)	1.33 (0.70, 2.53)	0.38
Malarone	3	28.3 (12.7)	1.08 (-13.00, 15.17)	0.88	3	1 (33.3)	1.13 (0.10, 12.81)	0.92
Other	11	39.5 (19.1)	10.82 (3.41, 18.21)	0.004	11	6 (54.6)	2.25 (0.67, 7.58)	0.19
Don't know	56	23.8 (8.6)	-4.92 (-8.68, -1.17)	0.01	56	11 (19.6)	0.51 (0.24, 1.05)	0.07

Adjusted for combat exposure, rank (enlisted v officer), sex, age (20-29, 30-39, 40+) and Service.

Bougainville

In Bougainville veterans the mean K10 score was 2.6 points higher in the group who used mefloquine, compared to the group who did not. This result was not statistically significant (p=0.07) (Table 13).

Table 13: K10 and PCL-C scores in mefloquine users in Bougainville

K10	N	Mean (SD)	Adj. Difference 95% CI	p- value	N	K10 ≥ 25 n (%)	Adj. Odds Ratio 95% CI	p- value
Used mefloquine	26	19.7 (7.5)	2.56 (-0.25, 5.37)	0.07	26	4 (15.4)	1.37 (0.46, 4.12)	0.58
Did not use mefloquine	1349	16.7 (7.0)	0 (Reference)		1366	166 (12.2)	1 (Reference)	
PCL-C	N	Mean (SD)	Adj. Difference 95% CI	p- value	N	PCL-C ≥ 29 n (%)	Adj. Odds Ratio 95% CI	p- value
Used mefloquine	23	32.2 (13.6)	3.81 (-0.89, 6.20)	0.11	23	14 (60.9)	3.20 (1.33, 7.70)	0.01
Did not use mefloquine	1301	26.6 (11.2)	0 (Reference)		1335	392 (29.4)	1 (Reference)	

Adjusted for combat exposure, rank (enlisted v officer), sex, age (20-29, 30-39, 40+) and Service.

Respondents who used mefloquine ‘mostly’ also reported a K10 score 4.1 points higher than members who ‘mostly’ used doxycycline (95% CI (0.44, 7.80), p=0.03). Members who used mefloquine ‘mostly’ had greater odds of scoring above 25 on the K10 scale (OR=3.13 (0.95, 10.36)), than those who used doxycycline, although this result was not statistically significant (p=0.06) (Table 14).

Bougainville veterans who used mefloquine ‘mostly’ reported higher PCL-C scores than the doxycycline group indicated by higher mean scores (6.43 95% CI (0.35, 12.50), p=0.03) and greater odds of scoring above the threshold of 29 (OR, 95% CI 3.73 (1.18, 11.80), p=0.03) (Table 14).

Table 14: K10 and PCL-C scores and anti-malarial drug used ‘mostly’ in Bougainville

K10	N	Mean (SD)	Adj. Difference 95% CI ¹	p- value	N	K10 ≥ 25 n (%)	Adj. Odds Ratio 95% CI ¹	p- value
Doxycycline	1198	16.7 (6.9)	0 (Reference)		1213	140 (11.5)	1 (Reference)	
Mefloquine	16	21.0 (8.8)	4.12 (0.44, 7.80)	0.03	16	4 (25.0)	3.13 (0.95, 10.36)	0.06
Malarone	9	17.4 (8.6)	1.26 (-3.33, 5.84)	0.59	10	2 (20.0)	2.06 (0.43, 9.90)	0.37
Other	14	16.9 (10.3)	0.17 (-3.51, 3.86)	0.93	14	2 (14.3)	1.35 (0.29, 6.17)	0.70
Don’t know	79	17.2 (7.7)	0.40 (-1.27, 2.08)	0.64	79	13 (16.5)	1.63 (0.84, 3.16)	0.15
PCL-C	N	Mean (SD)	Adj. Difference 95% CI ¹	p- value	N	PCL-C ≥ 29 n (%)	Adj. Odds Ratio 95% CI ¹	p- value
Doxycycline	1155	26.6 (11.2)	0 (Reference)		1186	350 (29.5)	1 (Reference)	
Mefloquine	14	34.9 (16.0)	6.43 (0.35, 12.50)	0.03	14	9 (64.3)	3.73 (1.18, 11.80)	0.03
Malarone	10	28.4 (11.7)	2.25 (-4.67, 9.17)	0.52	10	4 (40.0)	1.91 (0.52, 7.01)	0.33
Other	12	23.3 (6.8)	-3.01 (-9.33, 3.32)	0.35	12	2 (16.7)	0.50 (0.11, 2.36)	0.38
Don’t know	75	27.9 (12.6)	1.44 (-1.30, 4.19)	0.30	77	25 (32.5)	1.16 (0.68, 1.97)	0.59

Adjusted for combat exposure, rank (enlisted v officer), sex, age (20-29, 30-39, 40+) and Service

Primaquine

There was no evidence of an association between self-reported primaquine use and symptoms of psychological distress or PTSD in either the Bougainville or East Timor studies. Bougainville veterans who used primaquine were less likely to score above 25 on the K10 scale (p=0.01), compared to those who did not, however, this result was not replicated in East Timor veterans (Tables 15 and 16).

Table 15: Primaquine use and K10 scores¹

East Timor	Did not use primaquine	Used primaquine	‘Did not know’
N	229	992	257
Mean (SD)	17.2 (7.2)	17.3 (7.6)	17.4 (7.6)
Adj Difference 95% CI	0 (Reference)	-0.46 (-1.64, 0.73)	-0.18 (-1.54, 1.18)
p-value		0.45	0.79
N	232	1001	259
K10 ≥ 25 n (%)	38 (16.4)	148 (14.8)	39 (15.1)
Adj OR 95% CI	1 (Reference)	0.82 (0.53, 1.28)	0.88 (0.53, 1.48)
p-value		0.38	0.64
Bougainville	Did not use primaquine	Used primaquine	‘Did not know’
N	291	1230	277
Mean (SD)	17.0 (6.7)	16.5 (6.7)	17.1 (7.4)
Adj Difference 95% CI	0 (Reference)	-0.51 (-1.48, 0.47)	0.09 (-1.06, 1.23)
p-value		0.31	0.88
N	293	1249	281
K10 ≥ 25 n (%)	45 (15.4)	136 (10.9)	37 (13.2)
Adj OR 95% CI	1 (Reference)	0.60 (0.40, 0.90)	0.84 (0.52, 1.36)
p-value		0.01	0.47

¹Adjusted for combat exposure, rank (enlisted v officer), sex, age (20-29, 30-39, 40+) and Service.

Table 16: Primaquine use and PCL-C scores¹

East Timor	Did not use primaquine	Used primaquine	'Do not know'
N	226	955	245
Mean (SD)	27.9 (12.8)	27.3 (11.9)	28.2 (12.8)
Adj Difference 95% CI	0 (Reference)	-1.40 (-3.38, 0.57)	-0.39 (-2.66, 1.88)
p-value		0.16	0.74
N	227	998	256
PCL-C ≥ 29 n (%)	70 (30.8)	304 (30.8)	88 (34.4)
Adj OR 95% CI	1 (Reference)	0.89 (0.62, 1.27)	1.08 (0.72, 1.62)
p-value		0.51	0.72
Bougainville	Did not use primaquine	Used primaquine	'Do not know'
N	277	1186	269
Mean (SD)	27.0 (11.3)	26.5 (10.9)	26.7 (11.7)
Adj Difference 95% CI	0 (Reference)	-0.81 (-2.42, 0.80)	-0.23 (-2.11, 1.65)
p-value		0.32	0.81
N	286	1223	275
PCL-C ≥ 29 n (%)	85 (29.7)	363 (29.7)	81 (29.5)
Adj OR 95% CI	1 (Reference)	0.97 (0.71, 1.34)	0.96 (0.66, 1.40)
p-value		0.87	0.84

¹ Adjusted for combat exposure, rank (enlisted v officer), sex, age (20-29, 30-39, 40+) and Service.

3.4 Associations between use of anti-malarial drugs and physical health outcomes

Mefloquine

Veterans who used mefloquine on deployment in East Timor or Bougainville were slightly more likely to report 'fair or poor' general health compared to those who did not. However, these results were not statistically significant (Table 17).

Table 17: Mefloquine use and 'fair or poor' general health

	n	Fair or Poor health n (%)¹	OR 95% CI¹	p-value
East Timor				
Did not use mefloquine	928	199 (21.4)	1 (Reference)	
Used mefloquine	64	17 (26.6)	1.37 (0.76, 2.49)	0.30
Bougainville				
Did not use mefloquine	1296	233 (18.0)	1 (Reference)	
Used mefloquine	26	7 (26.9)	1.80 (0.74, 4.39)	0.19

¹ Adjusted for rank (enlisted v officer), sex, age (20-29, 30-39, 40+) and Service.

Veterans who used mefloquine 'mostly' on deployment in Bougainville were more likely to report 'fair or poor' general health compared to those who used doxycycline. No association between 'mostly' mefloquine use and poor general health was observed in the East Timor study (Table 18).

Table 18: Anti-malarial used mostly and 'fair or poor' general health

	n	Fair or Poor health n (%) ¹	OR 95% CI ¹	p-value
East Timor				
Doxycycline	878	187 (21.3)	1 (Reference)	
Mefloquine	46	13 (28.3)	1.49 (0.76, 2.94)	0.25
Malarone	3	0 (0)		
Other	12	7 (58.3)	4.43 (1.36, 14.44)	0.01
Don't know	56	9 (16.1)	0.45 (0.20, 0.99)	0.05
Bougainville				
Doxycycline	1208	209 (17.3)	1 (Reference)	
Mefloquine	16	6 (37.5)	3.13 (1.11, 8.85)	0.03
Malarone	10	3 (30.0)	2.33 (0.59, 9.28)	0.23
Other	13	2 (15.4)	0.79 (0.17, 3.61)	0.76
Don't know	79	21 (26.6)	1.54 (0.89, 2.68)	0.13

¹ Adjusted for rank (enlisted v officer), sex, age (20-29, 30-39, 40+) and Service.

Veterans who used mefloquine in Bougainville reported more health symptoms than Bougainville veterans who did not use mefloquine (Table 19). There was no association between mefloquine use and the mean number of health symptoms reported in East Timor veterans.

Table 19: Mefloquine use and mean number of health symptoms reported

	n	Mean (Std)	Adjusted ratio of means (95% CI) ¹	p-value
East Timor				
Did not use mefloquine	938	15.6 (12.4)	1 (Reference)	
Used mefloquine	65	16.8 (13.0)	1.05 (0.85, 1.30)	0.63
Bougainville				
Did not use mefloquine	1328	14.7 (11.7)	1 (Reference)	
Used mefloquine	27	21.7 (14.2)	1.47 (1.07, 2.04)	0.02

¹ Adjusted for rank (enlisted v officer), sex, age (20-29, 30-39, 40+) and Service.

Consistent with the results from Table 19, the prevalence of individual health symptoms reported in the previous month was higher in Bougainville veterans who used mefloquine on deployment, compared to those who did not take mefloquine (Figure 4). However, this pattern of reporting more symptoms was not observed in East Timor veterans (Figure 5).

In assessing five symptoms known to be common side-effects of mefloquine use (see Table 3), almost all of these individual symptoms were not significantly higher among mefloquine users. The exception was 'distressing dreams' which was reported more frequently in Bougainville veterans who used mefloquine (Table 20).

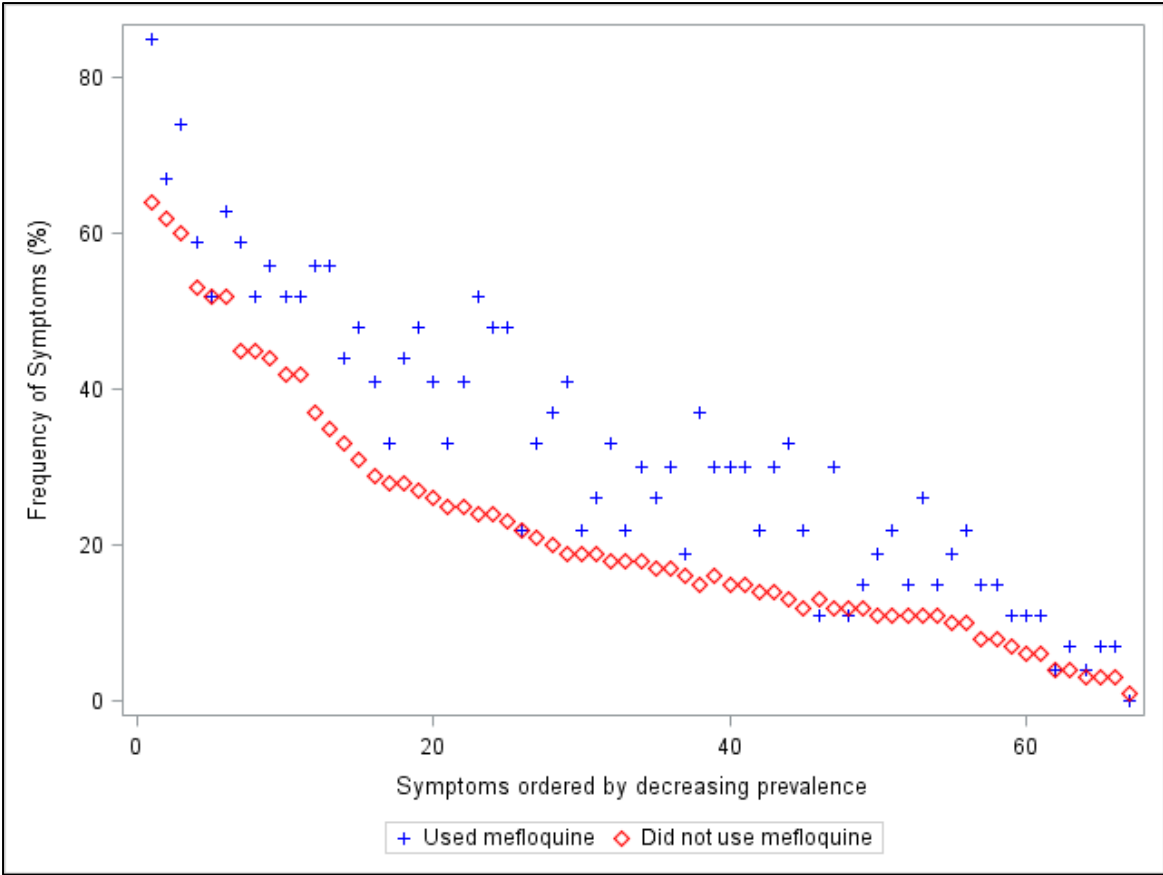


Figure 4: Health symptoms in Bougainville veterans by mefloquine use

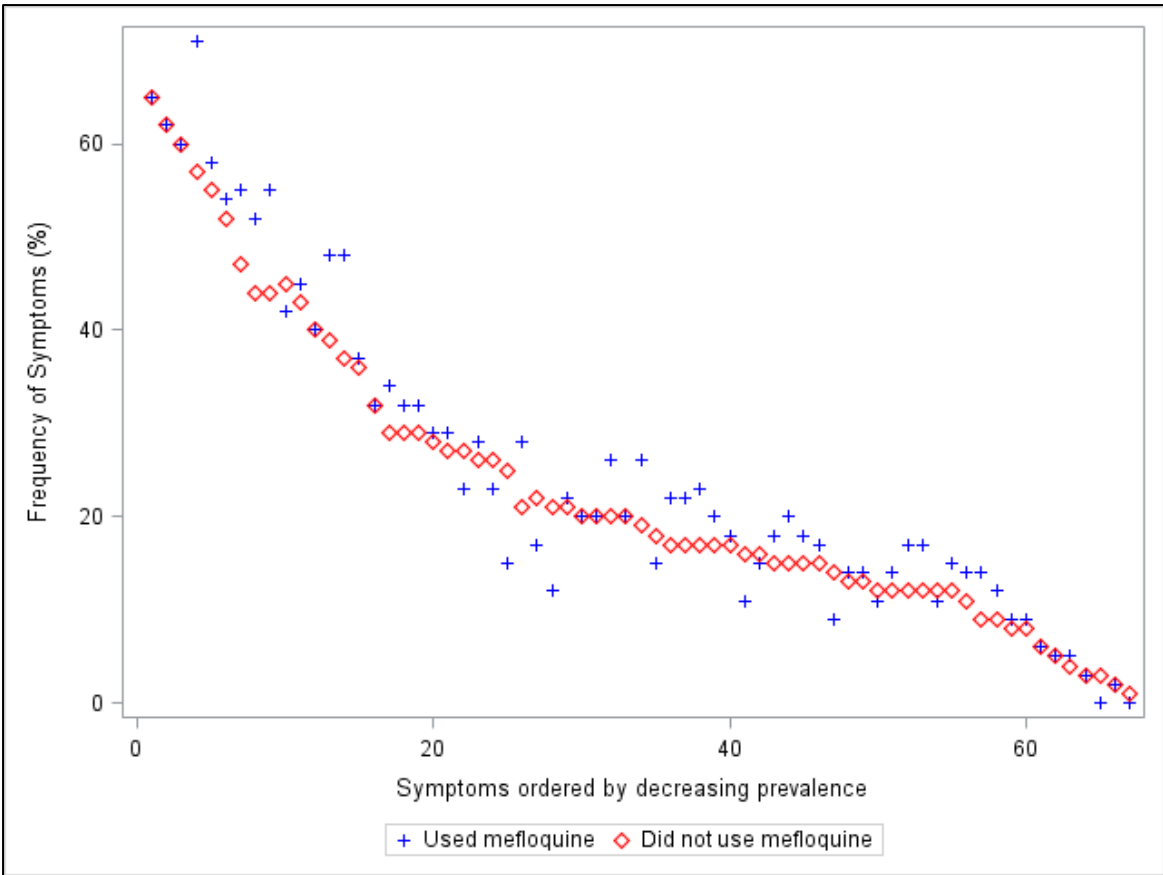


Figure 5: Health symptoms in East Timor veterans by mefloquine use

Table 20: Comparison of selected symptoms by mefloquine use

Symptom	East Timor			Bougainville		
	Mefloquine (n=65)	Non-mefloquine	OR 95% CI ¹	Mefloquine (n=27)	Non-mefloquine (n=1392)	OR 95% CI ¹
Sleeping difficulties	39 (60.0)	596 (60.3)	1.02 (0.60, 1.72)	20 (74.7)	837 (60.1)	1.99 (0.83, 4.77)
Headaches	35 (53.8)	516 (52.2)	1.06 (0.63, 1.76)	14 (51.9)	719 (51.7)	1.10 (0.51, 2.38)
Distressing dreams	19 (29.2)	280 (28.3)	0.99 (0.56, 1.73)	14 (51.9)	332 (23.9)	3.45 (1.60, 7.44)
Nausea	11 (16.9)	113 (11.4)	1.64 (0.82, 3.27)	5 (18.5)	158 (11.4)	1.92 (0.71, 5.20)
Dizziness, fainting or blackouts	11 (16.9)	117 (11.8)	1.42 (0.71, 2.83)	4 (14.8)	159 (11.4)	1.46 (0.49, 4.33)

¹ Adjusted for rank (enlisted v officer), sex, age (20-29, 30-39, 40+) and Service.

Primaquine

There was no association between primaquine use and poorer general health or increased symptom reporting in either Bougainville or East Timor veterans (Table 21 and 22).

Table 21: Primaquine use and 'fair or poor' general health

	n	Fair or Poor health n (%)	OR 95% CI ¹	p-value
East Timor				
Did not use primaquine	234	41 (17.5)	1 (Reference)	
Used primaquine	999	199 (19.9)	1.42 (0.94, 2.15)	0.09
Do not know	255	71 (27.8)	1.80 (1.15, 2.82)	0.01
Bougainville				
Did not use primaquine	292	59 (20.2)	1 (Reference)	
Used primaquine	1242	216 (17.4)	0.94 (0.66, 1.33)	0.71
Do not know	282	58 (20.6)	0.97 (0.65, 1.47)	0.90

¹ Adjusted for rank (enlisted v officer), sex, age (20-29, 30-39, 40+) and Service.

Table 22: Primaquine use and mean number of health symptoms reported

	n	Mean (Std)	Adjusted ratio of means (95% CI) ¹	p-value
East Timor				
Did not use primaquine	236	14.5 (12.0)	1 (Reference)	
Used primaquine	1012	15.3 (12.0)	1.05 (0.92, 1.19)	0.49
Do not know	259	16.2 (12.6)	1.08 (0.93, 1.25)	0.34
Bougainville				
Did not use primaquine	297	14.2 (12.2)	1 (Reference)	
Used primaquine	1272	14.6 (11.5)	1.04 (0.92, 1.17)	0.52
Do not know	286	15.2 (12.2)	1.05 (0.91, 1.21)	0.54

¹ Adjusted for rank (enlisted v officer), sex, age (20-29, 30-39, 40+) and Service.

3.5 Open-ended question responses about anti-malarial drugs

Six open-ended questions, shown in Figure 6, contained responses about anti-malarial drugs.

- Q22. Did you spend one or more nights under medical care during this deployment? If yes, please explain why.
- Q33. During the deployment, what do you consider to have been the major NEGATIVE experiences?
- Q42. Please list any other stressful experiences and fill in which best describes how much stress it caused (3 open-ended fields provided)
- Q48. Are there other important military experiences or exposures we have not asked you about? If yes, please give details in the space provided here.
- Q49. Are there other important health concerns we have not asked you about? If yes, please give details in the space provided here.
- Q50. Do you have any additional comments you would like to add? If yes, please give details in the space provided here or on additional pages.

Figure 6. Open-ended questions in the Bougainville and East Timor Health Studies that contained responses about anti-malarial drugs

Thirty East Timor Health Study respondents and 27 Bougainville Health Study respondents made at least one response about anti-malarial drugs in the open-ended questions. The majority of these responses were negative about the experience of taking these drugs. One respondent, however, provided a positive response and one provided a neutral response (both about the anti-malarial drug trials). Concerning mefloquine and the drug trials that tested mefloquine, 16 respondents conveyed a negative response. Of these 16, six had reported that they took mefloquine, while 10 took other drugs or did not know or answer which drugs they took.

Overall, most of the respondents were concerned with the effect of long-term use of doxycycline and whether symptoms they experienced post-deployment (resolved or ongoing) were related to the use of this drug.

Reason for medical care (n=6)

Three respondents reported spending time in medical care for a reaction to doxycycline. One respondent reported “a bad allergic reaction” with vomiting and indigestion, one had abdominal cramps and one had irregular heartbeats. One respondent conveyed that mefloquine caused them “*bad sleeping, massive mood shifts, altered conscious states*” (R749), while two respondents noted that anti-malarial drugs made them sick (reflux and vomiting, dizziness).

Negative experiences (n=8)

Of six respondents who took doxycycline, three noted that it made them prone to sunburn and had effects on their eyesight. One felt this was a long term effect: “*...the side effects that I have been left with...eyesight has deteriorated ever since Bougainville*” (R647). Two of the six just conveyed that taking the pills was a negative experience, while one believed that their suspected case of Crohn’s Disease was caused by the drug. Two respondents who took mefloquine stated this fact as a negative experience, with one writing: “*LARIUM!!!*” [The trade name for mefloquine] (R749) and the other: “*Trial drugs*” (R1050).

Stressful experiences (n=2)

Respondents R647 and R749 provided similar comments here as they did in the negative experiences questions.

Other military experiences/exposures (n=4)

Two respondents, both of whom didn't answer the question about which anti-malarial prophylaxis they took, stated that questions about the anti-malarial drug trials weren't asked in the survey, with one writing: *"Mefloquine anti-malarial drug effects"* (R633).

One respondent was confused, erroneously, about why they had been taking primaquine when in later deployments 'Primaquine was trialled' (tafenoquine was the trial drug, with primaquine the standard post-exposure prophylaxis as comparator), while another enjoyed the tafenoquine trial and hoped for its success over the *"complicated Primaquine"* (R123).

Other health concerns (n=31)

Fifteen respondents who took doxycycline discussed its impact on health post-deployment. Five respondents questioned 'effects of long-term use of Doxycycline' without elaboration.

Five believed the drug damaged their eyes, with one respondent (who also took mefloquine) stating: *"A study on repercussion of malarial drugs on eyesight should be carried out (R1840)"*. Two respondents felt that doxycycline damaged or had effects on their stomach, one said it caused them long-term sunburn sensitivity, one associated it with unexplained weight gain, and one who developed allergic reactions three years after their Bougainville deployment: *"was told that this could have been caused by being on Doxy"* (R1446).

Four respondents commented negatively on the mefloquine trials—two of these took mefloquine, one took doxycycline and one did not answer the prophylaxis question. Of those who took mefloquine, one associated the anger he felt after his deployment with the drug and noted that it: *"took a while to calm down from this"* (R1046), while the other questioned side effects: *"Trial drugs we were on – we were told there are no side effects – had problems with bowels and eyes and military say it's not from trial drugs"* (R1050). The respondent who took doxycycline wanted to know what happened to those given *"faulty tablets"* (R441) in the trial, while the respondent who did not answer the prophylaxis question felt questions should have been asked about trial side effects:

The questionnaire never addressed using Larium or Mefloquine to treat Malaria in East Timor, or if I experienced any side effects. Considering all the people I have heard with side effects, I think it's a large problem to be left out and possibly it was excluded because the Army does not want to accept liability (R284).

Four respondents (1 doxycycline, 1 mefloquine, 2 prophylaxis questions not answered) just stated the anti-malarial trials as an additional health concern, without elaboration, e.g.: *"Participant in drug trials while deployed"* (R1404).

Two respondents specifically discussed primaquine. One stated that they had: *“Primaquine induced Hepatitis”* (R1495), while the other questioned if it was primaquine that made them sick with appendicitis-like symptoms post-deployment. Of two respondents who took doxycycline but not primaquine in Bougainville, one stated that they had no problems from the tafenoquine trial, while the other stated: *“I believe I have side effects from the antimalaria tablets, I have not taken any action to date but will in the near future”* (R805).

Two respondents mentioned short-term adverse effects from doxycycline, ‘dreams’ in one case, with the other a: *“stomach ulcer due to taking doxy without adequate food whilst on patrol”* (R410).

One respondent who had bouts of dizziness and ‘minor stroke-like symptoms’ post-deployment was uncomfortable with Defence Medical’s response that these symptoms: *“must have been [their] body’s reaction to coming off”* (R600) doxycycline and primaquine. One respondent who did not answer the prophylaxis question but took primaquine stated: *“consequences of long term antimalarial therapy (R715)”* as an additional health concern.

Additional comments (n=7):

Three respondents who took doxycycline and primaquine wondered about the long-term effect of these drugs. One wondered if these drugs were associated with a liver tumour they developed, while another with ongoing issues with Irritable Bowel Syndrome post-deployment wondered if doxycycline was related to long-term digestion issues. The remaining respondent, who noted a PTSD diagnosis, believed: *“long time use of doxy must have a detrimental effect on health”* (R172).

Respondent R749 who stated that mefloquine was a negative and stressful experience of their deployment, expanded on this further here: *“LARIAM PROVED A DISASTER IN MANY RESPECTS TO MY LIFE! (R749)”*. Two other respondents, one who took mefloquine and one who did not answer the prophylaxis question felt that there was ‘not enough information given about anti-malarial drug side effects’. The final respondent (didn’t know which prophylaxis taken), was confused about the outcome of the mefloquine trials and wondered if the ‘trial pill did not work’ or *“worked but was too expensive for the government”* (R1089).

3.6 Descriptive findings from the Solomon Islands Health Study

Two respondents reported that mefloquine was the anti-malarial prophylaxis drug they mostly used during their Solomon Islands deployment/s. One respondent changed from using doxycycline during their deployment to mefloquine as they were found to be ‘allergic to doxycycline’ (respondent’s wording).

Twenty-four respondents reported a reaction to an anti-malarial drug on deployment—20 reactions were to doxycycline, two were to primaquine, one was to mefloquine and one respondent reported a reaction to both doxycycline and primaquine. Six respondents who reported a reaction to doxycycline detailed their reaction and this comprised four instances of ‘Doxy dreams’, one instance of a severe sore stomach and diarrhoea and one instance of tender lymph nodes in the neck. Two respondents detailed their reaction to primaquine and these both comprised upset stomachs/diarrhoea. The

respondent who reported a reaction to mefloquine detailed their reaction as: *“Suspected cause for sleeplessness (MO [medical officer] diagnosis) and cause for heightened aggression now (perceived by self)” (R64)*. Thirteen of the 24 respondents (54.2%) who reported a reaction to an anti-malarial drug sought medical attention for their reaction.

Three participants provided a response about anti-malarial drugs in the survey’s open-ended questions. One respondent who took doxycycline but not primaquine said that anti-malarial medication gave them bad mood swings. This comment was provided in the negative experiences of deployment question. One respondent who took doxycycline discussed their experience with this drug in the traumatic events question. They noted while *“there has been no lasting effect”*, they felt that periods of melancholia and ‘acid dreams’ were side effects of taking the drug.

One respondent who reported that mefloquine was the anti-malarial prophylaxis drug that they mostly used, discussed their concerns about this drug in the additional comments question. Their comment was:

I had no further follow-up initiated or concern raised by Medical Pers [personnel] in relation to issues I experienced (sleeplessness and anxiety) suspected to be side effect from the "Larium" anti-malarial drug. I don't know if anything was ever written on my Med Docs [medical documents] by the Deployment MO [medical officer] to raise concern or whether ADF is still utilising this drug following concerns by Army Pers [personnel] a couple of years [ago] who were placed on a trial program to utilise "Larium" and raised a group concern for the side effects experienced (R64).

4. Discussion

4.1 Summary of findings

1. Did deployed veterans who reported taking mefloquine during their deployment have different rates of mental health outcomes compared to veterans who reported taking Doxycycline, or other anti-malarial drugs?

Yes, there is some evidence that veterans who took mefloquine reported poorer mental health outcomes than those that did not, however the findings were below the level of clinical significance and are based on small numbers of personnel who reported taking mefloquine.

2. Did deployed veterans who reported taking mefloquine during their deployment have different rates of general health outcomes compared to veterans who reported taking doxycycline, or other anti-malarial drugs?

Yes, Bougainville veterans who took mefloquine reported more physical health symptoms than those who did not. The group who used mefloquine 'mostly' in Bougainville were also more likely to report 'fair or poor' general health than those who used doxycycline. These findings were based on a small number of veterans in the mefloquine group (n=27 and n=16 respectively). Among East Timor veterans there was no association between mefloquine use and the mean number of physical health symptoms reported or perceived general health.

3&4. Did deployed veterans who reported taking primaquine on return to Australia have different rates of mental/general health outcomes compared to veterans who reported they did not take primaquine on return to Australia?

No, there is no evidence that veterans who took primaquine had different rates of mental or general health outcomes than those who did not take primaquine.

5. Did deployed veterans report a significant reaction to anti-malarial drugs received during their deployment?

Yes, across the East Timor and Bougainville deployments, 4.5% of doxycycline users reported a reaction to doxycycline, 17.2% of mefloquine users reported a reaction to mefloquine, and 1.7% of primaquine users a reaction to primaquine. The reactions reported were consistent with the reactions reported from population surveillance sources.

6. Did deployed veterans mention previous use of anti-malarial drugs as an area of concern in response to open-ended questions, and what was the nature of responses?

Yes, across the East Timor and Bougainville deployments, a small number of veterans (1.6%, 57 out of 3,338 study responses) mentioned use of anti-malarial drugs as an area of concern in response to open-ended questions. Most respondents were concerned about the health effects of long-term use of doxycycline. Approximately a quarter of these respondents (n=16) provided responses that were negative about mefloquine or the anti-malarial drug trials.

4.2 Interpretation of findings

'Significant reactions' to mefloquine, self-described by the respondents, were reported more frequently than reactions to doxycycline or primaquine. This difference was greatest in the East Timor study where 20% (13/66) of mefloquine users reported side effects. Over half of the reactions to mefloquine described were related to nightmares and disturbed sleep, which are considered 'common' side effects [9]. In contrast, photosensitivity and nausea were the most commonly reported reactions to doxycycline and primaquine respectively, which are also known side effects of each medication [8, 10]. From the questions asked in the study we are unable to determine the duration of these reported side effects, however, between 56% and 64% of respondents sought medical advice for their reaction.

Members who reported that they 'mostly' used mefloquine generally had higher scores on the K10 and PCL-C scales, which measure symptoms of anxiety and depression, and post-traumatic stress respectively. However, these results were not consistently observed. For example, there was no association between using mefloquine and symptoms of PTSD in the East Timor study.

Clinical significance is defined as a change which has a noticeable effect on daily life [23]. While some comparisons showed mefloquine users had a statistically significantly higher mental health scale score compared to other groups, the differences observed were below the levels regarded as 'clinically significant' (K10 > 6.73, PCL-C >10) in studies of treatment and improvement in patients [24, 25]. The analyses undertaken did not show any association between doxycycline or primaquine use and self-reported mental health.

Bougainville veterans who used 'mostly' mefloquine on deployment were more likely to report their health as 'fair or poor' compared to those who used doxycycline (OR 3.13 95% CI (1.11, 8.85)). Bougainville veterans who used mefloquine also reported a higher number of mean health symptoms in the previous month compared to non-mefloquine users. Neither of these results were replicated in the East Timor study.

The reasons for the differences in the results between the East Timor and Bougainville studies is unknown. The numbers who reported changing from using doxycycline to mefloquine were similar in the East Timor (29%) and Bougainville groups (37%). Two trials of anti-malarial drugs that used mefloquine as a trial or comparator drug occurred during the East Timor deployment (mefloquine groups n=162 and n=1157) [4, 5], whereas mefloquine was not used in the tafenoquine trial which occurred in Bougainville [2]. Therefore members who received mefloquine in East Timor may have been more likely to have received this drug as part of a clinical trial compared to Bougainville veterans.

The analysis of open-ended question responses shows that in these 2007 and 2008 studies a small number of respondents (1.6%) raised concerns about anti-malarial drug use. The larger frequency of comments about doxycycline use is understandable given this was the most common anti-malarial drug used. Sixteen respondents in total provided a negative comment about the use of mefloquine or the anti-malarial drug trials. These results document that there was some concern about the use of anti-malarial drugs on deployment and the possible health effects in 2007-2008.

4.3 Comparison with similar research

The percentage of East Timor veterans who reported a 'significant reaction' to mefloquine (19.7%) was lower than the percentages reported to have had a moderate or severe 'adverse reaction' to mefloquine during one of the East Timor trials (30%) [4]. The current study collected this information a number of years after the deployment which may partly explain this difference in percentages.

Unlike the Schneiderman et al study [16], the present study did find some significant associations between adverse long-term mental and physical health outcomes and use of mefloquine. As noted, our findings are based on small numbers of veterans who reported taking mefloquine, whereas the Schneiderman study had an overall sample size of over 19,000 and a total of 346 who reported using mefloquine. Like this US study, the present study found minimal short-term and no long-term adverse health outcomes from the use of primaquine. Both studies used validated scales to measure health outcomes of concern (both used the PCL-C).

A US study of Peace Corps Volunteers found that psychiatric diagnoses were higher in a mefloquine group, but that these results were not replicated when participants with prior psychiatric illness were excluded from the analysis [32]. Eick-Cost et al. also undertook a large study of mefloquine exposure and neuropsychiatric outcomes. This study assessed outcomes for one year before and after a prescription of the drug. Overall this US study did not find an association between mefloquine use and neuropsychiatric diagnoses, but it was noted that mefloquine users with a previous neuropsychiatric diagnosis may be at increased risk of adverse outcomes [33].

The analyses presented in this report were unable to identify or exclude respondents who had a psychiatric illness prior to the deployment due to the cross-sectional design.

4.4 Strengths and limitations

A strength of this study is the time period in which data collection occurred, which was prior to extensive publicity regarding antimalarial drug use in the military. Presently, numerous military member perceptions of experiences with anti-malarial drugs, particularly mefloquine, can be found on social media platforms and in quotes provided to traditional media. A Google News Search performed in September 2018 revealed that sustained media interest in the topic of mefloquine use in the military is evident over the last decade [34].

The data collection for the Bougainville, Solomon Islands and East Timor Health Studies in 2007-2008 largely pre-dates the widespread use of social media platforms and media interest in the topic. Therefore, attributions of adverse reactions to mefloquine and responses to open-ended questions in the studies may be less socially influenced than if they had been obtained today. However, in 2004, a law firm announced plans to launch a class action against the ADF on behalf of Australian soldiers who took mefloquine and this received media attention [35]. An event like this, which predated the data collection for the current study, could have influenced some participant's self-reported responses collected in 2007-2008.

Recall bias may have been a limitation in this study. This study relied on self-reported questions on anti-malarial use and required respondents to recall types of medications taken a number of years

prior. Additionally it was difficult to examine the association between a specific anti-malarial drug and subsequent health, because most respondents reported taking an anti-malarial on deployment (e.g. doxycycline or mefloquine) *and* primaquine on return to Australia. Comparisons are further complicated by the possibility that respondents may have used different anti-malarial drugs on different deployments.

This study was a secondary exploratory analysis of data collected in 2007-2008, as opposed to a new study specifically designed and powered to assess the association between anti-malarial drug use and health outcomes. As such, this study was limited by small numbers of members who reported using mefloquine in each deployment location. As such the study had limited power to detect statistically significant differences between the mefloquine and doxycycline treatment groups, and the results presented are therefore largely descriptive in nature.

The cross-sectional design of the original studies allowed us to investigate associations between different types of anti-malarial use on deployment and self-reported physical and mental health outcomes. The data presented provides a snapshot of associations between anti-malarial use and health in 2007-2008. However, we do not know whether health problems may have predated the deployment or anti-malarial drug use, because the data collected was not longitudinal in design.

While we adjusted for self-reported traumatic exposures on deployment in our assessment of mental health outcomes, there are many other pathways through which a respondents' health may be affected by a military deployment (e.g. deployment stressors, injury on deployment, living conditions, exposure to environmental hazards) [36]. While the results presented highlight associations between some types of anti-malarial use and self-reported health, we are unable to investigate causal relationships from the available data due to small numbers and the cross-sectional design.

4.5 Discussion summary

Since 2006 mefloquine has been used as the third-line anti-malarial in the ADF, meaning it is only used when doxycycline or malarone is not available or appropriate [6]. The results presented in this report indicated that mefloquine users in Bougainville reported poorer self-rated health and more general health symptoms than the group who used doxycycline. However, these results were based on a small number of mefloquine users in Bougainville (n=27) and the findings were not replicated in the East Timor group.

It is recommended that any future trials of anti-malarial drug use in the ADF allow for an assessment of both short term and medium-term health following drug administration, as the Repatriation Medical Authority report highlighted that there were comparatively few studies designed to assess possible longer-term effects of anti-malarial drug use [1].

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