Cochrane
Library

Cochrane Database of Systematic Reviews

Mefloquine for preventing malaria in non-immune adult travellers (Review)

Croft AM, Garner P

Croft AM, Garner P.

Mefloquine for preventing malaria in non-immune adult travellers.

Cochrane Database of Systematic Reviews 2000, Issue 4. Art. No.: CD000138.

DOI: 10.1002/14651858.CD000138.pub2.

www.cochranelibrary.com

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	2
OBJECTIVES	3
METHODS	3
RESULTS	5
DISCUSSION	7
AUTHORS' CONCLUSIONS	8
ACKNOWLEDGEMENTS	10
REFERENCES	10
CHARACTERISTICS OF STUDIES	16
DATA AND ANALYSES	25
Analysis 1.1. Comparison 1 Mefloquine versus placebo or no drug, Outcome 1 Smear positive malarial illness.	26
Analysis 1.3. Comparison 1 Mefloquine versus placebo or no drug, Outcome 3 Withdrawal from study.	26
Analysis 1.4. Comparison 1 Mefloquine versus placebo or no drug, Outcome 4 Non-adherence at first assessment.	27
Analysis 1.5. Comparison 1 Mefloquine versus placebo or no drug, Outcome 5 Sleep disturbance.	27
Analysis 2.1. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 1 Smear-positive malarial illness.	28
Analysis 2.3. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 3 Withdrawal from study.	28
Analysis 2.4. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 4 Non-adherence at first assessment.	29
Analysis 2.5. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 5 Depression.	30
Analysis 2.6. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 6 Dreams.	31
Analysis 2.7. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 7 Fatigue.	32
Analysis 2.8. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 8 Headache.	33
Analysis 2.9. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 9 Insomnia.	34
Analysis 2.11. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 11 Abdominal pain.	35
Analysis 2.12. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 12 Anorexia.	36
Analysis 2.13. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 13 Diarrhoea.	37
Analysis 2.14. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 14 Nausea.	38
Analysis 2.15. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 15 Vomiting.	39
Analysis 2.17. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 17 Fever.	39
Analysis 2.18. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 18 Itch.	40
Analysis 2.20. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 20 Any symptom.	41
Analysis 2.21. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 21 Died or hospitalised (non-malaria).	41
ADDITIONAL TABLES	42
FEEDBACK	90
WHAT'S NEW	92
HISTORY	93
DECLARATIONS OF INTEREST	93
SOURCES OF SUPPORT	93
NOTES	94
INDEX TERMS	94

[Intervention Review]

Mefloquine for preventing malaria in non-immune adult travellers

Ashley M Croft¹, Paul Garner²

¹Surgeon General's Department, London, UK. ²International Health Group, Liverpool School of Tropical Medicine, Liverpool, UK

Contact address: Ashley M Croft, Surgeon General's Department, St. Georges's Court (Level 3 - Zone C), 2-12 Bloomsbury Way, London, WC1A 2SH, UK. ashleycroft@doctors.org.uk, Ashley.Croft410@mod.uk.

Editorial group: Cochrane Infectious Diseases Group.

Publication status and date: Unchanged, published in Issue 5, 2019.

Citation: Croft AM, Garner P. Mefloquine for preventing malaria in non-immune adult travellers. *Cochrane Database of Systematic Reviews* 2000, Issue 4. Art. No.: CD000138. DOI: 10.1002/14651858.CD000138.pub2.

Copyright © 2019 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Mefloquine is commonly prescribed to prevent malaria in travellers, and has replaced other drugs because *Plasmodium falciparum* is commonly resistant to them. However, mefloquine may be associated with neuropsychiatric harmful effects.

Objectives

To assess the effects of mefloquine in adult travellers compared to other regimens in relation to episodes of malaria, withdrawal from prophylaxis, and adverse events.

Search methods

We searched the Cochrane Infectious Diseases Group specialized trials register (September 2002), The Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 3, 2002), MEDLINE (1966 to September 2002), EMBASE (1980 to September 2002), LILACS (September 2002), Science Citation Index (1981 to September 2002), and bibliographies in retrieved papers and standard textbooks. We contacted researchers in the subject of malaria chemoprophylaxis, and pharmaceutical companies.

Selection criteria

Randomised trials comparing mefloquine with other standard prophylaxis or placebo in non-immune adult travellers, and in non-travelling volunteers. For adverse events, any published case reports were collected.

Data collection and analysis

We independently assessed trial quality and extracted data. Adverse events from observational studies were categorised by the study type. We also contacted study authors.

Main results

We included 10 trials involving 2750 non-immune adult participants. Five of these were field trials, and of these all were in mainly male soldiers. One trial comparing mefloquine with placebo showed mefloquine prevented malaria episodes in an area of drug resistance (Peto odds ratio 0.04, 95% confidence interval 0.02 to 0.08). Withdrawals in the mefloquine group were consistently higher in four placebo controlled trials (odds ratio 3.56, 95% confidence interval 1.67 to 7.60). In five trials comparing mefloquine with other chemoprophylaxis, no difference in tolerability was detected.

We found 516 published case reports of mefloquine adverse effects. 63 per cent of these published reports involved tourists and business travellers. There were four fatalities attributed to mefloquine.

Authors' conclusions

Mefloquine prevents malaria, but has adverse effects that limit its acceptability. There is evidence from non-randomised studies that mefloquine has potentially harmful effects in tourists and business travellers, and its use needs to be carefully balanced against this. Trials of comparative effects of antimalarial prophylaxis should include episodes of malaria and withdrawal from prophylaxis as outcomes.

PLAIN LANGUAGE SUMMARY

Mefloquine for preventing malaria in non-immune adult travellers

Malaria is a serious infectious disease of the tropics, spread by mosquitoes. Doctors have recommended various antimalaria drugs for travellers to these areas to take regularly to prevent infection. The problem is balancing good protection against the disease with the adverse effects of the drug. Due to some malaria becoming resistant to common drugs, there are fewer options for effective prevention.

Mefloquine is effective in preventing infection when compared to other drugs in areas with high levels of drug resistance, but it has adverse effects, including influences on mood, sleep and mental state. There remains considerable debate about how often these events occur, with a wide range of estimates. It is not disputed that these are true effects, and constrain the acceptability and tolerability of mefloquine for travellers.

BACKGROUND

Travellers and malaria

Malaria is an acute infectious disease of the tropics, spread by mosquitoes. The disease is caused by a protozoan infection of red blood cells with one of four species of the genus *Plasmodium*: *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae* (White 1996). The most severe form of the disease is cerebral malaria, which has a mortality in returned adult travellers of between 2-6 per cent (Murphy 1996).

Adults who do not normally live in malarious countries are at risk of contracting malaria when visiting tropical areas where the disease exists. Such travellers have no acquired immunity to malaria, whereas long-term residents of malaria-endemic regions typically develop partial immunity to the disease. Each year some 20 million people from the United States, and 50 million people from European countries, visit malaria-endemic regions (Koumans 1995, Huzly 1996). Travel specialists generally recommend chemoprophylaxis with an antimalaria drug to these groups, as well as simple measures to avoid mosquito bites.

Doctors recommend one of several chemoprophylactic regimens to travellers, depending on a journey-specific risk assessment, and on the individual traveller's preference. In general, an effective antimalaria drug is one which combines high protection against the parasite with high tolerability (Peto 1986). Drug side effects may

be acceptable in some circumstances, provided that the malaria risk is high, and that the drug adverse effects are temporary and not serious.

Mefloquine

Mefloquine emerged from the US Army's enormous drug discovery programme at the time of the Vietnam War, which between 1963 and 1976 screened over a quarter of a million potential anti-malaria compounds (White 1992). The earliest reported trials of mefloquine were carried out on US prisoners (Trenholme 1975, Clyde 1976).

Mefloquine first became generally available for European travellers in 1985 (Heimgartner 1986). The drug is manufactured by:

1. F Hoffmann-La Roche AG, Switzerland, under the trade name Lariam.
2. Mepha Pharma AG, Switzerland, under the trade name Mephaquin.

Since the late 1980s, mefloquine has become widely recommended for malaria chemoprophylaxis (CDC 1994, CDHSH 1995, WHO 1995, IG 1996, Ingram 1996, May 1996, Bradley 1997, Hatz 1997, Petersen 1997). Mefloquine has now largely replaced earlier chemoprophylactic drugs which, on account of parasite resistance, are no longer considered to be effective against all *Plasmodium* species. Combinations of mefloquine with other an-

timalaria agents have been developed mainly for use in therapy, in an attempt to delay the onset of parasite resistance to this relatively new drug. As well as being used to prevent malaria, mefloquine is also used at higher dosages to treat clinically confirmed malaria, especially that due to *P. falciparum* (White 1996).

The retail price of mefloquine varies from country to country. In general mefloquine is more expensive than alternative chemoprophylaxis (Hollyoak 1995). A course of eight tablets of mefloquine, sufficient for prophylaxis for a two-week package holiday to the tropics, costs approximately £20.00 at current prices (November 2000), compared to £5.00 for an equivalent course of chloroquine + proguanil, and £19 for a course of doxycycline.

As mefloquine is given to well people, doctors formulating national malaria prevention policies need to be confident that the regimen does more good than harm before it can be safely recommended to the public (Woolf 1996). Two studies have been influential in reaching a decision about recommending mefloquine:

- The Steffen study (Steffen 1993). This was a retrospective questionnaire survey of travellers returning to Europe from Kenya. This study reported a high level of tolerance for prophylactic mefloquine. However, some doubts have been raised about the reliability of the study methods and results (Held 1993, Milord 1993, Ingram 1996).
- The Lobel study (Lobel 1993). This was a retrospective questionnaire survey of young, fit, non-travelling US Peace Corps volunteers stationed in west Africa for a 12-month period. This study reported that mefloquine was well-tolerated. However, commentators on the study pointed out that the study population was not necessarily of the normal population of holiday makers and business personnel (Walker 1994), and that in any case, side effects and compliance cannot be verified with accuracy in retrospective surveys (Basco 1994).

The tolerability debate

The reported tolerability of mefloquine prophylaxis has been thrown into question by a series of recent observational studies which have found an excess of neuropsychiatric side effects in general travellers taking mefloquine, compared to travellers taking alternative chemoprophylaxis (Barrett 1996, Corbett 1996, Corominas 1997, Van Riemsdijk 1997, Durrheim 1999, Petersen 2000, Potasman 2000). In addition there are case reports describing neuropsychiatric adverse effects in mefloquine users which persisted for months, and even years (Folkerts 1992, Grupp 1994, Ronn 1994, Meszaros 1996, Heeringa 1998, Jensen 1998, Bygbjerg 1999, Fusetti 1999).

These concerns about the safety of mefloquine have led some experts to dissent from the official endorsement of the drug, and

to recommend that it should not be prescribed at all for malaria prophylaxis (Cook 1995, Perry 1995). The controversy has been particularly acute in the UK, Canada and the Netherlands, and has prompted parliamentary questions and intense media interest (Van Puijenbroek 1995, Choo 1996, Clift 1996, Anonymous 1997, Kondro 1999).

We carried out this systematic review of randomised trials in non-immune adults in order to synthesise current evidence on the effectiveness of mefloquine relative to alternative chemoprophylaxis. This review considers only prophylaxis for the non-immune, and does not address the problems of mass community prophylaxis in malaria-endemic regions.

OBJECTIVES

To evaluate mefloquine chemoprophylaxis in non-immune adult travellers on preventing malarial infection and adverse events.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised trials.

For severe adverse effects, we sought any published report.

Types of participants

Eligible trial participants were adults not immune to malaria who were travelling to endemic malarious regions and were given short-term drug regimens (<12 months) to protect them from malaria infection. Randomised tolerability studies carried out on pre-travel or non-travelling volunteers were also eligible for inclusion.

Types of interventions

Experimental arms: mefloquine, or mefloquine fixed drug combinations.

Control arms: doxycycline hyclate, chloroquine, chloroquine plus proguanil, placebo, no medication.

We excluded studies if either the experimental or control arm comprised a regimen no longer used for prophylaxis in travellers because of severe side effects, such as sulfadoxine-pyrimethamine (Bradley 1985, Miller 1986) and amodiaquine (Hatton 1986, MMWR 1986).

Types of outcome measures

PRIMARY

Malarial illness (confirmed by microscopic examination of blood).
Withdrawal from the study for any reason.

SECONDARY

Adherence at first assessment, in participants remaining in the study.

Self-reported or investigator-elicited symptoms at first assessment, in participants without clinical malaria and remaining in the study.

Any serious adverse events that are fatal, life threatening, or requiring hospitalisation.

Any adverse events that require discontinuation of treatment.

Search methods for identification of studies

TRIALS

Our primary source of trials was the Cochrane Infectious Diseases Group's register of trials. We searched the register up to September 2002. We carried out electronic searches for published trials in MEDLINE (1966 to September 2002), EMBASE (1980 to September 2002) and LILACS (September 2002) using the highly sensitive search strategy outlined in Appendix 5c of the Cochrane Handbook, and the search terms 'malaria' and 'prevention', and 'malaria' and 'prophylaxis'. We did not apply any time restrictions or language constraints.

We checked the Science Citation Index regularly and sought additional published and unpublished trials by:

- Citation tracking of all retrieved reports of chemoprophylaxis trials, review articles on malaria prevention, and standard textbooks of tropical medicine, searching for other relevant references.
- Hand searching two military medical journals from 1945 onwards (Croft 1999a, Hedger 1999). We looked specifically for early published trials of chemoprophylaxis which would not have been routinely indexed on any electronic database.
- Whenever we located a published trial, hand searching the correspondence pages of that same journal for several subsequent issues, to see if any commentator on the trial had referred to similar controlled studies, published or unpublished.
- Approaching drug companies for details of unpublished studies.
- Attending major international meetings, and scanning the conference proceedings of previous meetings.
- Corresponding directly with authors and investigators active in the field of malaria chemoprophylaxis.

We considered that all of the above measures were the minimum necessary to ensure that we had identified the full evidence base for

our systematic review of trials, and hence avoided possible publication bias at the outset (Chalmers 1992, Jadad 1993, Dickersin 1994).

CASE REPORTS

We compiled the database of published case reports of mefloquine adverse effects by:

- Searching MEDLINE between 1966 and July 2000 and EMBASE between 1980 and July 2000. We used the search terms 'meflo*', 'adverse effect*', 'poisoning' and 'toxicity'. We applied no language restrictions.
- Reading the Results section of all previously retrieved mefloquine trials and non-randomised studies, looking for nested case reports. We included only those reports where the authors were confident that the symptoms and signs elicited were causally related to mefloquine use. We carried out citation tracking of these and other relevant review articles.
- Consulting Martindale (Martindale 1999).
- Consulting Meyler's Side Effects of Drugs, and the Side Effects of Drugs Annual (SED 1996, SEDA 1999).

Data collection and analysis

TRIALS

We entered in the trial register 38 controlled trials of mefloquine prophylaxis.

We retrieved all the original trial reports, then independently applied the selection criteria to all these potentially eligible primary studies. We agreed independently that 10 of the 38 trials were eligible for inclusion in this review. The status of one trial remains undetermined, pending further information. In the event of an unresolved difference of opinion, a third person with no special expertise in the field of malaria chemoprophylaxis would have been approached for a deciding judgement.

To facilitate comparisons of tolerability between mefloquine and other regimens, we analysed three separate categories of symptoms: neuropsychiatric, gastrointestinal and 'other'. For the neuropsychiatric and gastrointestinal categories, we analysed only the five most commonly reported symptoms. These were: depression, dreams, fatigue, headache and insomnia (neuropsychiatric), and abdominal discomfort, anorexia, diarrhoea, nausea and vomiting (gastrointestinal). The two 'other' symptoms we analysed were fever and pruritus.

Some of the studies we identified included objective tests of psychomotor performance and neurobehavioural status. We have summarised these psychometric outcomes as they are described.

In addition to manually extracting data from published versions of the studies, we wrote twice to first authors asking them to supply data on outcomes that they had not reported in print or not reported on fully. Half responded (see the Acknowledgements section of this review). We are unable to assess whether non-response

indicated any bias in the published data by authors or simply reflected other priorities that researchers might have.

CASE REPORTS

We retrieved all the identified case reports of mefloquine adverse effects, and summarised the publication details of the reports in an annotated database, comprising two separate spreadsheets as follows:

- Published case reports of adverse effects from mefloquine prophylaxis.
- Published case reports of adverse effects from mefloquine treatment.

These two spreadsheets are included in this review as Additional Tables. For each table, we pooled incidence data from those studies where both a numerator and a denominator had been given. We were thus able to calculate a median frequency of observed adverse effects in both mefloquine prophylaxis (Table 1) and mefloquine treatment (Table 2).

RESULTS

Description of studies

10 randomised controlled trials of mefloquine chemoprophylaxis met the inclusion criteria (see Table of Characteristics of Included Studies). Two of these are currently unpublished (Croft 1997b, MacPherson 1997). The remaining eight were all published in English. Two studies (Arthur 1990, Croft 1997a) were reported in more than one journal.

The 10 trials represented a total of 2750 non-immune adult participants randomised to mefloquine prophylaxis, or to a control. Five of the trials were carried out as clinical toxicity studies in non-travellers. Five were field studies carried out in military personnel, who were >99 per cent male. The intensity of malaria exposure in these five field trials ranged from nil (Boudreau 1993) to high (Ohrt 1997). Only one trial (Ohrt 1997) yielded microscopically-confirmed cases of malaria.

Risk of bias in included studies

Researchers took adequate measures to conceal allocation in all trials. One trial (Kollaritsch 1997) was unblinded, and the remainder double blind.

Five trials reported an adequate method for generating random assignments. In four of the remaining five trials allocation was described simply as 'randomized'. In one trial (Boudreau 1993) the allocation sequence seemed to have been generated by a method that was non-random but unbiased.

All 10 trials carried out an intention to treat analysis, and had few or no losses to follow up.

Two published trials (Kollaritsch 1997, Ohrt 1997) included detailed reporting of the symptoms experienced by all participants. In the remaining trials, symptom reporting was variable and sometimes incomplete.

Of the ten included studies, four were funded wholly or in part by the manufacturer of mefloquine, and three were funded wholly or in part by the US military (see Table of Characteristics of Included Studies). There was thus, in our view, a potential for the reporting of important trial outcomes, such as dropouts, to be influenced by a commercial and/or an institutional bias. This potential for a bias in the evidence base is discussed further in the next section of this systematic review.

Effects of interventions

Placebo-controlled trials

Five trials compared outcomes between mefloquine and placebo. One trial in non-immune soldiers in Irian Jaya (Ohrt 1997) showed mefloquine to be highly protective (with no malaria cases in 202 person-months of exposure) compared with placebo (53 malaria cases in 109 person-months of exposure).

The four placebo-controlled trials reporting withdrawals showed a tendency for participants taking mefloquine to withdraw from the study. The meta-analysis of this was significant (Chi squared for heterogeneity not significant, Mantel-Haenszel OR based on a fixed effects model 3.56, 95% CI 1.67 to 7.6). The absolute risk of withdrawal, based on pooled withdrawal rates, was 3.3% (95% CI 4.4 to 1.1; using Yates' continuity correction, 95% CI 0.6% to 6%).

Analysis of other outcome measures of tolerability showed no significant pattern in relation to mefloquine or placebo, but the numbers were small.

Trials comparing mefloquine with other regimens

Six trials compared outcomes between mefloquine and alternative chemoprophylaxis. Of these, only one (Ohrt 1997) measured the relative incidence of malaria. Ohrt studied Indonesian soldiers in an area of high malaria transmission, and there were no cases of malaria in the 68 participants taking mefloquine compared with one case in the 67 participants taking doxycycline hyclate (Ohrt 1997). Because of the low incidence and small size of the study, this provides no information about the relative efficacy of the two drugs.

One study (Croft 1997b) sought evidence of recent malaria infection from antibody markers. 6/119 participants in the mefloquine group and 3/121 in the chloroquine-proguanil group showed immunological evidence of recent malaria infection. Again, the relatively low power of the study provided no conclusive evidence

as to whether mefloquine was more efficacious than chloroquine-proguanil in this setting (OR 2.09, 95% CI 0.51 to 8.55).

There was no obvious or significant difference in non-adherence at first assessment in the pooled data across the four studies that measured this outcome (Peto odds ratio 1.04, 95% CI 0.69 to 1.58). Withdrawal was higher in the mefloquine arm in three out of four studies, but the effect was not large and there was no significant difference between the groups if the data are pooled (OR 1.34, 95% CI 0.74 to 2.39), even though the absolute risk of withdrawal was only 0.95% (3.4% - 2.5%, 95% CI -0.89% to 2.6%).

Secondary evidence of tolerability from the outcome category 'reporting any symptom at first assessment' showed an overall incidence of adverse effects from mefloquine prophylaxis that was similar to the overall incidence from other chemoprophylaxis (Peto odds ratio 1.00, 95% CI 0.80 to 1.27).

In relation to neuropsychiatric symptoms, no consistent pattern emerged across the five variables analysed. However mefloquine was more likely to cause insomnia than other standard chemoprophylaxis (Peto odds ratio 1.64, 95% CI 1.18 to 2.28), and was more likely to cause fatigue (Peto odds ratio 1.57, 95% CI 1.01 to 2.45).

In relation to gastrointestinal symptoms, there was again no consistent pattern. Abdominal discomfort appeared to be more frequently reported in alternative regimens (mefloquine: 75/761; alternative regimens: 114/703; Peto odds ratio 0.57, 95% CI 0.42 to 0.77), as did anorexia and nausea. However, there was heterogeneity between trials, and the overall effect appears to be due to one particular study (Croft 1997a), where participants reported these symptoms more frequently in the chloroquine-proguanil group than in the mefloquine group.

The reporting of 'other' symptoms (fever, itch) were similar in the mefloquine and comparator arms.

Psychometric tests on trial participants

Boudreau and colleagues (Boudreau 1993) tested the following:

- Sleep. Sleep and wake cycles were monitored using actigraph recorders. Mefloquine users tended to sleep less (about 20 minutes less per night) than chloroquine users.

Vuurman and colleagues (Vuurman 1996) tested the following:

- Driving performance. Assessed through the standardized Highway Driving Test (HDT), and also the Car Following Test (CFT). The mefloquine group drove significantly better than the placebo group in HDT. There was no significant difference between groups in CFT.

- Postural sway. Measured by the standardized stabilometry method of the International Society of Posturography. Mefloquine and placebo groups showed about the same normal postural instability. After alcohol challenge, relative performance in the mefloquine group improved.

- Psychomotor performance. Assessed through the Critical Flicker/Fusion Frequency (CFF) test, and the Critical Instability Tracking (CIT) test. In both tests there was no significant difference between groups.

Schlagenhauf and colleagues (Schlagenhauf 1997) tested the following:

- Coordination. Simulated cockpit tasks were assessed through the Instrument Coordination Analyzer (ICA). There was no significant difference between the mefloquine and the placebo groups.

- Postural sway. A simplified postural sway meter force plate was used to assess balance. There was no significant difference between groups.

- Psychomotor performance. Assessed through the Neurobehavioural Evaluation System (NES), a battery of tests designed to provide quantitative neurobehavioural outcomes. There was no significant difference between groups.

- Sleep. Sleep and wake cycles were monitored using actigraph recorders. Mefloquine users tended to sleep less (34 minutes less per night) than placebo users.

Annotated database of mefloquine adverse effect reports

1. Published case reports of adverse effects from mefloquine prophylaxis.

We found 328 case reports of mefloquine adverse effects, published as 82 separate papers between 1976-2000. 56 of these papers were in English, and the remainder were in German (8), French (7), Dutch (4), Danish (2), Spanish (2), and Italian, Japanese and Swedish (1 of each). Of the 327 patients reported on, 254 were tourists and 12 were business travellers. The remainder were military (29), long-term residents of the tropics (16), experimental volunteers (12), prisoners (3) and aid workers (2).

2. Published case reports of adverse effects from mefloquine treatment.

We found 188 case reports of mefloquine adverse effects, published as 64 separate papers between 1981-2000. 44 of these papers were in English, and the remainder were in French (11), Danish (3), German (3), Italian (1), Japanese (1) and Spanish (1). Of the 188 patients reported on, 54 were tourists and 4 were business travellers. The remainder were long-term residents of the tropics (115), experimental volunteers (14), and military (1).

In total therefore we found 516 published case reports of mefloquine adverse effects, published from 1976 onwards in 136 separate papers (10 authors reported on prophylaxis and treatment adverse effects in the same paper). Tourists and business travellers comprised 324/516 (63 per cent) of the patients reported on. Although the median frequency was 4.9%, this is difficult to interpret as the estimates were very variable between studies, reflecting different populations, different exposure, and different sensitivity and reliability in detection.

An unexpected finding was that case reports published to date where the authors attributed death to mefloquine (Anonymous 1990, Nosten 1993, McBride 1997, Anonymous 1998). In addition, at least eight other cases are cited in the literature where mefloquine has been associated anecdotally with a fatal reaction (Smith 1999).

DISCUSSION

The 10 trials included in our review were well-designed and carefully executed. There were, however, some differences in the methodological quality of the trials and marked variation in the completeness of reporting of results. Not all trials, for example, included detailed reporting of withdrawals from prophylaxis. This diversity made it difficult at times to extract and synthesise outcomes data.

Our review identified two field trials which assessed the efficacy of mefloquine in preventing malaria. One of these trials (Ohrt 1997) showed an obvious effect of mefloquine in preventing malaria, compared with nothing. Two field trials (Croft 1997a and Croft 1997b) attempted to compare mefloquine efficacy against chloroquine-proguanil, but in the event could not do this as the incidence of clinical malaria in either group was nil.

Five trials assessed the tolerability of mefloquine compared with placebo, and withdrawal was greater in the mefloquine arm. This finding is consistent with anecdotal reports of side effects from mefloquine, but its significance is uncertain as all drugs given for malaria prophylaxis have side effects.

In calculating pooled withdrawal rates as our primary index of drug tolerability we used what is currently considered to be the most valid measure (Greenhalgh 1997). However we differ from some authors of the studies we included, who assessed the tolerability of their different study regimens through statistical tests of variance between a 'basket' of reported symptoms. In our view, this symptom-centred approach lacks objectivity and can result in invalid inferences that are derived from the background 'noise' of low-grade ill-health experienced by ostensibly well trial participants, and not from the pharmacological properties of the trial drugs themselves. Further comparative work is warranted to assess the validity of outcomes reflecting acceptability and tolerability of drugs in well patients.

'Symptom-counting' led some investigators (Boudreau 1993, MacPherson 1997, Ohrt 1997) to assert that the high number of mefloquine dropouts in their studies was unrelated to drug side effects. One investigator (Davis 1996) noted that 11/106 participants withdrew from his study but did not differentiate these dropouts by regimen or by gender, and instead based his analysis of drug tolerability solely on a comparison of 'diary symptoms'. Conclusions of this nature are difficult to validate, and to make

post-hoc judgements on why individuals drop out - thereby possibly excluding side effects as the cause of dropout - does not constitute an appropriate analysis. In trial analysis and in meta-analysis, participants should be analysed by intention to treat.

There is a debate about whether the strong protective effect of mefloquine shown in a trial of military participants can be generalised to tourists and business travellers. Extrapolating reported compliance in soldiers to the general public is difficult, since randomised field comparisons between mefloquine and alternative malaria prophylaxis have been conducted only in the military. We would surmise that adherence in soldiers to chemoprophylaxis tends to be unusually high for all regimens because of the military ethos of obedience to orders. Observational data support this hypothesis. Held et al found that travellers who were part of an organised group were more compliant with their malaria prophylaxis than were solo travellers or businessmen (Held 1994).

It may be that trials in the military actually underestimate the adverse effects of mefloquine and other drugs on the general public. The arguments are:

1. Fit subject effect: generalising tolerability findings in healthy soldiers to the general public (who will commonly have pre-existing illnesses, co-morbidities and concomitant medications) may underestimate the true incidence of these effects. Huzly et al have shown that travellers with chronic disorders are significantly more likely to report side effects from their antimalarials than healthy travellers (Huzly 1996).
2. Gender bias: in the military trials which we included, most participants (>99 per cent) were men. Observational studies in tourists and experimental volunteers have found that women experienced worse adverse effects from mefloquine prophylaxis than men (Weinke 1991, Bem 1992, Barrett 1996, Huzly 1996, Phillips 1996, Schlagenhauf 1996, Handschin 1997, Van Riemsdijk 1997, Kollaritsch 2000, Micheo 2000). Two studies have shown that adult women experience roughly twice as many adverse effects from mefloquine treatment as do adult men (Ter Kuile 1992, Ter Kuile 1995).
3. Age bias: conclusions reached in studies of young people cannot always be generalised to elderly people (Bugeja 1997); around 10 per cent of travellers to the tropics are aged 60 years or above (Steffen 1993, Huzly 1996).
4. Cultural or lifestyle differences between populations: one of the five field trials (Ohrt 1997) was carried out in Indonesian soldiers. There are some observational data to suggest that adverse events from mefloquine are more common in Caucasian and African patients than in Asian patients, though the reasons for this remain obscure (Phillips-Howard 1995, Ter Kuile 1992).
5. Dose effects: data from one observational study suggest that mefloquine is worse tolerated in low weight individuals (Corominas 1997). Trained soldiers are rarely of low body weight,

so that on these grounds also it is likely that their ability to tolerate prophylactic mefloquine is greater than that of civilian travellers.

These potential modifiers could mean that the results of this review systematically underestimate the adverse effects of any drug regimen. If adverse effects are more common with mefloquine, as has been suggested, these factors might explain why these trials did not detect this difference. However, this remains conjecture.

The importance of adverse effects is paramount, for two reasons. Firstly, adverse effects, and reports of them, strongly influence the general public. Secondly, any adverse drug effect may cause the user of that drug to stop his or her medication. Under these circumstances, users of malaria chemoprophylaxis who are at risk of developing malaria are left unprotected. This may mean that regimens that are well tolerated but less efficacious may actually perform better in practice than regimens that are shown to be highly efficacious in carefully controlled trials but which are poorly tolerated under their actual conditions of use.

Psychometric tests on trial participants

We believe that psychometric tests such as those used in some mefloquine trials can help to establish whether or not a prophylactic drug degrades specific technical skills (such as flying or driving), and are helpful for determining whether or not that drug should be taken by certain occupational subsets of travellers. We believe however that the preservation of technical skills while travelling is not an important outcome measure for most tourists or business travellers.

Annotated database of mefloquine adverse effect reports

We identified 516 published case reports of mefloquine adverse effects (including four fatal reactions). Most of these reports were in tourists and business travellers. We see this as indirect evidence of a problem with mefloquine adverse events, with the potential for rare but fatal effects, indicating the need for careful evaluation of risk from disease in those it is prescribed for. In a future update of this systematic review, we will include a detailed analysis of the phenomenology of the adverse effects associated with mefloquine, based on these 516 case reports.

AUTHORS' CONCLUSIONS

Implications for practice

Tolerability is important to travellers, and yet no-one appears to know whether mefloquine is well or poorly tolerated. Many of the standard textbooks of tropical medicine (Strickland 1991, Jernigan 1995, White 1996) assert that mefloquine is well tolerated in prophylaxis and that the only side effects of importance are neuropsychiatric reactions or seizures, experienced by around one in 10,000 users. This much-cited estimate of the frequency of neuropsychiatric side effects from mefloquine is based not on experimental data, but on spontaneous reports of severe adverse events in mefloquine users. As such, the one in 10,000 figure undoubtedly under-estimates the true incidence of undramatic but nevertheless unpleasant side effects from mefloquine (Christ 1991).

The main problem with mefloquine is that its tolerability is a major concern of the public, with questions raised repeatedly in the news media. Yet evidence to reassure the public, or confirm their fears, is not available (Croft 1998).

Despite the higher prophylactic efficacy of mefloquine suggested by one field trial in soldiers (Ohrt 1997), poor tolerability is likely to curtail the effectiveness of the drug in tourists and business travellers. Until the tolerability question is resolved, it would be premature to recommend mefloquine widely to general travellers, outside the context of a randomised controlled trial.

In the absence of this much-needed pivotal study in a heterogeneous travelling population, it can be argued that current research evidence indicates that mefloquine prophylaxis is only demonstrably useful in fit, highly-motivated occupational subgroups or individual travellers at high risk of infection with chloroquine-resistant *P. falciparum*. In our opinion, whilst waiting for the results of appropriate research, travellers who are at a lower risk of infection, and who have prompt access to high quality diagnostic and treatment services, can be given less efficacious regimens that are better tolerated.

On the above basis, we recommend that national malaria advisory bodies should revise their mefloquine prophylaxis advice in the light of experimental evidence, and stratify their recommendations according to high or low assessment of disease risk. This two-tier approach is consistent with the strategy originally recommended by Peto and Gilks for risk minimisation in malaria chemoprophylaxis (Peto 1986), and is in line also with more recent thinking on the need to very carefully balance the benefits and harms of medical interventions in low risk patients (Eddy 1990, Davey Smith 1994, Glasziou 1995).

Both high and low risk groups should be advised about the importance of effective measures to avoid mosquito bites (Croft 2000).

Process of implementing research findings

Process of implementing research findings

The malaria prevention guidelines issued by national advisory bodies differ from country to country, and it seems unlikely that they can all be correct. The lack of reproducibility of these national guidelines was demonstrated by a survey of 5489 European and North American travellers in Kenya, which found that 68 different drug regimens were being used for prophylaxis (Lobel 1990).

This lack of consistency between national malaria prevention guidelines can undermine the credibility of health advice to travellers, should those travellers meet in the course of their journeys and compare prophylaxis regimens. This can be a contributory factor in the lack of adherence to malaria prevention advice.

The controversy surrounding mefloquine demonstrates that at an international level there is a need to ensure that appropriate research is done, and that this research is used to develop valid, evidence-based guidelines on malaria prevention through an appropriately multiprofessional advisory panel. To achieve a balanced appraisal of which recommendations can be supported, and with what degree of certainty, the guideline development process should have the following characteristics:

1. The panel should optimally consist of between six to 10 members (Scott 1990, Woolf 1996). It should include representatives of key disciplines and interest groups (Bond 1995). Panel members need not necessarily have special expertise in the field of malaria prophylaxis, since excessive specialisation within a guidelines panel has been shown to introduce persuasive advocates and other subjectivities, and to act as a source of bias (Anonymous 1992, RCGP 1995, Woolf 1996). The production of any clinical guidelines must involve participants who are representative of the envisaged domain of practice (Leape 1992). Therefore at least one panel member should be a primary care physician (Lobach 1995).
2. Consumers should be represented on the panel (RCGP 1995).
3. The panel should use rigorous and pre-defined criteria for synthesising the best available research evidence (Woolf 1992).
4. The panel should evaluate the evidence base of all antimalaria strategies, i.e. bite avoidance measures, drugs, vaccines and environmental vector control. For each strategy, the strength of the scientific evidence should be quantified explicitly. Where uncertainty exists, this should be stated honestly (Haines 1992, CRD 1996).
5. Drugs should be systematically assessed according to their toxicity, efficacy, tolerability and convenience (Bero 1996, Greenhalgh 1997).
6. The guidelines issued by the panel should be risk-based, in that they should explicitly reflect the association between the degree of benefit resulting from different antimalarial strategies and the level of risk associated with each strategy (Davey Smith 1994).
7. At an early stage of their development, the guidelines should be submitted for scrutiny and comment by topic experts and interested agencies, both local and international (RCGP 1995). There should be a formal dissemination strategy for encouraging these agencies to assume ownership of the final product (AHCPR 1992, Haines 1992).
8. The language of the guidelines should be lucid, and the form and content should be accessible to all users. This can be achieved

by using a structured format, and through judicious use of brief checklists and key summaries (Haines 1992).

9. The guidelines must be continually updated to take account of new scientific evidence, and particularly the results of randomised controlled trials and systematic reviews (Haines 1992, Eccles 1996).

The evidence-based guidelines produced by this multiprofessional international panel should be translated into national recommendations, both internally valid and externally reproducible. These national guidelines should include information on the costs of different chemoprophylactic regimens, and the costs of other preventive strategies (Bero 1996, CRD 1996). The national guidelines should be made available to practitioners in electronic format, both for ease of updating and to act as prompts to good practice (Ornstein 1991, Litzelman 1993, Bargery 1994, Lobach 1995).

Consumers in each country should have ready access to the guidelines, and to a summary of the supporting evidence, so as to be empowered to make informed choices about their own health (RCGP 1995, Jacobson 1997, Liberati 1997).

Implications for research

It is often not possible to make a final risk-benefit assessment of a new drug until several years after marketing and broad clinical experience (Christ 1991). Where patients are healthy to start with, however (as is the case with most travellers), the pre-licensing evaluation of a drug must be as rigorous as possible. The case of mefloquine has shown that where an antimalarial drug which has not been adequately evaluated is recommended to members of the public this will result in avoidable morbidity, costly litigation and unfavourable publicity for the manufacturer of that drug. Poor national guidelines in this area have led to poor clinical practice, and this has undermined trust in the medical profession.

There is an urgent need for a pragmatic, randomised study which will assess the tolerability of mefloquine prophylaxis under field conditions, in a heterogeneous population of non-immune tourists and business travellers (Petersen 1990, Basco 1994, Cobelens 1997, Croft 1999b, Smith 1999). At present, no such trial exists, even though mefloquine prophylaxis has been prescribed to over eight million travellers worldwide (Handschin 1995).

As a lesson for the future, no candidate antimalaria agent should be licensed for routine use in prophylaxis until at least one pragmatic, randomised tolerability study has been carried out in a heterogeneous population of tourists and business travellers. This randomised study should have the following characteristics:

1. It should be of appropriate design and of sufficient power to show that the new compound is well tolerated by the target population under the anticipated conditions of use (Smith 1996).
2. Women, and also elderly travellers, must be well represented in the study population. Because this will introduce increased vari-

ance, the precision of the study estimates will be reduced, necessitating a larger sample or increased duration of drug use to achieve the same study power (Avorn 1997).

3. The study design must ensure that the drug is assessed against an appropriate standard comparator or comparators, and not simply against a different formulation of the drug itself (Henry 1995, Greenhalgh 1997).

4. The trial should be conducted according to a standardised scientific methodology (MacLean 1997), and should be reported completely. The Consolidated Standards of Reporting Trials (CONSORT), developed by an international panel of investigators, epidemiologists, biostatisticians and editors, currently provide the best available guidance on the correct reporting format for randomised controlled trials (Altman 1996, Begg 1996, Schulz 1996).

5. Withdrawals from prophylaxis, and low or non-adherence, should be reported as primary outcomes. The trial report should include a brief description of the patient characteristics, and

elicited symptoms and signs, in each dropout.

The fact that such field trials can be difficult to organise must not be used as an argument against their being attempted in the first place, particularly since amalgamated evidence from many small trials can be of great scientific value (Edwards 1997, Klebanoff 1997).

ACKNOWLEDGEMENTS

We thank Sir Iain Chalmers, Professor David Bradley and Dr Peter Gotzsche who refereed this review for their helpful comments, and Robert Baillie, Roger Brand, Sally Hannant and Sue Prescott for administrative support. We also thank those investigators (Drs Kollaritsch, MacPherson, Schlagenhauf and Vuurman) who responded to our requests for data which they had not previously reported in print.

REFERENCES

References to studies included in this review

Arthur 1990 *{published data only}*

Arthur JD, Echeverria P, Shanks GD, Karwacki J, Bodhidatta L, Brown JE. A comparative study of gastrointestinal infections in United States soldiers receiving doxycycline or mefloquine for malaria chemoprophylaxis. *Am J Trop Med Hyg* 1990;**43**:608–13.
Arthur JD, Shanks GD, Echeverria P. Mefloquine prophylaxis. *Lancet* 1990;**i**:972.

Boudreau 1993 *{published data only}*

Boudreau E, Schuster B, Sanchez J, Novakowski W, Johnson R, Redmond D, et al. Tolerability of prophylactic Lariam regimens. *Trop Med Parasitol* 1993;**44**:257–65.

Croft 1997a *{published and unpublished data}*

Croft AMJ. Toxicity of mefloquine is similar to that of other chemoprophylaxis. *BMJ* 1995;**311**:191.
Croft AMJ, Clayton TC, World MJ. Side effects of mefloquine prophylaxis for malaria: an independent randomized controlled trial. *Trans R Soc Trop Med Hyg* 1997;**91**:199–203.

Croft 1997b *{unpublished data only}*

Croft AMJ, Williams G, Docherty MJ. Mefloquine prophylaxis in British troops in Kenya: a follow-up, independent randomized controlled trial. Unpublished.
Croft AMJ, World MJ. Neuropsychiatric reactions with mefloquine chemoprophylaxis. *Lancet* 1996;**347**:326.

Davis 1996 *{published data only}*

Davis TME, Dembo LG, Kaye-Eddie SA, Hewitt BJ, Hislop RG, Batty KT. Neurological, cardiovascular and metabolic effects of mefloquine in healthy volunteers: a

double-blind, placebo-controlled trial. *Br J Clin Pharmacol* 1996;**42**:415–21.

Kollaritsch 1997 *{published data only}*

Kollaritsch H, Que JU, Kunz C, Wiedermann G, Herzog C, Cryz SJ. Safety and immunogenicity of live oral cholera and typhoid vaccines administered alone or in combination with antimalarial drugs, oral polio vaccine, or yellow fever vaccine. *J Infect Dis* 1997;**175**:871–5.

MacPherson 1997 *{unpublished data only}*

MacPherson D, Gamble K, Tessier D, Keystone J, Streiner D. Mefloquine tolerance: a randomized, double-blinded, placebo-controlled study using a loading dose of mefloquine in pre-exposed travelers. *Proceedings of the Fifth International Conference on Travel Medicine; Mar 24-27; Geneva*. Geneva: International Society of Travel Medicine, 1997.

Ohrt 1997 *{published data only}*

Ohrt C, Richie TL, Widjaja H, Shanks GD, Fitriadi J, Fryauff DJ, et al. Mefloquine compared with doxycycline for the prophylaxis of malaria in Indonesian soldiers. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1997;**126**:963–72.

Schlagenhauf 1997 *{published and unpublished data}*

Schlagenhauf P, Lobel H, Steffen R, Johnson R, Popp K, Tschopp A, et al. Tolerance of mefloquine by Swissair trainee pilots. *Am J Trop Med Hyg* 1997;**56**:235–40.

Vuurman 1996 *{published and unpublished data}*

Vuurman EFPM, Muntjewerff ND, Uiterwijk MMC, van Veggel LMA, Crevoisier C, Haglund L, et al. Effects of mefloquine alone and with alcohol on psychomotor and driving performance. *Eur J Clin Pharmacol* 1996;**50**: 475–82.

References to studies excluded from this review

Boudreau 1991 *{published data only}*

Boudreau EF, Pang LW, Chaikummao S, Witayarat C. Comparison of mefloquine, chloroquine plus pyrimethamine-sulfadoxine (Fansidar), and chloroquine as malarial prophylaxis in eastern Thailand. *Southeast Asian J Trop Med Public Health* 1991;**22**:183–9.

Bunnag 1992 *{published data only}*

Bunnag D, Malikul S, Chittamas S, Chindanon D, Harinasuta T, Fernex M, et al. Fansimef for prophylaxis of malaria: a double-blind randomized placebo-controlled trial. *Southeast Asian J Trop Med Public Health* 1992;**23**: 777–82.

Clyde 1976 *{published data only}*

Clyde DF, McCarthy VC, Miller RM, Hornick RB. Suppressive activity of mefloquine in sporozoite-induced human malaria. *Antimicrob Agents Chemother* 1976;**9**: 384–6.

Danis 1982 *{published data only}*

Danis M, et al. [Place de la mefloquine dans le traitement curatif et preventif du paludisme]. *Pathol Biol* 1982;**30**: 589–92.

Dos Santos 1993 *{published data only}*

Dos Santos JB, Prata A, Wanssa E. [Quimioprofilaxia da malaria com mefloquina na amazonia brasileira]. *Rev Soc Bras Med Trop* 1993;**26**:157–62.

Eamsila 1993 *{published data only}*

Eamsila C, Singharaj P, Yooyen P, Chatnugrob P, Ayuthya ANN, Webster HK, et al. Prevention of Plasmodium falciparum malaria by Fansimef and Lariam in the northeastern part of Thailand. *Southeast Asian J Trop Med Public Health* 1993;**24**:672–6.

Felix 1981 *{published data only}*

Felix H, Richard-Lenoble D, Danis M, Druille P, Brucker G, Gentilini M. [La Mefloquine. Rapport preliminaire]. *Medecine et Maladies Infectieuses* 1981;**11**(6b):392–9.

Heimgartner 1986 *{published data only}*

Heimgartner E. [Praktische Erfahrungen mit Mefloquin als Malariaprophylaktikum]. *Schweiz Rundsch Med Prax* 1986; **75**:459–62.

Kamolratanakul 1989 *{unpublished data only}*

Kamolratanakul P, Viputsiri O, Dhanamun B, Hirunabut S, Meksam A, Thongsawat P. The effectiveness of chemoprophylaxis against malaria for non-immune migrant workers in eastern Thailand. *Trans R Soc Trop Med Hyg* 1989;**83**:313–5.

Kollaritsch 1988 *{published data only}*

Kollaritsch H, Stemberger H, Mailer H, Krensmayr P, Kollaritsch R, Leimer R, et al. Tolerability of long-term malaria prophylaxis with the combination mefloquine + sulfadoxine + pyrimethamine (Fansimef): results of a double blind field trial versus chloroquine in Nigeria. *Trans R Soc Trop Med Hyg* 1988;**82**:524–9.

Leimer 1985a *{published data only}*

Leimer R. Randomized double-blind comparative study of acceptability and tolerability of the combination mefloquine + Fansidar (Ro 13-5112) versus mefloquine (Ro 21-5998) in visitors to tropical countries. Data on file, F Hoffmann-La Roche AG, Basel. 1985, unpublished.

Leimer 1985b *{published data only}*

Leimer R, Mittelholzer M. Randomized double-blind comparative study of acceptability and tolerability of the combination mefloquine + Fansidar (Ro 13-5112) versus mefloquine (Ro 21-5998) in visitors to tropical countries. Data on file, F Hoffmann-La Roche AG, Basel.

Lwin 1987 *{published data only}*

Lwin M, Win K, Htut Y, Thwe Y, Lwin TT, Win K. The use of immunofluorescence to evaluate the efficacy of malarial chemoprophylaxis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1987;**81**:896–8.

Mittelholzer 1989 *{published data only}*

Mittelholzer ML, Leimer R. Randomized double blind comparative study of acceptability and tolerability of 'Fansimef' versus 'Lariam' in visitors to tropical countries. Data on file, F Hoffmann-La Roche AG, Basel.

Mittelholzer 1990 *{published data only}*

Mittelholzer ML. Randomized double-blind multicenter trial comparing tolerability and acceptability of Fansimef (Ro 13-5112) and Lariam (mefloquine, Ro 21-5998) in tourists to tropical countries. Data on file, F Hoffmann-La Roche AG, Basel.

Navaratnam 1989 *{published data only}*

Navaratnam V, Mohammed M, Hussain S, Kumar A, Jamaludin A, Sulaiman I, et al. Chemosuppression of malaria by the triple combination mefloquine/sulfadoxine/pyrimethamine: a field trial in an endemic area in Malaysia. *Trans R Soc Trop Med Hyg* 1989;**83**:755–9.

Nosten 1994 *{published data only}*

Nosten F, ter Kuile F, Maelankiri L, Chongsuphajaisiddhi L, Nopdonrattakoon L, Tangkitchot S, et al. Mefloquine prophylaxis prevents malaria during pregnancy: a double-blind, placebo-controlled study. *J Infect Dis* 1994;**169**: 595–603.

Pearlman 1980 *{published data only}*

Pearlman EJ, Doberstyn EB, Sudsok S, Thiemanun W, Kennedy RS, Canfield CJ. Chemosuppressive field trials in Thailand. IV. The suppression of Plasmodium falciparum and Plasmodium vivax parasitemias by mefloquine (WR 142,490, a 4-quinolinemethanol). *Am J Trop Med Hyg* 1980;**29**:1131–7.

Prata 1984 *{published data only}*

Prata A, Barberino dos Santos J, Ferreira I, Leimer R. Suppressive treatment of malaria in the Amazon region. Proceedings of the Eleventh International Congress for Tropical Medicine and Malaria; 1984 Sep 16–22; Calgary (Canada). Vol. Calgary, issue Canada.

Reisinger 1989 *{published data only}*

Reisinger EC, Horstmann RD, Dietrich M. Tolerance of mefloquine alone and in combination with sulfadoxine-

pyrimethamine in the prophylaxis of malaria. *Trans R Soc Trop Med Hyg* 1989;**83**:474–7.

Rieckmann 1974 {published data only}

Rieckmann KH, Trenholme GM, Williams RL, Carson PE, Frischer H, Desjardins RE. Prophylactic activity of mefloquine hydrochloride (WR 142490) in drug-resistant malaria. *Bull World Health Organ* 1974;**51**:375–7.

Rombo 1993 {published data only}

Rombo L, Angel VH, Friman G, Hellgren U, Mittelholzer ML, Sturchler D. Comparative tolerability and kinetics during long-term intake of Lariam and Fansidar for malaria prophylaxis in nonimmune volunteers. *Trop Med Parasitol* 1993;**44**:254–6.

Salako 1992 {published data only}

Salako LA, Adio RA, Walker O, Sowunmi A. Mefloquine-sulphadoxine-pyrimethamine (Fansimef) in the prophylaxis of *Plasmodium falciparum* malaria: a double-blind, comparative, placebo-controlled study. *Ann Trop Med Parasitol* 1992;**86**:575–81.

Sossouhounto 1995 {published data only}

Sossouhounto RT, Soro BN, Coulibaly A, Mittelholzer ML, Stuerchler D, Haller L. Mefloquine in the prophylaxis of *P falciparum* malaria. *J Travel Med* 1995;**2**:221–4.

Steketee 1996 {published data only}

Steketee RW, Wirima JJ, Slutsker L, Khoromana CO, Breman JG, Heymann DL. Objectives and methodology in a study of malaria treatment and prevention in pregnancy in rural Malawi: the Mangochi Malaria Research Project. *Am J Trop Med Hyg* 1996;**55**:8–16.

Weiss 1995 {published data only}

Weiss WR, Oloo AJ, Johnson A, Koech D, Hoffman SL. Daily primaquine is effective for prophylaxis against *falciparum* malaria in Kenya: comparison with mefloquine, doxycycline and chloroquine plus proguanil. *J Infect Dis* 1995;**171**:1569–75.

Win 1985 {published data only}

Win K, Thwe Y, Lwin TT, Win K. Combination of mefloquine with sulfadoxine-pyrimethamine combinations in malaria chemoprophylaxis. *Lancet* 1985;**ii**:694–5.

References to studies awaiting assessment

Wolfensberger 1983 {unpublished data only}

Wolfensberger HR. Über die Vertraglichkeit bei prophylaktischer Einnahme von Mefloquin. Presented at the Tropenmedizinische Tagung, Garmisch-Partenkirchen (Germany), April 1983.

Additional references

AHCPR 1992

Agency for Health Care Policy and Research. Effective dissemination of health and clinical information and research findings. Grant announcement.

Altman 1996

Altman DG. Better reporting of randomised controlled trials: the CONSORT statement. *BMJ* 1996;**313**:570–1.

Anonymous 1990

Anonymous. Mefloquine for malaria. *Medical Letter on Drugs and Therapeutics* 1990;**31**:13–14.

Anonymous 1992

Anonymous. Guidelines for doctors in the new world [editorial]. *Lancet* 1992;**339**:1197–8.

Anonymous 1997

Anonymous. Malaria drug - Lariam safety in doubt as girl dies after foreign trip. *European Chemical News* 1997;**67**:18.

Anonymous 1998

Anonymous. Roche's Lariam linked to a suicide in UK. *Scrip* 1998;**2331**:23.

Avorn 1997

Avorn J. Including elderly people in clinical trials. Better information could improve their effectiveness and safety of drug use. *BMJ* 1997;**315**:1033–4.

Bargery 1994

Bargery A. New expert system will provide expertise at your elbow. *Practice Computing* 1994;**Summer**:20–2.

Barrett 1996

Barrett PJ, Emmins PD, Clarke PD, Bradley DJ. Comparison of adverse events associated with use of mefloquine and combination of chloroquine and proguanil as antimalarial prophylaxis: postal and telephone survey of travellers. *BMJ* 1996;**313**:525–8.

Basco 1994

Basco LK, Thor R, Le Bras J. Confused malaria chemoprophylaxis. *Lancet* 1994;**i**:550–551.

Begg 1996

Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomized controlled trials: the CONSORT statement. *JAMA* 1996;**276**:637–9.

Bem 1992

Bem L, Kerr L, Stuerchler D. Mefloquine prophylaxis: an overview of spontaneous reports of severe psychiatric reactions and convulsions. *J Trop Med Hyg* 1992;**95**:167–9.

Bero 1996

Bero LA, Rennie D. Influences on the quality of published drug studies. *Int J Technol Assess Health Care* 1996;**12**:209–37.

Bond 1995

Bond CM, Grimshaw JM. Multidisciplinary guideline development: a case study from community pharmacy. *Health Bull (Edinb)* 1995;**53**:29–36.

Bradley 1985

Bradley DJ, Hall AP, Peters W, Warhurst D. Fansidar in malaria prophylaxis. *BMJ* 1985;**291**:136.

Bradley 1997

Bradley DJ, Warhurst DC. Guidelines for the prevention of malaria in travellers from the United Kingdom. *Commun Dis Rep Rev* 1997;**7**:R137–52.

Bugeja 1997

Bugeja G, Kumar A, Banerjee AK. Exclusion of elderly people from clinical research: a descriptive study of published reports. *BMJ* 1997;**315**:1059.

Bygbjerg 1999

Bygbjerg IC, Ronn AM. [Langvarige neuropsykiatriske bivirkninger efter meflochinprofylakse]. *Ugeskrift for Læger* 1999;**161**(10):1422–1423.

CDC 1994

Centers for Disease Control. Health information for international travel. US Department of Health and Human Services, 1994.

CDHSH 1995

Commonwealth Department of Human Services and Health. Health information for international travel. CDHSH, 1995.

Chalmers 1992

Chalmers I, Dickersin K, Chalmers TC. Getting to grips with Archie Cochrane's agenda. All randomised controlled trials should be registered and reported. *BMJ* 1992;**305**:786–8.

Choo 1996

Choo V. Uncertainty about mefloquine will take time to resolve. *Lancet* 1996;**347**:891.

Christ 1991

Christ W, Esch B. Nutzen-Risiko-Abwägung bei Antiinfektiva aus der Sicht der Zulassungsbehörde. *Infection* 1991;**19**(1 Suppl):S65–71.

Clift 1996

Clift S, Grabowski P. Malaria prophylaxis and the media. *BMJ* 1996;**348**:344.

Cobelens 1997

Cobelens FGJ, van Thiel PPAM. [Niet meer klachten bij mefloquinegebruik dan bij malariaprofylaxe met andere middelen]. *Nederlands Tijdschrift voor Geneeskunde* 1997;**141**:794.

Cook 1995

Cook GC. Mefloquine toxicity should limit its use to treatment alone. *BMJ* 1995;**311**:190–1.

Corbett 1996

Corbett EL, Doherty JF, Behrens RH. Study in returned travellers confirms authors' findings. *BMJ* 1996;**313**:1552.

Corominas 1997

Corominas N, Gascon J, Mejias T, Caparros F, Quinto L, Codina C, et al. Reacciones adversas asociadas a la quimioprofilaxis antipaludica. *Med Clin (Barc)* 1997;**108**:772–5.

CRD 1996

Centre for Reviews and Dissemination. Undertaking systematic reviews of research on effectiveness. CRD guidelines for those carrying out or commissioning reviews. CRD Report 4. NHS Centre for Reviews and Dissemination, 1996.

Croft 1998

Croft AM, Garner P, Squire B. Malaria prevention for travelers. *Journal of the American Medical Association* 1998;**279**:990.

Croft 1999a

Croft AMJ, Vassallo DJ, Rowe M. Handsearching the Journal of the Royal Army Medical Corps for trials. *Journal of the Royal Army Medical Corps* 1999;**145**:20–2.

Croft 1999b

Croft AM, Whitehouse DP. More studies of mefloquine prophylaxis must be done in tourists. *British Medical Journal* 1999;**318**:1139–1140.

Croft 2000

Croft A. Malaria: prevention in travellers. *British Medical Journal* 2000;**321**:154–160.

Davey Smith 1994

Davey Smith G, Egger M. Who benefits from medical interventions? Treating low risk patients can be a high risk strategy. *BMJ* 1994;**308**:72–4.

Dickersin 1994

Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994;**309**:1286–91.

Durrheim 1999

Durrheim DN, Gammon S, Waner S, Braack LEO. Antimalarial prophylaxis - use and adverse events in visitors to the Kruger National Park. *South African Medical Journal* 1999;**89**(2):170–175.

Eccles 1996

Eccles M, Clapp Z, Grimshaw J, Adams PC, Higgins B, Purves I, et al. North of England evidence based guidelines development project: methods of guideline development. *BMJ* 1996;**312**:760–2.

Eddy 1990

Eddy DM. Comparing benefits and harms: the balance sheet. *JAMA* 1990;**263**:2239–43.

Edwards 1997

Edwards SJL, Lilford RJ, Braunholtz D, Jackson J. Why “underpowered” trials are not necessarily unethical. *Lancet* 1997;**350**:804–7.

Evans 1996

Evans MR. Adverse events associated with mefloquine. Patients may start to take cheaper over the counter regimens. *BMJ* 1996;**313**:1554.

Folkerts 1992

Folkerts H, Kuhs H. Psychotische Episode infolge Malariaprofylaxe mit Mefloquin. *Nervenarzt* 1992;**63**:300–2.

Fusetti 1999

Fusetti M, Eibenstein A, Corridore V, Hueck S, Chiti-Batelli S. [Meflochina ed ototossicità: descrizione di tre casi]. *Clinica Terapeutica* 1999;**150**:379–382.

Glasziou 1995

Glasziou PP, Irwig LM. An evidence based approach to individualising treatment. *BMJ* 1995;**311**:1356–9.

Greenhalgh 1997

Greenhalgh T. Papers that report drug trials. *BMJ* 1997;**315**:480–3.

Grupp 1994

Grupp D, Rauber A, Froscher W. Neuropsychiatrische Störungen nach Malariaprophylaxe mit Mefloquin. *Aktuel Neurol* 1994;**21**:134–6.

Haines 1992

Haines A, Feder G. Guidance on guidelines. Writing them is easier than making them work. *BMJ* 1992;**305**:785–6.

Handschin 1995

Handschin J, Crevoisier C, Sturchler D. Mefloquine in malaria prophylaxis: low efficacy or low compliance?. *Lancet* 1995;**346**:1294.

Handschin 1997

Handschin JC, Wall M, Steffen R, Sturchler D. Tolerability and effectiveness of malaria chemoprophylaxis with mefloquine or chloroquine with or without co-medication. *Journal of Travel Medicine* 1997;**4**:121–127.

Hatton 1986

Hatton CSR, Peto TEA, Bunch C, Pasvol G, Russell SJ, Singer CRJ, et al. Frequency of severe neutropenia associated with amodiaquine prophylaxis against malaria. *Lancet* 1986;**1**:411–4.

Hatz 1997

Hatz C, Gyr N. Reiseprophylaxe. *Therapiewoche Schweiz* 1997;**13**:203–4.

Hedger 1999

Hedger NA, Croft AM, Rowe M. Handsearching the Journal of the Royal Naval Medical Service for Trials. *Journal of the Royal Naval Medical Service* 1999;**164**:712–7.

Heeringa 1998

Heeringa M, Kuster JAM, Meyboom RHB, Bouvy M. [Convulsies tijdens profylactisch gebruik van mefloquine]. *Nederlands Tijdschrift voor Geneeskunde* 1998;**142**(45): 2477–2480.

Heimgartner 1986

Heimgartner E. [Praktische erfahrungen mit mefloquin als malariaprophylaktikum]. *Schweizerische Rundschau fur Medizin Praxis* 1986;**75**:459–62.

Held 1993

Held TK, Weinke T, Trautmann M, Mansmann U, Pohle HD. Malaria chemoprophylaxis. *Lancet* 1993;**342**:503.

Held 1994

Held TK, Weinke T, Mansmann U, Pohle HD. Malaria prophylaxis: identifying risk groups for non-compliance. *Q J Med* 1994;**87**:17–22.

Henry 1995

Henry D, Hill S. Comparing treatments. *BMJ* 1995;**310**: 1279.

Hollyoak 1995

Hollyoak V. Prophylaxis against malaria. *BMJ* 1995;**310**: 1329.

Huzly 1996

Huzly D, Schonfeld C, Beurle W, Bienzle U. Malaria chemoprophylaxis in German tourists: a prospective study on compliance and adverse reactions. *J Travel Med* 1996;**3**: 148–55.

IG 1996

Inspectie voor de Gezondheidszorg. Malariaprofylaxe. Inspectie voor de Gezondheidszorg, 1996.

Ingram 1996

Ingram RJH, Ellis-Pegler RB. Health advice for overseas travellers. Ministry of Health, 1996.

Jacobson 1997

Jacobson LD, Edwards GK, Granier SK, Butler CC. Evidence-based medicine and general practice. *Br J Gen Pract* 1997;**47**:449–52.

Jadad 1993

Jadad AR, McQuay HJ. Be systematic in your searching. *BMJ* 1993;**307**:66.

Jensen 1998

Jensen JB. [Meflochin: de neuropsychiatriske bivirkninger er ofte alvorlige og kan persistere laenge efter ophor med medicinen]. *Ugeskrift for Laeger* 1998;**160**(16):2413.

Jernigan 1995

Jernigan JA, Pearson RD. Antiparasitic agents. In: Mandell GL, Bennett GL, Dolin R, editors. Principles and practice of infectious diseases. 4th ed. 472.

Klebanoff 1997

Klebanoff M, Levine RJ, DerSimonian R. Large trials vs meta-analysis of smaller trials. *JAMA* 1997;**277**:376–7.

Kollaritsch 2000

Kollaritsch H, Karbwang J, Wiedermann G, Mikolasek A, Na-Bangchang K, Wernsdorfer WH. Mefloquine concentration profiles during prophylactic dose regimens. *Wiener Klinische Wochenschrift* 2000;**112**:441–447.

Kondro 1999

Kondro W. Canadian military malarial prophylaxis under scrutiny. *Lancet* 1999;**353**:1507.

Koumans 1995

Koumans EHA, Zucker JR. Update on malaria. Prevention for children and pregnant women. *Report Pediatr Infect Dis* 1995;**5**:1–2.

Leape 1992

Leape LL, Park RE, Kahan JP. Group judgments of appropriateness: the effect of panel composition. *Qual Assur Health Care* 1992;**4**:151–5.

Liberati 1997

Liberati A. Consumer participation in health and health care. *BMJ* 1997;**315**:499.

Litzelman 1993

Litzelman DK, Dittus RS, Miller ME, Tierney WM. Requiring physicians to respond to computerized reminders improves their compliance with preventive care protocols. *J Gen Intern Med* 1993;**8**:311–7.

Lobach 1995

Lobach DF. A model for adapting clinical guidelines for electronic implementation in primary care. 581–5.

Lobel 1990

Lobel HO, Phillips-Howard PA, Brandling-Bennett AD, Steffen R, Campbell CC, Huong AY, et al. Malaria incidence and prevention among European and North American travellers to Kenya. *Bull WHO* 1990;**68**:209–15.

Lobel 1993

Lobel HO, Miani M, Eng T, Bernard KW, Hightower AW, Campbell CC. Long-term malaria prophylaxis with weekly mefloquine. *Lancet* 1993;**341**:848–51.

MacLean 1997

MacLean M, Anderson J, Davies C. Making malaria research bite. *Nature Med* 1997;**3**:14–6.

Martindale 1999

Parfitt K, ed. *Martindale - the Complete Drug Reference*. 2nd Edition. London: Pharmaceutical Press, 1999.

May 1996

May J, Schonfeld C, Meyer CG. Leitlinien zum Malaria-Schutz. *Munch Med Wschr* 1996;**138**:776–8.

McBride 1997

McBride SR, Lawrence CM, Reid CA. Fatal toxic epidermal necrolysis associated with mefloquine antimalarial prophylaxis. *Lancet* 1997;**349**:101.

Meszaros 1996

Meszaros K, Kasper S. [Psychopathologische Phänomene im Langzeitverlauf einer akuten Psychose nach Mefloquinprophylaxe (Lariam)]. *Nervenarzt* 1996;**67**:404–406.

Micheo 2000

Micheo C, Arias C, Rovira A. Adverse effects and compliance with mefloquine or chloroquine + proguanil malaria chemoprophylaxis. Proceedings of the Second European Conference on Travel Medicine; 2000 Mar 29–31; Venice, Italy. Venice: Fondazione Cini, 2000.

Miller 1986

Miller KD, Lobel HO, Satriale RF, Kuritsky IH, Stern R, Campbell CC. Severe cutaneous reactions among American travelers using pyrimethamine-sulfadoxine (Fansidar) for malaria prophylaxis. *Am J Trop Med Hyg* 1986;**35**:451–8.

Milord 1993

Milord F, Allard R, Gyorkos TW. Malaria chemoprophylaxis. *Lancet* 1993;**342**:502.

MMWR 1986

Morbidity and Mortality Weekly Reports. Agranulocytosis associated with use of amodiaquine for malaria prophylaxis. *MMWR* 1986;**35**:165–6.

Murphy 1996

Murphy GS, Oldfield EC. Falciparum malaria. *Infectious Disease Clinics of North America* 1996;**10**:747–775.

Nosten 1993

Nosten F, ter Kuile FO, Luxemburger C, Woodrow C, Kyle DE, Chongsuphajaisiddhi T, et al. Cardiac effects of

antimalarial treatment with halofantrine. *Lancet* 1993;**341**:1054–1056.

Ornstein 1991

Ornstein SM, Garr DR, Jenkins RG, Rust PF, Arnon A. Computer-generated physician and patient reminders. Tools to improve population adherence to selected preventive services. *J Fam Pract* 1991;**32**:82–90.

Perry 1995

Perry IC. Malaria prophylaxis. *BMJ* 1995;**310**:1673.

Petersen 1990

Petersen E, Hogh B, Bygbjerg IC, Black FT. Malaria chemoprophylaxis: why mefloquine?. *Lancet* 1990;**i**:811.

Petersen 1997

Petersen E. Malariaprofylakse. *Ugeskr Laeger* 1997;**159**:2723–30.

Petersen 2000

Petersen E, Ronne T, Ronn A, Bygbjerg I, Larsen SO. Reported side effects to chloroquine, chloroquine plus proguanil, and mefloquine as chemoprophylaxis against malaria in Danish travelers. *Journal of Travel Medicine* 2000;**7**:79–84.

Peto 1986

Peto TEA, Gilks CF. Strategies for the prevention of malaria in travellers: comparison of drug regimens by means of risk-benefit analysis. *Lancet* 1986;**i**:1256–61.

Phillips 1996

Phillips MA, Kass RB. User acceptability patterns for mefloquine and doxycycline malaria chemoprophylaxis. *J Travel Med* 1996;**3**:40–5.

Phillips-Howard 1995

Phillips-Howard P, ter Kuile FO. CNS adverse events associated with antimalarial agents - fact or fiction?. *Drug Saf* 1995;**12**:370–83.

Potasman 2000

Potasman I, Beny A, Seligmann H. Neuropsychiatric problems in 2,500 long-term young travelers to the tropics. *Journal of Travel Medicine* 2000;**7**(1):5–9.

RCGP 1995

Royal College of General Practitioners. The development and implementation of clinical guidelines: report of the Clinical Guidelines Working Group. Report from General Practice Paper 26. Royal College of General Practitioners, 1995.

Ronn 1994

Ronn AM, Bygbjerg IC. [Akut hjernesyndrom efter meflokinbehandling]. *Ugeskrift for Laeger* 1994;**156**(41):6044–6045.

Schlagenhauf 1996

Schlagenhauf P, Steffen R, Lobel H, Johnson R, Letz R, Tschopp A, et al. Mefloquine tolerability during chemoprophylaxis: focus on adverse event assessments, stereochemistry and compliance. *Trop Med Int Health* 1996;**1**:485–94.

Schulz 1996

Schulz KF. Randomised trials, human nature, and reporting guidelines. *Lancet* 1996;**348**:596–8.

Scott 1990

Scott M, Marinker ML. Small group work. In: Marinker ML, editor. *Medicine audit and general practice*. 1st ed. 180–95.

SED 1996

Dukes MNG, editor. *Meyler's side effects of drugs*. 13th Edition. Amsterdam: Elsevier, 1996.

SEDA 1999

Aronson JK, editor. *Side Effects of Drugs Annual 22*. Amsterdam: Elsevier, 1998.

Smith 1996

Smith PG, Morrow RH. Field trials of health interventions in developing countries: a toolbox. 44.

Smith 1999

Smith HR, Croft AM, Black MM. Dermatological adverse effects with the antimalarial drug mefloquine: a review of 74 published case reports. *Clinical and Experimental Dermatology* 1999;**24**:249–254.

Steffen 1993

Steffen R, Fuchs E, Schildknecht J, Naef U, Funk M, Schlagenhauf P, et al. Mefloquine compared with other malaria chemoprophylactic regimens in tourists visiting East Africa. *Lancet* 1993;**341**:1299–303.

Strickland 1991

Strickland GT. Malaria. In: Strickland GT, editor. *Hunter's tropical medicine*. 7th ed. 605.

Ter Kuile 1992

Ter Kuile FO, Nosten F, Thieren M, Luxemburger C, Edstein MD, Chongsuphajaisiddhi T, et al. High-dose mefloquine in the treatment of multidrug-resistant falciparum malaria. *Journal of Infectious Diseases* 1992;**166**: 1393–400.

Ter Kuile 1995

Ter Kuile FO, Nosten F, Luxemburger C, Kyle D, Teja-Isavatharm P, Phaipun L, et al. Mefloquine treatment of acute falciparum malaria: a prospective study of non-serious adverse effects in 3673 patients. *Bulletin of the World Health Organization* 1995;**73**(5):631–42.

Trenholme 1975

Trenholme GM, Williams RL, Desjardins RE, Frischer H, Carson PE, Rieckmann KH. Mefloquine (WR 142,490)

in the treatment of human malaria. *Science* 1975;**190**: 792–794.

Van Puijenbroek 1995

Van Puijenbroek EP, Bouvy M. Mefloquine (Lariam) in het nieuws. *Pharmaceutisch Weekblad* 1995;**130**:912.

Van Riemsdijk 1997

Van Riemsdijk MM, van der Klauw MM, van Heest JAC, Reedeker FR, Ligthelm RJ, Herings RMC, et al. Neuropsychiatric effects of antimalarials. *Eur J Clin Pharmacol* 1997;**52**:1–6.

Walker 1994

Walker E, Calvert L, Raeside F. Confused malaria prophylaxis. *Lancet* 1994;**i**:551.

Weinke 1991

Weinke T, Trautmann M, Held T, Weber G, Eichenlaub D, Fleischer K, et al. Neuropsychiatric side effects after the use of mefloquine. *American Journal of Tropical Medicine* 1991; **45**(1):86–91.

White 1992

White NJ. Antimalarial drug resistance: the pace quickens. *J Antimicrob Chemother* 1992;**30**:571–85.

White 1996

White NJ. Malaria. In: Cook GC, editor. *Manson's tropical diseases*. 20th ed. 1147.

WHO 1995

World Health Organization. International travel and health. Vaccination requirements and health advice. WHO Office of Information, 1995.

Woolf 1996

Woolf SH, DiGuseppi C, Atkins D, Kamerow DB. Developing evidence-based clinical practice guidelines: lessons learned by the US Preventive Services Task Force. *Annu Rev Public Health* 1996;**17**:511–38.

References to other published versions of this review**Croft 1997**

Croft A, Garner P. Mefloquine to prevent malaria: a systematic review of trials. *BMJ* 1997;**315**:1412–6.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Arthur 1990

Methods	Double-blind controlled trial. Field trial. Duration of chemoprophylaxis - 6 weeks. Randomisation method adequate (i.e. a computer-generated random numbers list)	
Participants	US soldiers (all males) temporarily in Thailand for military training. EXCLUSIONS: soldiers with previous history of gastrointestinal illness	
Interventions	Mefloquine 250 mg weekly (n=134) compared with doxycycline hyclate 100 mg daily (n = 119)	
Outcomes	Inferred non-compliance, reported symptoms	
Notes	Period of study - July to August 1988. Study carried out in area of Thailand with low malaria endemicity. Primary purpose of the study was to determine the efficacy of doxycycline in preventing diarrhoea Possible conflict of interest: US Army support.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Boudreau 1993

Methods	Double-blind controlled trial. Field trial. Duration of active treatment - 13 weeks. ALLOCATION METHOD NON-RANDOM BUT REPORTEDLY UNBIASED (i.e. this was done by "major subordinate command", such that equal proportions of each study group would be represented)	
Participants	US Marines (all males) stationed in Hawaii, and meeting military weight standards. EXCLUSIONS: any Marines being treated with beta-blocking agents or other cardiotropic drugs; history of cardiac arrhythmia, anaemia or psychotic/neurological problems within previous five years; impaired hepatic/renal function; underlying chronic disease; women	
Interventions	Mefloquine loading dose of 250 mg daily for 3 days, followed by 250 mg weekly (n = 46) compared with mefloquine normal regimen i.e. 250 mg weekly (n = 157) compared with chloroquine 300 mg weekly (n = 156)	
Outcomes	Withdrawals from study, symptom assessment (physician interview and standard questionnaires). ONE PSYCHOMETRIC PARAMETER TESTED: sleep	
Notes	Year study was carried out - not stated. Estimated as 1992. Study carried out in US state (Hawaii) with no indigenous malaria. Possible conflicts of interest: US Army support.	

Boudreau 1993 (Continued)

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Croft 1997a

Methods	Double-blind controlled trial, with double-dummy technique. Field trial. Duration of chemoprophylaxis - 12 weeks. Randomisation method adequate (i.e. a computer-generated random numbers list). Tablets were issued in opaque, sealed, individually-numbered packets	
Participants	British soldiers (all males) temporarily in Kenya for military training. EXCLUSIONS: soldiers with previous neuropsychiatric histories; soldiers taking beta-adrenergic blocking drugs; female personnel; aircrew	
Interventions	Mefloquine hydrochloride 250 mg weekly (n = 317) compared with chloroquine sulphate 300 mg weekly + proguanil hydrochloride 200 mg daily (n = 307)	
Outcomes	Withdrawals from study, numbers non-compliant (self-reported), self-reported symptoms, numbers hospitalised from any cause	
Notes	Period of study - December 1994 to March 1995. Study carried out in a highland region of Kenya with low malaria endemicity Possible conflict of interest: none.	

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Croft 1997b

Methods	Double-blind controlled trial, with double-dummy technique. Field trial. Duration of chemoprophylaxis - 12 weeks. Randomisation method adequate (a computer-generated random numbers list). Tablets were issued in opaque, sealed, individually-numbered packets	
Participants	British soldiers (2 females) temporarily in Kenya for military training. EXCLUSIONS: soldiers with previous neuropsychiatric histories; soldiers taking beta-adrenergic blocking drugs; aircrew	
Interventions	Mefloquine hydrochloride 250 mg weekly (n = 275) compared with chloroquine sulphate 150 mg twice weekly + proguanil hydrochloride 200 mg daily (n = 268)	
Outcomes	Antibody markers of recent Plasmodium infection, withdrawals from study, numbers non-compliant (self-reported), self-reported symptoms, deaths (non-malaria), numbers hospitalised from any cause	

Croft 1997b (Continued)

Notes	Period of study - October 1995 to January 1996. Study carried out in a highland region of Kenya with low malaria endemicity Possible conflict of interest: none.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Davis 1996

2025-1998

Methods	Double-blind, placebo-controlled trial. Clinical toxicity study. Duration of active treatment - 4 weeks. Tablets were prepared in individually-numbered but otherwise unlabelled containers. Randomisation method adequate (i.e. a random number code generated by independent hospital staff)	
Participants	Healthy adult staff and students at teaching hospitals in Perth, Western Australia. EXCLUSIONS: volunteers with past history of psychiatric conditions; history of neurological, cardiac, hepatic or renal disease; pregnant or breastfeeding women; any volunteer who had taken mefloquine in the 3 months preceding the study	
Interventions	Mefloquine 250 mg weekly (n = 46) compared with placebo one tablet weekly (n = 49)	
Outcomes	Daily symptom diary, measured biochemical variables, electrocardiography, audiometry, psychometric tests	
Notes	Period of study - April to August 1994. Study carried out in temperate state (Western Australia) with no indigenous malaria. Eleven participants (unspecified) withdrew from study - FURTHER DETAILS BEING SOUGHT FROM INVESTIGATORS Possible conflict of interest: financial support from F Hoffmann-La Roche	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Kollaritsch 1997

Methods	Unblinded controlled trial. Clinical toxicity study. Duration of active treatment - 2 weeks. ADEQUACY OF RANDOMISATION METHOD UNCLEAR	
Participants	Healthy adult students, male and female, at the University of Vienna. EXCLUSIONS: volunteers with acute febrile illness, history of allergies, recent immunizations, recent use of antibiotics, treatment with immunosuppressive drugs, underlying immunodeficiency state, epilepsy, clinical depression, recent recipients of an experimental drug or blood product, use of beta-blockers, acute or chronic gastrointestinal illness, current participation in another trial	

Kollaritsch 1997 (Continued)

Interventions	Mefloquine 250 mg weekly (n = 60) compared with chloroquine 250 mg weekly (n = 60)	
Outcomes	Self-recorded symptoms and any other clinically relevant event	
Notes	Year study was carried out - not stated. Estimated as 1995. Study carried out in country (Austria) with no indigenous malaria. Primary purpose of the study was to investigate the role of antimalarial drugs in suppressing the immune response to live oral vaccines. A third, proguanil, arm to the study has not been analysed in this systematic review since proguanil alone is no longer used as standard chemoprophylaxis Possible conflict of interest: none.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

MacPherson 1997

Methods	Double-blind, placebo-controlled trial. Clinical toxicity study. Duration of active treatment - one month. ADEQUACY OF RANDOMISATION METHOD UNCLEAR	
Participants	Non-immune, male and female, pre-travel adult Canadian volunteers. EXCLUSIONS - FURTHER DETAILS BEING SOUGHT FROM INVESTIGATORS	
Interventions	Mefloquine loading dose of 250 mg daily for 3 days followed by 250 mg weekly as from Day 8 (n = 251) compared with placebo “loading dose” as above followed by one tablet weekly as from Day 8 (n = 238)	
Outcomes	Withdrawals from study, self-reported symptoms	
Notes	Period of study - September 1996 to February 1997. Study carried out in country (Canada) with no indigenous malaria Possible conflict of interest: none.	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Ohrt 1997

Methods	Double-blind, placebo-controlled trial. Field trial. Duration of chemoprophylaxis - approximately 13 weeks. Randomisation method adequate (i.e. blocked randomisation was utilized, with soldiers assigned consecutive study drug numbers, and individually labelled drug packages)	
Participants	Indonesian soldiers (all male, all non-immune) temporarily stationed in northeastern Irian Jaya. EXCLUSIONS: soldiers with history of frequent travel; chronic illness; allergy to a study drug; G6PD deficiency	

Ohrt 1997 (Continued)

Interventions	Mefloquine loading dose of 250 mg daily for 3 days followed by 250 mg once weekly (n = 68) compared with placebo 'loading dose' as above followed by one placebo tablet weekly (n = 69) compared with doxycycline hyclate 100 mg daily (n = 67)	
Outcomes	Smear-positive malarial illness, withdrawals from study, numbers non-compliant, spontaneously-reported symptoms (NO DATA GIVEN ON SYMPTOMS EXPERIENCED BY PLACEBO USERS - FURTHER DETAILS BEING SOUGHT FROM INVESTIGATORS)	
Notes	Period of study - April to August 1994. Study carried out in geographical area of Indonesia with very high malaria endemicity The ethics of using a placebo in such a high-risk setting are questionable (although accepted by the investigators) Possible conflicts of interest: (1) US Army grant support, (2) grant support and free mefloquine from F Hoffmann-La Roche, (3) free doxycycline huclate from Pfizer	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Schlagenhauf 1997

Methods	Placebo-controlled crossover study. Clinical toxicity study. Duration of active treatment - 4 weeks. AD-EQUACY OF RANDOMISATION METHOD UNCLEAR. Each participant served as his/her own control	
Participants	Swissair trainee pilots (one female). EXCLUSIONS: any pilots with past history of seizures, psychosis or severe depression; known allergy or sensitivity to mefloquine; concurrent use of cardioactive medication; compromised renal or hepatic function; pregnancy; use of mefloquine in the 2 months before study; use of hypnotics or tranquillizers in the 2 weeks before study; use of alcohol during the 12 hours before testing	
Interventions	Mefloquine loading dose of 250 mg daily for three days followed by 250 mg once weekly as from Day 8 (n = 23) compared with placebo “loading dose” as above followed by one tablet weekly as from Day 8 (n = 23)	
Outcomes	Withdrawals from study, symptom assessment (investigator interview). FOUR PSYCHOMETRIC PA-RAMETERS TESTED: coordination, postural sway, psychomotor performance, sleep	
Notes	Period of study - July 1993 to September 1994. Study carried out in country (Switzerland) with no indigenous malaria Possible conflict of interest: study sponsored by F Hoffmann-La Roche	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement

Schlagenhauf 1997 (Continued)

Allocation concealment?	Unclear risk	B - Unclear
-------------------------	--------------	-------------

Vuurman 1996

Methods	Two-arm double-blind trial with parallel group design. Clinical toxicity study. Duration of active treatment - 4 weeks. ADEQUACY OF RANDOMISATION METHOD UNCLEAR. 20 volunteers were "assigned to each group"
Participants	Adult Caucasians (20 males, 20 females) living in the Netherlands and holding a driver's licence. EXCLUSIONS: volunteers with clinically relevant blood test abnormalities; impaired visual acuity; known hypersensitivity to any drug; history of chronic gastrointestinal, hepatic, renal or neurological disease; evidence of drug or alcohol abuse; excessive alcohol or nicotine use; blood donation or participation in other trial within previous 2 months; pregnancy, lactation or possibility of pregnancy in near future
Interventions	Mefloquine loading dose of 250 mg daily for 3 consecutive days followed by 250 mg once weekly as from Day 8 (n = 20) compared with placebo "loading dose" as above followed by one tablet weekly as from Day 8 (n = 20)
Outcomes	Withdrawals from study, self-reported adverse events. THREE PSYCHOMETRIC PARAMETERS TESTED: driving performance, postural sway, psychomotor performance
Notes	Period of study - April to September 1994. Study carried out in country (Netherlands) with no indigenous malaria Possible conflict of interest: study sponsored by F Hoffmann-La Roche

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Boudreau 1991	Participants were semi-immune.
Bunnag 1992	Participants were semi-immune.
Clyde 1976	Allocation of participants to mefloquine arm or no treatment appears to have been non-random
Danis 1982	Participants were semi-immune children.
Dos Santos 1993	Participants were semi-immune.

(Continued)

Eamsila 1993	Mefloquine and mefloquine plus sulfadoxine-pyrimethamine compared with chloroquine plus sulfadoxine-pyrimethamine (the latter not now used for malaria chemoprophylaxis in travellers)
Felix 1981	Participants were semi-immune.
Heimgartner 1986	Mefloquine compared only with a mefloquine combination (mefloquine plus sulfadoxine-pyrimethamine - the latter not now used for malaria chemoprophylaxis in travellers)
Kamolratanakul 1989	Mefloquine plus sulfadoxine-pyrimethamine compared with sulfadoxine-pyrimethamine (now not used for malaria chemoprophylaxis in travellers)
Kollaritsch 1988	Mefloquine plus sulfadoxine-pyrimethamine (the latter now not used for malaria chemoprophylaxis in travellers) compared with chloroquine
Leimer 1985a	Mefloquine compared only with a mefloquine combination (mefloquine plus sulfadoxine-pyrimethamine - the latter not now used for malaria chemoprophylaxis in travellers)
Leimer 1985b	Mefloquine compared only with a mefloquine combination (mefloquine plus sulfadoxine-pyrimethamine - the latter now not used for malaria chemoprophylaxis in travellers)
Lwin 1987	Mefloquine plus sulfadoxine-pyrimethamine compared with sulfadoxine-pyrimethamine (now not used for malaria chemoprophylaxis in travellers)
Mittelholzer 1989	Mefloquine compared only with a mefloquine combination (mefloquine plus sulfadoxine-pyrimethamine - the latter not now used for malaria chemoprophylaxis in travellers)
Mittelholzer 1990	Mefloquine compared only with a mefloquine combination (mefloquine plus sulfadoxine-pyrimethamine - the latter now not used for malaria chemoprophylaxis in travellers)
Navaratnam 1989	Mefloquine plus sulfadoxine-pyrimethamine at two dosages compared with sulfadoxine-pyrimethamine (now not used for malaria chemoprophylaxis in travellers)
Nosten 1994	Participants were semi-immune.
Pearlman 1980	Participants were semi-immune.
Prata 1984	Participants were semi-immune.
Reisinger 1989	Mefloquine compared only with a mefloquine combination (mefloquine plus sulfadoxine-pyrimethamine - the latter now not used for malaria chemoprophylaxis in travellers)
Rieckmann 1974	Allocation of participants to mefloquine arm or no treatment appears to have been non-random
Rombo 1993	Mefloquine compared with sulfadoxine-pyrimethamine (now not used for malaria chemoprophylaxis)
Salako 1992	Participants were semi-immune.

(Continued)

Sossouhounto 1995	Participants were semi-immune.
Steketee 1996	Allocation of participants to mefloquine or control arm was non-random
Weiss 1995	Participants were semi-immune children.
Win 1985	Mefloquine plus sulfadoxine-pyrimethamine (the latter now not used for malaria chemoprophylaxis in travellers) compared with chloroquine

DATA AND ANALYSES

Comparison 1. Mefloquine versus placebo or no drug

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Smear positive malarial illness	1	137	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.04 [0.02, 0.08]
3 Withdrawal from study	4	1382	Odds Ratio (M-H, Fixed, 95% CI)	3.56 [1.67, 7.60]
4 Non-adherence at first assessment	1	137	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.61 [0.47, 122.95]
5 Sleep disturbance	1	46	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.11 [0.80, 82.12]
6 Gastrointestinal symptoms (add)	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. Mefloquine versus alternative chemoprophylaxis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Smear-positive malarial illness	1	135	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.00, 6.72]
3 Withdrawal from study	4	1661	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.33 [0.75, 2.36]
4 Non-adherence at first assessment	4	1238	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.69, 1.58]
5 Depression	3	1209	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.74 [0.44, 1.22]
6 Dreams	4	1344	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.71 [0.46, 1.08]
7 Fatigue	4	1344	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.57 [1.01, 2.45]
8 Headache	6	1717	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.77, 1.33]
9 Insomnia	4	1344	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.64 [1.18, 2.28]
11 Abdominal pain	5	1464	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.57 [0.42, 0.77]
12 Anorexia	4	1444	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.64 [0.43, 0.95]
13 Diarrhoea	6	1717	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.58 [0.45, 0.74]
14 Nausea	6	1717	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.74 [0.57, 0.96]
15 Vomiting	4	1599	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.81 [0.48, 1.38]
17 Fever	2	494	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.95 [1.00, 3.80]
18 Itch	3	985	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.85 [0.55, 1.33]
20 Any symptom	4	1344	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.80, 1.27]
21 Died or hospitalised (non-malaria)	2	850	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.50 [0.05, 4.79]

Analysis 1.1. Comparison 1 Mefloquine versus placebo or no drug, Outcome 1 Smear positive malarial illness.

Review: Mefloquine for preventing malaria in non-immune adult travellers

Comparison: 1 Mefloquine versus placebo or no drug

Outcome: 1 Smear positive malarial illness

Analysis 1.3. Comparison 1 Mefloquine versus placebo or no drug, Outcome 3 Withdrawal from study.

Review: Mefloquine for preventing malaria in non-immune adult travellers

Comparison: 1 Mefloquine versus placebo or no drug

Outcome: 3 Withdrawal from study

Analysis 1.4. Comparison 1 Mefloquine versus placebo or no drug, Outcome 4 Non-adherence at first assessment.

Review: Mefloquine for preventing malaria in non-immune adult travellers

Comparison: 1 Mefloquine versus placebo or no drug

Outcome: 4 Non-adherence at first assessment

Analysis 1.5. Comparison 1 Mefloquine versus placebo or no drug, Outcome 5 Sleep disturbance.

Review: Mefloquine for preventing malaria in non-immune adult travellers

Comparison: 1 Mefloquine versus placebo or no drug

Outcome: 5 Sleep disturbance

Analysis 2.1. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 1 Smear-positive malarial illness.

Review: Mefloquine for preventing malaria in non-immune adult travellers

Comparison: 2 Mefloquine versus alternative chemoprophylaxis

Outcome: 1 Smear-positive malarial illness

Analysis 2.3. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 3 Withdrawal from study.

Review: Mefloquine for preventing malaria in non-immune adult travellers

Comparison: 2 Mefloquine versus alternative chemoprophylaxis

Outcome: 3 Withdrawal from study

Analysis 2.4. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 4 Non-adherence at first assessment.

Review: Mefloquine for preventing malaria in non-immune adult travellers

Comparison: 2 Mefloquine versus alternative chemoprophylaxis

Outcome: 4 Non-adherence at first assessment

Analysis 2.5. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 5 Depression.

Review: Mefloquine for preventing malaria in non-immune adult travellers

Comparison: 2 Mefloquine versus alternative chemoprophylaxis

Outcome: 5 Depression

Analysis 2.6. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 6 Dreams.

Review: Mefloquine for preventing malaria in non-immune adult travellers

Comparison: 2 Mefloquine versus alternative chemoprophylaxis

Outcome: 6 Dreams

Analysis 2.7. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 7 Fatigue.

Review: Mefloquine for preventing malaria in non-immune adult travellers

Comparison: 2 Mefloquine versus alternative chemoprophylaxis

Outcome: 7 Fatigue

Analysis 2.8. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 8 Headache.

Review: Mefloquine for preventing malaria in non-immune adult travellers

Comparison: 2 Mefloquine versus alternative chemoprophylaxis

Outcome: 8 Headache

Analysis 2.9. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 9 Insomnia.

Review: Mefloquine for preventing malaria in non-immune adult travellers

Comparison: 2 Mefloquine versus alternative chemoprophylaxis

Outcome: 9 Insomnia

Analysis 2.11. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 11 Abdominal pain.

Review: Mefloquine for preventing malaria in non-immune adult travellers

Comparison: 2 Mefloquine versus alternative chemoprophylaxis

Outcome: 11 Abdominal pain

Analysis 2.12. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 12 Anorexia.

Review: Mefloquine for preventing malaria in non-immune adult travellers

Comparison: 2 Mefloquine versus alternative chemoprophylaxis

Outcome: 12 Anorexia

Analysis 2.13. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 13 Diarrhoea.

Review: Mefloquine for preventing malaria in non-immune adult travellers

Comparison: 2 Mefloquine versus alternative chemoprophylaxis

Outcome: 13 Diarrhoea

Analysis 2.14. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 14 Nausea.

Review: Mefloquine for preventing malaria in non-immune adult travellers

Comparison: 2 Mefloquine versus alternative chemoprophylaxis

Outcome: 14 Nausea

Analysis 2.15. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 15 Vomiting.

Review: Mefloquine for preventing malaria in non-immune adult travellers

Comparison: 2 Mefloquine versus alternative chemoprophylaxis

Outcome: 15 Vomiting

Analysis 2.17. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 17 Fever.

Review: Mefloquine for preventing malaria in non-immune adult travellers

Comparison: 2 Mefloquine versus alternative chemoprophylaxis

Outcome: 17 Fever

Analysis 2.18. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 18 Itch.

Review: Mefloquine for preventing malaria in non-immune adult travellers

Comparison: 2 Mefloquine versus alternative chemoprophylaxis

Outcome: 18 Itch

Analysis 2.20. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 20 Any symptom.

Review: Mefloquine for preventing malaria in non-immune adult travellers

Comparison: 2 Mefloquine versus alternative chemoprophylaxis

Outcome: 20 Any symptom

Analysis 2.21. Comparison 2 Mefloquine versus alternative chemoprophylaxis, Outcome 21 Died or hospitalised (non-malaria).

Review: Mefloquine for preventing malaria in non-immune adult travellers

Comparison: 2 Mefloquine versus alternative chemoprophylaxis

Outcome: 21 Died or hospitalised (non-malaria)

ADDITIONAL TABLES

Table 1. Published case reports of adverse effects from mefloquine prophylaxis, 1976-2000

Study identifier	Publication year	Publication language	Study design	Setting	Numerator	Denominator	Incidence (%)	Reference
Clyde 1976	1976	English	Case series	Prisoner	3			Clyde DF, et al. Suppressive activity of mefloquine in sporozoite-induced human malaria. <i>Antimicrobial Agents and Chemotherapeutics</i> 1976; 9: 384-38
Coulaud 1983	1983	French	Cohort study	Tourist	2	53	3.8	Coulaud JP, et al. Traitement du paludisme d'importation par la méfloquine. <i>Annales du Société Belge de la Médecine Tropicale</i> 1983; 63: 247-257
Heimgartner 1986	1986	German	Cohort study	Tourist	10	30	33.3	Heimgartner E. Praktische Erfahrungen mit Mefloquin als Malaria-prophylaxe.

Table 1. Published case reports of adverse effects from mefloquine prophylaxis, 1976-2000 (Continued)

								laktikum. Schweiz- erische Rundschau für Medi- zin Praxis (Bern) 1986; 75: 459-462
Castot 1988	1988	French	Case report	Tourist	1		-	Castot A, et al. Réflexions sur les effets secondaires de la mefloquine. Le Concours Médicale 1988; 110: 4003
Jallon 1988	1988	English	Case report	Tourist	1		-	Jallon P. Use of meflo- quine in epileptic pa- tients. Jour- nal of Neu- rology, Neu- rosurgery and Psychia- try 1988; 51: 733-739
Kollaritsch 1988	1988	English	RCT	Business traveller	9	81	11.1	Kollaritsch H, et al. Tolerability of long- term malaria prophylaxis with the combina- tion meflo- quine + sul- fadoxine + pyrimethamine (Fansimef) : results of

Table 1. Published case reports of adverse effects from mefloquine prophylaxis, 1976-2000 (Continued)

								a double blind field trial versus chloroquine in Nigeria. Transactions of the Royal Society of Tropical Medicine and Hygiene 1988; 82: 524-529
Hellgren 1989	1989	Swedish	Case report	Tourist	1		-	Hellgren U, et al. Neurologiska biverkningar av meflokin: implikationer för profylax och egenbehandling. Läkartidningen (Stockholm) 1989; 86: 4592
Navaratnam 1989	1989	English	RCT	Military	5	310	1.6	Navaratnam V, et al. Chemo-suppression of malaria by the triple combination mefloquine/ sulfadoxine/ pyrimethamine: a field trial in an endemic area in Malaysia. Transactions of the Royal Society of

Table 1. Published case reports of adverse effects from mefloquine prophylaxis, 1976-2000 (Continued)

								Tropical Medicine and Hygiene 1989; 83: 755-759
Reisinger 1989	1989	English	RCT	Tourist	6	175	3.4	Reisinger EC, et al. Tolerance of mefloquine alone and in combi- nation with sulfadoxine- pyrimethamine in the prophylaxis of malaria. Transactions of the Royal Society of Tropical Medicine and Hygiene 1989; 83: 474-477
WHO 1989	1989	English	Case series	Tourist	6		-	World Health Or- ganization. Central ner- vous system reactions re- lated to the antimalarial drug, meflo- quine. Geneva: World Health Or- ganiza- tion; 1989. Report No: WHO/ MAL/89/ 1054
Anonymous 1990	1990	English	Case report	Tourist	1		-	Anony- mous.

Table 1. Published case reports of adverse effects from mefloquine prophylaxis, 1976-2000 (Continued)

								Mefloquine for malaria. Medical Letter on Drugs and Therapeutics 1990; 31: 13-14
Rodor 1990	1990	French	Case report	Tourist	1		-	Rodor F, et al. Manifestations psychiatriques récidivantes lors d'une prophylaxie antipaludique par méfloquine. A propos d'un cas. Therapie 1990; 45: 433-434
Steffen 1990	1990	English	Cohort study	Tourist	1	2780	0.0	Steffen R, et al. Malaria chemoprophylaxis among European tourists in tropical Africa: use, adverse reactions and efficacy. Bulletin of the World Health Organization 1990; 68: 313-322
Besser 1991	1991	German	Case report	Tourist	1		-	Besser R, et al. Verdacht auf anfallfördernde

Table 1. Published case reports of adverse effects from mefloquine prophylaxis, 1976-2000 (Continued)

								Wirkung von Mefloquin (Lariam®). Nervenarzt 1991; 62: 760-761
Hennequin 1991	1991	English	Case report	Tourist	1		-	Hennequin C, et al. Agranulocytosis during treatment with mefloquine. Lancet 1991; 337: 984
Shlim 1991	1991	English	Case report	Tourist	1		-	Shlim DR. Severe facial rash associated with mefloquine. Journal of the American Medical Association 1991; 266: 2560
Singh 1991	1991	English	Case report	Tourist	1		-	Singh K, et al. Seizures after mefloquine. Annals of Internal Medicine 1991; 114: 994
Van den Enden 1991	1991	English	Case report	Tourist	1		-	Van den Enden E, et al. Mefloquine induced Stevens-Johnson syndrome.

Table 1. Published case reports of adverse effects from mefloquine prophylaxis, 1976-2000 (Continued)

								Lancet 1991; 337: 683
Weinke 1991	1991	English	Cohort study	Tourist	4	52000	0.0	Weinke T, et al. Neuropsy- chiatric side effects after the use of mefloquine. American Jour- nal of Tropi- cal Medicine and Hygiene 1991; 45: 86-9
WHO 1991	1991	English	Case series	Tourist	14		-	World Health Or- ganization. Review of central ner- vous system adverse events re- lated to the antimalar- ial drug, mefloquine (1985- 1990). Geneva: World Health Organiza- tion; 1991. Report No: WHO/ MAL/91. 1063
Bem 1992	1992	English	Case series	Tourist	54		-	Bem JL, et al. Meflo- quine pro- phylaxis: an overview of spontaneous

Table 1. Published case reports of adverse effects from mefloquine prophylaxis, 1976-2000 (Continued)

								reports of severe psychiatric reactions and convulsions. Journal of Tropical Medicine and Hygiene 1992; 95: 167-179
Caillon 1992	1992	English	Case report	Tourist	1		-	Caillon E, et al. Acute depressive symptoms after mefloquine treatment. American Journal of Psychiatry 1992; 149: 5
Folkerts 1992	1992	German	Case report	Business traveller	1		-	Folkerts H, et al. Psychotische Episode infolge Malaria-prophylaxe mit Mefloquin. Eine kasuistische Mitteilung. Nervenarzt (Berlin) 1992; 63: 300-302
Olson 1992	1992	English	Case report	Military	1		-	Olson PE, et al. Paresthesias and mefloquine prophylaxis. Annals of Internal Medicine 1992; 117: 1058-1059

Table 1. Published case reports of adverse effects from mefloquine prophylaxis, 1976-2000 (Continued)

Boudreau 1993	1993	English	RCT	Military	2	203	1.0	Boudreau E, et al. Tolerability of prophylactic Lariam regimens. Tropical Medicine and Parasitology 1993; 44: 257-265
Burke 1993	1993	English	Case report	Business traveller	1		-	Burke BM. Mefloquine. Lancet 1993; 341: 1605-1606
Conget 1993	1993	Spanish	Case report	Tourist	1		-	Conget JI, et al. Alteración del perfil hormonal tiroideo tras la administración profiláctica de mefloquina. Medicina Clínica (Barcelona) 1993; 100: 516
Gascon 1993	1993	Spanish	Case report	Tourist	1		-	Gascón J, et al. Reacción neuropsiquiátrica grave tras la toma de mefloquina. Medicina Clínica (Barcelona) 1993; 101: 515-516

Table 1. Published case reports of adverse effects from mefloquine prophylaxis, 1976-2000 (Continued)

Gullahorn 1993	1993	English	Case series	Military	3		-	Gul- lahorn GM, et al. Anaes- thesia emer- gence delir- ium after mefloquine prophy- laxis. Lancet 1993; 341: 632
Kozarsky 1993	1993	English	Cohort study	Tourist	16	144	11.1	Kozarsky P, et al. Use of mefloquine for malarial chemopro- phylaxis in its first year of avail- ability in the United States. Clin- ical In- fectious Dis- eases 1993; 16: 185-186
Marsepoil 1993	1993	French	Case report	Tourist	1		-	Marsepoil T, et al. Encéphalopathie et troubles amnésiques au cours des traite- ments par la méfloquine. Revue de la Médecine Interne (Paris) 1993; 14: 788-791
Martin 1993	1993	English	Case report	Tourist	1		-	Martin GJ, et al. Ex- foliative der- matitis dur- ing malarial

Table 1. Published case reports of adverse effects from mefloquine prophylaxis, 1976-2000 (Continued)

								prophylaxis with mefloquine. Clinical Infectious Diseases 1993; 16; 341-342
Ries 1993	1993	German	Case report	Tourist	1		-	Ries S. Zerebrale Krampfanfälle während einer Malaria prophylaxe mit Mefloquin. Deutsche Medizinische Wochenschrift (Stuttgart) 1993; 118: 1911-1912
Rombo 1993	1993	English	RCT	Resident	4	105	3.8	Rombo L, et al. Comparative intake and tolerability during long-term intake of Lariam and Fansidar for malaria prophylaxis in nonimmune volunteers. Tropical Medicine and Parasitology 1993; 44: 254-256
Scerri 1993	1993	English	Case report	Tourist	1		-	Scerri L, et al. Mefloquine-as-

Table 1. Published case reports of adverse effects from mefloquine prophylaxis, 1976-2000 (Continued)

								sociated cutaneous vasculitis. International Journal of Dermatology 1993; 32: 517-518
Grupp 1994	1994	German	Case report	Tourist	1		-	Grupp D, et al. Neuropsychiatrische Störungen nach Malariaprophylaxe mit Mefloquin. Aktuelle Neurologie (Stuttgart) 1994; 21: 134-136
Hennequin 1994	1994	English	Case report	Tourist	1		-	Hennequin C, et al. Severe psychiatric side effects observed during prophylaxis and treatment with mefloquine. Archives of Internal Medicine 1994; 154: 2360-2362
Nosten 1994	1994	English	RCT	Resident	1	171	0.6	Nosten F, et al. Mefloquine prophylaxis prevents malaria during

Table 1. Published case reports of adverse effects from mefloquine prophylaxis, 1976-2000 (Continued)

								pregnancy: a double-blind, placebo-controlled study. Journal of Infectious Diseases 1994; 169: 595-603
Phillips 1994	1994	English	Case series	Tourist	5		-	Phillips M. Antimalarial mefloquine. The Medical Journal of Australia 1994; 161: 227-228
Ruff 1994	1994	English	Case report	Tourist	1		-	Ruff TA, et al. Seizure associated with mefloquine for malaria prophylaxis. Medical Journal of Australia 1994; 161: 453
Stracher 1994	1994	English	Case report	Tourist	1		-	Stracher AR, et al. Aplastic anemia during malarial prophylaxis with mefloquine. Clinical Infectious Diseases 1994; 18: 263-264
Takeshima 1994	1994	Japanese	Cohort study	Military	16	48	33.3	Takeshima S. Side

Table 1. Published case reports of adverse effects from mefloquine prophylaxis, 1976-2000 (Continued)

								effects with mefloquin for long-term malaria prophylaxis. Japanese Journal of Tropical Medicine and Hygiene 1994; 22: 193-198
Hessen-Söderman 1995	1995	English	Cohort study	Experimental volunteer	1	10	10.0	Hessén-Söderman A, et al. Mefloquine prophylaxis and hearing, postural control, and vestibular functions. Journal of Travel Medicine 1995; 2: 66-69
Hollweg 1995	1995	German	Case report	Tourist	1		-	Hollweg M. Mefloquininduzierte Psychosen - Probleme der Kausalzuordnung anhand zweier kasuistischer Berichte. Psychiatrische Praxis (Stuttgart) 22: 33-36

Table 1. Published case reports of adverse effects from mefloquine prophylaxis, 1976-2000 (Continued)

Lench 1995	1995	English	Case report	Aid worker	1		-	Lench P. Psychological problems after mefloquine and chloroquine. British Medical Journal 1995; 311: 192
Pous 1995	1995	English	Case report	Tourist	1		-	Pous E, et al. Mefloquine-induced grand mal seizure during malaria chemoprophylaxis in a non-epileptic subject. Transactions of the Royal Society of Tropical Medicine and Hygiene 1995; 89: 434
Sos-souhounto 1995	1995	English	RCT	Resident	10	204	4.9	Sos-souhounto RT, et al. Mefloquine in the prophylaxis of <i>P falciparum</i> malaria. Journal of Travel Medicine 1995; 2: 221-224
Van Puijenbroek 1995	1995	Dutch	Case series	Tourist	6		-	van Puijenbroek EP, et al. Slaapstoornissen

Table 1. Published case reports of adverse effects from mefloquine prophylaxis, 1976-2000 (Continued)

								tijdens het gebruik van mefloquine. Pharmaceutisch Weekblad 1995; 130: 477-479
White 1995	1995	English	Case report	Tourist	1		-	White AC, et al. Cutaneous vasculitis associated with mefloquine. Annals of Internal Medicine 1995; 123: 894
Wittes 1995	1995	English	Case report	Business traveller	1		-	Wittes RC, et al. Adverse reaction to mefloquine associated with ethanol ingestion. Canadian Medical Association Journal 1995; 152: 515-517
Barrett 1996	1996	English	Cohort study	Tourist	10	1214	0.8	Barrett PJ, et al. Comparison of adverse events associated with use of mefloquine and combination of chloroquine

Table 1. Published case reports of adverse effects from mefloquine prophylaxis, 1976-2000 (Continued)

								and proguanil as antimalar- ial prophylaxis: postal and telephone survey of travellers. British Medical Journal 1996; 313: 525-528
Carme 1996	1996	French	Case series	Tourist	5		-	Carme B, et al. Intolérance neuropsychique au cours de la chimio-prophylaxie antipalustre par la méfloquine. A propos de 5 observations. Médecine et Maladies Infectieuses 1996; 26: 728-729
Constable 1996	1996	English	Case series	Tourist	2		-	Constable P. Lariam. Pharmaceutical Journal 1996; 256: 212
Croft 1996	1996	English	Case report	Military	1		-	Croft AMJ, et al. Neuropsychiatric reactions with mefloquine chemoprophylaxis.

Table 1. Published case reports of adverse effects from mefloquine prophylaxis, 1976-2000 (Continued)

								laxis. Lancet 1996; 347: 326
Fonteyne 1996	1996	English	Case report	Tourist	1		-	Fonteyne W, et al. Atrial flutter with 1:1 conduction after administration of the anti-malarial drug mefloquine. Clinical Cardiology 1996; 19: 967-968
Meszaros 1996a	1996	English	Case report	Tourist	1		-	Meszaros K. Acute psychosis caused by mefloquine prophylaxis? Canadian Journal of Psychiatry 1996; 41: 196
Meszaros 1996b	1996	German	Case report	Tourist	1		-	Meszaros K. Psychopathological symptoms in the long-term course of an acute psychosis after intake of mefloquine
Phillips 1996	1996	English	Cohort study	Tourist	4	285	1.4	Phillips MA, et al. User acceptability patterns for mefloquine and doxycycline malaria

Table 1. Published case reports of adverse effects from mefloquine prophylaxis, 1976-2000 (Continued)

								chemoprophylaxis. Journal of Travel Medicine 1996; 3: 40-45
Piening 1996	1996	English	Case report	Military	1		-	Piening RB, et al. Mefloquine-induced psychosis. Annals of Emergency Medicine 1996; 27: 792-793
Vuurman 1996	1996	English	RCT	Experimental volunteer	2	20	10.0	Vuurman EFPM, et al. Effects of mefloquine alone and with alcohol on psychomotor and driving performance. European Journal of Clinical Pharmacology 1996; 50: 475-482
Anonymous 1997	1997	Dutch	Case series	Tourist	19		-	Anonymous. Toegenomen transpiratie met mefloquine (Lariam®). Geneesmiddelen Bulletin 1997; 31: 97

Table 1. Published case reports of adverse effects from mefloquine prophylaxis, 1976-2000 (Continued)

Bauer 1997	1997	English	Case report	Aid worker	1		-	Bauer WM, et al. Acute psychotic reactions in an aid worker following separate administration of mefloquine and iodoquinol. Proceedings of the Fifth International Conference on Travel Medicine; 1997 Mar 24-27; Geneva. Geneva: International Society of Travel Medicine, 1997
Carme 1997	1997	French	Case series	Tourist	36		-	Carme B, et al. Chimio-prophylaxie du paludisme: tolérance et observance de la méfloquine et de l'association proguanil/chloroquine chez des touristes français. Bulletin de la Société de

Table 1. Published case reports of adverse effects from mefloquine prophylaxis, 1976-2000 (Continued)

								Pathologie Exotique (Paris) 1997; 90: 273-276
Clattenburg 1997	1997	English	Case report	Tourist	1		-	Clattenburg RN, et al. Case study: neuropsychiatric symptoms associated with the antimalarial agent mefloquine. Journal of the American Academy of Child and Adolescent Psychiatry 1997; 36: 1606-1608
De Beer 1997	1997	Dutch	Case report	Resident	1		-	De Beer PAM. Niet meer klachten bij mefloquinegebruik dan bij malariaprofylaxe met andere middelen. Nederlands Tijdschrift voor Geneeskunde (Amsterdam) 1997; 141: 795
Kollaritsch 1997	1997	English	RCT	Experimental volunteer	4	60	6.7	Kollaritsch H, et al. Safety and im-

Table 1. Published case reports of adverse effects from mefloquine prophylaxis, 1976-2000 (Continued)

								munogenicity of live oral cholera and typhoid vaccines administered alone or in combination with antimalarial drugs, oral polio vaccine, or yellow fever vaccine. Journal of Infectious Diseases 1997; 175: 871-875
Lafitte 1997	1997	French	Case report	Tourist	1		-	Lafitte E. Crise convulsive à la méfloquine en prophylaxe. Médecine Tropicale (Marseille) 1997; 57: 307
McBride 1997	1997	English	Case report	Tourist	1		-	McBride SR, et al. Fatal toxic epidermal necrolysis associated with mefloquine anti-malarial prophylaxis. Lancet 1997; 349: 101
Ravera 1997	1997	English	Case series	Tourist	2		-	Ravera M. Se-

Table 1. Published case reports of adverse effects from mefloquine prophylaxis, 1976-2000 (Continued)

								vere adverse reactions to prophylactic use of mefloquine in nonimmune travellers in Hoima District, Uganda. Journal of Travel Medicine 1997; 4: 153-154
Richter 1997	1997	English	Case report	Tourist	1		-	Richter J. Aberrant atrioventricular conduction triggered by antimalarial prophylaxis with mefloquine. Lancet 1997; 349: 101
Schlagenhauf 1997	1997	English	RCT	Experimental volunteer	4	23	17.4	Schlagenhauf P, et al. Tolerance of mefloquine by Swissair trainee pilots. American Journal of Tropical Medicine and Hygiene 1997; 56(2): 235-240
Thorsten 1997	1997	English	Case report	Tourist	1		-	Thorsten O, et al. Acute necrotizing pancreatitis possibly

Table 1. Published case reports of adverse effects from mefloquine prophylaxis, 1976-2000 (Continued)

								caused by mefloquine for malaria prophylaxis. Proceedings of the Fifth International Conference on Travel Medicine; 1997 Mar 24-27; Geneva. Geneva: International Society of Travel Medicine, 1997
Anonymous 1998	1998	English	Case report	Tourist	1		-	Anony-mous. Roche's Lar-iam linked to a suicide in UK. Scrip 1998; 2331: 23
Drent 1998	1998	English	Case report	Tourist	1		-	Drent M. Drug-in-duced pneu-monia asso-ciated with hemizygote glucose-6-phosphate dehydro-genase defi-ciency. Eu-ropean Jour-nal of Haema-tology 1998; 61: 218-220
Heeringa 1998	1998	Dutch	Case series	Tourist	6		-	Heeringa M, et al. Con-

Table 1. Published case reports of adverse effects from mefloquine prophylaxis, 1976-2000 (Continued)

								vulsies ti- jdens profy- lactisch gebruik van meflo- quine. Ned- erlands Tijd- schrift voor Ge- neeskunde (Amster- dam) 1998; 142: 2477- 2478
Jensen 1998	1998	Danish	Case series	Tourist	5		-	Jensen JB. Meflochin: de neurop- sykiatriske bivirkninger er ofte alvorlige og kan per- sistere længe efter ophør med medici- nen. Ugeskrift for Læger (Copen- hagen) 1998; 159: 241
Lysack 1998	1998	English	Case report	Tourist	1		-	Lysack JT. A severe adverse reac- tion to mefloquine and chloro- quine prophylaxis. Aus- tralian Fam- ily Physician 1998; 27: 1119-1120

Table 1. Published case reports of adverse effects from mefloquine prophylaxis, 1976-2000 (Continued)

Potashman 1998	1998	English	Case report	Tourist	1		-	Potashman I, et al. A unique case of mefloquine-induced psoriasis. Journal of Travel Medicine 1998; 5: 156
Bygbjerg 1999	1999	Danish	Case report	Tourist	1		-	Bygbjerg IC, et al. Langvarige neuropsykiske bivirkninger efter meflochin-profylakse. Ugeskrift for Læger (Copenhagen) 1999; 161: 1422-1423
Fusetti 1999	1999	Italian	Case series	Tourist	3		-	Fusetti M, et al. Meflochina ed ototoxicità: descrizione di tre casi. Clinica Terapeutica (Roma) 1999; 150: 379-382
Grieco 1999	1999	English	Case report	Tourist	1		-	Grieco A, et al. Acute fatty liver after malaria prophylaxis with mefloquine. Lancet

Table 1. Published case reports of adverse effects from mefloquine prophylaxis, 1976-2000 (Continued)

								1999; 353: 295-296
Kollaritsch 2000	2000	German	RCT	Experimental volunteer	1	12	8.3	Kollaritsch H, et al. Mefloquine concentration profiles during prophylactic dose regimes. Wiener Klinische Wochenschrift 2000; 112: 441-447

Table 2. Published case reports of adverse effects from mefloquine treatment, 1981-2000

Study identifier	Publication year	Publication language	Study design	Setting	Numerator	Denominator	Incidence (%)	Reference
Felix 1981	1981	French	Case series	Resident	4	?	-	Felix H, et al. La méfloquine. Rapport préliminaire. Médecine et Maladies Infectieuses 1981; 11: 392-399
Ekue 1983	1983	English	RCT	Resident	3	50	6.0	Ekue JM, et al. A double-blind comparative clinical trial

Table 2. Published case reports of adverse effects from mefloquine treatment, 1981-2000 (Continued)

								of mefloquine and chloroquine in symptomatic falciparum malaria. Bulletin of the World Health Organization 1983; 61: 713-718
Harinasuta 1983	1983	English	RCT	Resident	4	147	2.7	Hari-nasuta T, et al. A phase II clinical trial of mefloquine in patients with chloroquine-resistant falciparum malaria in Thailand. Bulletin of the World Health Organization 1983; 61: 299-305
Li 1984	1984	English	RCT	Resident	8	65	12.3	Li G, et al. Randomised comparative study of mefloquine, qinghaosu, and pyrimethamine-sulfadoxine in patients with falciparum malaria. Lancet 1984; ii: 1360-1361

Table 2. Published case reports of adverse effects from mefloquine treatment, 1981-2000 (Continued)

Ekue 1985	1985	English	RCT	Resident	1	150	0.7	Ekue JMK, et al. A double-blind clinical trial of a combination of mefloquine, sulfadoxine and pyrimethamine in symptomatic falciparum malaria. Bulletin of the World Health Organisation 1985; 63: 339-343
Harinasuta 1985	1985	English	RCT	Resident	1	58	1.7	Harinasuta T, et al. Trials of mefloquine in vivax and of mefloquine plus 'Fansidar' in falciparum malaria. Lancet 1985; i: 885-888
Bernard 1987	1987	French	Case report	Tourist	1	?	-	Bernard J, et al. Encéphalopathie toxique à la méfloquine? La Presse Médicale (Paris) 1987; 16: 1654-1655
De Souza 1987	1987	English	RCT	Resident	5	150	3.3	De Souza JM, et al. A phase II/

Table 2. Published case reports of adverse effects from mefloquine treatment, 1981-2000 (Continued)

								III double-blind, dose-finding clinical trial of a combination of mefloquine, sulfadoxine, and pyrimethamine (Fansimef) in falciparum malaria. Bulletin of the World Health Organization 1987; 65: 357-36
Ekue 1987	1987	English	RCT	Resident	2	50	4.0	Ekue JMK, et al. A double-blind trial of a fixed combination of mefloquine plus sulfadoxine-pyrimethamine compared with sulfadoxine-pyrimethamine alone in symptomatic falciparum malaria. Bulletin of the World Health Organization 1987; 65: 369-373
Nosten 1987	1987	English	Cohort study	Resident	1	5192	0.0	Nosten F, et al. Malaria

Table 2. Published case reports of adverse effects from mefloquine treatment, 1981-2000 (Continued)

								on the Thai-Burmese border: treatment of 5192 patients with mefloquine-sulfadoxine-pyrimethamine. Bulletin of the World Health Organization 1987; 65: 891-896
Guo 1988	1988	English	RCT	Resident	2	60	3.3	Guo XB, et al. Double-blind dose finding study of mefloquine-sulfadoxine pyrimethamine in children with acute falciparum malaria. Transactions of the Royal Society of Tropical Medicine and Hygiene 1988; 82: 538-540
Bernard 1989	1989	French	Case series	Tourist	2	?	-	Bernard J, et al. Encéphalopathie toxique à la méfloquine: à propos de trois observations. Médecine et Armées 1989; 17: 209-211

Table 2. Published case reports of adverse effects from mefloquine treatment, 1981-2000 (Continued)

Lapras 1989	1989	French	Case report	Tourist	1	?	-	Lapras J, et al. Trouble transitoire de mémoire au décours d'un accès palustre. Responsabilité de la méfloquine? Presse Médicale (Paris) 1989; 18: 776
Rouveix 1989	1989	English	Case series	Tourist	5	?	-	Rouveix B, et al. Mefloquine and an acute brain syndrome. Annals of Internal Medicine 1989; 110: 577-578
Stuiver 1989	1989	English	Case series	Tourist	2	?	-	Stuiver PC, et al. Acute psychosis after mefloquine. Lancet 1989; ii: 282
WHO 1989	1989	English	Case series	Tourist	14	?	-	World Health Organization. Central nervous system reactions related to the antimalarial drug, mefloquine. Geneva: World Health Or-

Table 2. Published case reports of adverse effects from mefloquine treatment, 1981-2000 (Continued)

								ganiza- tion; 1989. Report No: WHO/ MAL/89/ 1054
Ajana 1990	1990	French	Case report	Resident	1	?	-	Ajana F, et al. Pro- phylaxie par mefloquine et neurotox- icité. À pro- pos d'une observation. Semaine des Hôpitaux de Paris 1990; 66: 918-919
Anh 1990	1990	English	RCT	Resident	2	80	2.5	Anh TK, et al. Dou- ble-blind studies with mefloquine alone and in combi- nation with sulfadoxine- pyrimethamine in 120 adults and 120 chil- dren with falciparum malaria in Vietnam. Journal of Tropical Medicine and Hygiene 1990; 84: 50-53
Bourgeade 1990	1990	French	Case report	Business traveller	1	?	-	Bourgeade A, et al. In- tox- ication acci- dentelle à la

Table 2. Published case reports of adverse effects from mefloquine treatment, 1981-2000 (Continued)

								mefloquine. La Presse Médicale 1990; 19: 1903
Gascon 1990	1990	Spanish	Case series	Tourist	3	?	-	Gascón J, et al. Efectos secundarios del antipalúdico mefloquina. Presentación de 20 casos. Medicina Clínica (Barcelona) 1990; 95: 277
Held 1991	1991	German	Case series	Tourist	2	?	-	Held T, et al. Klinische Erfahrungen mit Mefloquin bei Malaria tropica - eine prospektive Studie. Immunität und Infektion 1991; 19: 83-86
Hellgren 1991	1991	English	Case series	Resident	8	?	-	Hellgren U, et al. Standard and reduced doses of mefloquine for treatment of Plasmodium falciparum in Tanzania: whole blood con-

Table 2. Published case reports of adverse effects from mefloquine treatment, 1981-2000 (Continued)

								centrations in relation to adverse reactions, in vivo response, and in vitro susceptibility. American Journal of Tropical Medicine and Hygiene 1991; 45: 254-262
Karbwang 1991	1991	English	RCT	Experimental volunteer	14	20	70.0	Karbwang J, et al. Pharmacokinetics and pharmacodynamics of mefloquine in Thai patients with acute falciparum malaria. Bulletin of the World Health Organization 1991; 69: 207-212
Luxemburger 1991	1991	English	Cohort study	Resident	8	95013	0.1	Luxemburger C, et al. Mefloquine for multidrug-resistant malaria. Lancet 1991; 338: 1268
Nosten 1991	1991	English	RCT	Resident	1	395	0.3	Nosten F, et al. Mefloquine-resistant fal-

Table 2. Published case reports of adverse effects from mefloquine treatment, 1981-2000 (Continued)

								ciparum malaria on the Thai-Burmese border. Lancet 1991; 337: 1140-1143
Weinke 1991	1991	English	Cohort study	Tourist	8	1720	0.5	Weinke T, et al. Neuropsychiatric side effects after the use of mefloquine. American Journal of Tropical Medicine and Hygiene 1991; 45: 86-91
WHO 1991	1991	English	Case series	Resident	8	?	-	World Health Organization. Review of central nervous system adverse events related to the antimalarial drug, mefloquine (1985-1990). Geneva: World Health Organization; 1991. Report No: WHO/MAL/91.1063

Table 2. Published case reports of adverse effects from mefloquine treatment, 1981-2000 (Continued)

Bem 1992	1992	English	Case series	Tourist	2	?	-	Bem JL, et al. Mefloquine prophylaxis: an overview of spontaneous reports of severe psychiatric reactions and convulsions. Journal of Tropical Medicine and Hygiene 1992; 95: 167-179
Bunnag 1992	1992	English	RCT	Resident	3	51	5.9	Bunnag D, et al. Clinical trials of mefloquine with tetracycline. Southeast Asian Journal of Tropical Medicine and Public Health 1992; 23: 377-382
Caillon 1992	1992	English	Case report	Tourist	1	?	-	Caillon E, et al. Acute depressive symptoms after mefloquine treatment. American Journal of Psychiatry 1992; 149: 5
De Gennes 1992	1992	French	Case report	Business traveller	1	?	-	De Gennes C, et al. Attaque de panique au

Table 2. Published case reports of adverse effects from mefloquine treatment, 1981-2000 (Continued)

								décours d'un traitement curatif par la méfloquine. Annales de la Médecine Interne (Paris) 1992; 142: 631
Doumbo 1992	1992	French	Case series	Resident	12	?	-	Doumbo O, et al. Efficacité et tolérance de la triple association méfloquine + pyriméthamine + sulfadoxine (Fansimef®) dans le traitement des accès palustres graves à Plasmodium falciparum au Mali (à propos de 100 cas). Médecine d'Afrique Noire 1992; 39: 458-462
Karbwang 1992a	1992	English	RCT	Resident	1	8	12.5	Karbwang J, et al. Pharmacokinetics of mefloquine in the presence of primaquine. European Journal of Clinical Pharmacology 1992; 42: 1-6

Table 2. Published case reports of adverse effects from mefloquine treatment, 1981-2000 (Continued)

								cology 1992; 42: 559-560
Karbwang 1992b	1992	English	RCT	Resident	5	12	41.7	Karbwang J, et al. Compar- ison of oral artemether and meflo- quine in acute un- complicated falciparum malaria. Lancet 1992; 340: 1245-1248
Looa- reesuwan 1992	1992	English	RCT	Resident	1	85	1.2	Looa- reesuwan S, et al. Ran- domised trial of artesunate and meflo- quine alone and in sequence for acute un- complicated falciparum malaria. Lancet 1992; 339: 821-824
Win 1992	1992	English	RCT	Resident	1	74	1.4	Win K, et al. Compari- son of com- binations of parenteral artemisinin derivatives plus oral meflo- quine with intravenous

Table 2. Published case reports of adverse effects from mefloquine treatment, 1981-2000 (Continued)

								quinine plus oral tetracycline for treating cerebral malaria. Bulletin of the World Health Organization 1992; 70: 777-782
Burgmann 1993	1993	German	Case report	Tourist	1	?	-	Burgmann H, et al. Mefloquin und Sul-fadoxin/Pyrimethamin-Überdosierung bei Malaria tropica. Wiener Medizinische Wochenschrift (Wien) 1993; 105: 61-63
Danis 1993	1993	French	Case series	Resident	3	?	-	Danis M, et al. Fièvre bilieuse hémoglobinurique après prise de méfloquine - 3 observations. La Presse Médicale (Paris) 1993; 22: 80
Marsepoil 1993	1993	French	Case report	Tourist	1	?	-	Marsepoil T, et al.

Table 2. Published case reports of adverse effects from mefloquine treatment, 1981-2000 (Continued)

								Encéphalopathie et troubles amnésiques au cours des traitements par la méfloquine. Revue de la Médecine Interne (Paris) 1993; 14: 788-791
Nosten 1993	1993	English	Case series	Resident	2	?	-	Nosten F, et al. Cardiac effects of antimalarial treatment with halofantrine. Lancet 1993; 341: 1054-1056
Recasens 1993	1993	French	Case report	Tourist	1	?	-	Recasens C, et al. Un épisode psychotique au retour d'un voyage en Afrique: implication possible de la méfloquine. Annales Psychiatriques 1993; 8: 100-103
Sowunmi 1993	1993	English	RCT	Resident	9	303	3.0	Sowunmi A, et al. Neuropsychiatric side effects of mefloquine in Africans. Transac-

Table 2. Published case reports of adverse effects from mefloquine treatment, 1981-2000 (Continued)

								tions of the Royal Society of Tropical Medicine and Hygiene 1993; 87: 462-463
Axmann 1994	1994	English	Case report	Military	1	?	-	Axmann A, et al. Long-term malaria prophylaxis with Lariam in Cambodia, 1993. Travel Medicine International 1994; 12: 13-18
Gram 1994	1994	Danish	Case series	Tourist	2	?	-	Gram LF. Mefloquin (Lariam) og depression/mani. Ugeskrift for Læger (Copenhagen) 1994; 156: 2434
Hennequin 1994	1994	English	Case report	Tourist	1	?	-	Hennequin C, et al. Severe psychiatric side effects observed during prophylaxis and treatment with mefloquine. Archives of Internal Medicine 1994; 154: 2360-2362

Table 2. Published case reports of adverse effects from mefloquine treatment, 1981-2000 (Continued)

Karbwang 1994	1994	English	Case report	Resident	1	?	-	Karbwang J, et al. Quinine toxicity when given with doxycycline and mefloquine. Southeast Asian Journal of Tropical Medicine and Public Health 1994; 25: 397-400
Luxemburger 1994	1994	English	RCT	Resident	3	552	0.5	Luxemburger C, et al. Single day mefloquine-artesunate combination in the treatment of multi-drug resistant falciparum malaria. Transactions of the Royal Society of Tropical Medicine and Hygiene 1994; 88: 213-217
Nosten 1994	1994	English	RCT	Resident	1	652	0.2	Nosten F, et al. Treatment of multidrug-resistant Plasmodium falciparum malaria with 3-day arte-

Table 2. Published case reports of adverse effects from mefloquine treatment, 1981-2000 (Continued)

								unate-mefloquine combination. Journal of Infectious Diseases 1994; 170: 971-977
Ronn 1994	1994	Danish	Case report	Tourist	1	?	-	Rønn AM, et al. Akut hjernesyndrom efter meflokinbehandling. Ugeskrift for Læger (Copenhagen) 1994; 156: 6044-6045
Sowunmi 1994	1994	English	Case report	Resident	1	?	-	Sowunmi A. Acute psychosis after mefloquine: a case report. East African Medical Journal 1994; 71: 818-819
Speich 1994	1994	English	Case report	Tourist	1	?	-	Speich R, et al. Central anticholinergic syndrome with the antimalarial mefloquine. New England Journal of Medicine 1994; 331: 57-58
Assan 1995	1995	English	Case report	Tourist	1	?	-	Assan R, et al.

Table 2. Published case reports of adverse effects from mefloquine treatment, 1981-2000 (Continued)

								Mefloquine-associated hypoglycaemia in a cachectic AIDS patient. Diabete et Metabolisme (Paris) 1995; 21: 54-57
Hollweg 1995	1995	German	Case report	Tourist	1	?	-	Hollweg M. Mefloquininduzierte Psychosen - Probleme der Kausalzuordnung anhand zweier kasuistischer Berichte. Psychiatrische Praxis (Stuttgart) 1995; 22: 33-36
Miyashita 1995	1995	Japanese	Case report	Business traveller	1	?	-	Miyashita T. A case of mefloquine resistant Plasmodium falciparum malaria with convulsion after antimalarial treatment. Kansenshogaku Zasshi (Tokyo) 1995; 68: 152-156

Table 2. Published case reports of adverse effects from mefloquine treatment, 1981-2000 (Continued)

Sowunmi 1995	1995	English	Case series	Resident	5	?	-	Sowunmi A, et al. Acute psychosis after mefloquine. Report of six cases. Tropical and Geographical Medicine 1995; 47: 179-180
Ter Kuile 1995	1995	English	Cohort study	Resident	1	3673	0.0	ter Kuile FO, et al. Mefloquine treatment of acute falciparum malaria: a prospective study of non-serious adverse events in 3673 patients. Bulletin of the World Health Organization 1995; 73: 631-642
Alin 1996	1996	English	RCT	Resident	1	20	5.0	Alin MH. Clinical efficacy and pharmacokinetics of artemisinin monotherapy and in combination with mefloquine in patients with

Table 2. Published case reports of adverse effects from mefloquine treatment, 1981-2000 (Continued)

								falciparum malaria. British Journal of Clinical Pharmacology 1996; 41: 587-592
Garg 1996	1996	English	Case report	Resident	1	?	-	Garg MR, et al. Mefloquine induced grand mal seizure in a case of uncomplicated falciparum malaria. Journal of the Association of Physicians of India 1996; 44: 750
Arndt 1997	1997	English	Case report	Tourist	1	?	-	Arndt PA. Immune hemolytic anemia associated with mefloquine. Transfusion 1997; 37: 1220-1221
Bregani 1998	1998	Italian	Case report	Business traveller	1	?	-	Bregani ER, et al. Mefloquine-induced grand mal seizure in tubercular meningitis. Panminerva Medica (Torino) 1998; 40: 345-346

Table 2. Published case reports of adverse effects from mefloquine treatment, 1981-2000 (Continued)

Jensen 1998	1998	Danish	Case series	Tourist	2	?	-	Jensen JB. Meflochin: de neuropsykiatriske bivirkninger er ofte alvorlige og kan persistere længe efter ophør med medicinen. Ugeskrift for Læger (Copenhagen) 1998; 159: 241
Van den Ende 1998	1998	English	Case report	Resident	1	?	-	van den Ende E, et al. Mefloquine induced Stevens-Johnson syndrome. Lancet 1991; 337: 683
Mangalvedhekar 1999	1999	English	Case series	Resident	3	?	-	Mangalvedhekar SS, et al. Convulsions in non-epileptics due to mefloquine-fluoroquinolone co-administration. National Medical Journal of India 2000; 13: 47

Table 2. Published case reports of adverse effects from mefloquine treatment, 1981-2000 (Continued)

Haval- dar 2000	2000	English	Case report	Resident	1	?	-	Haval- dar PV, et al. Mefloquine- induced psy- chosis. The Pediatric In- fectious Dis- ease Journal 2000; 19: 166-167

FEEDBACK

Herxheimer

Summary

Methods

1. The four outcomes you list are not evidence of efficacy and tolerability, but evidence of INefficacy and INtolerability.

Reply: This comment is strictly speaking quite correct (though it doesn't alter our results and conclusions). We have included this as a passing observation in our Methods section.

2. You analysed only the 5 most commonly reported symptoms in the neuropsych and g.i. categories. Does this mean you ignored the "other" symptoms reported within these categories? I think they should be analysed as "other neurops" and "other g.i." symptoms - otherwise you may get potentially serious distortion, esp. since several different terms are likely to have been used for essentially similar symptoms and what is "most commonly reported" will be partly determined by the terms used and how they are categorised/lumped.

Reply: This is a helpful suggestion, although the analysis would not be at all likely to alter our conclusions. We will endeavour to carry out this analysis in a later update of the review, which will also include an analysis of all the "adverse effects" case reports (which in the latest update is simply presented as an annotated bibliography).

4. Half the authors responded to your request for unreported outcomes, but you don't say which of those 5 actually sent you unreported data, and which replied "sorry, ain't got none". In the acknowledgments you collectively thank those who sent you unpublished data, but I think you should name them individually.

Reply: We are somewhat reluctant to "name and shame" those who never replied to us, as there might be perfectly good reasons for this (eg, death of the investigator, or change of post), and we wouldn't want to be seen to be witch-hunting! However the idea of thanking those who did respond with unpublished data is a good one, and we have included their names in our Acknowledgments section.

Characteristics of included studies

Did you come across any possible conflict of interest? The institutional investment in many of these trials was very important - whether Roche, WHO TMP, armed forces, and should be remembered in evaluating these studies. If no report acknowledged funding or conflict of interest, that is also worth saying.

Reply: Very helpful suggestion. We have included a short comment where appropriate in the Notes column of the "Characteristics of Included Studies" table.

Results

1. The Ohrt trial comparing mefloquine against placebo raises a serious question about the ethics of using a placebo in such a high-risk setting. Was this approved by an ethics committee? What information were the participants given about the trial? Did they volunteer, or just get orders? The ethical aspects of the other placebo-controlled trials also deserve discussion.

Reply: The authors of the Ohrt trial reported that “Our study was conducted in accordance with U.S. Army, U.S. Navy and republic of Indonesia regulations governing the protection of human participants.” They also state that “All volunteers gave written, informed consent.” There is no mention of an ethics committee, as such.

We have included a note about the somewhat worrying ethics of this trial, in the “Characteristics of Included Studies” table.

2. I am uncomfortable about your lumping together all the alternative regimens without any discussion or explicit justification.

Reply: We are uncomfortable about this also, although it does help to show, in a clear visual format, that there is a consistent tendency for mefloquine to be less well tolerated than all the standard alternatives. We may drop this lumping in a future update of the review, and separate out all the interventions being compared.

No action taken at the moment.

3a. You report “slightly more withdrawals from the study in the mefloquine group than with the alternative regimens but this is not significant”. You should say “not statistically significant”.

Reply: We have changed the text, as suggested.

3b. Were the reasons for withdrawal and non-compliance not tabulated in any of the trials? That is surely important evidence. Worth saying that too in Para 5 of Implications for research, where you merely make the general accounting point without saying that we need to know the reasons why.

Reply: We have modified the text at several points, to reflect these suggestions.

4. The review skirts around the issue of ADR profiles. It is important and potentially revealing to compare the detailed ADR profiles for mefloquine (and other drugs, not necessarily in this review) derived from observational studies, from your high-grade RCTs, and from the excluded trials. Where they all point the same way they will strengthen each other, where they don't they will point us towards questions that need sharper investigation.

Reply: We have now “enriched” the review with much more data about the adverse effects - initially as an annotated bibliography of case reports. Future updates of the review will carry some detailed analysis of these case reports.

5. The 10 trials differed interestingly in that five began with a loading dose and five did not. I would expect a higher incidence of adverse reactions, and a greater intensity of those reactions in the groups given loading doses, and also that the rate of ADRs would then after say 4 to 8 weeks gradually drop back to the level of the groups that got no loading dose. There might even be a difference in ADR profile, though I hesitate to predict that.

Reply: It seems that the use of a mefloquine loading dose was being promoted by the manufacturer, but has not been approved anywhere for use by travellers, other than military. The reason seems to be that yes, it is less well-tolerated than the once-weekly dose.

If the mefloquine loading dose starts to come into general use, we will investigate it in detail and report on it further. At this stage, we have included simply a brief observation about the loading dose, in our Discussion section.

Discussion

The observational findings that women report mefloquine side effects more commonly than men. An obvious difference is in mean weight, so they receive higher mean dose/kg, and the accumulation due to the long half-life of mefloquine means that the sex differential is likely to widen with duration of treatment. This view could be tested by looking at time-to-ADR-report data for the two sexes.

Reply: Given that 98% of the participants in the included studies are male, we cannot draw any robust conclusions at this stage on what might or might not be the explanation for this gender difference in the tolerability of mefloquine. Where appropriate, however, we have included a comment on the gender of dropouts in the Notes column of the “Characteristics of Included Studies” table.

Conclusions

In implications for research, Para 3, you propose at least one RCT in travellers etc, but then say dogmatically that they should not be native-English or native-Dutch speakers! The reason you give seems to me far from cogent. The publicity would make such a trial harder to do but no less necessary. The central issue is decent reliable balanced information for the public and a fortiori for trial participants. Much more effort has to go into composing and providing that.

Reply: This is a very valid comment, and we have now modified the pertinent section of our Conclusions section.

Reply

See replies to statements in the Summary section.

Contributors

Contributors
Andrew Herxheimer
Jan 27 1998

Erny

Summary

Results

1. Higher withdrawal rates with mefloquine were only shown in comparison with placebo but not when mefloquine was compared with alternative chemoprophylaxis such as doxycycline or chloroquine and proguanil.

Reply: This is a reasonable comment, and we have included this observation in our Discussion section.

2. The use of withdrawal rates is a problematic measure of tolerability because the reasons for withdrawal from controlled trials are frequently unrelated to the study drug... It is misleading to use withdrawal rates as a direct measure of tolerability without considering the reasons that led participants to abandon the study.

Reply: Systematic reviews of clinical interventions commonly use withdrawal rates as a measure of the tolerability or otherwise of the study interventions. In randomised controlled trials participants are allocated at random between the arms, and if the tolerability of each arm is the same, the number of withdrawals from each arm should also be equal. This effect is not shown with mefloquine prophylaxis.

No action taken on this comment.

Discussion

1. All the drugs available today for malaria prophylaxis have adverse effects - the seriousness of malaria warrants tolerating certain temporary adverse effects.

Reply: We accept the first half of this statement. However the “enhanced” systematic review we have now published (which includes data about adverse effects from non-randomised studies) shows that some of the adverse effects that have been associated with mefloquine prophylaxis have lasted months or years - and hence have not been “temporary”. This is cause for concern.

2. If more severe adverse effects occur, travelers need to seek medical advice and if justified need another drug prescribed, so that they don't remain without a protection for the rest of their journey.

Reply: We accept this statement, and have incorporated it into the Discussion section of our review.

3. Alarmist reports on adverse effects that are based on weak grounds must be challenged by evidence based recommendations. Otherwise travellers' lives will be put at risk unnecessarily, through under-utilisation of efficacious prophylactic drugs.

Reply: We agree that recommendations on anti-malarial drug use should be based on good evidence (which is why we prepared this review in the first place!). We do not accept that drawing attention to drug adverse effects is “alarmist”. By studying and discussing adverse effects honestly, clinicians can be helped to prescribe drugs more safely.

No action taken on this comment.

Conclusion

Croft and Garner's meta-analysis is inconclusive. The interpretation of this inconclusive body of evidence is, however, clearly biased.

Reply: We accept that in the absence of appropriate research, our review is inconclusive (and we have said so in our Conclusions section). We do not believe that it is “clearly biased”.

Reply

See replies to statements in the Summary section.

Contributors

Samuel Erny
September 25 1998

WHAT'S NEW

Date	Event	Description
9 November 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 1996

Review first published: Issue 2, 1997

Date	Event	Description
12 November 2007	Amended	Review withdrawn as of Issue 1, 2008
15 May 2005	New search has been performed	New studies sought but none found
28 August 2000	New citation required and conclusions have changed	Substantive amendment
27 August 2000	New search has been performed	Substantive amendment

DECLARATIONS OF INTEREST

We certify that we have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of the review (e.g. employment, consultancy, stock ownership, honoraria, expert testimony).

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.
- Defence Secondary Care Agency, UK.
- Army Medical Services Research Executive, UK.

External sources

- Department for International Development, UK.

NOTES

The Editor withdrew this review as of Issue 1, 2008. This review has been updated and replaced following the publication of a new review: Jacquerioz FA, Croft AM Jacquerioz FA, Croft AM. Drugs for preventing malaria in travellers. Cochrane Database of Systematic Reviews 2009 , Issue 4 . Art. No.: CD006491. DOI: 10.1002/14651858.CD006491.pub2 .

INDEX TERMS

Medical Subject Headings (MeSH)

Antimalarials [*adverse effects]; Malaria [immunology; *prevention & control]; Malaria, Falciparum [immunology; prevention & control]; Mefloquine [*adverse effects]; Randomized Controlled Trials as Topic; Travel; Treatment Outcome

MeSH check words

Adult; Female; Humans; Male