# Drugs for preventing malaria in travellers (Review)

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[Intervention Review]

# Drugs for preventing malaria in travellers

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## ABSTRACT

### Background

Malaria infects 10,000 to 30,000 international travellers each year. It can be prevented through anti-mosquito measures and drug prophylaxis. However, antimalaria drugs have adverse effects which are sometimes serious.

### Objectives

To compare the effects of currently used antimalaria drugs when given as prophylaxis to non-immune adult and child travellers who are travelling to regions with *Plasmodium falciparum* resistance to chloroquine. Specifically, to assess the efficacy, safety, and tolerability of atovaquone-proguanil, doxycycline, and mefloquine compared to each other, and also when compared to chloroquine-proguanil and to primaquine.

### Search strategy

In August 2009 we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (*The Cochrane Library* 2008, Issue 4), MEDLINE, EMBASE, LILACS, BIOSIS, *m*RCT, and reference lists. We handsearched conference proceedings and one specialist journal, and contacted researchers and drug companies. We searched PubMed for drug-related deaths.

### Selection criteria

Randomized and quasi-randomized controlled trials of any antimalaria drug regimen currently used by non-immune international travellers.

### Data collection and analysis

We independently extracted data and assessed eligibility and risk of bias using a standardized data collection form. We resolved any disagreement through discussion. We combined dichotomous outcomes using risk ratio (RR) and continuous data using mean difference (MD), presenting both with 95% confidence intervals (CI).

### Main results

Eight trials (4240 participants) met the inclusion criteria. Evidence on comparative efficacy from head-to-head comparisons was limited. Atovaquone-proguanil compared to doxycycline had similar adverse events reported. Compared to mefloquine, atovaquone-proguanil users had fewer reports of any adverse effect (RR 0.72, 95% CI 0.6 to 0.85), gastrointestinal adverse effects (RR 0.54, 95% CI 0.42 to 0.7), neuropsychiatric adverse events (RR 0.86, 95% CI 0.75 to 0.99), and neuropsychiatric adverse effects (RR 0.49, 95% CI

0.38 to 0.63), besides a better total mood disturbance score (MD -7.20, 95% CI -10.79 to -3.61). Similarly, doxycycline users had fewer reported neuropsychiatric events than mefloquine users (RR 0.84, 95% CI 0.73 to 0.96). We also examined these three regimens against chloroquine-proguanil; this latter regimen had more reports of any adverse effect (RR 0.84, 95% CI 0.73 to 0.96) and of gastrointestinal adverse effects (RR 0.71, 95% CI 0.6 to 0.85).

**Authors' conclusions**

Atovaquone-proguanil and doxycycline are the best tolerated regimens, and mefloquine is associated with adverse neuropsychiatric outcomes.

## PLAIN LANGUAGE SUMMARY

**Drugs for preventing malaria in travellers**

Malaria is a mosquito-transmitted disease which commonly infects international travellers, sometimes fatally. Deaths from malaria are usually caused by *Plasmodium falciparum*.

Malaria can be prevented through a range of anti-mosquito precautions (barrier measures), and by taking antimalaria drugs (chemoprophylaxis). Chloroquine is effective chemoprophylaxis in those parts of the world where *P. falciparum* has not developed resistance to chloroquine. For most malaria-endemic regions, however, travellers must take a newer and stronger drug regimen. These newer antimalaria regimens have unpredictable adverse effects, including severe illness or death.

This review was designed to assess the efficacy, safety, and tolerability of atovaquone-proguanil, doxycycline, and mefloquine (the three currently available chemoprophylaxis choices for regions with *P. falciparum* resistance) compared to each other, and also when compared to chloroquine-proguanil (an older drug combination) and to primaquine (a candidate for chemoprophylaxis).

We found eight trials (4240 participants). Overall the evidence base was small, and we found no evidence to support the use of primaquine. There was only limited evidence on which of the three currently available drugs is most effective in preventing malaria. While none of the eight trials reported any serious adverse events (which are usually rare) all trials reported common adverse events from antimalaria drugs.

Atovaquone-proguanil and doxycycline are well tolerated by most travellers, and they are less likely than mefloquine to cause neuropsychiatric adverse events. Chloroquine-proguanil causes more gastrointestinal adverse events than other chemoprophylaxis. In other respects, the common unwanted effects of currently available drugs are similar.

As well as the eight trials, we also found 22 published case reports of deaths, including five suicides, associated with mefloquine use at normal dosages. No other currently used drugs were reported as causing death, at normal dosages.

In conclusion, there were differences in the common unwanted effects of the drugs which are currently available to prevent malaria, in adult and child travellers. However, the quality of evidence was overall low. Atovaquone-proguanil and doxycycline are the best tolerated regimens. Mefloquine has more adverse effects than other drugs, and these adverse effects are sometimes serious. However mefloquine may still be an appropriate choice for those travellers who have taken it previously, without any adverse events. Other factors should be considered by prescribers, in addition to tolerability: cost, ease of administration, possible drug-drug interactions, travel itinerary, and the additional protection that may be afforded by doxycycline against other infections, besides malaria.

## SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

**Atovaquone-proguanil compared to Mefloquine for Non immune child and adult travellers**

**Patient or population:** Non immune child and adult travellers
**Settings:** International travel
**Intervention:** Atovaquone-proguanil
**Comparison:** Mefloquine

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Mefloquine | Atovaquone-proguanil | | | | |
| **Any adverse effect** | **422 per 1000** | **304 per 1000** (253 to 359) | **RR 0.72** (0.6 to 0.85) | 976 (1 study) | ⊕⊕◯◯ **low**[1,2] | |
| **Gastrointestinal adverse effect** | **288 per 1000** | **156 per 1000** (121 to 202) | **RR 0.54** (0.42 to 0.7) | 976 (1 study) | ⊕⊕◯◯ **low**[1,3] | |
| **Neuropsychiatric adverse event** | **771 per 1000** | **663 per 1000** (578 to 763) | **RR 0.86** (0.75 to 0.99) | 317 (1 study) | ⊕⊕⊕◯ **moderate**[4] | |
| **Neuropsychiatric adverse effect** | **288 per 1000** | **141 per 1000** (109 to 181) | **RR 0.49** (0.38 to 0.63) | 976 (1 study) | ⊕⊕◯◯ **low**[1,3] | |
| **Total Mood Disturbance (TMD) scores** Scale from: -20 to 108. | | The mean Total Mood Disturbance (TMD) scores in the intervention groups was **7.2 lower** (10.79 to 3.61 lower) | | 119 (1 study) | ⊕⊕◯◯ **low**[4,5] | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Serious indirectness. The trial enrolled both adults and children (>= 3 years), but it was unclear how many participants were children as data were not reported separately.

[2] Serious imprecision.The 95% CI of the pooled estimate includes appreciable benefit (<0.75) and non-appreciable benefit (>= 0.75 and <=1.00) with atovaquone-proguanil

[3] Serious limitation in design (selective reporting bias). It is unclear if both adverse events and adverse effects for dermatological, gastrointestinal, and neuropsychiatric were measured, but only the adverse effects reported.

[4] Serious indirectness. The trial enrolled only adults.

[5] Serious limitation in design. High risk of bias due to incomplete outcome data (>10%). Some reasons for attrition and exclusion were likely to be related to true outcome (adverse events).

# BACKGROUND

## Malaria

Malaria is a common and life-threatening disease in many tropical and subtropical areas (WHO 2008). Worldwide, more than two billion people are at risk of malaria, and there are approximately 500 million clinical cases of malaria each year and one million deaths (Greenwood 2008).

Malaria is caused by a blood parasite of the genus *Plasmodium*, transmitted by the bite of infected female anopheline mosquitoes. Four species of *Plasmodium* commonly infect humans: *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae* (White 2009). Malaria parasites cause a wide variety of symptoms, ranging from no or mild symptoms to severe disease and death, depending on the infecting parasite species, the patient's immune status, prior use or non-use of chemoprophylaxis, and the timeliness and nature of any treatment administered (Chiodini 2007).

The most dangerous form of malaria is that due to *P. falciparum*. This has a variable presentation often characterized by a spiking fever, chills, headache, muscular aching and weakness, vomiting, cough, and diarrhoea. Without prompt diagnosis and treatment, this often progresses to circulatory and major organ failure, generalized convulsions, coma, and death (Freedman 2008).

Uncomplicated malaria occurs with all four *Plasmodium* species and starts as a non-specific flu-like illness. This often results in misdiagnosis and delayed treatment (Jong 2003; Bausch 2005).

## Malaria and travellers

Malaria is endemic in 109 countries, and these countries are visited by more than 125 million travellers each year (White 2009). International travellers from non-endemic areas lack immunity to malaria, and every year between 10,000 and 30,000 of these travellers fall ill with malaria after returning home (WHO 2008). Around 150 returning travellers die each year from imported malaria, usually due to *P. falciparum* infection (Wellems 2003).

Since the mid-1990s, the incidence of malaria in travellers has increased in the context of a spectacular growth in tourism to tropical destinations, along with a reverse population flow of migrants from malaria-endemic regions to industrialized countries (Jelinek 2002; Askling 2005; Eliades 2005; WTO 2006). Similar trends are seen in both North America and Europe. In pooled studies in non-immune travellers and migrants, the case-fatality rate for *P. falciparum* infection was estimated as 1% to 1.3% (Genton 2001; Newman 2004). In North America, around half of all malaria infections are due to imported *P. falciparum*, while in European countries the proportion of *P. falciparum* infection varies from 44% in Greece to 82% in France (Muentener 1999). This variability reflects national differences in common travel destinations.

The risk of malaria during travel is determined by the immunological characteristics of the individual traveller (the person), by the travel destination (the place), and by the use of preventive anti-mosquito measures and adequate chemoprophylaxis (prevention without and with drugs).

## Malaria risk and person

Traveller groups at risk of malaria include not only non-immune tourists, aid workers, and military and business travellers to the tropics but also an important group of travellers visiting their friends and relatives abroad (known as VFR travellers). This category describes former residents of malaria-endemic areas, whose partial immunity to the infection has weakened while living in industrialized countries, and who then return to their country of origin to visit friends and family (Jelinek 2002; Loutan 2003; Lalloo 2008). Many VFR travellers regard malaria as a non-threatening disease, and as a group they are less likely to seek pre-travel counselling, to adopt anti-mosquito measures, and to take antimalaria drugs (Schlagenhauf 2003b; Bacaner 2004; Askling 2005; Leder 2006).

Travellers who are naturally vulnerable because of lowered immunity (such as young children, people with chronic diseases, elderly people, and pregnant women) are now travelling more frequently, and consequently imported malaria is more often seen in these subgroups (Loutan 2003; Leder 2004). They are also at greater risk of severe disease.

## Malaria risk and place

A recent study found that Swedish travellers have a *P. falciparum* malaria risk of 302 per 100,000 persons when visiting West Africa, 46 per 100,000 when visiting South Africa, 7.2 per 100,000 when visiting South America, and 2 per 100,000 when visiting Thailand (Askling 2005). Other studies on traveller populations from different industrialized countries found results consistent with this range and showed that the highest risk of acquiring *P. falciparum* malaria is from travel to sub-Saharan Africa, followed by travel to South and South-East Asia (especially Oceania), then to Central and South America. The lowest risk of acquiring *P. falciparum* malaria is from travel to the Caribbean, North Africa, and the Middle East (Phillips-Howard 1990; Kofoed 2003; Loutan 2003; Leder 2004; Leder 2006; Freedman 2008; Schlagenhauf 2008, Behrens 2009).

The risk of malaria is particularly difficult to estimate in regions of unstable transmission, since risk in such regions is likely to change over time due to various environmental and climatic factors (White 2009).

*P. vivax* malaria is especially frequent in travellers returning from Oceania (Jelinek 2002; Leder 2004). However, the risk of *P. vivax* infection exists in all malaria-endemic regions, except Haiti and the Dominican Republic (White 2009). The dormant liver stage parasites (hypnozoites) that characterize *P. vivax* infection mean

that the risk of primary presentation or of relapse can persist for years after visiting any country endemic for this form of malaria.

## Preventing malaria without drugs

Anopheline mosquitoes bite mainly in the evening and at night. Malaria prevention while travelling is therefore based on simple measures to prevent mosquito biting after dusk (Croft 2005). These preventive measures include:

- sleeping under an insecticide-treated bed net;
- wearing clothes that have been pretreated with insecticide;
- wearing long-sleeved treated clothing when outdoors in the evening and at night;
- applying insect repellent regularly to exposed skin.

When used consistently and simultaneously, these barrier measures for preventing malaria are highly effective (Croft 2001). Cochrane Reviews on the impact of insecticide-treated bed nets to prevent malaria in populations living in endemic areas of Africa have shown that bed nets alone significantly reduce childhood mortality and morbidity from malaria, and improve pregnancy outcomes (Lengeler 2004; Gamble 2006).

Barrier measures have the additional advantage of protecting against other mosquito-transmitted infections, such as dengue fever, Japanese encephalitis, and yellow fever (Lalloo 2008).

There is currently no effective vaccine against malaria (Graves 2006a; Graves 2006b; Graves 2006c). A useful vaccine is unlikely to be available for many years, owing to the complex biology and antigenic diversity of *P. falciparum*.

## Preventing malaria with drugs (chemoprophylaxis)

In areas of intense malaria transmission, prophylaxis with drugs (chemoprophylaxis) remains an important strategy for preventing malaria (Croft 2000).

Antimalaria drugs as prophylaxis may have adverse outcomes including, in extreme cases, the death of the user (Cook 1986). These effects may limit adherence in travellers who were healthy before travelling (Croft 2002a; van Riemsdijk 2002; Moore 2004). If travellers stop taking prophylaxis, they are at risk of malaria. Mefloquine prophylaxis is unpopular with some travellers on account of its tendency to induce neuropsychiatric reactions (Akhtar 1993; Nosten 1999; Toovey 2009). This has resulted in legal action against drug manufacturers in a number of countries (Croft 2007; Croft 2008b).

An additional difficulty with drug prophylaxis against malaria is that all drug regimens must be taken scrupulously during travel, and most regimens must then be continued for some weeks after returning from the malaria-endemic area; this is so that the agent can continue to act against the erythrocytic forms of *Plasmodium* that are only gradually released from the liver into the bloodstream. This requires considerable personal discipline, and persisting with drugs after travel is counterintuitive; hence, travellers often discontinue their antimalaria drugs soon after returning home, and develop malaria as a result (Genton 2001; Askling 2005). The inappropriate use or early discontinuation of chemoprophylaxis is likely to be an important factor in malaria acquisition, and may also worsen the severity of imported cases. In the USA, 75% of fatal cases occurred in people who either were not taking malaria chemoprophylaxis or else were prescribed inappropriate drugs or drug regimens (Filler 2003). Similar data have been reported from Europe (Raglio 1994; Jelinek 2002; Schoneberg 2003; Corne 2004; Askling 2005).

In many parts of the world *P. falciparum* has developed resistance to chloroquine. There are still six regions of the tropics and subtropics, encompassing 23 malaria-endemic countries (Appendix 1), where there has been no reported *P. falciparum* drug resistance to chloroquine, and where most authorities still recommend chloroquine alone as prophylaxis (Arguin 2008; WHO 2008).

At present, the antimalaria drugs used as chemoprophylaxis by travellers to regions with *P. falciparum* resistance to chloroquine comprise three main regimens:

1. atovaquone-proguanil;
2. doxycycline; and
3. mefloquine.

Not all the above drugs are licensed for use as malaria chemoprophylaxis in all industrialized countries (Appendix 2). However, in this review we refer to these three main regimens as 'standard chemoprophylaxis'.

## Standard chemoprophylaxis: atovaquone-proguanil

Atovaquone-proguanil (Malarone®) is a relatively new fixed-dose combination that is taken once daily (Jong 2003; McCarthy 2005). Atovaquone-proguanil is currently not recommended as prophylaxis in pregnancy, due to insufficient data on its safety for this indication (CDC 2005). This regimen can be administered as prophylaxis to children of $\geq$ 11 kg body weight.

The principal stated advantage of atovaquone-proguanil is that in addition to being a suppressive drug, it is a causal hepatic stage prophylactic agent. It therefore needs only be taken for one week after leaving the malaria-endemic area (Shanks 2005). Atovaquone-proguanil is currently the most costly antimalaria drug licensed for prophylaxis (Bryan 2006).

## Standard chemoprophylaxis: doxycycline

Doxycycline is an off-patent product (Appendix 3) and a long-acting antimicrobial agent of the tetracycline class (Hawkes 2008).

It is a once-daily drug that may be safe in early pregnancy, although data are currently insufficient to recommend this drug to pregnant women in their first trimester (CDC 2005). It has been claimed that doxycycline may cause tooth staining in children aged < 8 years, but some authorities doubt that this is a true effect (Volovitz 2007).

Doxycycline is an important drug in travel medicine since it may protect not only against malaria, but also against other travel-associated infections such as leptospirosis (Takafuji 1984; Sehgal 2000), Lyme disease (Nadelman 2001), lymphatic filariasis (Taylor 2005), scrub typhus (Twartz 1982), tick-borne relapsing fever ( Hasin 2006), and travellers' diarrhoea (Sack 1979; Freeman 1983; Sack 1986; Diemert 2006).

As a prophylactic drug, doxycycline is only effective in suppressing the blood stages of *Plasmodium*. It therefore needs to be taken before travel, during travel, and for one month after leaving the malaria-endemic area (Shanks 2005). In terms of affordability, a prophylactic course of doxycycline is similar in cost to mefloquine, and much cheaper than atovaquone-proguanil (Bryan 2006).

### Standard chemoprophylaxis: mefloquine

Mefloquine is an off-patent product (Appendix 4) and a once-weekly drug that has been in general use for malaria prophylaxis since the late 1980s (Behrens 2009). Mefloquine may be used as prophylaxis during the second and third trimesters of pregnancy, and in some countries it is considered safe enough to use in the first trimester also (Chiodini 2007). Like any other drug, mefloquine carries the risk of adverse events. The neuropsychiatric character of the adverse events popularly associated with mefloquine has resulted in controversy about its use (Toovey 2009).

As a prophylactic drug, mefloquine is effective in suppressing the blood stages of *Plasmodium*. It therefore needs to be taken before travel, during travel, and for one month after leaving the malaria-endemic area (Shanks 2005).

### Other available drugs: chloroquine-proguanil and primaquine

Chloroquine-proguanil was formerly recommended by some authorities as prophylaxis for travel to regions of *P. falciparum* resistance to chloroquine. Chloroquine-proguanil is a complex two-drug regimen and is no longer widely used, but it is still occasionally considered for travellers visiting West Africa, and for pregnant women (Croft 2008a). Chloroquine-proguanil is also safe for travellers with mild hepatic impairment (Chiodini 2006).

Primaquine is a drug that has only modest activity against *P. falciparum,* but which is thought to protect against *P. vivax* infection. This drug is recommended by some authorities as chemoprophylaxis in non-immune travellers to those regions, such as Oceania, where *P. vivax* predominates (Schwartz 2008). Primaquine is contra-indicated in persons with glucose-6-phosphate dehydrogenase (G6PD) deficiency, and during pregnancy and lactation.

### Discontinued drugs

A number of older drugs and fixed-dose combinations (amodiaquine, chloroquine-primaquine, doxycycline-primaquine, pyrimethamine-dapsone, pyrimethamine-sulfadoxine) were formerly prescribed as malaria chemoprophylaxis, but they are no longer used in travellers for this indication because of concerns around their safety (Croft 2002b). Other drugs (azithromycin, proguanil used alone) are not now recommended to travellers as chemoprophylaxis because they no longer effectively suppress *P. falciparum* (Anderson 1995; Parzy 1997).

### Cochrane Reviews of malaria chemoprophylaxis

This review replaces the existing Cochrane Review on mefloquine for preventing malaria in non-immune adult travellers (Croft 2008b).

Malaria prophylaxis in children living in endemic areas, chemoprophylaxis in pregnant women, and malaria prevention in persons suffering from sickle cell disease are all reviewed elsewhere (Garner 2006; Oniyangi 2006; Meremikwu 2008).

### Scope of this review

This review is concerned with chemoprophylaxis to prevent malaria in non-immune adult and child populations. The primary concern was to identify the safest and best-tolerated drug regimen for travel to regions with *P. falciparum* resistance to chloroquine; these regions include all of sub-Saharan Africa, all of South and South-East Asia, and most of tropical South America (Arguin 2008).

As we were interested in assessing the effects of drugs in non-immune populations, we did not include trials conducted on semi-immune populations and decided to limit this review to trials assessing the drugs of interest through head-to-head comparisons. This review does not address the following:

- malaria chemoprophylaxis in pregnant travellers;
- the use by travellers of emergency standby malaria treatment; or
- the use by travellers of alternative medications (such as homeopathic agents, herbs) to prevent malaria.

This review aims to contribute to a better understanding of the effects of drugs currently used as malaria prophylaxis in non-immune travellers, and will highlight the research questions that need to be addressed through future trials of malaria chemoprophylaxis.

We were aware that efficacy decisions are often made on known drug sensitivity patterns regionally and locally, and that travellers (and prescribers) are particularly concerned with adverse outcomes. With this in mind, we summarized what information was available on efficacy, and analysed adverse outcome data carefully.

# OBJECTIVES

To compare the efficacy, safety, and tolerability of currently used antimalaria drugs when given as prophylaxis to non-immune adult and child travellers, travelling to regions with known *P. falciparum* resistance to chloroquine.

# METHODS

## Criteria for considering studies for this review

### Types of studies

Randomized and quasi-randomized controlled trials.

### Types of participants

Non-immune adult and child travellers visiting malaria-endemic areas for a limited period of time (< 3 months), or non-travelling non-immune adult volunteers.

### Types of interventions

#### Intervention

Atovaquone-proguanil, doxycycline, and mefloquine.

#### Control

Interventions compared with each other (atovaquone-proguanil, doxycycline, and mefloquine) or to chloroquine-proguanil or primaquine.

### Types of outcome measures

#### Clinical outcomes

Clinical cases of malaria, confirmed by microscopy or by polymerase chain reaction (PCR).

#### Adverse outcomes

#### Adverse events

- Any adverse event.*
- Dermatological adverse events.*
- Gastrointestinal adverse events.*
- Neuropsychiatric adverse events.*
- Serious adverse events (fatal, life-threatening, or requiring hospitalization).

**regardless of their level of severity.*
'Serious adverse event' in the above list refers to safety as defined in the Cochrane Collaboration glossary (Cochrane Glossary 2008). We used the Uppsala Monitoring Centre's definition of an adverse event, namely "any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment" ( Uppsala 2001).

#### Adverse effects

- Any adverse effect.*
- Dermatological adverse effects.*
- Gastrointestinal adverse effects.*
- Neuropsychiatric adverse effects.*

**regardless of their level of severity.*
We used the Cochrane Handbook's definition of an adverse effect, namely "an adverse event for which the causal relation between the intervention and the event is at least a reasonable possibility" (Loke 2008).

#### Secondary outcomes

- Discontinuation of study drug at any time, for any reason.
- Changes in Profile of Mood States (POMS) score (McNair 1992).

## Search methods for identification of studies

We attempted to find all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

### Electronic searches

On 2 August 2009 we searched the following databases, using the search terms and strategy described in Appendix 5: the Cochrane Infectious Diseases Group Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL) (3rd quarter of 2009), published in *The Cochrane Library* (2009,Issue 3); MEDLINE (1950 to July week 5, 2009); EMBASE; LILACS; and BIOSIS. We also searched the *meta*Register of Controlled Trials (*m*RCT) using malaria, atovaquone, chloroquine, doxycycline, mefloquine, and primaquine as our search terms.

On 6 January 2009 we searched PubMed, using the search terms and strategy described in Appendix 6, to identify published case reports of deaths causally associated with currently used malaria chemoprophylaxis, when taken at normal dosages.

### Searching other resources

#### Handsearching

We searched the following conference proceedings for relevant abstracts: MIM Pan-African Malaria Conference; American Society of Tropical Medicine and Hygiene meetings; European Conference on Travel Medicine; Interscience Conference on Antimicrobial Agents and Chemotherapy meetings; Conference of the International Society of Travel Medicine; Annual Malaria Meeting of the British Society for Parasitology; European Congress on Tropical Medicine and International Health. The dates and locations of recurring conferences are in Appendix 7.

Ashley Croft (AC) handsearched the journal *Military Medicine* (1955 to 2008) for relevant trials.

#### Correspondence

For unpublished and ongoing trials, Frédérique Jacquerioz (FJ) contacted individual researchers working in the field and searched the clinical trial registries of the following pharmaceutical companies: F Hoffmann-La Roche AG, Switzerland (May 2008); GlaxoSmithKline, UK (May 2008); Mepha Pharma, Switzerland (June 2008); and Pfizer, UK (May 2008).

#### Reference lists

FJ retrieved and checked the reference lists of all studies identified through the above searches.

## Data collection and analysis

### Selection of studies

FJ screened the results of the literature search for potentially relevant trials, retrieved the hard copy reports of those trials, and looked for multiple publications from the same dataset.

AC and FJ independently assessed identified trials for inclusion in the review. We resolved any disagreements through discussion, and we report below our reasons for excluding any studies.

### Data extraction and management

AC and FJ independently extracted data using a standardized data collection form. We resolved any disagreement through discussion. For dichotomous data, we extracted the numbers of events and the numbers of participants analyzed in each intervention group, and calculated risk ratios. For continuous data, we extracted the mean change from the baseline and a standard deviation for this change for each treatment group, and the number of participants analysed in each group; we then calculated the mean difference of the change in the mean from baseline across treatment groups.

Whenever possible, we extracted the overall result for adverse events or effects belonging to the same category, and regardless of severity. When results were presented only separately in each category, or by level of severity, we reported the most frequent adverse events per category, or the combined level of severity (see 'Characteristics of included studies'). The true number of events might have been underestimated in these circumstances.

### Assessment of risk of bias in included studies

AC and FJ independently assessed the risk of bias of each trial using The Cochrane Collaboration's 'Risk of bias' tool (Higgins 2008). We followed the guidance for making judgements on the risk of bias in five domains: sequence generation; allocation concealment; blinding (of participants, personnel, and outcome assessors); incomplete outcome data (for adverse outcomes); and selective outcome reporting (for adverse outcomes). We categorized these judgements as 'Yes' (low risk of bias), 'No' (high risk of bias), or 'Unclear'.

Where biases due to incomplete outcome data and selective outcome reporting appeared to be present, we approached the trial authors for further details.

### Dealing with missing data

We analysed data extracted from the trials on an intention-to-treat basis where there were no missing data. We contacted trial investigators if data were incomplete or unclear.Otherwise, we used the complete-case analysis approach, using the number of participants for whom outcomes were available (Gamble 2005).

### Assessment of heterogeneity

We tested for statistical heterogeneity between trials using the Chi $^2$ test ($P < 0.1$) and the $I^2$ statistic ($I^2 > 50\%$), along with a visual inspection of the forest plots. If we identified substantial heterogeneity, and it was appropriate to combine data, we used the random-effects model. Otherwise, we did not combine the data in a meta-analysis.

### Data synthesis

We carried out statistical analyses using Review Manager 5. We compared dichotomous variables using the risk ratio (RR) and continuous variables using the mean difference (MD), and presented each result with a 95% confidence interval (CI).

We attempted to make head-to-head comparisons and stratified the analyses by using the following hierarchy:

- atovaquone-proguanil versus doxycycline;
- atovaquone-proguanil versus mefloquine;
- doxycycline versus mefloquine;
- any of the three standard drugs versus chloroquine-proguanil;
- any of the three standard drugs versus primaquine.

### Subgroup analysis and investigation of heterogeneity

We intended to explore possible sources of heterogeneity using subgroup analyses (i.e. children versus adults, female versus male travellers, soldiers versus non-soldiers, short-duration versus long-duration travel).

### Sensitivity analysis

We included all eligible trials in the initial analysis and aimed to carry out sensitivity analyses to evaluate the robustness of the results, by including only those trials with no risk of selective reporting bias in the reported trial results (i.e. reported adverse events and adverse effects).

## RESULTS

### Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

From the 163 studies identified by the search strategy, we retrieved 13 published reports.

Eight trials met the inclusion criteria (see 'Characteristics of included studies'). Three of these trials were in soldiers (Arthur 1990a; Croft 1997; Ohrt 1997), and the remaining five trials were in tourists and general travellers (Høgh 2000; Overbosch 2001; van Riemsdijk 2002; Schlagenhauf 2003a; Camus 2004).

One trial had four arms (Schlagenhauf 2003a), yielding four separate comparisons. Thus, the total number of comparisons evaluated is 11 (Appendix 8). Seven trials were randomized, double-blind studies (Arthur 1990a; Croft 1997; Ohrt 1997; Høgh 2000; Overbosch 2001; van Riemsdijk 2002; Schlagenhauf 2003a). The eighth trial was reported as a randomized, open-label study (Camus 2004).

All the studies were published in English. Four trials were multicentre studies, selecting their participants from travel clinics in North America and Europe (Høgh 2000; Overbosch 2001; Schlagenhauf 2003a; Camus 2004). One trial was conducted in a single travel clinic in the Netherlands (van Riemsdijk 2002).

The commonest travel destination was sub-Saharan Africa, accounting for about three-quarters of all the travel documented.

We excluded five studies out of the 13 reports retrieved (see 'Characteristics of excluded studies'); in three instances this was because the allocation of participants was not random or quasi-randomized (Rieckmann 1993; Carme 1997; van Genderen 2007); and in two instances because randomization by clustering was inadequate (Baudon 1999; Pages 2002).

### Participants

The review includes 4240 randomized participants, of whom 1098 were soldiers, and the rest tourists and general travellers. All participants were non-immune persons travelling to malaria-endemic countries.

Among the tourists and general travellers, adults and children aged $\geq$ 3 years were recruited in two trials (Overbosch 2001; van Riemsdijk 2002), adults and children aged $\geq$14 years in one trial (Høgh 2000), exclusively children in one (Camus 2004), and exclusively adults in one (Schlagenhauf 2003a). Tourist travellers were of both genders. All of the soldiers in the military studies were adult males (Arthur 1990a; Croft 1997; Ohrt 1997).

### Interventions

Atovaquone-proguanil was compared against doxycycline in one trial (Schlagenhauf 2003a) and against mefloquine in three trials (Overbosch 2001; van Riemsdijk 2002; Schlagenhauf 2003a). Doxycycline was compared against mefloquine in three trials (Arthur 1990a; Ohrt 1997; Schlagenhauf 2003a). Four trials compared any of the above drugs against chloroquine-proguanil (Croft 1997; Høgh 2000; Schlagenhauf 2003a; Camus 2004). No trial directly compared primaquine to any of the other study drugs (see Appendix 8).

### Outcomes

#### Clinical outcomes

Clinical cases of malaria were reported in six trials. Three trials used results of blood smear and/or *P. falciparum* DNA detected by polymerase chain reaction (PCR) (Ohrt 1997; Høgh 2000; Camus 2004); one trial used results from serological testing (antibodies to blood stage malaria parasites) (Overbosch 2001); and two trials did not report the method used (Arthur 1990a; Croft 1997). Only one trial included a placebo arm (Ohrt 1997).

### Adverse outcomes

This group of outcomes is further divided into two categories: 'adverse event' and 'adverse effect'. The later includes what was reported by the authors as 'side effect' (Arthur 1990a; Croft 1997) or 'adverse event attributed to study drug' (Høgh 2000; Overbosch 2001; Camus 2004). With the exception of serious adverse events, or unless otherwise reported, each category of adverse outcomes includes all level of severity together (mild, moderate, and severe).

### Adverse events

Five trials reported the frequency of any adverse events (Ohrt 1997; Høgh 2000; Overbosch 2001; Schlagenhauf 2003a; Camus 2004).
Three trials reported organ-specific adverse events and categorized these as dermatological, gastrointestinal and neuropsychiatric ( Ohrt 1997; Schlagenhauf 2003a; Camus 2004).
Serious adverse events were measured in five studies (Ohrt 1997; Høgh 2000; Overbosch 2001; Schlagenhauf 2003a; Camus 2004).

### Adverse effects

Four trials reported any adverse effect (Croft 1997; Høgh 2000; Overbosch 2001; Camus 2004).
Five trials reported organ-specific adverse effects and categorized these as dermatological, gastrointestinal, and neuropsychiatric ( Arthur 1990a; Croft 1997; Høgh 2000; Overbosch 2001; Camus 2004).
Croft 1997 reported only the adverse effects for each of the above categories that were 'severe' and 'very severe'.

### Secondary outcomes

We extracted from seven trials the outcome 'discontinuation of study drug at any time for any reason'. This outcome has a broader definition than 'withdrawal due to study drug related adverse events', and includes withdrawal for all reasons.
Two trials reported the effects of malaria prophylaxis on moods and feelings (van Riemsdijk 2002; Schlagenhauf 2003a), using the Profile of Mood States (POMS) standardized questionnaire (McNair 1992). POMS scores from Schlagenhauf's trial has been also recently published in more details (Schlagenhauf 2009). In this review, we used the composite outcome, 'total mood disturbance score', which is derived by summing the scores for tension, anger, fatigue, and depression and subtracting the score for vigour. The individual scores for total mood disturbance could not be extracted from Schlagenhauf 2003a or Schlagenhauf 2009, the study authors merely stating in their text that there was no difference between drugs.

## Risk of bias in included studies

Our judgements on the risk of bias in each trial are summarized in the 'Risk bias' tables (see under 'Characteristics of included studies') and are presented in Figure 1 and Figure 2.

**Figure 1.**

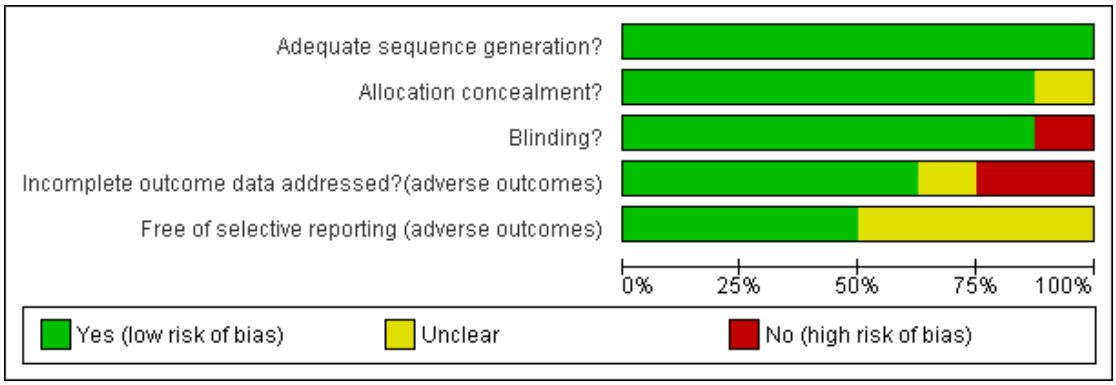
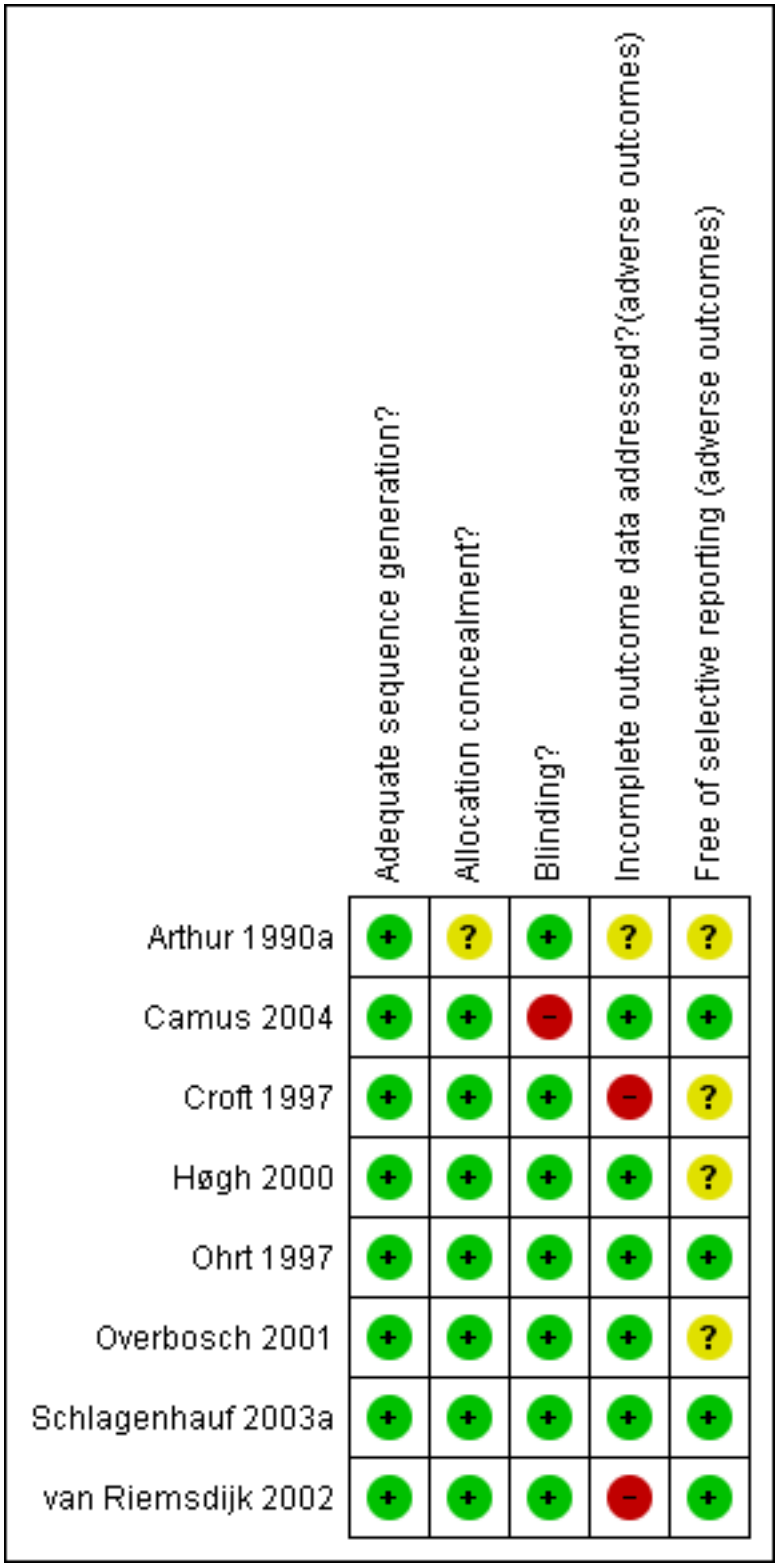


**Figure 2.**



### Allocation

Sequence generation was adequately performed and reported in all trials. Allocation concealment was adequate in seven trials and unclear in one (Arthur 1990a), where the method used was not described. We estimated the risk of bias from these two domains and across trials to be low.

### Blinding

All trials were described as double-blind, except one which was an open-label study (Camus 2004). We considered this trial to have a high risk of bias, since care providers assessing adverse events could have been aware of drug assignment.

### Incomplete outcome data

This criterion was applied to adverse outcomes.
Five trials excluded participants after randomization if they did not receive the study drug. Reasons such as "did not travel", "lost to follow up", and "withdrew consent" were balanced between groups, were unlikely to have been related to the outcome of interest, and in all cases represented < 10% of the randomized participants. Missing outcome data accounted for > 10% of the data in three trials (Arthur 1990a; Croft 1997; van Riemsdijk 2002). In Arthur 1990a, there was insufficient reporting of reasons for attrition and exclusion and how missing data were addressed in the analysis. We judged the risk of bias to be unclear. In Croft 1997, the explanation for missing data lay in the low response rate to the questionnaire. This low response rate occurred similarly in both arms of the study and was unlikely to have been related to the outcome of interest. However at eight weeks 54% of the participants in both arms did not have available outcome data (Croft 1997). The third trial reported the exclusion of some participants from analysis due to adverse events and because of suspicion they had switched study drugs (van Riemsdijk 2002). For these two last studies, we estimated the missing data to have been at high risk of bias.

### Selective reporting

This criterion was applied to adverse outcomes.
For Høgh 2000 and Overbosch 2001 it was unclear if both adverse events and adverse effects were measured in the dermatological, gastrointestinal, and neuropsychiatric categories, but only the adverse effects were reported. We judged these two trials to have an unclear risk of selective reporting bias. A third trial from the same group of investigators reported both the organ-related adverse events and the organ-related adverse effects (Camus 2004). One trial did not report the adverse effects associated with each drug (Arthur 1990a), and this information was retrieved from another publication by the same investigator referring to this study (Arthur 1990b). Another trial did not report mild or moderate adverse effects (Croft 1997). The risk of bias due to selective reporting was estimated to be unclear for both Arthur 1990a and Croft 1997.

### Other potential sources of bias

Except for two trials (Croft 1997; van Riemsdijk 2002), all the trials in this review were funded wholly or in part by pharmaceutical companies. The exact nature of this funding was not always clear or available. It was therefore difficult for us to assess the degree of influence which the commercial sponsors of the studies might have had in the subsequent presentation by the investigators of their outcomes data. Thus, we decided simply to report the information in the 'Characteristics of included studies' tables, without assessing the potential for bias.

## Effects of interventions

See: **Summary of findings for the main comparison** Atovaquone-proguanil compared to Mefloquine for Non immune child and adult travellers; **Summary of findings 2** Doxycycline compared to Mefloquine for Non Immune Child and Adult Travellers; **Summary of findings 3** Any standard drugs compared to Chloroquine-proguanil for Non Immune Child and Adult Travellers

### Atovaquone-proguanil versus doxycycline

One trial made this comparison (Schlagenhauf 2003a).

#### Clinical outcomes

No clinical outcomes were evaluated.

#### Adverse outcomes

For this comparison, only *adverse events* are available. Adverse events were very commonly reported in both arms, but no difference in effect was shown for any adverse events (317 participants, Analysis 1.1), dermatological adverse events (317 participants, Analysis 1.2), gastrointestinal adverse events (317 participants, Analysis 1.3), and neuropsychiatric adverse events (317 participants, Analysis 1.4).
For *serious adverse events*, no event was reported.

### Secondary outcomes

No difference was detected between the drugs in the number of discontinuations of the study drug for any reason (317 participants, Analysis 1.5).

## Atovaquone-proguanil versus mefloquine

Overbosch 2001, Schlagenhauf 2003a, and van Riemsdijk 2002 compared these drugs.

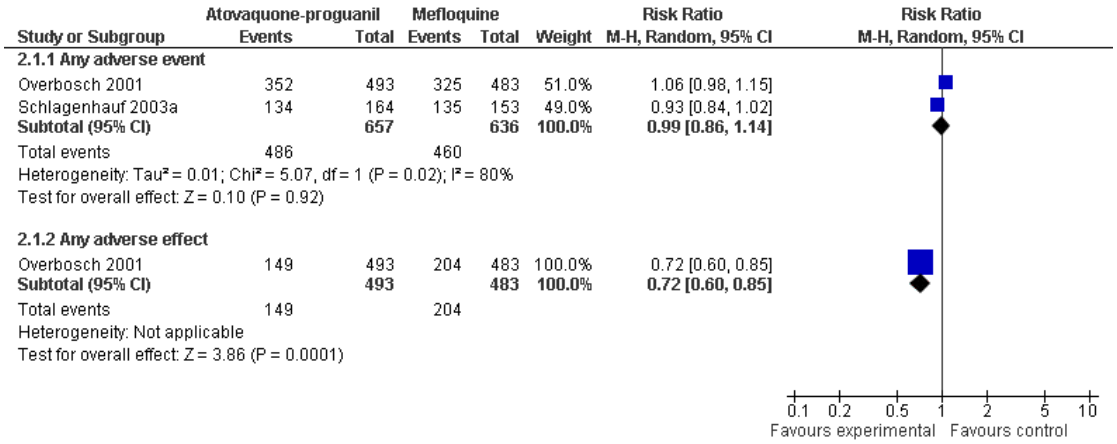
### Clinical outcomes

Clinical outcome was reported in Overbosch 2001, and there were no clinical cases of malaria in either group.

### Adverse outcomes

*Any adverse outcome* (Analysis 2.1, Figure 3) - Adverse events and effects were common in both arms. We found no apparent difference in effect between the drugs in the number of any adverse events (1293 participants, two trials). There were fewer any adverse effects (RR 0.72, 95% CI 0.60 to 0.85; 976 participants) in the atovaquone-proguanil group compared to mefloquine.

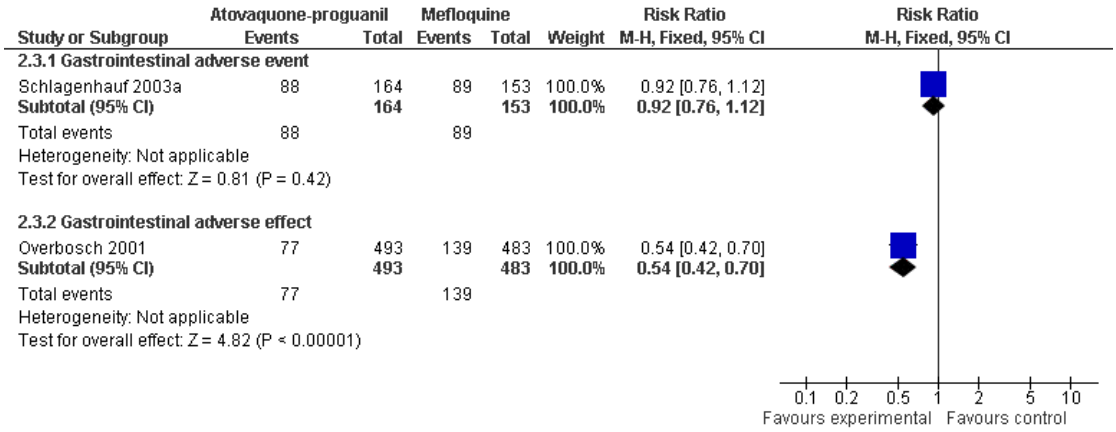
**Figure 3. Forest plot of comparison: 2 Atovaquone-proguanil vs mefloquine, outcome: 2.1 Any adverse outcome.**




*Dermatological adverse outcome* (Analysis 2.2) - We found no apparent difference in effect between the drugs in the number of dermatological adverse events (317 participants, one trial) and in the number of dermatological adverse effects (976 participants, one trial).

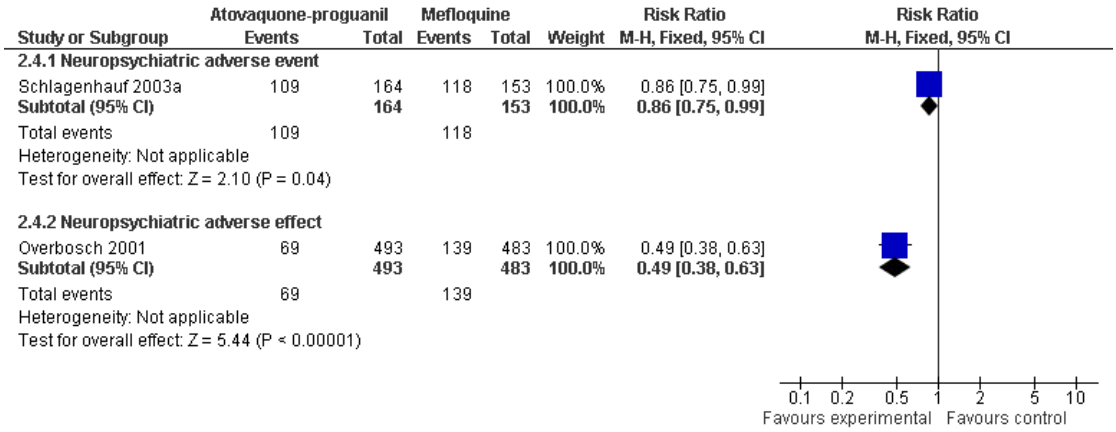
*Gastrointestinal adverse outcome* (Analysis 2.3, Figure 4) - We found no apparent difference in effect between the drugs in the number of gastrointestinal adverse events (317 participants, one trial). There were fewer gastrointestinal adverse effects (RR 0.54, 95% CI 0.42 to 0.70; 976 participants) in the atovaquone-proguanil group compared to mefloquine.

**Figure 4. Forest plot of comparison: 2 Atovaquone-proguanil vs mefloquine, outcome: 2.3 Any gastrointestinal adverse outcome.**




*Neuropsychiatric adverse outcome* (Analysis 2.4, Figure 5) - There were fewer neuropsychiatric adverse events (RR 0.86, 95% CI 0.75 to 0.99; 317 participants) and fewer neuropsychiatric adverse effects (RR 0.49, 95% CI 0.38 to 0.63; 976 participants) in the atovaquone-proguanil group compared to mefloquine.

**Figure 5. Forest plot of comparison: 2 Atovaquone-proguanil vs mefloquine, outcome: 2.4 Any neuropsychiatric adverse outcome.**




*Serious adverse event* - We found no apparent difference in effect between the drugs in the number of any serious adverse event (1293 participants, two trials, Analysis 2.5).

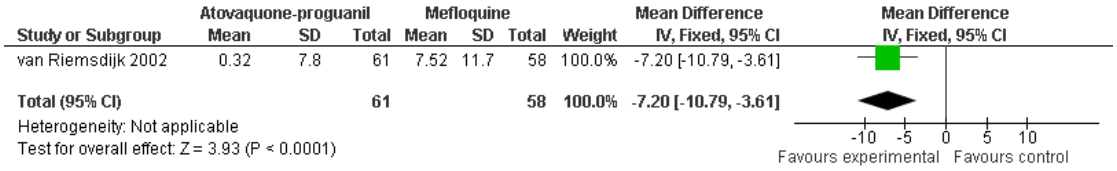
### Secondary outcomes

We found no apparent difference in effect between the drugs in the number of discontinuations of the study drug for any reason (1293 participants, two trials, Analysis 2.6).

One trial measured total mood disturbance scores (van Riemsdijk 2002). The score clearly favoured participants taking atovaquone-

proguanil compared to mefloquine (MD -7.20, 95% CI -10.79 to -3.61; 119 participants, Analysis 2.7, Figure 6).

**Figure 6. Forest plot of comparison: 2 Atovaquone-proguanil vs mefloquine, outcome: 2.7 Total Mood Disturbance (TMD) scores.**




### Doxycycline versus mefloquine

Three trials made this comparison (Arthur 1990a; Ohrt 1997; Schlagenhauf 2003a).

#### Clinical outcomes

Clinical outcome was reported in Arthur 1990a and Ohrt 1997. There was one case of clinical malaria in the doxycycline arm and none in the mefloquine arm (388 participants, two trials, Analysis 3.1), so no difference is detected due to small numbers.

#### Adverse outcomes

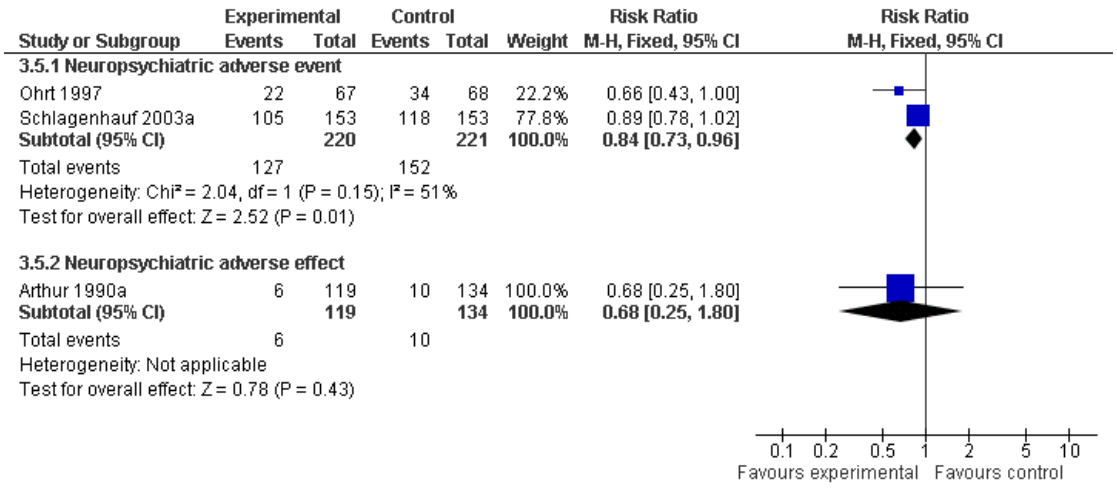
*Any adverse outcome* (Analysis 3.2) - No apparent difference was detected in any adverse event between the drugs (441 participants, two trials).

*Dermatological adverse outcome* (Analysis 3.3) - No apparent difference was detected in dermatological adverse events (441 participants, two trials)

*Gastrointestinal adverse outcome* (Analysis 3.4) - No apparent difference was detected in gastrointestinal adverse events (441 participants, two trials) and in gastrointestinal adverse effects (253 participants, one trial)

*Neuropsychiatric adverse outcome* (Analysis 3.5, Figure 7) - There were fewer neuropsychiatric adverse events (RR 0.84, 95% CI 0.73 to 0.96; 441 participants, two trials) in the doxycycline group compared with mefloquine. There was no apparent difference in effect between the drugs in the number of neuropsychiatric adverse effects (253 participants, one trial).

**Figure 7. Forest plot of comparison: 3 Doxycycline vs mefloquine, outcome: 3.5 Any neuropsychiatric adverse outcome.**



For *serious adverse event*, no event was reported in any of the three trials.

### Secondary outcomes

No apparent difference in effect was found in the number of discontinuations of study drugs for any reason (441 participants, two trials, Analysis 3.6).

## Any of the three standard drugs versus chloroquine-proguanil

Camus 2004, Croft 1997, Høgh 2000, and Schlagenhauf 2003a compared either atovaquone-proguanil, doxycycline, or mefloquine to chloroquine-proguanil.

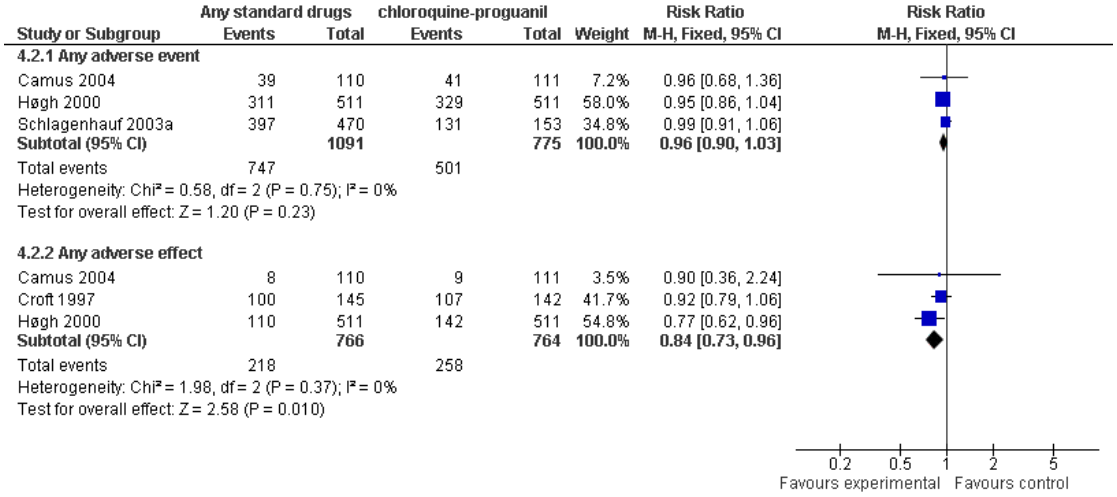
### Clinical outcomes

Clinical outcome was reported in Camus 2004, Croft 1997, and Høgh 2000. There were no clinical cases of malaria in the standard chemoprophylaxis group and three cases in the chloroquine-proguanil group (1853 participants, three trials, Analysis 4.1). The results were inconclusive.

### Adverse outcomes

*Any adverse outcome* (Analysis 4.2, Figure 8) - Adverse events were commonly reported in both arms. There was no apparent difference in effect between the drugs in the number of any adverse event (1866 participants, three trials). There were fewer any adverse effects (RR 0.84, 95% CI 0.73 to 0.96; 1530 participants, three trials) in all standard regimens compared with chloroquine-proguanil.

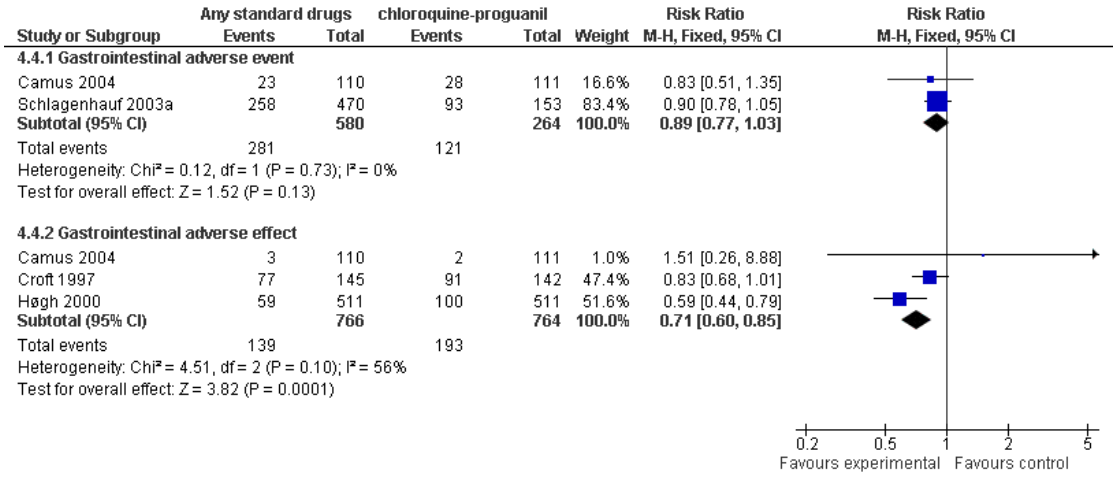
**Figure 8. Forest plot of comparison: 4 Any standard drugs vs chloroquine-proguanil, outcome: 4.2 Any adverse outcome.**



*Dermatological adverse outcome* (Analysis 4.3) - There was no apparent difference in effect between the drugs in the number of dermatological adverse events (623 participants, one trial) and the number of dermatological adverse effects (1309 participants, two trials).

*Gastrointestinal adverse outcome* (Analysis 4.4, Figure 9) - There was no apparent difference in effect between the drugs in the number of gastrointestinal adverse events (844 participants, two trials). There were fewer gastrointestinal adverse effects (RR 0.71, 95% CI 0.60 to 0.85; 1530 participants, three trials) in all standard regimens compared with chloroquine-proguanil.

**Figure 9. Forest plot of comparison: 4 Any standard drugs vs chloroquine-proguanil, outcome: 4.4 Any gastrointestinal adverse outcome.**




*Neuropsychiatric adverse outcome* (Analysis 4.5) - There was no apparent difference in effect between the drugs in the number of neuropsychiatric adverse events (844 participants, two trials) and the number of neuropsychiatric adverse effects (1530 participants, three trials).

*Serious adverse event* - There was no apparent difference in effect between the drugs in the number of serious adverse events (1866 participants, three trials, Analysis 4.6). There were no serious adverse events reported by Camus 2004 or by Schlagenhauf 2003a. Høgh 2000 reported 12 serious adverse events: six were in the standard chemoprophylaxis group and six in the chloroquine-proguanil group. None of them was considered by the investigators to be related to the study drug.

### Secondary outcomes

No apparent difference in effect was found in the number of discontinuations of study drugs for any reason (2490 participants, four trials, Analysis 4.7).

### Any of the three standard drugs versus primaquine

We found no trials on the comparative effects of primaquine through head-to-head comparisons.

### Subgroup analyses (adverse outcomes)

We did not perform additional subgroup analyses (children versus adults, male versus female travellers) owing to paucity of data. One small trial with child participants only (Camus 2004) showed inconclusive results for all outcomes in the comparison of atovaquone-proguanil versus chloroquine-proguanil. Child participants in other trials could not be identified separately.

**Sensitivity analyses (adverse outcomes)**

We did not performed selective analyses owing to paucity of data.

## ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

**Doxycycline compared to Mefloquine for Non Immune Child and Adult Travellers**

**Patient or population:** Non Immune Child and Adult Travellers
**Settings:** International travel
**Intervention:** Doxycycline
**Comparison:** Mefloquine

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Mefloquine | Doxycycline | | | | |
| **Neuropsychiatric adverse event** | **688 per 1000** | **578 per 1000** (502 to 660) | **RR 0.84** (0.73 to 0.96) | 441 (2 studies) | ⊕⊕◯◯ **low**[1,2] | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Serious indirectness. Both trials enrolled only adults.
[2] Serious imprecision. The 95% CI of the pooled estimate includes appreciable benefit (<0.75) and non-appreciable benefit (>=0.75 and <=1.00) with doxycycline.

**Any standard drugs compared to Chloroquine-proguanil for Non Immune Child and Adult Travellers**

**Patient or population:** Non Immune Child and Adult Travellers
**Settings:** International travel
**Intervention:** Any standard drugs
**Comparison:** Chloroquine-proguanil

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Chloroquine-proguanil | Any standard drugs | | | | |
| **Any adverse effect** | **338 per 1000** | **284 per 1000** (247 to 324) | **RR 0.84** (0.73 to 0.96) | 1530 (3 studies) | ⊕◯◯◯ **very low**[1,2,3] | |
| **Gastrointestinal adverse effect** | **253 per 1000** | **180 per 1000** (152 to 215) | **RR 0.71** (0.6 to 0.85) | 1530 (3 studies) | ⊕◯◯◯ **very low**[2,3,4] | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Serious limitation in design. One trial is open label. In one trial, incomplete outcome data is largely >10% and it is unclear if mild and moderate side effects were measured but not reported in the results.
[2] Serious indirectness. One trial included children only, one trial adult soldiers, and one trial adults and children (>= 14 years).
[3] Serious imprecision. The 95% CI of the pooled estimate includes appreciable benefit (<0.75) and non-appreciable benefit (>=0.75 and <=1.00) with any standard drugs (atovaquone-proguanil, doxycycline, mefloquine).

[4] Serious limitation in design. One trial is open label. In one trial, incomplete outcome data is largely >10% and it is unclear if mild and moderate side effects were measured but not reported in the results. For the third trial, it is unclear if both adverse events and adverse effects for dermatological, gastrointestinal, and neuropsychiatric were measured, but only adverse effects reported.

# DISCUSSION

## Summary of main results

This is a systematic review of malaria chemoprophylaxis in non-immune persons. The review was designed to assess the comparative effects of atovaquone-proguanil, doxycycline, and mefloquine compared to each other, and to compare any of these three standard prophylactic drugs to chloroquine-proguanil or primaquine, examining adverse outcomes in particular.

### Protection - clinical outcome

This review provides **inconclusive evidence** about which currently recommended drug is most effective in preventing malaria in non-immune populations travelling to regions with *P. falciparum* resistance to chloroquine.

### Safety - serious adverse events

This review provides **inconclusive evidence** about which currently recommended drug is safest in non-immune populations travelling to regions with *P. falciparum* resistance to chloroquine.

### Adverse outcomes

The review provides some evidence that atovaquone-proguanil and doxycycline have a better profile of tolerability in comparison to mefloquine; and all three drugs compared to chloroquine-proguanil. However, the quality of evidence ranges from very low to moderate (Summary of findings for the main comparison, Summary of findings 2, Summary of findings 3). Thus the findings have to be interpreted with caution.

***Compared to mefloquine*** , atovaquone-proguanil and doxycycline users had fewer neuropsychiatric adverse events. Atovaquone-proguanil users also had fewer any adverse effects, fewer gastrointestinal adverse effects, fewer neuropsychiatric adverse effects, and better total mood disturbance scores.

There was no difference in effect between ***atovaquone-proguanil*** and ***doxycycline*** for any of the outcomes.

***Compared to chloroquine-proguanil*** , users of any of the three standard prophylactic drugs had fewer any adverse effects and fewer gastrointestinal adverse effects.

### Discontinuation of study drug for any reason

***In all four comparisons*** we found no difference in effect for 'discontinuation of study drug for any reason'.

## Overall completeness and applicability of evidence

We found studies for all comparisons of interest, except for the comparison between any of the three standard prophylactic regimens and primaquine.

The included studies address all of the objectives of the review. However, many were designed to investigate the frequency of common adverse events and effects as their primary outcome, and were not powered to assess effectiveness (i.e. clinical cases of malaria), or serious and hence by definition rare adverse events. Thus, for these outcomes, the review provides inconclusive or no results about which drug regimen is the most effective or the safest in non-immune adult and child travellers.

With regard to common adverse events and effects regardless of severity (any, dermatological, gastrointestinal, and neuropsychiatric), the review provides some relevant evidence for the target population of non-immune adult and child travellers.

All studies were conducted in non-immune individuals visiting malaria-endemic areas, the commonest travel destination (for around 75% of the participants) being sub-Saharan Africa. However, over one-quarter of the participants in the eight included trials were male soldiers (1098/4240). The remaining participants were tourists and general travellers. Soldiers are a healthy and disciplined study population who, compared to non-soldiers, are likely to under-report adverse events (Croft 1999). There is therefore likely to be some systematic under-estimation throughout this review of the true frequencies of the common unwanted effects of antimalaria drugs.

In addition, and owing to the lack of adequately differentiated data, we were not able to perform sensitivity analyses or subgroup analyses of adults versus children, or of male versus female travellers, or of soldiers versus non-soldiers. Consequently, there is continuing uncertainty about the likely harms and benefits of malaria chemoprophylaxis for each of these travelling subgroups.

## Quality of the evidence

We found eight trials (4240 participants); one trial compared atovaquone-proguanil to doxycycline (317 participants), two trials compared atovaquone-proguanil to mefloquine (1293 participants), three trials compared doxycycline to mefloquine (694 participants), four trials compared any standard prophylactic regimen to chloroquine-proguanil (2490 participants), and no trials compared any standard regimen to primaquine.

The body of evidence that we found was disappointingly small, and the quality of the evidence (Guyatt 2008) ranged from very low to moderate (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3). The main reason for the lower quality of the evidence was indirectness, as data for children and adults were reported separately and imprecision in the effect estimates (i.e. large 95% confidence intervals), which in turn was due to the small number of studies per comparison and to the limited number of participants/events per study.

Other factors that impair the quality of evidence include methodological limitations and, in particular, the risk of selective reporting of adverse outcomes in some studies (see 'Risk of bias' tables in 'Characteristics of included studies'). Adverse effect by defini-

tion includes "any event for which the causal relation between the intervention and the event is at least a reasonable possibility (Loke 2008 )." Findings for this category are clinically more relevant than those for the broader category of adverse events. However, the risk of bias is also higher when attributability of the event to the study drug is performed post hoc by unblinded assessors and/or measured outcomes are not fully reported. In addition, criteria for attributability were usually not reported in detail in published articles. In this review, this has resulted in a lower quality of evidence.

As a result of the above factors, it is the case that with many of the comparisons made in this review it is not possible to know whether the intervention is beneficial, harmful, or without effect.

### Potential biases in the review process

Among the limitations of this review are the selection criteria which excluded placebo-controlled trials and also studies conducted on semi-immune populations. This has limited heterogeneity among the studies and enhanced the generalizability to our target population of non-immune travellers, but has also excluded potentially useful data on drug effectiveness.

Another limitation of this review lies in our inability, in most cases, to obtain additional relevant information from study authors when important data were lacking or else were presented unclearly in the authors' published reports. In all such cases, we contacted the corresponding and/or the first author, but the response rate to our enquiries was low.

The strength of this review lies in its systematic identification of all relevant chemoprophylaxis trials, and in its meta-analysis of trial outcomes, which can usefully inform clinical decision-making for non-immune travellers to malaria-endemic regions. Other strengths include independent data extraction by two authors and a systematic centralized electronic search at the Cochrane editorial base.

### Agreements and disagreements with other studies or reviews

#### Protection - clinical outcome

With malaria, and because the effects are so massive, the effectiveness of malaria chemoprophylaxis can often be inferred from simple observational studies. With atovaquone-proguanil, doxycycline, and mefloquine the protective efficacy has been demonstrated through placebo-controlled trials carried out in non-immune migrants and soldiers (Ohrt 1997; Ling 2002; Soto 2006), and also and more commonly in trials carried out in semi-immune populations (Sossouhounto 1995; Weiss 1995; Andersen 1998; Lell 1998; Shanks 1998; Sukwa 1999) and from observational studies. Likewise, some evidence on the protective efficacy of primaquine can be found in placebo-controlled trials carried out in non-immune populations (Fryauff 1995; Soto 1998; Baird 2001). Doxycycline appears to be an exceptionally useful drug for travellers due to the fact that it might protect against other infections associated with the travel destination, besides malaria.

Widespread *P. falciparum* resistance to chloroquine raises concerns about the continuing protective efficacy of chloroquine-proguanil as prophylaxis (Klement 2001; Sutherland 2007; Croft 2008a).

#### Safety - serious adverse events

The main controversy around the use of mefloquine as prophylaxis is the potential risk of neuropsychiatric adverse events, and in particular serious events that can be distressing for previously healthy travellers. This review shows that there is a lack of data from randomized controlled trials to usefully inform the debate around mefloquine's safety. Since serious adverse events are by definition rare, only a trial with a very large study population, or the pooling of data from a large number of smaller but comparable studies, would yield the statistical power needed to assess this outcome in head-to-head comparisons. However very large randomized trials are difficult to conduct, for both logistical and financial reasons.

To examine safety from a different perspective, we performed a search to identify published case reports of deaths attributed to any of the study drugs at normal dosages (Appendix 6). We found 22 published case reports of deaths associated with the use of mefloquine at normal dosages, including five reported suicides (Appendix 9), and no case reports of deaths attributed to any of the other drugs. This result might partly be explained by reporting bias, reflecting strong consumer concerns around the safety of mefloquine (Eaton 1997).

As it is probably impractical to have a very large, multicentre randomized controlled trial powered to assess rare serious adverse events with mefloquine compared to other prophylactic drugs, then information from pharmacovigilance is very important.

#### Adverse outcomes

For common adverse outcomes (any, dermatological, gastrointestinal, and neuropsychiatric), the evidence found on mefloquine to some extent reflects what we already know from non-Cochrane reviews, individual placebo trials and from non-randomized studies, which is that mefloquine users have more common neuropsychiatric adverse outcomes than users of other chemoprophylaxis (Toovey 2009).

## AUTHORS' CONCLUSIONS

## Implications for practice

Overall, the data do not provide evidence of comparative protective efficacy between drugs used for malaria prevention during travel to regions of chloroquine-resistant *P. falciparum*. Decision-making here will depend on other data, including knowledge of regional and local drug sensitivities.

Adverse events and effects are commonly reported for all drugs. Limited evidence shows that mefloquine users have worse total mood disturbance scores and experience more neuropsychiatric adverse outcomes (events and effects) than users of atovaquone-proguanil or doxycycline. There is no evidence from head-to-head comparisons to support primaquine use as primary prophylaxis in travellers.

It follows that the choice of whether to prescribe atovaquone-proguanil or doxycycline (or, exceptionally, mefloquine) should be made by health professionals through taking into account additional factors such as cost, known contraindications to any of the drugs in question (for example, pregnancy, breastfeeding, age), known rare serious adverse events, previous use of the drugs, possible drug-drug interactions, ease of administration, and travel itinerary.

## Implications for research

Better quality research is needed into malaria chemoprophylaxis in non-immune travellers, in order to better assess drug effectiveness and drug safety. The development of new prophylactic drugs should be a high priority in the research agenda, since parasite resistance to currently used agents will increase, and questions around the safety of mefloquine are likely to remain unanswered.

Participants in future trials of chemoprophylaxis should represent the general population of travellers. Trial participants should be male and female non-immune adult and child travellers. They should not normally be soldiers, since tolerability evidence in non-soldiers can readily be generalized to soldiers, but not vice-versa. Trial data for adults and children, and for males and females, should be reported separately.

As a minimum, future trials of chemoprophylaxis should include the following adverse outcome categories:

- any adverse event and effect;
- dermatological adverse events and effect;
- gastrointestinal adverse events and effects;
- neuropsychiatric adverse events and effects;
- serious adverse events; and
- discontinuation of study drug for any reason at any time.

The Profile of Mood States (POMS) questionnaire (McNair 1992) has been a useful instrument for assessing antimalaria drug effects on mood and on feelings.

All adverse outcomes in chemoprophylaxis trials should be reported as they occur, without post hoc investigator judgements on attributability, unless criteria for attributability in all outcomes are fully reported. Dermatological, gastrointestinal, and neuropsychiatric adverse events or effects should be defined in accordance with the Uppsala organ system taxonomy of adverse drug reactions (Uppsala 2001), and should be clearly reported at publication. Serious adverse events should be defined as those that are fatal, life-threatening, or requiring hospitalization. Deaths attributed to antimalaria drugs taken at normal dosages should be published as case reports (Morris 1989).

The safety or otherwise of doxycycline in children aged < 8 years needs to be more rigorously investigated.

Primaquine is recommended by some authorities as first-line chemoprophylaxis. It should be investigated for this indication in head-to-head comparisons with other currently used drugs.

Investigators in future trials of malaria chemoprophylaxis in non-immune travellers should make their full outcome datasets freely available to other researchers, and to systematic reviewers.

Where trials are funded wholly or in part by pharmaceutical companies, the exact nature of the funding should be made explicit in the published report.

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Sack RB, Froehlich JL, Zulich AW, Hidi DS, Kapikian AZ, Orskov F, et al.Prophylactic doxycycline for travelers' diarrhea: results of a prospective double-blind study of Peace Corps volunteers in Morocco. *Gastroenterology* 1979;**76**:1368–73.

**Sack 1986**
Sack RB. Antimicrobial prophylaxis of travelers' diarrhea: a selected summary. *Reviews of Infectious Diseases* 1986;**8 Suppl 2**:160–6.

**Schlagenhauf 2003b**
Schlagenhauf P, Steffen R, Loutan L. Migrants as a major risk group for imported malaria in European countries. *Journal of Travel Medicine* 2003;**10**(2):106–7.

**Schlagenhauf 2008**
Schlagenhauf P, Petersen E. Malaria chemoprophylaxis: strategies for risk groups. *Clinical Microbiology Reviews* 2008;**21**(3):466–72.

**Schlagenhauf 2009**
Schlagenhauf P, Johnson R, Schwartz E, Nothdurft HD, Steffen R. Evauation of mood profiles during malaria chemoprophylaxis: a randomized, double-blind, four-arm study. *Journal of Travel Medicine* 2009;**16**(1):42–5.

**Schoneberg 2003**
Schoneberg I, Krause G, Ammon A, Strobel H, Stark K. Malaria surveillance in Germany 2000/2001 - results and experience with a new reporting system. *Gesundheitswesen* 2003;**65**(4):263–9.

**Schwartz 2008**
Schwartz E. Primaquine. In: Schlagenhauf-Lawlor P editor(s). *Travelers' malaria*. 2nd Edition. Hamilton, Ontario: Decker, 2008: 155–9.

**Sehgal 2000**
Sehgal SC, Sugunan AP, Murhekar MV, Sharma S, Vijayachari P. Randomized controlled trial of doxycycline prophylaxis against leptospirosis in an endemic area. *International Journal of Antimicrobial Agents* 2000;**13**(4):249–55.

**Shanks 1998**
Shanks GD, Gordon DM, Klotz FW, Aleman GM, Oloo AJ, Sadie D, et al.Efficacy and safety of atovaquone/proguanil as suppressive prophylaxis for *Plasmodium falciparum* malaria. *Clinical Infectious Diseases* 1998;**27**:494–9.

**Shanks 2005**
Shanks GD, Edstein MD. Modern malaria chemoprophylaxis. *Drugs* 2005;**65**(15):2091–110.

**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**: 249–54.

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

**Soto 1998**
Soto J, Toledo J, Rodriquez M, Sanchez J, Herrera R, Padilla J, et al.Primaquine prophylaxis against malaria in nonimmune Colombian soldiers: efficacy and toxicity. *Annals of Internal Medicine* 1998;**129**:241–4.

**Soto 2006**
Soto J, Toledo J, Luzz M, Gutierrez P, Berman J, Duparc S. Randomized, double-blind, placebo-controlled study of Malarone for malaria prophylaxis in non-immune Colombian soldiers. *American Journal of Tropical Medicine and Hygiene* 2006;**75**:430–3.

**Sukwa 1999**
Sukwa TY, Mulenga M, Chisdaka N, Roskell NS, Scott TR. A randomized, double-blind, placebo-controlled field trial to determine the efficacy and safety of Malarone (atovaquone/ proguanil) for the prophylaxis of malaria in Zambia. *American Journal of Tropical Medicine and Hygiene* 1999;**60**:521–5.

**Sutherland 2007**
Sutherland CS, Haustein T, Gadalla N, Armstrong M, Doherty JF, Chiodini PL. Chloroquine-resistant Plasmodium falciparum infections among UK travellers returning with malaria after chloroquine prophylaxis. *Journal of Antimicrobial Chemotherapy.* 2007;**59**(6):1197–9.

**Takafuji 1984**
Takafuji ET, Kirkpatrick JW, Miller RN, Karwacki JJ, Kelley PW, Gray MR, et al.An efficacy trial of doxycycline chemoprophylaxis against leptospirosis. *New England Journal of Medicine* 1984;**310**: 497–500.

**Taylor 2005**
Taylor MJ, Makunde WH, McGarry HF, Turner JD, Mand S, Hoerauf A. Macrofilaricidal activity of Wuchereria bancrofti: a double-blind, randomized placebo-controlled trial. *Lancet* 2005; **365**(9477):2116–21.

**Toovey 2009**
Toovey S. Mefloquine neurotoxicity: a literature review. *Travel Medicine and Infectious Disease* 2009;**7**:2–6.

**Twartz 1982**
Twartz JC, Shirai A, Selvaraju G, Saunders JP, Huxsoll DL, Groves MG. Doxycycline prophylaxis for human scrub typhus. *Journal of Infectious Diseases* 1982;**146**(6):811–8.

**Uppsala 2001**
Uppsala Monitoring Centre. *WHO Adverse Reaction Terminology (WHO-ART)*. Uppsala: Uppsala Monitoring Centre, 2001.

**van Riemsdijk 2002**
van Riemsdijk MM, Ditters JM, Sturkenboom MC, Tulen JH, Ligthelm RJ, Overbosch D, et al.Neuropsychiatric events during prophylactic use of mefloquine before travelling. *European Journal of Clinical Pharmacology* 2002;**58**(6):441–5.

**Volovitz 2007**
Volovitz B, Shkap R, Amir J, Calderon S, Varsano I, Nussinovitch M. Absence of tooth staining with doxycycline treatment in young children. *Clinical Pediatrics (Philadelphia)* 2007;**46**:121–6.

**Weiss 1995**
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. *Journal of Infectious Diseases* 1995;**171**:1569–75.

**Wellems 2003**

Wellems TE, Miller LH. Two worlds of malaria. *New England Journal of Medicine* 2003;**349**(16):1496–8.

**White 2009**

White NJ. Malaria. In: Cook GC, Zumla AI editor(s). *Mansons tropical diseases*. 22nd Edition. London: Saunders Elsevier, 2009: 1201–300.

**WHO 2008**

Anonymous. *International travel and health*. Geneva, Switzerland: World Health Organization, 2008.

**WTO 2006**

World Tourism Organization. Historical perspective of world tourism. www.world-tourism.org/facts/wtb.html (accessed January 2006).

* *Indicates the major publication for the study*

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies *[ordered by study ID]*

**Arthur 1990a**

| | |
|---|---|
| Methods | Design: randomized controlled trial<br>Duration: June to August 1988<br>Duration of exposure to malaria: 5 weeks |
| Participants | Non-immune US Army soldiers (age 18 to 40, average 24), all male<br>Number enrolled: 310<br>Inclusion criteria: soldiers awaiting deployment to Thailand<br>Exclusion criteria: previous history of gastrointestinal illness |
| Interventions | 1. Doxycycline (1 capsule containing doxycycline hyclate 100 mg) once daily, starting 1 week before travel and continuing throughout the period of deployment<br>2. Mefloquine (1 x 250 mg tablet) once weekly, starting 1 week before travel and continuing throughout the period of deployment<br>*For each drug regimen, a matched placebo* |
| Outcomes | 1. Clinical cases of malaria (not defined)<br>2. Gastrointestinal side effect* (diarrhoea, nausea, vomiting)<br>3. Neuropsychiatric side effect (dizziness)<br>4. Serious side effect<br>**Gastrointestinal adverse events were reported separately. The most frequent adverse event (diarrhoea) is considered in the review. The true number of events might be underestimated.*<br>**Not assessed in the review:**<br>5. Incidence of diarrhoea<br>6. Infection with enterotoxigenic *Escherichia coli* (ETEC)<br>7. Infection with *Campylobacter* spp.<br>8. Withdrawal due to study drug related adverse event |
| Notes | Location: Korat, Thailand<br>Setting: military overseas training exercise<br>Funding sources: Pfizer Inc supplied active and placebo doxycycline; Hoffman-La Roche Inc supplied active and placebo mefloquine |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Adequate sequence generation? | Yes | "Computer-generated random numbers list" |
| Allocation concealment? | Unclear | Comment: information not provided |
| Blinding?<br>Any adverse event | Yes | "Soldiers receiving mefloquine also received identical appearing doxycycline placebo capsules daily, and those receiving |

**Arthur 1990a** (*Continued*)

| | | |
|---|---|---|
| | | doxycycline received weekly mefloquine placebo tablets..."<br>Participants and providers were blinded |
| Incomplete outcome data addressed?(adverse outcomes)?<br>Adverse outcomes | Unclear | 310 enrolled, 253 analysed (119 in the doxycycline arm and 134 in the mefloquine arm)<br>Comment: insufficient reporting of reasons for attrition and exclusion and how missing data were addressed in the analysis to permit judgement of 'Yes' or 'No' |
| Free of selective reporting (adverse outcomes)?<br>Adverse outcomes | Unclear | Comment: assessment of side effects and clinical case of malaria not described in the Methods section. Results for side effects not presented by drug and retrieved from another article from the same investigator. |

**Camus 2004**

| | |
|---|---|
| Methods | Randomized open-label trial<br>Multicentre study: Canada, Denmark, France, Germany, The Netherlands, United Kingdom<br>Duration of study: May 1999 to November 2000<br>Mean duration of exposure to malaria: 15 days |
| Participants | Non-immune paediatric travellers, 43% female<br>Number enrolled: 232<br>Inclusion criteria: non-immune children (age 3 to 16, weight 11 to 50kg) with planned travel of $\leq$ 28 days to areas with a substantial risk of *P. falciparum* infection<br>Exclusion criteria: pregnancy/lactation; cardiac, renal, hepatic, neurological disorders/impairment; travel to area when prophylaxis with chloroquine-proguanil would be inappropriate; clinical malaria within previous 12 months; travel to malaria endemic area within previous 60 days |
| Interventions | 1. Atovaquone-proguanil (1 combined tablet containing 250 mg atovaquone and 100 mg proguanil hydrochloride, or alternatively 1 combined paediatric tablet containing 62.5 mg atovaquone and 25 mg proguanil hydrochloride) once daily, starting 1 to 2 days before travel and continuing for 7 days after travel<br>2. Chloroquine (one 250 mg tablet, containing the equivalent of 155 mg chloroquine base) once weekly, starting $\geq$ 1 week before travel and continuing for 4 weeks after travel; and proguanil (one 100 mg tablet) once daily, starting 1 to 2 days before travel and continuing for 4 weeks after travel<br>*For each drug regimen, a matched placebo* |
| Outcomes | 1. Clinical cases of malaria (malaria smears, parasite DNA analysis)<br>2. Any adverse event[$]<br>3. Gastrointestinal adverse event *[$] (diarrhoea, abdominal pain, vomiting, nausea, oral |

| | |
|---|---|
| | ulceration)<br>4. Neuropsychiatric adverse event*$ (dreams, visual impairment, dizziness)<br>5. Serious adverse event$<br>6. Any adverse event attributed to study drug$<br>7. Gastrointestinal adverse event attributed to study drug*$ (diarrhoea, abdominal pain, vomiting, nausea, oral ulceration)<br>8. Neuropsychiatric adverse event attributed to study drug*$ (dreams, lethargy)<br>9. Discontinuation of study drug for any reason<br>**Gastrointestinal and neuropsychiatric adverse events/effects were reported separately. For each category, the most frequent adverse events/effects (diarrhoea, dreams) are considered in the review. The number of events might be underestimated.*<br>$ *Exposure period: start of travel through seventh day after travel*<br>**Not assessed in the review:**<br>10. Compliance with study drug (pre-travel, during travel and post-travel)<br>11. Withdrawal due to study drug related adverse event<br>12. Exposure to malaria (circumsporozoite antibody testing) |
| Notes | Location: various malaria endemic destinations (85% in Africa)<br>Setting: travel clinics<br>Funding source: GlaxoSmithKline (manufacturer of atovaquone-proguanil) gave financial support |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Adequate sequence generation? | Yes | "Participants were randomized (ratio, 1:1) "<br>Comment: information not provided. Probably done, since report of similar intervention in adults from same authors and the Malarone International Study Team describe use of a computer generated random numbers. |
| Allocation concealment? | Yes | Comment: information not provided. Probably done, since report of similar intervention in adults from same authors and the Malarone International Study Team describe use of "opaque sealed envelopes". |
| Blinding?<br>Any adverse event | No | Open label |
| Incomplete outcome data addressed?(adverse outcomes)?<br>Adverse outcomes | Yes | 232 randomized, 221 received study drugs and were analysed (110 in the atovaquone-proguanil arm and 111 in the chloroquine-proguanil arm)<br>Comment: reasons for attrition or ex- |

**Camus 2004** (*Continued*)

| | | |
|---|---|---|
| | | clusion were reported, balanced between groups and unlikely to be related to true outcome. Thus, the risk of bias is defined as low. |
| Free of selective reporting (adverse outcomes)?<br>Adverse outcomes | Yes | - |

**Croft 1997**

| | |
|---|---|
| Methods | Randomized controlled trial<br>Duration of study: December 1994 to March 1995<br>Duration of exposure to malaria: 6 weeks |
| Participants | Non-immune British Army soldiers, all male<br>Number enrolled: 624<br>Inclusion criteria: soldiers awaiting deployment to Kenya<br>Exclusion criteria: aviators, neuropsychiatric history, use of ß-adrenergic blocking drugs |
| Interventions | 1. Chloroquine (one 300 mg tablet) once weekly, starting 2 weeks before travel and continuing throughout the period of deployment; and proguanil (two 100 mg tablets) once daily, starting 1 to 2 days before travel and continuing for 28 days after travel<br>2. Mefloquine (one 250 mg tablet) once weekly, starting 1 week before travel and continuing throughout the period of deployment<br>*For each drug regimen, a matched placebo* |
| Outcomes | 1. Clinical cases of malaria (not defined)<br>2. Any side effect<br>3. Dermatological side effect (skin rash, pruritus) - *severe and very severe*<br>4. Gastrointestinal side effect (anorexia, nausea, vomiting, abdominal pain, diarrhoea, buccal ulceration) - *severe and very severe*<br>5. Neuropsychiatric side effect (sleep disturbance, memory disturbance, blurred vision, dizziness, motor disturbance, hallucination, alteration of mood, abnormal feeling, abnormal tiredness) - *severe and very severe*<br>6. Discontinuation of study drug for any reason<br>**Not assessed in the review**:<br>8. Self-reported compliance with study drug<br>9. Withdrawal due to study drug related adverse event |
| Notes | Location: Kenya<br>Setting: military overseas training exercise<br>Funding source: British Army Medical Services Research Executive gave financial support |

***Risk of bias***

| **Item** | **Authors' judgement** | **Description** |
|---|---|---|

**Croft 1997** (*Continued*)

| | | |
|---|---|---|
| Adequate sequence generation? | Yes | "Assigned randomly on the basis of computer-generated random numbers" |
| Allocation concealment? | Yes | "Opaque, sealed, individually-numbered packet" |
| Blinding?<br>Any adverse event | Yes | "All took 3 tablets weekly and 2 tablet daily without knowing which prophylactic regimen each was receiving"<br>Participants and providers blinded |
| Incomplete outcome data addressed?(adverse outcomes)?<br>Adverse outcomes | No | 624 randomized, 287 analysed at 8 weeks (145 in the mefloquine arm and 142 in the chloroquine-proguanil arm)<br>Comment: reasons for attrition and exclusion were not reported. The number of missing data is large. Thus, the risk of bias is defined as high. |
| Free of selective reporting (adverse outcomes)?<br>Adverse outcomes | Unclear | Comment: mild and moderate side effects were measured but not reported in the results |

**Høgh 2000**

| | |
|---|---|
| Methods | Randomized controlled trial<br>Multicentre study: Canada, Denmark, France, Germany, The Netherlands, South Africa, United Kingdom<br>Duration of study: April to November 1999<br>Mean duration of exposure to malaria: 2.5 weeks |
| Participants | Non-immune tourists and general travellers, 48% female<br>Number enrolled: 1083<br>Inclusion criteria: travellers aged $\geq$ 14 years and weighing > 50 kg with planned travel of $\leq$ 28 days to *P. falciparum* endemic areas<br>Exclusion criteria: poor general health; drug hypersensitivity (to atovaquone, chloroquine or proguanil); history of alcoholism, seizures or psychiatric or severe neurological disorders; generalized psoriasis; severe blood disorders; pregnancy/lactation; renal, hepatic or cardiac dysfunction; clinical malaria within previous 12 months; travel to malaria endemic area within previous 60 days |
| Interventions | 1. Atovaquone-proguanil (1 combined tablet containing 250 mg atovaquone and 100 mg proguanil hydrochloride) once daily, starting 1 to 2 days before travel and continuing for 7 days after travel<br>2. Chloroquine (one 250 mg tablet, containing the equivalent of 155 mg chloroquine base) once weekly, starting 7 days before travel and continuing for 4 weeks after travel; and proguanil (one 100 mg tablet) once daily, starting 1 to 2 days before travel and continuing for 28 days after travel |

**Høgh 2000** (*Continued*)

| | |
|---|---|
| | *For each drug regimen, a matched placebo* |
| Outcomes | 1. Clinical cases of malaria (malaria smear, parasite DNA analysis)<br>2. Any adverse event<br>3. Serious adverse event<br>4. Any adverse event attributed to study drug<br>5. Dermatological adverse event attributed to study drug (itching)<br>6. Gastrointestinal adverse event attributed to study drug (diarrhoea, nausea, abdominal pain, mouth ulcers, vomiting)<br>7. Neuropsychiatric adverse event attributed to study drug (dizziness, strange or vivid dreams, insomnia, visual difficulties, anxiety, depression)<br>8. Discontinuation of study drug for any reason<br>**Not assessed in the review**:<br>9. Non-compliance<br>10. Withdrawal due to study drug related adverse event<br>11. Exposure to malaria (circumsporozoite antibody testing) |
| Notes | Location: various malaria endemic destinations (63% in Africa)<br>Setting: travel clinics<br>Funding source: GlaxoSmithKline (manufacturer of atovaquone-proguanil) gave financial support |

***Risk of bias***

| **Item** | **Authors' judgement** | **Description** |
|---|---|---|
| Adequate sequence generation? | Yes | "Computer-generated code" |
| Allocation concealment? | Yes | "Treatment codes were provided to investigators in opaque sealed envelopes" |
| Blinding?<br>Any adverse event | Yes | "For each active drug, capsules or film-coated tablets were identical in appearance to the matching placebo"<br>Participants and providers were blinded |
| Incomplete outcome data addressed?(adverse outcomes)?<br>Adverse outcomes | Yes | 1083 randomized, 1022 received study drugs and were analysed (511 in the atovaquone-proguanil arm and 511 in the chloroquine-proguanil arm),1008 completed the trial (501 in the atovaquone-proguanil arm and 507 in the chloroquine-proguanil arm).<br>Comment: reasons for attrition and exclusion were reported. It is unclear how missing data for participants included in the analysis were addressed. However the total number of missing data is low and we judge the risk of bias to be low. |

**Høgh 2000** (*Continued*)

| | | |
|---|---|---|
| Free of selective reporting (adverse outcomes)?<br>Adverse outcomes | Unclear | Comment: it is unclear if dermatological, gastrointestinal, and neuropsychiatric adverse events were measured, but not reported |

**Ohrt 1997**

| | |
|---|---|
| Methods | Randomized controlled trial<br>Duration of study: May to July 1994<br>Duration of exposure to malaria: approximately 13 weeks |
| Participants | Non-immune Indonesian Army soldiers, all male<br>Number enrolled: 204<br>Inclusion criteria: soldiers in military posts with a high malaria attack rate<br>Exclusion criteria: history of frequent travel, allergy to one of the study drugs, glucose-6-phosphate dehydrogenase deficiency, history of underlying illness |
| Interventions | 1. Doxycycline hyclate (one 100 mg capsule) once daily<br>2. Mefloquine (one 250 mg tablet, containing the equivalent of 228 mg mefloquine base) once weekly (after a loading dose of 250 mg per day for 3 days).<br>3. Placebo<br>*Matched placebo for all 3 arms* |
| Outcomes | 1. Clinical cases of malaria (malaria smear)<br>2. Any adverse event<br>3. Dermatological adverse event (skin related)<br>4. Gastrointestinal adverse event (nausea, vomiting, abdominal pain, diarrhoea, constipation, anorexia)<br>5. Neuropsychiatric adverse event (insomnia, somnolence, dreams, dizziness, palpitations, sexual dysfunction, headache)<br>6. Serious adverse event<br>7. Discontinuation of study drug for any reason |
| Notes | Location: North-Eastern Irian Jaya, Indonesia<br>Setting: military posts<br>Funding source: Pfizer Indonesia supplied active and placebo doxycycline; F. Hoffman-La Roche supplied active and placebo mefloquine, and gave financial support; US Army Medical Research and Materiel Command gave financial support; US Naval Medical Research and Development Command gave financial support |

***Risk of bias***

| **Item** | **Authors' judgement** | **Description** |
|---|---|---|
| Adequate sequence generation? | Yes | "Block randomization was used (block size, 15)" |

**Ohrt 1997** (*Continued*)

| | | |
|---|---|---|
| Allocation concealment? | Yes | "The randomization code was stored in individual envelopes in a locked box at the study site" |
| Blinding?<br>Any adverse event | Yes | "Double dummy technique," "placebo capsules were identical in appearance"<br>Participants and providers were blinded |
| Incomplete outcome data addressed?(adverse outcomes)?<br>Adverse outcomes | Yes | 204 randomized and analysed. "Twelve of the 204 participants did not complete the study".<br>Comment: reasons for attrition were reported. It is unclear how missing data were addressed in the analysis. However, the percent of missing data is low and we judge the risk of bias to be low. |
| Free of selective reporting (adverse outcomes)?<br>Adverse outcomes | Yes | - |

**Overbosch 2001**

| | |
|---|---|
| Methods | Randomized controlled trial<br>Multicentre study: Canada, Germany, The Netherlands, South Africa, United Kingdom<br>Duration of study: April to October 1999<br>Mean duration of exposure to malaria: 2.5 weeks |
| Participants | Non-immune tourists and general travellers, 45% female<br>Number enrolled: 1013<br>Inclusion criteria: travellers aged $\geq$ 3 years and weighing $\geq$ 11 kg with planned travel of $\leq$ 28 days to a malaria-endemic area<br>Exclusion criteria: poor general health; drug hypersensitivity (to atovaquone, chloroquine or proguanil); history of alcoholism, seizures or psychiatric or severe neurological disorders; generalized psoriasis; severe blood disorders; pregnancy/lactation; renal, hepatic or cardiac dysfunction; clinical malaria within previous 12 months; travel to malaria endemic area within previous 60 days |
| Interventions | 1. Atovaquone-proguanil (1 combined tablet containing 250 mg atovaquone and 100 mg proguanil hydrochloride; or alternatively 1 to 3 combined paediatric tablets according to body weight, each tablet containing 62.5 mg atovaquone and 25 mg proguanil hydrochloride) once daily, starting 1 to 2 days before travel and continuing for 1 week after leaving the malaria-endemic area<br>2. Mefloquine (one 250 mg tablet; or alternatively one-fourth, one half or three-fourths of a tablet, according to body weight) once weekly, starting 7 days before travel and continuing for 4 weeks after travel<br>*For each drug regimen, a matched placebo* |

**Overbosch 2001** (*Continued*)

| | |
|---|---|
| Outcomes | 1. Clinical cases of malaria (antibody to blood-stage malaria parasites)<br>2. Any adverse event<br>3. Serious adverse event<br>4. Adverse event attributed to study drug<br>5. Dermatological adverse event attributed to study drug (itching)<br>6. Gastrointestinal adverse event attributed to study drug (diarrhoea, nausea, abdominal pain, mouth ulcers, vomiting)<br>7. Neuropsychiatric adverse event attributed to study drug (strange or vivid dreams, insomnia, dizziness or vertigo, visual difficulties, anxiety, depression)<br>8. Discontinuation of study drug for any reason<br>**Not assessed in the review:**<br>9. Compliance with study drug (pre-travel, during travel and post-travel)<br>10. Withdrawal due to study drug related adverse event<br>11. Exposure to malaria (circumsporozoite antibody testing) |
| Notes | Location: various malaria endemic destinations worldwide (63% in Africa)<br>Setting: travel clinics<br>Funding source: GlaxoSmithKline (manufacturer of atovaquone-proguanil) gave financial support |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Adequate sequence generation? | Yes | "Study conduct described elsewhere [Høgh 2000]"<br>Comment: computer-generated random numbers |
| Allocation concealment? | Yes | "Study conduct described elsewhere [Høgh 2000]"<br>Comment: opaque sealed envelopes |
| Blinding?<br>Any adverse event | Yes | "Ato-<br>vaquone-proguanil or matching placebo...<br>Mefloquine or matching placebo..."<br>Participants and providers were blinded |
| Incomplete outcome data addressed?(adverse outcomes)?<br>Adverse outcomes | Yes | 1083 randomized, 976 received study drug and were analysed (493 in the atovaquone-proguanil arm and 483 in the mefloquine arm), 966 completed the trial (489 in the atovaquone-proguanil arm and 477 in the mefloquine arm)<br>Comment: reasons for attrition and exclusion were reported. It is unclear how missing data for participants included in the analysis were addressed. However, the total |

**Overbosch 2001** (*Continued*)

| | | |
|---|---|---|
| | | number of missing data is low and we judge the risk of bias to be low. |
| Free of selective reporting (adverse outcomes)?<br>Adverse outcomes | Unclear | Comment: it is unclear if dermatological, gastrointestinal, and neuropsychiatric adverse events were measured, but not reported |

**Schlagenhauf 2003a**

| | |
|---|---|
| Methods | Randomized controlled trial<br>Multicentre study: Germany, Israel, Switzerland<br>Duration of study: 1998 to 2001<br>Mean duration of exposure to malaria: unclear |
| Participants | Non-immune tourists and general travellers, 49% female<br>Number enrolled: 674<br>Inclusion criteria: adult travellers aged 18 to 70 years, with planned travel of 1 to 3 weeks to a malaria-endemic area, and consulting at a travel clinic $\geq$ 17 days before departure<br>Exclusion criteria: glucose-6-phosphate dehydrogenase deficiency; contraindication to or severe adverse events from any of the 4 study regimens; pregnancy or risk of pregnancy; severe renal or hepatic dysfunction; history of seizures, psychiatric disorders or photosensitivity; concurrent or recent vaginal infections or bacterial enteric disorder |
| Interventions | 1. Atovaquone-proguanil (1 combined capsule containing 250 mg atovaquone and 100 mg proguanil hydrochloride) once daily, starting 17 days before travel and continuing for 1 week after travel<br>2. Chloroquine-proguanil (1 combined capsule containing chloroquine diphosphatase 161.21 mg, equivalent to chloroquine 100 mg base; and 200 mg proguanil hydrochloride) once daily, starting 17 days before travel and continuing for 4 weeks after travel<br>3. Doxycycline (1 capsule containing doxycycline monohydrate 100 mg) once daily, starting 17 days before travel and continuing for 4 weeks after travel<br>4. Mefloquine (1 capsule containing mefloquine hydrochloride 274.09 mg, equivalent to mefloquine 250 mg base) once weekly, starting 7 days before travel and continuing for 4 weeks after travel<br>*For each drug regimen, either a matched placebo (atovaquone-proguanil, mefloquine) or identical capsules* |
| Outcomes | 1. Any adverse event<br>2. Dermatological adverse event (itching, abnormal reddening of skin)<br>3. Gastrointestinal adverse event (nausea, diarrhoea, mouth ulcers)<br>4. Neuropsychiatric adverse event (strange or vivid dreams, headache, dizziness, anxiety, depression, visual disturbances, fits or seizures)<br>5. Serious adverse event<br>6. Discontinuation of study drug for any reason<br>7. Profile of Mood States (POMS) score<br>**Not assessed in the review:**<br>8. Quality of life score |

**Schlagenhauf 2003a** (*Continued*)

| | |
|---|---|
| Notes | Location: sub-Saharan Africa (mainly Kenya and South Africa)<br>Setting: travel clinics<br>Funding sources: GlaxoSmithKline supplied atovaquone-proguanil and gave financial support; Zeneca supplied chloroquine-proguanil; Pfizer supplied doxycycline; Roche supplied mefloquine and gave financial support. |

***Risk of bias***

| Item | Authors' judgement | Description |
|---|---|---|
| Adequate sequence generation? | Yes | "Randomization was from a computer generated table to numbers in permuted blocks of five" |
| Allocation concealment? | Yes | "Allocation concealment was by sealed envelope" |
| Blinding?<br>Any adverse event | Yes | "Drugs were provided as identical capsules... by the company that packed the study drugs"<br>Participants and providers blinded |
| Incomplete outcome data addressed?(adverse outcomes)?<br>Adverse outcomes | Yes | 674 randomized, 634 received study drug, 623 were analysed (164 in the atovaquone-proguanil arm, 153 in the chloroquine-proguanil arm, 153 in the doxycycline arm, and 153 in the mefloquine arm), 569 completed all evaluations (154 in the atovaquone-proguanil arm, 135 in the chloroquine-proguanil arm, 142 in the doxycycline arm, and 138 in the mefloquine arm)<br>Comment: reasons for attrition and exclusion were reported |
| Free of selective reporting (adverse outcomes)?<br>Adverse outcomes | Yes | - |

**van Riemsdijk 2002**

| | |
|---|---|
| Methods | Randomized controlled trial<br>Duration of study: unclear<br>Mean duration of exposure to malaria: 19 days |
| Participants | Non-immune tourists and general travellers, 38% female<br>Number enrolled: 140<br>Inclusion criteria: travellers aged $\geq$ 3 years and weighing $\geq$ 11 kg with planned travel of $\leq$ 28 days to a malaria-endemic area |

| | |
|---|---|
| | Exclusion criteria: poor general health; drug hypersensitivity (to atovaquone, chloroquine or proguanil); history of alcoholism, seizures, psychiatric disorders, severe neurological disorders, severe blood disorders; renal, hepatic or cardiac dysfunction; clinical malaria within previous 12 months; travel to malaria-endemic area within previous 60 days; risk factors for concentration impairment (e.g. use of opioids, hypnotics, or tranquillizers; or use of alcohol 4 hours before testing) |
| Interventions | 1. Atovaquone-proguanil (1 combined tablet containing 250 mg atovaquone and 100 mg proguanil hydrochloride; or alternatively 1 to 3 combined paediatric tablets according to body weight, each tablet containing 62.5 mg atovaquone and 25 mg proguanil hydrochloride) once daily, starting 1 to 2 days before travel and continuing for 1 week after leaving the malaria-endemic area<br>2. Mefloquine (1 250 mg tablet; or else one-fourth, one half or three-fourths of a tablet, according to body weight) once weekly, starting 7 days before travel and continuing for 4 weeks after travel<br>*For each drug regimen, a matched placebo* |
| Outcomes | 1. Profile of mood states (POMS) score<br>**Not assessed in the review:**<br>2. Neurobehavioural evaluation system score |
| Notes | Location: various malaria endemic destinations (66% in Africa, 13% South America, 24% other)<br>Setting: Rotterdam Travel Clinic, the Netherlands<br>Funding source: Netherlands Inspectorate for Healthcare gave financial support |

***Risk of bias***

| **Item** | **Authors' judgement** | **Description** |
|---|---|---|
| Adequate sequence generation? | Yes | "This study was independently performed in a sample of patients from one center that participated in the MAL30010 multicenter clinical trial, the methods of which have been described in detail elsewhere." (Høgh 2000; Overbosch 2001)<br>Comment: computer-generated random numbers |
| Allocation concealment? | Yes | "This study was independently performed in a sample of patients from one center that participated in the MAL30010 multicenter clinical trial, the methods of which have been described in detail elsewhere" (Høgh 2000; Overbosch 2001)<br>Comment: opaque sealed envelopes |

**van Riemsdijk 2002** (*Continued*)

| | | |
|---|---|---|
| Blinding?<br>Any adverse event | Yes | "All placebo treatment regimens were identical to the aforementioned scheme for the active ingredient of mefloquine and atovaquone plus chloroguanide" |
| Incomplete outcome data addressed?(adverse outcomes)?<br>Adverse outcomes | No | 140 randomized, 119 analysed (61 in the atovaquone-proguanil arm and 58 in the mefloquine arm)<br>Comment: reasons for attrition and exclusion were balanced between groups. However, some reasons were likely to be related to true outcome (adverse outcomes). Thus, the risk of bias was defined as high. |
| Free of selective reporting (adverse outcomes)?<br>Adverse outcomes | Yes | - |

## Characteristics of excluded studies *[ordered by study ID]*

| | |
|---|---|
| Baudon 1999 | Randomization of 4 companies of soldiers stratified by country, but with results reported at individual level - inappropriate number of clusters |
| Carme 1997 | Allocation of participants to mefloquine versus chloroquine-proguanil was not random |
| Pages 2002 | Randomization of 4 companies of soldiers stratified by country, but with results reported at individual level - inappropriate number of clusters |
| Rieckmann 1993 | Allocation of participants to either mefloquine, doxycycline, doxycycline plus primaquine, or doxycycline plus chloroquine was not random |
| van Genderen 2007 | Allocation of participants to atovaquone-proguanil or mefloquine was not random |

## DATA AND ANALYSES

### Comparison 1. Atovaquone-proguanil vs doxycycline

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Any adverse outcome | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 1.1 Any adverse event | 1 | 317 | Risk Ratio (M-H, Fixed, 95% CI) | 0.98 [0.88, 1.08] |
| 2 Dermatological adverse outcome | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 2.1 Dermatological adverse event | 1 | 317 | Risk Ratio (M-H, Fixed, 95% CI) | 0.88 [0.58, 1.33] |
| 3 Gastrointestinal adverse outcome | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 3.1 Gastrointestinal adverse event | 1 | 317 | Risk Ratio (M-H, Fixed, 95% CI) | 1.01 [0.82, 1.25] |
| 4 Neuropsychiatric adverse outcome | 1 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 4.1 Neuropsychiatric adverse event | 1 | 317 | Risk Ratio (M-H, Fixed, 95% CI) | 0.97 [0.83, 1.13] |
| 5 Discontinuation of study drug for any reason | 1 | 317 | Risk Ratio (M-H, Fixed, 95% CI) | 0.75 [0.20, 2.73] |

### Comparison 2. Atovaquone-proguanil vs mefloquine

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Any adverse outcome | 2 | | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 1.1 Any adverse event | 2 | 1293 | Risk Ratio (M-H, Random, 95% CI) | 0.99 [0.86, 1.14] |
| 1.2 Any adverse effect | 1 | 976 | Risk Ratio (M-H, Random, 95% CI) | 0.72 [0.60, 0.85] |
| 2 Dermatological adverse outcome | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 2.1 Dermatological adverse event | 1 | 317 | Risk Ratio (M-H, Fixed, 95% CI) | 0.88 [0.58, 1.33] |
| 2.2 Dermatological adverse effect | 1 | 976 | Risk Ratio (M-H, Fixed, 95% CI) | 0.78 [0.37, 1.66] |
| 3 Gastrointestinal adverse outcome | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 3.1 Gastrointestinal adverse event | 1 | 317 | Risk Ratio (M-H, Fixed, 95% CI) | 0.92 [0.76, 1.12] |
| 3.2 Gastrointestinal adverse effect | 1 | 976 | Risk Ratio (M-H, Fixed, 95% CI) | 0.54 [0.42, 0.70] |
| 4 Neuropsychiatric adverse outcome | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 4.1 Neuropsychiatric adverse event | 1 | 317 | Risk Ratio (M-H, Fixed, 95% CI) | 0.86 [0.75, 0.99] |
| 4.2 Neuropsychiatric adverse effect | 1 | 976 | Risk Ratio (M-H, Fixed, 95% CI) | 0.49 [0.38, 0.63] |
| 5 Serious adverse event | 2 | 1293 | Risk Ratio (M-H, Fixed, 95% CI) | 0.39 [0.12, 1.24] |

| | | | | |
|---|---|---|---|---|
| 6 Discontinuation of study drug for any reason | 2 | 1293 | Risk Ratio (M-H, Fixed, 95% CI) | 0.79 [0.59, 1.06] |
| 7 Total Mood Disturbance (TMD) scores | 1 | 119 | Mean Difference (IV, Fixed, 95% CI) | -7.20 [-10.79, -3.61] |

## Comparison 3. Doxycycline vs mefloquine

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Clinical cases of malaria | 2 | 388 | Risk Ratio (M-H, Fixed, 95% CI) | 3.04 [0.13, 73.42] |
| 2 Any adverse outcome | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 2.1 Any adverse event | 2 | 441 | Risk Ratio (M-H, Fixed, 95% CI) | 0.97 [0.90, 1.04] |
| 3 Dermatological adverse outcome | 2 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 3.1 Dermatological adverse event | 2 | 441 | Risk Ratio (M-H, Fixed, 95% CI) | 0.96 [0.72, 1.28] |
| 4 Gastrointestinal adverse outcome | 3 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 4.1 Gastrointestinal adverse event | 2 | 441 | Risk Ratio (M-H, Fixed, 95% CI) | 0.82 [0.68, 1.00] |
| 4.2 Gastrointestinal adverse effect | 1 | 253 | Risk Ratio (M-H, Fixed, 95% CI) | 1.02 [0.79, 1.32] |
| 5 Neuropsychiatric adverse outcome | 3 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 5.1 Neuropsychiatric adverse event | 2 | 441 | Risk Ratio (M-H, Fixed, 95% CI) | 0.84 [0.73, 0.96] |
| 5.2 Neuropsychiatric adverse effect | 1 | 253 | Risk Ratio (M-H, Fixed, 95% CI) | 0.68 [0.25, 1.80] |
| 6 Discontinuation of study drug for any reason | 2 | 441 | Risk Ratio (M-H, Random, 95% CI) | 0.67 [0.31, 1.46] |

## Comparison 4. Any standard drugs vs chloroquine-proguanil

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Clinical cases of malaria | 3 | 1853 | Risk Ratio (M-H, Fixed, 95% CI) | 0.14 [0.01, 2.79] |
| 2 Any adverse outcome | 4 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 2.1 Any adverse event | 3 | 1866 | Risk Ratio (M-H, Fixed, 95% CI) | 0.96 [0.90, 1.03] |
| 2.2 Any adverse effect | 3 | 1530 | Risk Ratio (M-H, Fixed, 95% CI) | 0.84 [0.73, 0.96] |
| 3 Dermatological adverse outcome | 3 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 3.1 Dermatological adverse event | 1 | 623 | Risk Ratio (M-H, Fixed, 95% CI) | 0.86 [0.63, 1.18] |
| 3.2 Dermatological adverse effect | 2 | 1309 | Risk Ratio (M-H, Fixed, 95% CI) | 1.19 [0.67, 2.13] |
| 4 Gastrointestinal adverse outcome | 4 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |

| | | | | |
|---|---|---|---|---|
| 4.1 Gastrointestinal adverse event | 2 | 844 | Risk Ratio (M-H, Fixed, 95% CI) | 0.89 [0.77, 1.03] |
| 4.2 Gastrointestinal adverse effect | 3 | 1530 | Risk Ratio (M-H, Fixed, 95% CI) | 0.71 [0.60, 0.85] |
| 5 Neuropsychiatric adverse outcome | 4 | | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 5.1 Neuropsychiatric adverse event | 2 | 844 | Risk Ratio (M-H, Fixed, 95% CI) | 1.00 [0.89, 1.13] |
| 5.2 Neuropsychiatric adverse effect | 3 | 1530 | Risk Ratio (M-H, Fixed, 95% CI) | 1.02 [0.81, 1.27] |
| 6 Serious adverse event | 3 | 1866 | Risk Ratio (M-H, Fixed, 95% CI) | 1.0 [0.32, 3.08] |
| 7 Discontinuation of study drug for any reason | 4 | 2490 | Risk Ratio (M-H, Fixed, 95% CI) | 1.05 [0.75, 1.47] |

**Analysis 1.1. Comparison 1 Atovaquone-proguanil vs doxycycline, Outcome 1 Any adverse outcome.**

Review: Drugs for preventing malaria in travellers

Comparison: 1 Atovaquone-proguanil vs doxycycline

Outcome: 1 Any adverse outcome

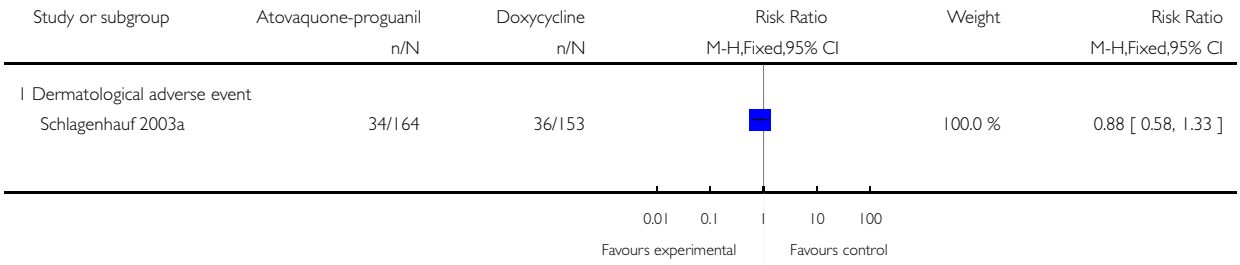
| Study or subgroup | Atovaquone-proguanil n/N | Doxycycline n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Any adverse event | | | | | |
| Schlagenhauf 2003a | 134/164 | 128/153 | | 100.0 % | 0.98 [ 0.88, 1.08 ] |

### Analysis 1.2. Comparison 1 Atovaquone-proguanil vs doxycycline, Outcome 2 Dermatological adverse outcome.

Review: Drugs for preventing malaria in travellers

Comparison: 1 Atovaquone-proguanil vs doxycycline

Outcome: 2 Dermatological adverse outcome

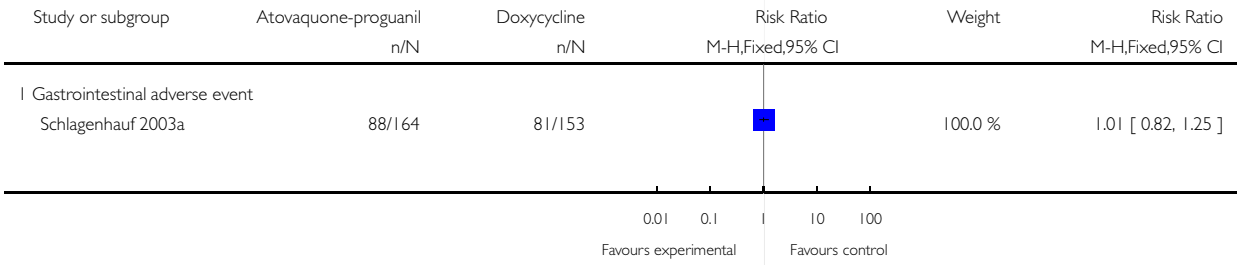



### Analysis 1.3. Comparison 1 Atovaquone-proguanil vs doxycycline, Outcome 3 Gastrointestinal adverse outcome.

Review: Drugs for preventing malaria in travellers

Comparison: 1 Atovaquone-proguanil vs doxycycline

Outcome: 3 Gastrointestinal adverse outcome

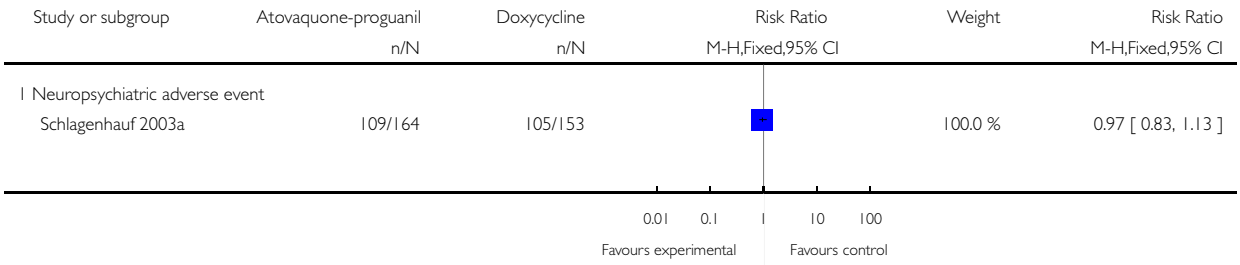


### Analysis 1.4. Comparison 1 Atovaquone-proguanil vs doxycycline, Outcome 4 Neuropsychiatric adverse outcome.

Review: Drugs for preventing malaria in travellers

Comparison: 1 Atovaquone-proguanil vs doxycycline

Outcome: 4 Neuropsychiatric adverse outcome

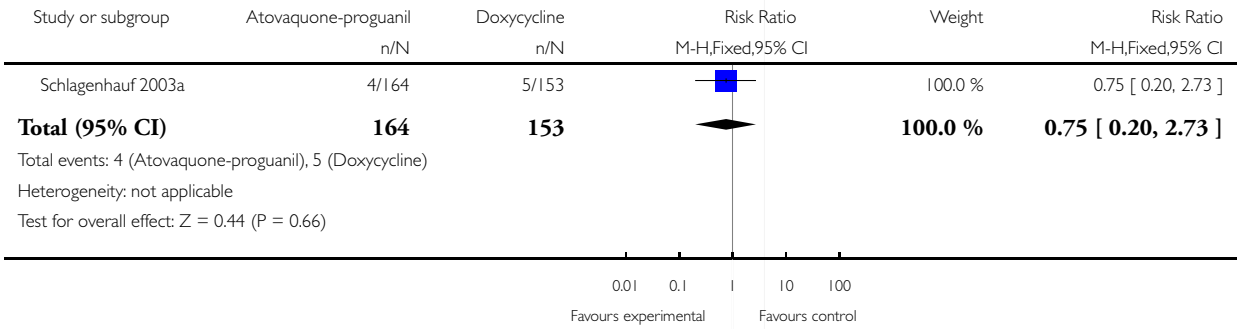



### Analysis 1.5. Comparison 1 Atovaquone-proguanil vs doxycycline, Outcome 5 Discontinuation of study drug for any reason.

Review: Drugs for preventing malaria in travellers

Comparison: 1 Atovaquone-proguanil vs doxycycline

Outcome: 5 Discontinuation of study drug for any reason



### Analysis 2.1. Comparison 2 Atovaquone-proguanil vs mefloquine, Outcome 1 Any adverse outcome.

Review: Drugs for preventing malaria in travellers

Comparison: 2 Atovaquone-proguanil vs mefloquine

Outcome: 1 Any adverse outcome

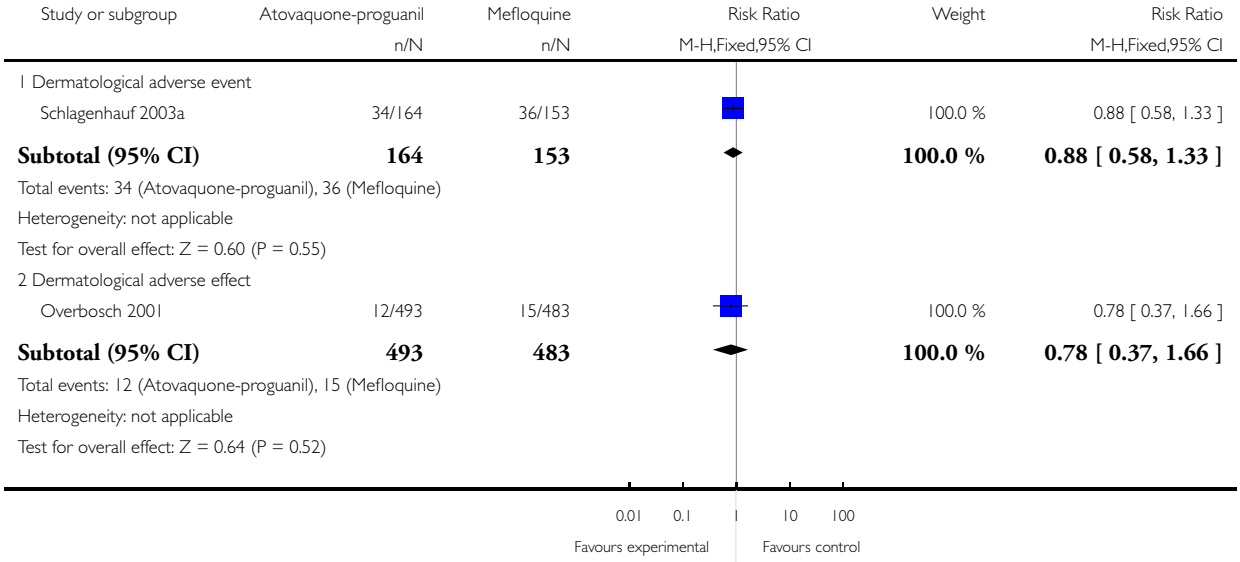
| Study or subgroup | Atovaquone-proguanil n/N | Mefloquine n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| 1 Any adverse event | | | | | |
| Overbosch 2001 | 352/493 | 325/483 | | 51.0 % | 1.06 [ 0.98, 1.15 ] |
| Schlagenhauf 2003a | 134/164 | 135/153 | | 49.0 % | 0.93 [ 0.84, 1.02 ] |
| **Subtotal (95% CI)** | **657** | **636** | | **100.0 %** | **0.99 [ 0.86, 1.14 ]** |
| Total events: 486 (Atovaquone-proguanil), 460 (Mefloquine) | | | | | |
| Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 5.07$, df = 1 (P = 0.02); $I^2 = 80\%$ | | | | | |
| Test for overall effect: Z = 0.10 (P = 0.92) | | | | | |
| 2 Any adverse effect | | | | | |
| Overbosch 2001 | 149/493 | 204/483 | | 100.0 % | 0.72 [ 0.60, 0.85 ] |
| **Subtotal (95% CI)** | **493** | **483** | | **100.0 %** | **0.72 [ 0.60, 0.85 ]** |
| Total events: 149 (Atovaquone-proguanil), 204 (Mefloquine) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 3.86 (P = 0.00011) | | | | | |

### Analysis 2.2. Comparison 2 Atovaquone-proguanil vs mefloquine, Outcome 2 Dermatological adverse outcome.

Review: Drugs for preventing malaria in travellers

Comparison: 2 Atovaquone-proguanil vs mefloquine

Outcome: 2 Dermatological adverse outcome

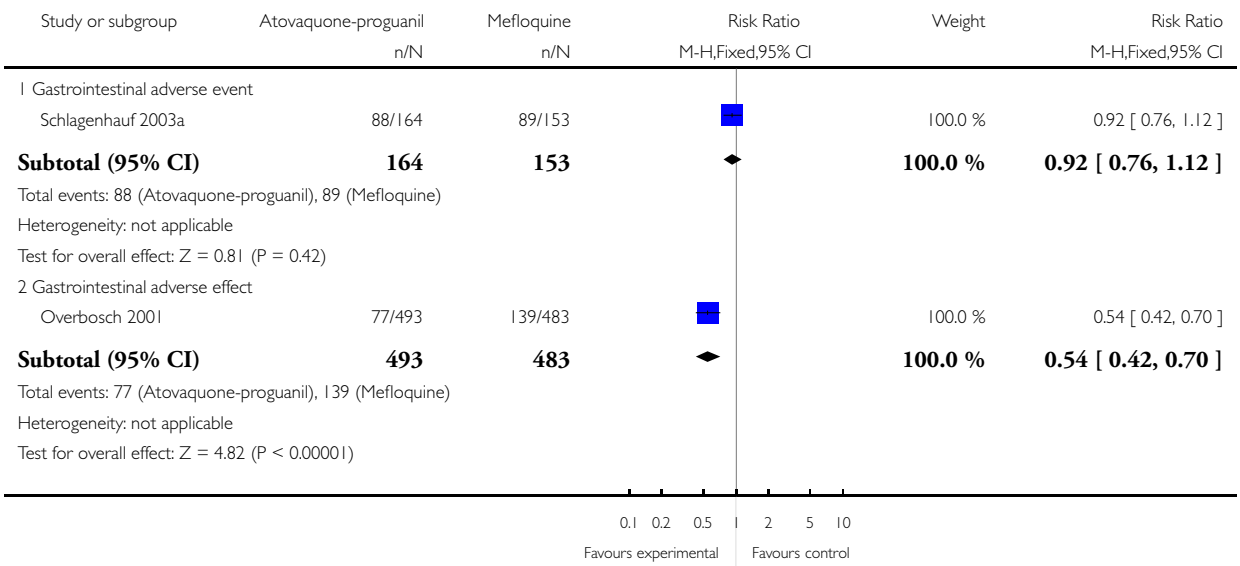


### Analysis 2.3. Comparison 2 Atovaquone-proguanil vs mefloquine, Outcome 3 Gastrointestinal adverse outcome.

Review: Drugs for preventing malaria in travellers

Comparison: 2 Atovaquone-proguanil vs mefloquine

Outcome: 3 Gastrointestinal adverse outcome



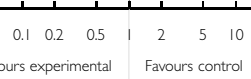
### Analysis 2.4. Comparison 2 Atovaquone-proguanil vs mefloquine, Outcome 4 Neuropsychiatric adverse outcome.

Review: Drugs for preventing malaria in travellers

Comparison: 2 Atovaquone-proguanil vs mefloquine

Outcome: 4 Neuropsychiatric adverse outcome

| Study or subgroup | Atovaquone-proguanil n/N | Mefloquine n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Neuropsychiatric adverse event | | | | | |
| Schlagenhauf 2003a | 109/164 | 118/153 | | 100.0 % | 0.86 [ 0.75, 0.99 ] |
| **Subtotal (95% CI)** | **164** | **153** | | **100.0 %** | **0.86 [ 0.75, 0.99 ]** |
| Total events: 109 (Atovaquone-proguanil), 118 (Mefloquine) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 2.10 (P = 0.036) | | | | | |
| 2 Neuropsychiatric adverse effect | | | | | |
| Overbosch 2001 | 69/493 | 139/483 | | 100.0 % | 0.49 [ 0.38, 0.63 ] |
| **Subtotal (95% CI)** | **493** | **483** | | **100.0 %** | **0.49 [ 0.38, 0.63 ]** |
| Total events: 69 (Atovaquone-proguanil), 139 (Mefloquine) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 5.44 (P < 0.00001) | | | | | |



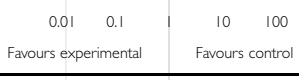

### Analysis 2.5. Comparison 2 Atovaquone-proguanil vs mefloquine, Outcome 5 Serious adverse event.

Review: Drugs for preventing malaria in travellers

Comparison: 2 Atovaquone-proguanil vs mefloquine

Outcome: 5 Serious adverse event

| Study or subgroup | Atovaquone-proguanil n/N | Mefloquine n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Overbosch 2001 | 4/493 | 10/483 | | 0.39 [ 0.12, 1.24 ] |
| Schlagenhauf 2003a | 0/164 | 0/153 | | 0.0 [ 0.0, 0.0 ] |
| **Total (95% CI)** | **657** | **636** | | **0.39 [ 0.12, 1.24 ]** |
| Total events: 4 (Atovaquone-proguanil), 10 (Mefloquine) | | | | |
| Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0% | | | | |
| Test for overall effect: Z = 1.59 (P = 0.11) | | | | |



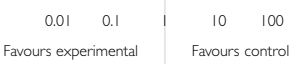
### Analysis 2.6. Comparison 2 Atovaquone-proguanil vs mefloquine, Outcome 6 Discontinuation of study drug for any reason.

Review: Drugs for preventing malaria in travellers

Comparison: 2 Atovaquone-proguanil vs mefloquine

Outcome: 6 Discontinuation of study drug for any reason

| Study or subgroup | Atovaquone-proguanil n/N | Mefloquine n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Schlagenhauf 2003a | 4/164 | 8/153 | | 9.7 % | 0.47 [ 0.14, 1.52 ] |
| Overbosch 2001 | 64/493 | 76/483 | | 90.3 % | 0.83 [ 0.61, 1.12 ] |
| **Total (95% CI)** | **657** | **636** | | **100.0 %** | **0.79 [ 0.59, 1.06 ]** |
| Total events: 68 (Atovaquone-proguanil), 84 (Mefloquine) | | | | | |
| Heterogeneity: $Chi^2$ = 0.84, df = 1 (P = 0.36); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 1.55 (P = 0.12) | | | | | |



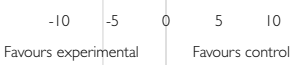

### Analysis 2.7. Comparison 2 Atovaquone-proguanil vs mefloquine, Outcome 7 Total Mood Disturbance (TMD) scores.

Review: Drugs for preventing malaria in travellers

Comparison: 2 Atovaquone-proguanil vs mefloquine

Outcome: 7 Total Mood Disturbance (TMD) scores

| Study or subgroup | Atovaquone-proguanil N | Mean(SD) | Mefloquine N | Mean(SD) | Mean Difference IV,Fixed,95% CI | Weight | Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| van Riemsdijk 2002 | 61 | 0.32 (7.8) | 58 | 7.52 (11.7) | | 100.0 % | -7.20 [ -10.79, -3.61 ] |
| **Total (95% CI)** | **61** | | **58** | | | **100.0 %** | **-7.20 [ -10.79, -3.61 ]** |
| Heterogeneity: not applicable | | | | | | | |
| Test for overall effect: Z = 3.93 (P = 0.000085) | | | | | | | |

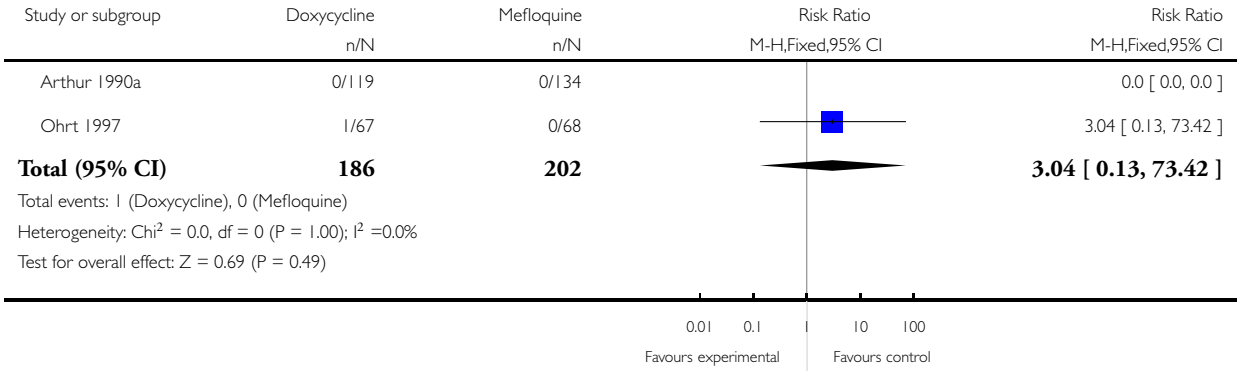


### Analysis 3.1. Comparison 3 Doxycycline vs mefloquine, Outcome 1 Clinical cases of malaria.

Review: Drugs for preventing malaria in travellers

Comparison: 3 Doxycycline vs mefloquine

Outcome: 1 Clinical cases of malaria

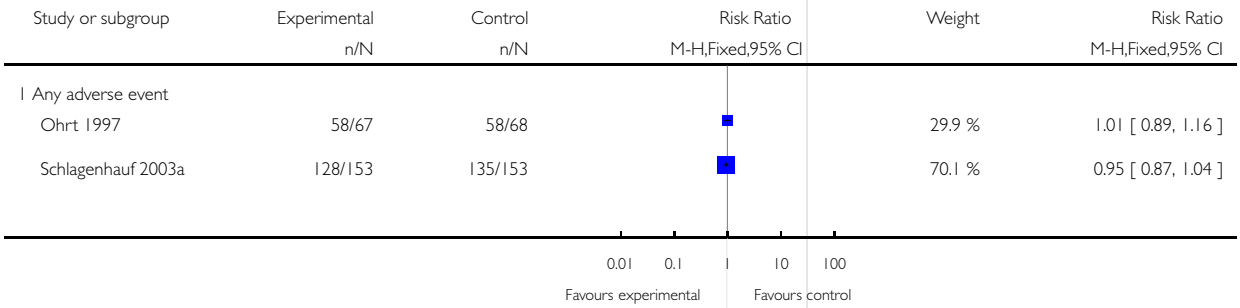



### Analysis 3.2. Comparison 3 Doxycycline vs mefloquine, Outcome 2 Any adverse outcome.

Review: Drugs for preventing malaria in travellers

Comparison: 3 Doxycycline vs mefloquine

Outcome: 2 Any adverse outcome



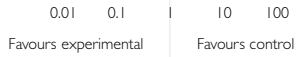
### Analysis 3.3. Comparison 3 Doxycycline vs mefloquine, Outcome 3 Dermatological adverse outcome.

Review: Drugs for preventing malaria in travellers

Comparison: 3 Doxycycline vs mefloquine

Outcome: 3 Dermatological adverse outcome

| Study or subgroup | Experimental n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Dermatological adverse event | | | | | |
| Ohrt 1997 | 22/67 | 22/68 | | 32.7 % | 1.01 [ 0.62, 1.65 ] |
| Schlagenhauf 2003a | 42/153 | 45/153 | | 67.3 % | 0.93 [ 0.65, 1.33 ] |



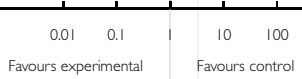

### Analysis 3.4. Comparison 3 Doxycycline vs mefloquine, Outcome 4 Gastrointestinal adverse outcome.

Review: Drugs for preventing malaria in travellers

Comparison: 3 Doxycycline vs mefloquine

Outcome: 4 Gastrointestinal adverse outcome

| Study or subgroup | Experimental n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Gastrointestinal adverse event | | | | | |
| Ohrt 1997 | 16/67 | 29/68 | | 24.4 % | 0.56 [ 0.34, 0.93 ] |
| Schlagenhauf 2003a | 81/153 | 89/153 | | 75.6 % | 0.91 [ 0.74, 1.11 ] |
| **Subtotal (95% CI)** | **220** | **221** | | **100.0 %** | **0.82 [ 0.68, 1.00 ]** |
| Total events: 97 (Experimental), 118 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 3.15, df = 1 (P = 0.08); $I^2$ =68% | | | | | |
| Test for overall effect: Z = 1.99 (P = 0.046) | | | | | |
| 2 Gastrointestinal adverse effect | | | | | |
| Arthur 1990a | 58/119 | 64/134 | | 100.0 % | 1.02 [ 0.79, 1.32 ] |
| **Subtotal (95% CI)** | **119** | **134** | | **100.0 %** | **1.02 [ 0.79, 1.32 ]** |
| Total events: 58 (Experimental), 64 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.16 (P = 0.88) | | | | | |



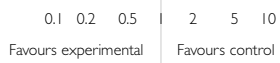
### Analysis 3.5. Comparison 3 Doxycycline vs mefloquine, Outcome 5 Neuropsychiatric adverse outcome.

Review: Drugs for preventing malaria in travellers

Comparison: 3 Doxycycline vs mefloquine

Outcome: 5 Neuropsychiatric adverse outcome

| Study or subgroup | Experimental n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Neuropsychiatric adverse event | | | | | |
| Ohrt 1997 | 22/67 | 34/68 | | 22.2 % | 0.66 [ 0.43, 1.00 ] |
| Schlagenhauf 2003a | 105/153 | 118/153 | | 77.8 % | 0.89 [ 0.78, 1.02 ] |
| **Subtotal (95% CI)** | **220** | **221** | | **100.0 %** | **0.84 [ 0.73, 0.96 ]** |
| Total events: 127 (Experimental), 152 (Control) | | | | | |
| Heterogeneity: $Chi^2$ = 2.04, df = 1 (P = 0.15); $I^2$ =51% | | | | | |
| Test for overall effect: Z = 2.52 (P = 0.012) | | | | | |
| 2 Neuropsychiatric adverse effect | | | | | |
| Arthur 1990a | 6/119 | 10/134 | | 100.0 % | 0.68 [ 0.25, 1.80 ] |
| **Subtotal (95% CI)** | **119** | **134** | | **100.0 %** | **0.68 [ 0.25, 1.80 ]** |
| Total events: 6 (Experimental), 10 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.78 (P = 0.43) | | | | | |



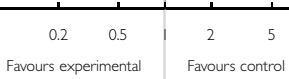

### Analysis 3.6. Comparison 3 Doxycycline vs mefloquine, Outcome 6 Discontinuation of study drug for any reason.

Review: Drugs for preventing malaria in travellers

Comparison: 3 Doxycycline vs mefloquine

Outcome: 6 Discontinuation of study drug for any reason

| Study or subgroup | Doxycycline n/N | Mefloquine n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Ohrt 1997 | 5/67 | 7/68 | | 49.9 % | 0.72 [ 0.24, 2.17 ] |
| Schlagenhauf 2003a | 5/153 | 8/153 | | 50.1 % | 0.63 [ 0.21, 1.87 ] |
| **Total (95% CI)** | **220** | **221** | | **100.0 %** | **0.67 [ 0.31, 1.46 ]** |
| Total events: 10 (Doxycycline), 15 (Mefloquine) | | | | | |
| Heterogeneity: $Tau^2$ = 0.0; $Chi^2$ = 0.04, df = 1 (P = 0.85); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 1.00 (P = 0.32) | | | | | |



### Analysis 4.1. Comparison 4 Any standard drugs vs chloroquine-proguanil, Outcome 1 Clinical cases of malaria.

Review: Drugs for preventing malaria in travellers

Comparison: 4 Any standard drugs vs chloroquine-proguanil

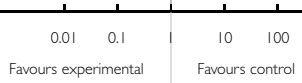
Outcome: 1 Clinical cases of malaria

| Study or subgroup | Any standard drugs n/N | chloroquine-proguanil n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Camus 2004 | 0/110 | 0/111 | | 0.0 [ 0.0, 0.0 ] |
| Croft 1997 | 0/317 | 0/307 | | 0.0 [ 0.0, 0.0 ] |
| Hgh 2000 | 0/501 | 3/507 | | 0.14 [ 0.01, 2.79 ] |
| **Total (95% CI)** | **928** | **925** | | **0.14 [ 0.01, 2.79 ]** |

Total events: 0 (Any standard drugs), 3 (chloroquine-proguanil)

Heterogeneity: $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 1.28 (P = 0.20)



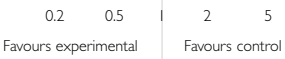
### Analysis 4.2. Comparison 4 Any standard drugs vs chloroquine-proguanil, Outcome 2 Any adverse outcome.

Review: Drugs for preventing malaria in travellers

Comparison: 4 Any standard drugs vs chloroquine-proguanil

Outcome: 2 Any adverse outcome

| Study or subgroup | Any standard drugs n/N | chloroquine-proguanil n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Any adverse event | | | | | |
| Camus 2004 | 39/110 | 41/111 | | 7.2 % | 0.96 [ 0.68, 1.36 ] |
| Hgh 2000 | 311/511 | 329/511 | | 58.0 % | 0.95 [ 0.86, 1.04 ] |
| Schlagenhauf 2003a | 397/470 | 131/153 | | 34.8 % | 0.99 [ 0.91, 1.06 ] |
| **Subtotal (95% CI)** | **1091** | **775** | | **100.0 %** | **0.96 [ 0.90, 1.03 ]** |
| Total events: 747 (Any standard drugs), 501 (chloroquine-proguanil) | | | | | |
| Heterogeneity: $Chi^2$ = 0.58, df = 2 (P = 0.75); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 1.20 (P = 0.23) | | | | | |
| 2 Any adverse effect | | | | | |
| Camus 2004 | 8/110 | 9/111 | | 3.5 % | 0.90 [ 0.36, 2.24 ] |
| Croft 1997 | 100/145 | 107/142 | | 41.7 % | 0.92 [ 0.79, 1.06 ] |
| Hgh 2000 | 110/511 | 142/511 | | 54.8 % | 0.77 [ 0.62, 0.96 ] |
| **Subtotal (95% CI)** | **766** | **764** | | **100.0 %** | **0.84 [ 0.73, 0.96 ]** |
| Total events: 218 (Any standard drugs), 258 (chloroquine-proguanil) | | | | | |
| Heterogeneity: $Chi^2$ = 1.98, df = 2 (P = 0.37); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 2.58 (P = 0.0097) | | | | | |

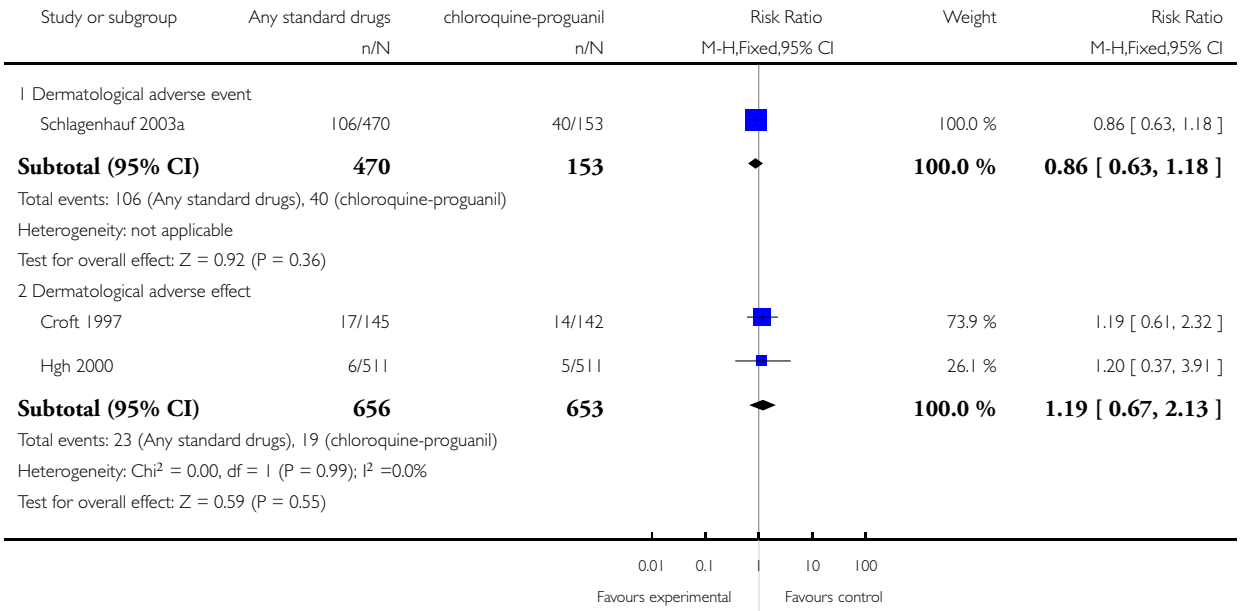


### Analysis 4.3. Comparison 4 Any standard drugs vs chloroquine-proguanil, Outcome 3 Dermatological adverse outcome.

Review: Drugs for preventing malaria in travellers

Comparison: 4 Any standard drugs vs chloroquine-proguanil

Outcome: 3 Dermatological adverse outcome



### Analysis 4.4. Comparison 4 Any standard drugs vs chloroquine-proguanil, Outcome 4 Gastrointestinal adverse outcome.

Review: Drugs for preventing malaria in travellers

Comparison: 4 Any standard drugs vs chloroquine-proguanil

Outcome: 4 Gastrointestinal adverse outcome

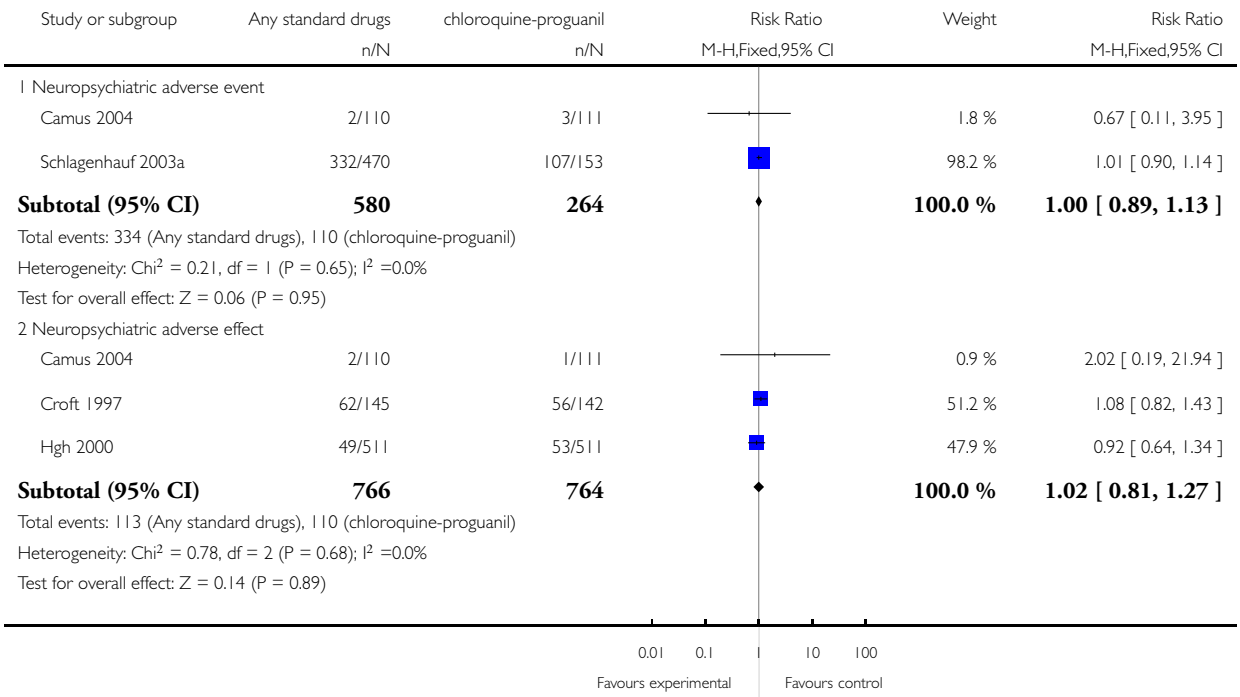
| Study or subgroup | Any standard drugs n/N | chloroquine-proguanil n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| 1 Gastrointestinal adverse event | | | | | |
| Camus 2004 | 23/110 | 28/111 | | 16.6 % | 0.83 [ 0.51, 1.35 ] |
| Schlagenhauf 2003a | 258/470 | 93/153 | | 83.4 % | 0.90 [ 0.78, 1.05 ] |
| **Subtotal (95% CI)** | **580** | **264** | | **100.0 %** | **0.89 [ 0.77, 1.03 ]** |
| Total events: 281 (Any standard drugs), 121 (chloroquine-proguanil) | | | | | |
| Heterogeneity: $Chi^2$ = 0.12, df = 1 (P = 0.73); $I^2$ =0.0% | | | | | |
| Test for overall effect: Z = 1.52 (P = 0.13) | | | | | |
| 2 Gastrointestinal adverse effect | | | | | |
| Camus 2004 | 3/110 | 2/111 | | 1.0 % | 1.51 [ 0.26, 8.88 ] |
| Croft 1997 | 77/145 | 91/142 | | 47.4 % | 0.83 [ 0.68, 1.01 ] |
| Hgh 2000 | 59/511 | 100/511 | | 51.6 % | 0.59 [ 0.44, 0.79 ] |
| **Subtotal (95% CI)** | **766** | **764** | | **100.0 %** | **0.71 [ 0.60, 0.85 ]** |
| Total events: 139 (Any standard drugs), 193 (chloroquine-proguanil) | | | | | |
| Heterogeneity: $Chi^2$ = 4.51, df = 2 (P = 0.10); $I^2$ =56% | | | | | |
| Test for overall effect: Z = 3.82 (P = 0.00013) | | | | | |

### Analysis 4.5. Comparison 4 Any standard drugs vs chloroquine-proguanil, Outcome 5 Neuropsychiatric adverse outcome.

Review: Drugs for preventing malaria in travellers

Comparison: 4 Any standard drugs vs chloroquine-proguanil

Outcome: 5 Neuropsychiatric adverse outcome



### Analysis 4.6. Comparison 4 Any standard drugs vs chloroquine-proguanil, Outcome 6 Serious adverse event.

Review: Drugs for preventing malaria in travellers

Comparison: 4 Any standard drugs vs chloroquine-proguanil

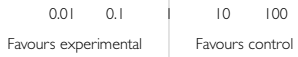
Outcome: 6 Serious adverse event

| Study or subgroup | Any standard drugs n/N | chloroquine-proguanil n/N | Risk Ratio M-H,Fixed,95% CI | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|
| Camus 2004 | 0/110 | 0/111 | | 0.0 [ 0.0, 0.0 ] |
| Hgh 2000 | 6/511 | 6/511 | | 1.00 [ 0.32, 3.08 ] |
| Schlagenhauf 2003a | 0/470 | 0/153 | | 0.0 [ 0.0, 0.0 ] |
| **Total (95% CI)** | **1091** | **775** | | **1.00 [ 0.32, 3.08 ]** |

Total events: 6 (Any standard drugs), 6 (chloroquine-proguanil)

Heterogeneity: $Chi^2$ = 0.0, df = 0 (P = 1.00); $I^2$ =0.0%

Test for overall effect: Z = 0.0 (P = 1.0)




### Analysis 4.7. Comparison 4 Any standard drugs vs chloroquine-proguanil, Outcome 7 Discontinuation of study drug for any reason.

Review: Drugs for preventing malaria in travellers

Comparison: 4 Any standard drugs vs chloroquine-proguanil

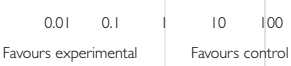
Outcome: 7 Discontinuation of study drug for any reason

| Study or subgroup | Any standard drugs n/N | chloroquine-proguanil n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Camus 2004 | 1/110 | 4/111 | | 6.5 % | 0.25 [ 0.03, 2.22 ] |
| Croft 1997 | 6/317 | 2/307 | | 3.3 % | 2.91 [ 0.59, 14.28 ] |
| Hgh 2000 | 49/511 | 43/511 | | 70.4 % | 1.14 [ 0.77, 1.68 ] |
| Schlagenhauf 2003a | 17/470 | 8/153 | | 19.8 % | 0.69 [ 0.30, 1.57 ] |
| **Total (95% CI)** | **1408** | **1082** | | **100.0 %** | **1.05 [ 0.75, 1.47 ]** |

Total events: 73 (Any standard drugs), 57 (chloroquine-proguanil)

Heterogeneity: $Chi^2$ = 4.38, df = 3 (P = 0.22); $I^2$ =32%

Test for overall effect: Z = 0.30 (P = 0.77)



# APPENDICES

## Appendix 1. Malaria-endemic regions with no *Plasmodium falciparum* resistance to chloroquine

| *Region* | Malaria-endemic countries with no *P. falciparum resistance to chloroquine* |
|---|---|
| *Central American/Caribbean* | Belize, Costa Rica, Dominican Republic, El Salvador, Guatemala, Haiti, Honduras, Mexico, Nicaragua |
| *South American* | Argentina, Paraguay |
| *North African* | Algeria, Morocco, Western Sahara |
| *Middle Eastern* | Egypt, Iraq, Syria, Turkey |
| *Central Asian* | Kyrgyzstan, Turkmenistan, Uzbekistan |
| *Far Eastern* | North Korea, South Korea |

### Footnotes

1. Table adapted from Arguin 2008.
2. The appropriate chemoprophylaxis for adult and child travellers to all malaria-endemic areas in the above countries is **chloroquine alone** Croft 2008a.

## Appendix 2. Available malaria chemoprophylaxis in selected industrialized countries

| *Country* | Atovaquone-proguanil | Chloroquine alone | Chloroquine-proguanil | Doxycycline | Mefloquine | Primaquine | Proguanil alone | Tafenoquine |
|---|---|---|---|---|---|---|---|---|
| *Australia* | L | L | L | L | L | NL | L | NL |
| *Canada* | L | L | NL | L | L | L | NL | NL |
| *France* | L | L | L | L | L | NL | L | NL |
| *Germany* | L | L | L | NL | L | NL | L | NL |
| *Japan* | NL | L | NL | NL | L | NL | NL | NL |
| *Switzerland* | L | L | L | L | L | NL | L | NL |
| *United Kingdom* | L | L | L | L | L | NL | L | NL |

(*Continued*)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| *United States* | L | L | NL | L | L | NL | NL | NL |

**Footnotes**

1. Key: L - licensed (though with age restrictions for some regimens, in some countries); NL - not licensed.
2. Table adapted from Chen 2007.
3. Tafenoquine (formerly called etaquine) is a synthetic analogue of primaquine.

## Appendix 3. Doxycycline international brand names

| ***Brand name*** | **Country** |
|---|---|
| *Adoxa* | US |
| *Amermycin* | HK, TH |
| *Apo-Doxy* | CA |
| *Apo-Doxy Tabs* | CA |
| *Azudoxat* | DE |
| *Bactidox* | PH |
| *Banndoclin* | ID |
| *Bassado* | IT |
| *Biodoxi* | IN |
| *Biomixin* | MX |
| *Bronmycin* | MY |
| *Ciclonal* | MX |
| *Cyclidox* | ZA |
| *Cytragen* | PH |
| *Dagracycline* | NL |
| *Dagramycine* | LU |

(*Continued*)

| | |
|---|---|
| *Dentistar* | KP |
| *Deoxymykoin* | CZ |
| *Docyl* | TH |
| *Doinmycin* | TW |
| *Doksiciklin* | HR |
| *Doline* | MY |
| *Domiken* | MX |
| *Doryx* | AU, NZ, US |
| *Dotur* | PL |
| *Doxacin* | ID |
| *Doxat* | AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, QA, SA, SY, YE |
| *Doxibiotic* | IL |
| *Doxiclat* | ES |
| *Doxilin-100* | SG |
| *Doximed* | FI |
| *Doximycin* | CZ, FI |
| *Doxin* | ID, PH, TH |
| *Doxine* | NZ, SG |
| *Doxsig* | AU |
| *Doxy* | HK, MY, NZ |
| *Doxy 200* | LU |
| *Doxy Komb* | LU |
| *Doxy M* | EE |
| *Doxy SMB* | LU |

(*Continued*)

| | |
|---|---|
| *Doxy-1* | IN |
| *Doxy-100* | DE, NZ, US |
| *Doxycap* | SG |
| *Doxycin* | CA |
| *Doxycline* | LU, TH |
| *Doxycyclin AL* | HU |
| *Doxycyclin Stada* | PL |
| *Doxycycline* | BE |
| *Doxycycline-Ethypharm* | LU |
| *Doxycycline-Eurogenerics* | LU |
| *Doxycyclinum* | PL |
| *Doxyhexal* | AU, HU, LU |
| *Doxylag* | AE, BB, BF, BH, BJ, BM, BS, BZ, CI, CY, EG, ET, GH, GM, GN, GY, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW |
| *Doxylcap* | TH |
| *Doxylets* | LU |
| *Doxylin* | AU, IL, NO, TH |
| *Doxyline* | SG |
| *Doxylis* | FR |
| *Doxymycin* | NL, TW, ZA |
| *Doxymycine* | LU |
| *Doxypharm* | HU |
| *Doxyratio* | PL |

(*Continued*)

| | |
|---|---|
| *Doxytec* | CA |
| *Dumoxin* | AE, BH, CY, EG, ID, IL, IQ, IR, JO, KW, LB, LY, NL, NO, OM, QA, SA, SY, YE |
| *Etidoxina* | CO |
| *Frakas* | AU |
| *Genobiotic-Doxi* | MX |
| *Gewacyclin* | AT |
| *Granudoxy* | FR, LU |
| *Harvellin* | PH |
| *Hiramicin* | HR |
| *Interdoxin* | ID |
| *Linexine* | PE |
| *Madoxy* | TH |
| *Medomycin* | BF, BJ, CI, ET, GH, GM, GN, HK, KE, LR, MA, ML, MR, MU, MW, MY, NE, NG, SC, SD, SG, SL, SN, TH, TN, TW, TZ, UG, ZA, ZM, ZW |
| *Miraclin* | IT |
| *Monocin* | KP |
| *Monodox* | CO, US |
| *Novo-Doxylin* | CA |
| *Nu-Doxycycline* | CA |
| *Oracea* | US |
| *Periostat* | CA, GB, IE, IL, US |
| *Radox* | AE, BF, BH, BJ, CI, CY, EG, ET, GH, GM, GN, IL, IQ, IR, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, OM, QA, SA, SC, SD, SL, SN, SY, TN, TZ, UG, YE, ZA, ZM, ZW |
| *Remycin* | TW |
| *Servidoxine* | EC |
| *Servidoxyne* | MY, TH |

(*Continued*)

| | |
|---|---|
| *Siadocin* | TH |
| *Sigadoxin* | AT, PT |
| *Supracyclin* | AT, CH, PL |
| *Supramycina* | CR, DO, GT, HN, NI, PA, PY, SV |
| *Tenutan* | BB, BM, BS, BZ, GY, JM, NL, SR, TT |
| *Tetradox* | PL |
| *Tolexine* | FR |
| *Tolexine Ge* | FR |
| *Torymycin* | TH |
| *Unidox* | AE, BH, CY, EG, IL, IQ, IR, JO, KW, LB, LY, OM, PL, QA, SA, SY, YE |
| *Veemycin* | TH |
| *Viadoxin* | ID |
| *Vibra-S* | NL |
| *Vibra-Tabs* | AU, US |
| *Vibrabiotic* | GR |
| *Vibradox* | DK, PT |
| *Vibramicina* | AR, CO, CR, DO, GT, HN, MX, NI, PA, PE, PT, SV, UY |
| *Vibramicina C* | VE |
| *Vibramycin* | AE, AT, AU, BB, BF, BG, BH, BJ, BM, BS, BZ, CH, CI, CY, CZ, DE, EG, ET, GB, GH, GM, GN, GR, GY, HK, HN, HU, ID, IE, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, MY, NE, NG, NL, NO, OM, PH, PK, PL, QA, RU, SA, SC, SD, SE, SL, SN, SR, SY, TH, TN, TT, TW, TZ, UG, US, YE, ZA, ZM, ZW |
| *Vibramycin-N* | KP |
| *Vibramycine* | BE, FR |
| *Vibratab* | HN |
| *Vibraveineuse* | FR |

(*Continued*)

| | |
|---|---|
| *Vibravenos* | DE |
| *Vivradoxil* | MX |
| *Wanmycin* | HK |
| *Zadorin* | AE, BB, BF, BH, BJ, BM, BS, BZ, CI, CY, EG, ET, GH, GM, GN, GY, IL, IQ, IR, JM, JO, KE, KW, LB, LR, LY, MA, ML, MR, MU, MW, NE, NG, NL, OM, QA, SA, SC, SD, SL, SN, SR, SY, TN, TT, TZ, UG, YE, ZA, ZM, ZW |

### Footnotes

1. Table adapted from Merck 2009a.

## Appendix 4. Mefloquine international brand names

| ***Brand name*** | **Country** |
|---|---|
| *Apo-Mefloquine* | CA |
| *Lariam* | AE, AT, AU, BE, BF, BG, BH, BJ, CA, CH, CI, CN, CY, CZ, DE, DK, EG, ES, ET, FI, FR, GB, GH, GM, GN, GR, HK, HN, HU, IE, IL, IQ, IR, IT, JO, KE, KW, LB, LR, LU, LY, MA, ML, MR, MU, MW, NE, NG, NL, NO, OM, PE, PH, PL, PT, QA, RU, SA, SC, SD, SE, SL, SN, SY, TN, TR, TW, TZ, UG, US, UY, YE, ZA, ZM, ZW |
| *Laricam* | JP |
| *Larimef* | IN |
| *Mefliam* | ZA |
| *Mephaquin* | BB, BM, BR, BS, BZ, CH, CR, EC, GT, GY, HK, HN, IL, JM, NI, NL, PE, PT, SG, SR, SV, TT |
| *Mequin* | TH |
| *Suton* | TW |
| *Tropicur* | AR |

### Footnotes

1. Table adapted from Merck 2009b.

## Appendix 5. Search strategy - malaria chemoprophylaxis

| Search set | Databases: all |
|---|---|
| 1 | malaria |
| 2 | prophylaxis |
| 3 | chemoprophylaxis |
| 4 | prevention |
| 5 | 2 or 3 or 4 |
| 6 | atovaquone |
| 7 | proguanil |
| 8 | malarone |
| 9 | chloroquine |
| 10 | doxycycline |
| 11 | vibramycin |
| 12 | mefloquine |
| 13 | lariam |
| 14 | mephaquine |
| 15 | primaquine |
| 16 | 6-15/or |
| 17 | 1 and 5 and 16 |

### Footnotes

1. Date of search: 2 August 2009.
2. Note: search terms for MEDLINE, EMBASE, and LILACS used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (Lefebvre 2008).

## Appendix 6. Search strategy - deaths associated with chemoprophylaxis

| Search set | Databases: PUBMED, no time limits |
|---|---|
| 1 | ("Mefloquine/adverse effects" [Mesh] OR "mefloquine/toxicity" [Mesh]) AND malaria AND (case report OR case series OR observational OR cohort) |
| 2 | (atovaquone-proguanil OR malarone) AND malaria AND (case report OR case series OR observational OR cohort OR toxicity OR safety OR adverse) |
| 3 | ("Primaquine/adverse effects" [Mesh] OR "Primaquine/toxicity" [Mesh]) AND malaria AND (case report OR case series OR observational OR cohort) |
| 4 | ("Doxycycline/adverse effects" [Mesh] OR "Doxycycline/toxicity" [Mesh]) AND malaria AND (case report OR case series OR observational OR cohort) |
| 5 | (chloroquin*-proguanil AND malaria AND (case report OR case series OR observational OR cohort OR toxicity OR safety OR adverse) |

### Footnotes

1. Date of search: 6 January 2009.

## Appendix 7. Search dates for conference proceedings

| *Conference* | Number | Date | Location |
|---|---|---|---|
| *Multilateral Initiative on Malaria Pan-African Malaria Conference* | 3rd MIM | 17 to 22 November 2002 | Arusha, Tanzania |
| | 4th MIM | 13 to 18 November 2005 | Yaoundé, Cameroon |
| *American Society of Tropical Medicine and Hygiene meetings* | ASTMH-49 | 29 October to 2 November 2000 | Houston, USA |
| | ASTMH-50 | 11 to 15 November 2001 | Atlanta, USA |
| | ASTMH-51 | 10 to 14 November 2002 | Denver, USA |
| | ASTMH-52 | 3 to 7 December 2003 | Philadelphia, USA |
| | ASTMH-53 | 7 to 11 November 2004 | Miami, USA |
| | ASTMH-54 | 11 to 15 December 2005 | Washington DC, USA |

(*Continued*)

| | | | |
|---|---|---|---|
| | ASTMH-55 | 12 to 16 November 2006 | Atlanta, USA |
| | ASTMH-56 | 5 to 8 November 2007 | Philadelphia, USA |
| *European Conference on Travel Medicine* | ECTM-1 | 25 to 27 March 1998 | Venice, Italy |
| | ECTM-2 | 29 to 31 March 2000 | Venice, Italy |
| | ECTM-3 | 15 to 18 May 2002 | Florence, Italy |
| | ECTM-4 | 29 to 31 March 2004 | Rome, Italy |
| | ECTM-5 | 23 to 25 March 2006 | Venice, Italy |
| | ECTM-6 | 28 to 30 April 2008 | Rome, Italy |
| *Interscience Conference on Antimicrobial Agents and Chemotherapy* | 40th ICAAC | 17 to 20 September 2000 | Toronto, Canada |
| | 41st ICAAC | 16 to 19 December 2001 | Chicago, USA |
| | 42nd ICAAC | 27 to 30 September 2002 | San Diego, USA |
| | 43rd ICAAC | 14 to 17 September 2003 | Chicago, USA |
| | 44th ICAAC | 30 October to 2 November 2004 | Washington DC, USA |
| | 45th ICAAC | 21 to 24 December 2005 | Washington DC, USA |
| | 46th ICAAC | 27 to 30 September 2006 | San Francisco, USA |
| | 47th ICAAC | 17 to 20 September 2007 | Chicago, USA |
| *Conference of the International Society of Travel Medicine* | CISTM5 | 24 to 27 March 1997 | Geneva, Switzerland |
| | CISTM6 | 6 to 10 June 1999 | Montréal, Canada |
| | CISTM7 | 27 to 31 May 2001 | Innsbruck, Austria |
| | CISTM8 | 7 to 11 May 2003 | New York, USA |
| | CISTM9 | 1 to 5 May 2005 | Lisbon, Portugal |
| | CISTM10 | 20 to 24 May 2007 | Vancouver, Canada |

(*Continued*)

| | | | |
|---|---|---|---|
| | CISTM11 | 24 to 28 May 2009 | Budapest, Hungary |
| | AECTM 2004 | | Webpage disabled |
| | AECTM 2006 | 7 to 10 June 2006 | Edinburgh, Scotland |
| Combined conference<br>*Medicine and Health in the Tropics*<br>*XVI International Congress for Tropical Medicine and Malaria*<br>*IV European Congress on Tropical Medicine and International Health*<br>*VII Congrès International de la Société de Pathologie Exotique* | | 11 to 15 September 2005 | Marseille, France |

## Appendix 8. Comparisons evaluated in the trials

| Intervention | Control | Trials |
|---|---|---|
| Atovaquone-proguanil | Doxycycline | Schlagenhauf 2003a |
| Atovaquone-proguanil | Mefloquine | Overbosch 2001; van Riemsdijk 2002; Schlagenhauf 2003a |
| Doxycycline | Mefloquine | Arthur 1990a,; Ohrt 1997; Schlagenhauf 2003a |
| Any of the previous three drugs | Chloroquine-proguanil | Camus 2004; Croft 1997; Høgh 2000, Schlagenhauf 2003a |
| Any of the previous three drugs | Primaquine | - |

## Appendix 9. Published case reports of deaths causally associated with chemoprophylaxis, taken at normal dosages

| *Regimen* | Total number of deaths causally associated with chemoprophylaxis regimen | References |
|---|---|---|
| *Atovaquone-proguanil* | 0 | - |
| *Chloroquine-proguanil* | 0 | - |

(*Continued*)

| | | |
|---|---|---|
| *Doxycycline* | 0 | - |
| *Mefloquine* | 22 | Anonymous 1990 (1 death)<br>Anonymous 1998 (1 suicide)<br>Anonymous 2000 (1 suicide)<br>CDC 2000 (1 death)<br>FDA 2008 (1 death)<br>Jousset 2006 (1 suicide)<br>McBride 1997 (1 death)<br>Meier 2004 (2 suicides)<br>Nosten 1993 (1 death)<br>Nosten 1999 (4 deaths)<br>Smith 1999 (8 deaths) |
| *Primaquine* | 0 | - |

## WHAT'S NEW

Last assessed as up-to-date: 6 August 2009.

| | | |
|---|---|---|
| 16 June 2010 | Amended | In-text links to appendices corrected |

## HISTORY

Protocol first published: Issue 2, 2007

Review first published: Issue 4, 2009

| | | |
|---|---|---|
| 9 November 2009 | Amended | Tables moved to appendices in order to enhance readability. |

## CONTRIBUTIONS OF AUTHORS

AC and FJ wrote the review, extracted the data, assessed trial eligibility and risk of bias, analysed the data, reported the outcomes, jointly drafted the discussion, and agreed the conclusions.

## DECLARATIONS OF INTEREST

AC is an investigator on one of the included trials.

## SOURCES OF SUPPORT


### Internal sources

- Center for Evidence-Based Global Health, Tulane University, USA.
- Commander Regional Forces, UK.

### External sources

- Department for International Development, UK.


## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol, only adverse events were considered. However, a few authors used the terms 'adverse event', 'adverse effect', or 'side effect' interchangeably and loosely. For the sake of clarity, we considered two categories of adverse outcomes: 'adverse event' and 'adverse effect'. This latter category encompassed reporting by authors of 'adverse effect', 'side effect', and 'adverse event attributed to the study drug'. Both categories of adverse outcomes were further divided into any, dermatological, gastrointestinal, and neuropsychiatric adverse event or effect. We used the Uppsala Monitoring Centre's definition of an adverse event, namely "any event that may present while taking the chemoprophylaxis but which does not necessarily have a causal relationship with the drug" (Uppsala 2001) and the Cochrane Handbook's definition of an adverse effect , namely "any event for which the causal relation between the intervention and the event is at least a reasonable possibility" (Loke 2008).

We chose to report "discontinuation of study drug at any time for any reason" instead of "withdrawal due to study drug related adverse events", to avoid selective bias. When not explicitly reported by the investigators, we extracted results for this outcome from the study flow charts and/or from the published text of the trial.

We added POMS score (McNair 1992) to the outcomes. Two trials measured this outcome, which is consistent with the objective of the review.

Cochrane guidelines for evaluating the risk of bias (i.e. methodological quality) of trials ('Risk of bias' tables) and also the quality of evidence ('Summary of findings' tables) changed between the publication of our protocol in 2007 and the preparation of this review. We updated our methods to reflect these changes.

## NOTES

This review replaces the previously published (now withdrawn) review: 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.

## INDEX TERMS

### Medical Subject Headings (MeSH)

*Travel; Antimalarials [adverse effects; *therapeutic use]; Atovaquone [adverse effects; therapeutic use]; Chloroguanide [adverse effects; therapeutic use]; Chloroquine [adverse effects; therapeutic use]; Doxycycline [adverse effects; therapeutic use]; Drug Resistance; Drug Therapy, Combination [methods]; Malaria, Falciparum [*prevention & control]; Mefloquine [adverse effects; therapeutic use]; Primaquine [adverse effects; therapeutic use]; Randomized Controlled Trials as Topic

### MeSH check words

Adult; Child; Humans