Human Parasitic Diseases

CONSISE REVIEW

Drugs to Prevent Malaria in Travellers: A Systematic Review of Randomized Controlled Trials

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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. We did a systematic review to assess the effects of currently used antimalaria drugs, given as prophylaxis to non-immune adult and child travellers to regions with chloroquine-resistant *Plasmodium falciparum* malaria.

Methods: We included randomized and quasi-randomized controlled trials of any antimalaria drug regimen currently used by international travellers, compared against any other currently used regimen. In August 2009 we searched MEDLINE, EMBASE, LILACS, BIOSIS, *m*RCT, and the Cochrane Register of Controlled Trials (CENTRAL), without time restrictions. We searched reference lists, conference proceedings and one specialist journal, and contacted researchers and drug companies. We summarized the characteristics of the eligible trials, assessed their quality using standard criteria, and extracted relevant outcomes data. Where appropriate, we combined the results of different trials.

Results: Eight trials (4240 participants) were included. One-quarter of trial participants were soldiers. Duration of exposure to malaria ranged from 15 days to 13 weeks. All trials reported common adverse events from antimalaria drugs. Atovaquone-proguanil users and doxycycline users had similar frequencies of reported adverse effects. Atovaquone-proguanil users had fewer reports of any adverse effect than mefloquine users (RR 0.72, 95% CI 0.6 to 0.85), also fewer gastrointestinal adverse effects (RR 0.54, 95% CI 0.42 to 0.7), and fewer neuropsychiatric adverse effects (RR 0.49, 95% CI 0.38 to 0.63). Chloroquine-proguanil users had more reports of any adverse effect than users of other drugs (RR 0.84, 95% CI 0.73 to 0.96), also more gastrointestinal adverse effects (RR 0.71, 95% CI 0.6 to 0.85). We found no evidence on primaquine in travellers.

Conclusions: There is limited evidence on which currently available drug is most effective in preventing malaria. Atovaquone-proguanil and doxycycline are the best tolerated regimens. Doxycycline monohydrate appears exceptionally useful due to its good safety profile, low cost and protective efficacy against many travel-related infections, besides malaria. Mefloquine is associated with adverse neuropsychiatric outcomes. Chloroquine-proguanil is associated with adverse gastrointestinal outcomes. There is no evidence to support the use of primaquine as prophylaxis in travellers.

Keywords: malaria, prophylaxis, systematic review, travellers

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Background

Malaria and travellers

Malaria is endemic in 109 countries, and these countries are visited by more than 125 million travellers each year.[1] 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.[2] Around 150 returning travellers die each year from imported malaria, usually due to *Plasmodium falciparum* infection.[3]

Female anopheline mosquitoes, which transmit malaria, bite mainly in the evening and at night. Malaria prevention while travelling is therefore based on simple measures to prevent mosquito biting after dusk.[4] 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.[5] Cochrane Reviews on the impact of insecticide-treated bed nets to prevent malaria in populations living in endemic areas of Africa show that treated bed nets alone significantly reduce childhood mortality and morbidity from malaria, and improve pregnancy outcomes.[6,7]

Barrier measures against malaria have the additional advantage of protecting against other mosquito-transmitted infections, such as dengue fever, Japanese encephalitis, and yellow fever.[8]

Prophylactic drugs (i.e. chemoprophylaxis) give additional protection against malaria. The antimalaria drugs recommended for travellers to regions with *P. falciparum* resistance to chloroquine comprise three main regimens:

- Atovaquone-proguanil.
- Doxycycline.
- Mefloquine.

Chloroquine-proguanil was formerly recommended by some authorities as prophylaxis for travel to these regions of chloroquine-resistant *P. falciparum* disease, but is no longer widely used. Primaquine is a candidate drug for chemoprophylaxis.

Not all the currently-available drugs are licensed for use as malaria chemoprophylaxis in all industrialized countries (Table 1). There are differences also in the recommendations issued to travellers by national expert advisory bodies. Even when two national expert bodies agree to recommend the same prophylactic drug, they are likely to recommend the drug for different sub-groups of travellers, and to impose widely differing temporal, age-dependent and occupational restrictions on its use.[9]

All of the above has led to confusion amongst travellers and prescribers.[10]

Objective

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.

Table 1. Available malaria chemoprophylaxis in selected industrialized countries.*

Country	Atovaquone-proguanil	Chloroquine alone	Chloroquine-proguanil	Doxycycline	Mefloquine	Primaquine
Australia	L	L	L	L	L	NL
Canada	L	L	NL	L	L	L
France	L	L	L	L	L	NL
Germany	L	L	L	NL	L	NL
Japan	NL	L	NL	NL	L	NL
Switzerland	L	L	L	L	L	NL
United Kingdom	L	L	L	L	L	NL
United States	L	L	NL	L	L	NL

Key: L, licensed (though often with differing temporal, age-dependent and occupational restrictions on the agent's use, in different countries); NL, not licensed.
*Table adapted from Reference.[62]

Methods

Our methods are reported in full in the *Cochrane Library*,[11] and are summarized in this report.

Criteria for including studies in the review

We sought randomized and quasi-randomized controlled trials without time restrictions in non-immune adult and child travellers visiting malaria-endemic areas for <3 months, or in non-travelling non-immune adult volunteers, comparing atovaquone-proguanil, doxycycline and mefloquine either against each other or against chloroquine-proguanil or primaquine.

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

Adverse outcomes were of two classes:

- Adverse events. These were any adverse event, dermatological adverse events, gastrointestinal adverse events, neuropsychiatric adverse events and serious adverse events (i.e. fatal, life-threatening, or requiring hospitalization).
- Adverse effects. These were any adverse effect, dermatological adverse effects, gastrointestinal adverse effects and neuropsychiatric adverse effects.

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."[12]

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."[13]

Search methods for identification of studies

On 2 August 2009 we searched the following electronic databases, using a 17-step search strategy which we describe in full in the *Cochrane Library*:[11]

- The Cochrane Infectious Diseases Group Specialized Register.
- The Cochrane Central Register of Controlled Trials (CENTRAL) (2009, Issue 3).
- MEDLINE (1950 to July [Week 5] 2009).
- EMBASE.
- LILACS.
- BIOSIS.

We also searched the *meta*Register of Controlled Trials (*m*RCT) using malaria, atovaquone, chloroquine, doxycycline, mefloquine, and primaquine as our search terms.

We searched the following conference proceedings for relevant abstracts:

- American Society of Tropical Medicine and Hygiene meetings (2000–2007).
- Annual Malaria Meeting of the British Society for Parasitology (2000–2008).
- Conference of the International Society of Travel Medicine (1997–2009).
- European Conference on Travel Medicine (1998–2008).
- European Congress on Tropical Medicine and International Health (1999–2007).
- Interscience Conference on Antimicrobial Agents and Chemotherapy meetings (2000–2007).
- MIM Pan-African Malaria Conference (2000–2008).

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

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).
- Pfizer, UK (May 2008).

FJ retrieved and checked the reference lists of all studies identified through the above searches. FJ screened the results of the literature searches for potentially relevant trials, retrieved the hard copy reports of the trials, and looked for duplicate 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 intervention group, and the numbers of participants analyzed 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 (Figs. 1 and 2). The true numbers 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.[14] 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 analyzed 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 numbers of participants for whom outcomes were available.[15]

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 v.5.[16] 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).

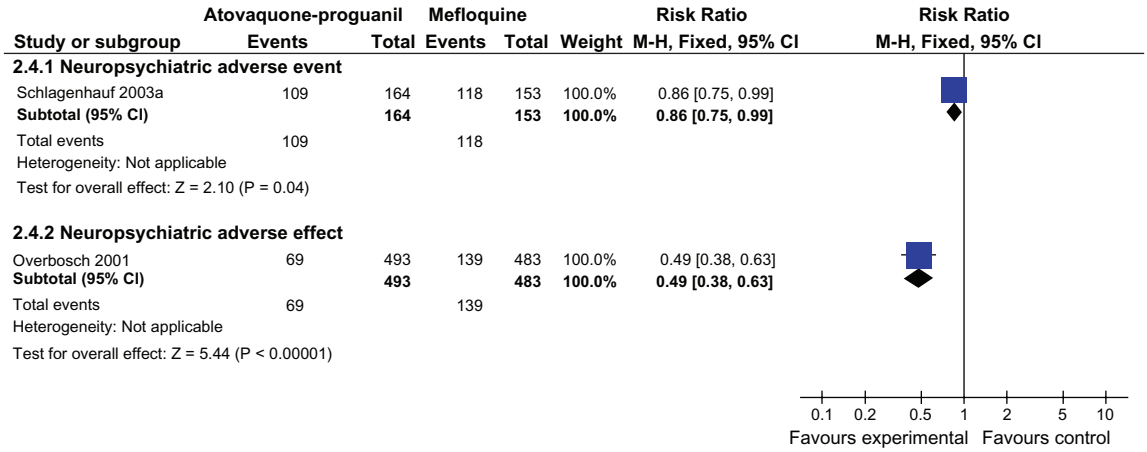

Figure 1. Forest plot of atovaquone-proguanil versus mefloquine: any neuropsychiatric adverse outcome.

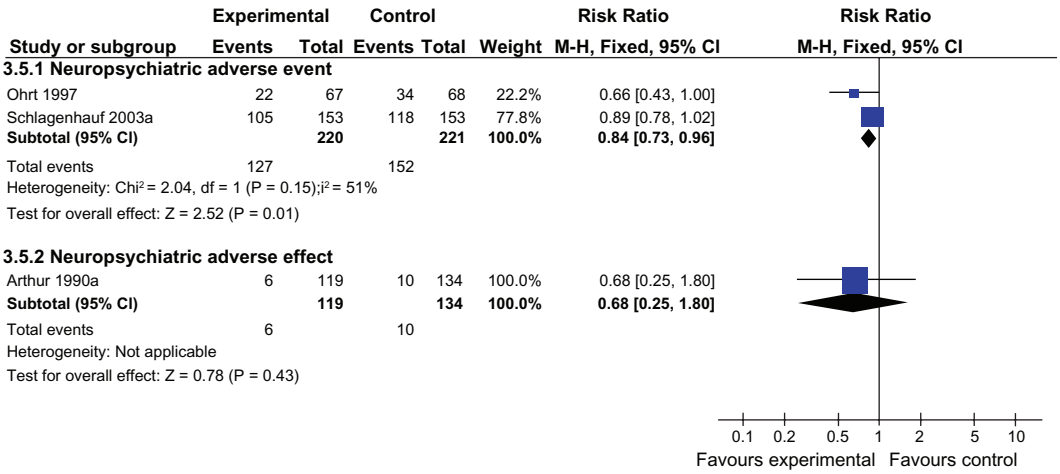

Figure 2. Forest plot of doxycycline versus mefloquine: any neuropsychiatric adverse outcome.

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 and sensitivity analyses

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). We also 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

From the 169 studies identified through the search strategy, we retrieved 13 published reports.[17–29] We found no trials on primaquine.

Eight out of the 13 published reports met the inclusion criteria (Table 2). We excluded five studies:

- In three instances because the allocation of participants was not random or quasi-randomized.[18,19,29]
- In two instances because randomization by clustering was inappropriate in the context of our review.[22,25]

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 ≥3 years were recruited in two trials,[24,26] adults and children aged ≥14 years in one trial,[23] exclusively children in one,[28] and exclusively adults in one.[27] Tourist travellers were of both genders. All of the soldiers in the military studies were adult males.[17,20,21]

Interventions

Atovaquone-proguanil was compared against doxycycline in one trial,[27] and against mefloquine in three trials.[24,26,27] Doxycycline was compared against mefloquine in three trials.[17,21,27] Four trials compared any of the above drugs against chloroquine-proguanil.[20,23,27,28] No trial directly compared primaquine to any of the other study drugs.

Clinical outcomes

Duration of exposure to malaria ranged from a mean of 15 days in Camus et al[28] to approximately 13 weeks in Ohrt et al.[21]

Table 2. Characteristics of included studies.

Study	Methods	Participants	Interventions	Outcomes	Notes
Arthur 1990a	Design: randomized controlled trial Duration: June to August 1988 Duration of exposure to malaria: 5 weeks	Non-immune US Army soldiers (age 18 to 40, average 24), all male Number enrolled: 310 Inclusion criteria: soldiers awaiting deployment to Thailand Exclusion criteria: previous history of gastrointestinal illness	1. Doxycycline (1 capsule containing doxycycline hyclate 100 mg) once daily, starting 1 week before travel and continuing throughout the period of deployment 2. Mefloquine (1 × 250 mg tablet) once weekly, starting 1 week before travel and continuing throughout the period of deployment *For each drug regimen, a matched placebo*	1. Clinical cases of malaria (not defined) 2. Gastrointestinal side effect* (diarrhoea, nausea, vomiting) 3. Neuropsychiatric side effect (dizziness) 4. Serious side effect **Not assessed in the review:* 5. Incidence of diarrhoea 6. Infection with enterotoxigenic *Escherichia coli* (ETEC) 7. Infection with *Campylobacter* spp. 8. Withdrawal due to study drug related adverse event **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.*	Location: Korat, Thailand Setting: military overseas training exercise Funding sources: Pfizer Inc supplied active and placebo doxycycline; Hoffman-La Roche Inc supplied active and placebo mefloquine
Camus 2004	Randomized open-label trial Multicentre study: Canada, Denmark, France, Germany, The Netherlands, United Kingdom Duration of study: May 1999 to November 2000	Non-immune paediatric travellers, 43% female Number enrolled: 232 Inclusion criteria: non-immune children (age 3 to 16, weight 11 to 50 kg) with planned travel of ≤28 days to areas with a substantial risk of *P. falciparum* infection	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	1. Clinical cases of malaria (malaria smears, parasite DNA analysis) 2. Any adverse event[$] 3. Gastrointestinal adverse event*[$] (diarrhoea, abdominal pain, vomiting, nausea, oral ulceration) 4. Neuropsychiatric adverse event*[$] (dreams, visual impairment, dizziness) 5. Serious adverse event[$]	Location: various malaria endemic destinations (85% in Africa) Setting: travel clinics Funding source: GlaxoSmithKline (manufacturer of atovaquone-proguanil) gave financial support

Mean duration of exposure to malaria: 15 days	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	2. Chloroquine (one 250 mg tablet, containing the equivalent of 155 mg chloroquine base) once weekly, starting ≥ 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 *For each drug regimen, a matched placebo*	6. Any adverse event attributed to study drug[$] 7. Gastrointestinal adverse event attributed to study drug*[$] (diarrhoea, abdominal pain, vomiting, nausea, oral ulceration) 8. Neuropsychiatric adverse event attributed to study drug*[$] (dreams, lethargy) 9. Discontinuation of study drug for any reason **Gastrointestinal and neuropsychiatric adverse events/ effects were reported separately. For each category, the most frequent adverse events/ effects (diarrhoea, dreams) are considered in the review. The number of events might be underestimated.* *[$]Exposure period: start of travel through seventh day after travel* **Not assessed in the review:** 10. Compliance with study drug (pre-travel, during travel and post-travel) 11. Withdrawal due to study drug related adverse event 12. Exposure to malaria (circumsporozoite antibody testing)

(*Continued*)

Table 2. (*Continued*)

Study	Methods	Participants	Interventions	Outcomes	Notes
Croft 1997	Randomized controlled trial Duration of study: December 1994 to March 1995 Duration of exposure to malaria: 6 weeks	Non-immune British Army soldiers, all male Number enrolled: 624 Inclusion criteria: soldiers awaiting deployment to Kenya Exclusion criteria: aviators, neuropsychiatric history, use of ß-adrenergic blocking drugs	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 2. Mefloquine (one 250 mg tablet) once weekly, starting 1 week before travel and continuing throughout the period of deployment *For each drug regimen, a matched placebo*	1. Clinical cases of malaria (not defined) 2. Any side effect 3. Dermatological side effect (skin rash, pruritus)—*severe and very severe* 4. Gastrointestinal side effect (anorexia, nausea, vomiting, abdominal pain, diarrhoea, buccal ulceration)—*severe and very severe* 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* 6. Discontinuation of study drug for any reason **Not assessed in the review**: 8. Self-reported compliance with study drug 9. Withdrawal due to study drug related adverse event	Location: Kenya Setting: military overseas training exercise Funding source: British Army Medical Services Research Executive gave financial support
Høgh 2000	Randomized controlled trial Multicentre study: Canada, Denmark, France, Germany, The Netherlands, South Africa, United Kingdom Duration of study: April to November 1999 Mean duration of exposure to malaria: 2.5 weeks	Non-immune tourists and general travellers, 48% female Number enrolled: 1083 Inclusion criteria: travellers aged $\geq$ 14 years and weighing $>$ 50 kg with planned travel of $\leq$28 days to *P. falciparum* endemic areas	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	1. Clinical cases of malaria (malaria smear, parasite DNA analysis) 2. Any adverse event 3. Serious adverse event 4. Any adverse event attributed to study drug	Location: various malaria endemic destinations (63% in Africa) Setting: travel clinics

		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	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 *For each drug regimen, a matched placebo*	5. Dermatological adverse event attributed to study drug (itching) 6. Gastrointestinal adverse event attributed to study drug (diarrhoea, nausea, abdominal pain, mouth ulcers, vomiting) 7. Neuropsychiatric adverse event attributed to study drug (dizziness, strange or vivid dreams, insomnia, visual difficulties, anxiety, depression) 8. Discontinuation of study drug for any reason **Not assessed in the review:** 9. Non-compliance 10. Withdrawal due to study drug related adverse event 11. Exposure to malaria (circumsporozoite antibody testing)	Funding source: GlaxoSmithKline (manufacturer of atovaquone-proguanil) gave financial support
Ohrt 1997	Randomized controlled trial Duration of study: May to July 1994 Duration of exposure to malaria: approximately 13 weeks	Non-immune Indonesian Army soldiers, all male Number enrolled: 204 Inclusion criteria: soldiers in military posts with a high malaria attack rate Exclusion criteria: history of frequent travel, allergy to one of the study drugs, glucose-6-phosphate dehydrogenase deficiency, history of underlying illness	1. Doxycycline hyclate (one 100 mg capsule) once daily 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) 3. Placebo *Matched placebo for all 3 arms*	1. Clinical cases of malaria (malaria smear) 2. Any adverse event 3. Dermatological adverse event (skin related) 4. Gastrointestinal adverse event (nausea, vomiting, abdominal pain, diarrhoea, constipation, anorexia) 5. Neuropsychiatric adverse event (insomnia, somnolence, dreams, dizziness, palpitations, sexual dysfunction, headache)	Location: North-Eastern Irian Jaya, Indonesia Setting: military posts

(*Continued*)

Table 2. (*Continued*)

Study	Methods	Participants	Interventions	Outcomes	Notes
				6. Serious adverse event 7. Discontinuation of study drug for any reason	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
Overbosch 2001	Randomized controlled trial Multicentre study: Canada, Germany, The Netherlands, South Africa, United Kingdom Duration of study: April to October 1999 Mean duration of exposure to malaria: 2.5 weeks	Non-immune tourists and general travellers, 45% female Number enrolled: 1013 Inclusion criteria: travellers aged ≥ 3 years and weighing ≥ 11 kg with planned travel of ≤28 days to a malaria-endemic area 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	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	1. Clinical cases of malaria (antibody to blood-stage malaria parasites) 2. Any adverse event 3. Serious adverse event 4. Adverse event attributed to study drug 5. Dermatological adverse event attributed to study drug (itching) 6. Gastrointestinal adverse event attributed to study drug (diarrhoea, nausea, abdominal pain, mouth ulcers, vomiting) 7. Neuropsychiatric adverse event attributed to study drug (strange or vivid dreams, insomnia, dizziness or vertigo, visual difficulties, anxiety, depression)	Location: various malaria endemic destinations worldwide (63% in Africa) Setting: travel clinics Funding source: GlaxoSmithKline (manufacturer of atovaquone-proguanil) gave financial support

			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 *For each drug regimen, a matched placebo*	8. Discontinuation of study drug for any reason **Not assessed in the review:** 9. Compliance with study drug (pre-travel, during travel and post-travel) 10. Withdrawal due to study drug related adverse event 11. Exposure to malaria (circumsporozoite antibody testing)	
Schlagenhauf 2003	Randomized controlled trial Multicentre study: Germany, Israel, Switzerland Duration of study: 1998 to 2001 Mean duration of exposure to malaria: unclear	Non-immune tourists and general travellers, 49% female Number enrolled: 674 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 ≥17 days before departure 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	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 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 3. Doxycycline (1 capsule containing doxycycline monohydrate 100 mg) once daily, starting 17 days before travel and continuing for 4 weeks after travel	1. Any adverse event 2. Dermatological adverse event (itching, abnormal reddening of skin) 3. Gastrointestinal adverse event (nausea, diarrhoea, mouth ulcers) 4. Neuropsychiatric adverse event (strange or vivid dreams, headache, dizziness, anxiety, depression, visual disturbances, fits or seizures) 5. Serious adverse event 6. Discontinuation of study drug for any reason 7. Profile of Mood States (POMS) score **Not assessed in the review:** 8. Quality of life score	Location: sub-Saharan Africa (mainly Kenya and South Africa) Setting: travel clinics Funding sources: GlaxoSmithKline supplied atovaquone-proguanil and gave financial support; Zeneca supplied chloroquine-proguanil; Pfizer supplied doxycycline; Roche supplied mefloquine and gave financial support

(*Continued*)

Table 2. (*Continued*)

Study	Methods	Participants	Interventions	Outcomes	Notes
			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 *For each drug regimen, either a matched placebo (atovaquone-proguanil, mefloquine) or identical capsules*		
van Riemsdijk 2002	Randomized controlled trial Duration of study: unclear Mean duration of exposure to malaria: 19 days	Non-immune tourists and general travellers, 38% female Number enrolled: 140 Inclusion criteria: travellers aged ≥ 3 years and weighing ≥ 11 kg with planned travel of ≤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)	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 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 *For each drug regimen, a matched placebo*	1. Profile of mood states (POMS) score **Not assessed in the review:** 2. Neurobehavioural evaluation system score	Location: various malaria endemic destinations (66% in Africa, 13% South America, 24% other) Setting: Rotterdam Travel Clinic, the Netherlands Funding source: Netherlands Inspectorate for Healthcare gave financial support

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);[21,23,28] one trial used results from serological testing (antibodies to blood stage malaria parasites);[24] and two trials did not report the method used.[17,20] Only one trial included a placebo arm.[21]

Adverse events

Five trials reported the frequency of any adverse event.[21,23,24,27,28]

Three trials reported organ-specific adverse events and categorized these as dermatological, gastrointestinal and neuropsychiatric.[21,27,28]

Serious adverse events were measured in five studies.[21,23,24,27,28]

Adverse effects

Four trials reported any adverse effect.[20,23,24,28]

Five trials reported organ-specific adverse effects and categorized these as dermatological, gastrointestinal, and neuropsychiatric.[17,20,23,24,28]

Croft et al reported only the adverse effects for each of the above categories that were 'severe' and 'very severe'.[20]

Risk of bias in included studies

Sequence generation was adequately performed and reported in all trials. Allocation concealment was adequate in seven trials and unclear in one,[17] where the method used was not described. We estimated the risk of bias from these two domains and across trials to be low.

All trials were described as double-blind, except one which was an open-label study.[28] We considered this trial to have a high risk of bias, since care providers assessing adverse events could have been aware of drug assignment.

In respect of incomplete outcome data, 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 outcomes data accounted for $>10\%$ of the data in three trials, as follows:

- In Arthur et al, there was insufficient reporting of reasons for exclusion and attrition, and on how missing data were addressed in the analysis.[17] We judged the risk of bias to be unclear.
- In Croft et al, the explanation for missing data lay in the low response rate to the questionnaire.[20] 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 outcomes data.[20]
- The third trial, van Riemsdijk et al, reported the exclusion of some participants from analysis due to adverse events and because of investigator suspicion that they had switched study drugs.[26]

For the latter two studies, Croft and van Riemsdijk, we estimated the missing data to have been at high risk of bias.[20,26]

In respect of selective reporting, for Høgh and Overbosch it was unclear if both adverse events and adverse effects were measured in the dermatological, gastrointestinal, and neuropsychiatric categories; however only the adverse effects were reported.[23,24] 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.[28]

One trial did not report the adverse effects associated with each drug, and this information was retrieved from a duplicate publication by the same investigators.[17,30] Another trial did not report mild or moderate adverse effects.[20] The risk of bias due to selective reporting was estimated to be unclear for both these trials.[17,20]

There was a further potential source of bias in that, except for two trials,[20,26] all the trials in this review were funded wholly or in part by drug 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 over the investigators, in their presentation of the outcomes data. Thus we decided simply to simply record the sponsorship information as disclosed in the published reports (Table 2, right-hand column), without grading the potential for serious reporting bias.

Effects of interventions

The effects of interventions are reported in full in the *Cochrane Library*,[11] and are summarized at Table 3.

Discussion

Strengths of this review

This is a systematic review of malaria chemoprophylaxis in non-immune travellers. This is the first review of its kind and its strength lies in its systematic identification of all relevant chemoprophylaxis trials, and in its meta-analysis of those trial outcomes which can usefully inform clinical decision-making for non-immune travellers to malaria-endemic regions.

This review provides some evidence that atovaquone-proguanil and doxycycline are better tolerated than mefloquine, and that all three drugs are better tolerated than chloroquine-proguanil. However, the quality of evidence ranges from very low to moderate. Thus, the findings have to be interpreted with caution.

Doxycycline in particular seems an exceptionally useful drug for travellers, due to the fact that it protects against other travel-associated infections, besides malaria. These other infections for which doxycycline is protective include:

- Leptospirosis.[31,32]
- Lyme disease.[33]
- Lymphatic filariasis.[34]
- *Mansonella perstans* infection.[35]
- Scrub typhus.[36]
- Tick-borne relapsing fever.[37]
- Travellers' diarrhoea.[38–41]

Doxycycline is a derivative of tetracycline and is a once-daily, off-patent drug, which travellers may find more convenient than once-weekly chemoprophylaxis, such as with chloroquine or mefloquine. In terms of affordability, a prophylactic course of doxycycline is similar in cost to mefloquine, and much cheaper than atovaquone-proguanil.[42]

Doxycycline may be safe in early pregnancy, although data are currently insufficient to recommend this drug to pregnant women in their first trimester.[43]

Because of its short half-life of 15–22 hours, travellers who forget to take their daily doxycycline dose, or who experience vomiting and/or diarrhoea in conjunction with taking prophylaxis, may be insufficiently protected. In these circumstances it is sometimes recommended that travellers take a double dose of doxycycline the following day, and this approach was used by Ohrt and all with good protective results.[21,46]

It has been suggested that doxycycline may cause tooth staining in children aged <8 years, but there is evidence that this may not be a true effect.[44,45] Empirical evidence indicates that the monohydrate formulation of doxycycline is better tolerated by travellers than the hyclate form, which in non-randomised studies has been associated with a 6% withdrawal rate due to gastrointestinal adverse effects.[46]

Limitations of this review

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. It is nevertheless the case that with malaria, and because the effects are so massive, the effectiveness of chemoprophylaxis can often be inferred from simple observational studies.

With atovaquone-proguanil, doxycycline, and mefloquine protective efficacy has been demonstrated through the following:

- Placebo-controlled trials carried out in non-immune migrants and soldiers.[21,47,48]
- Trials carried out in semi-immune populations.[49–54]
- Observational studies.

Likewise, some evidence on the protective efficacy of primaquine can be inferred from placebo-controlled trials carried out in non-immune populations.[55–57]

Widespread *P. falciparum* resistance to chloroquine raises concerns about the continuing protective efficacy of chloroquine-proguanil as prophylaxis.[58–60]

Potential biases in this review

Overall the body of evidence for this review was small, and the quality of the evidence ranged from 'very low' to 'low' to 'moderate'. Our definitions of these terms are as follows:[14]

- Very low quality. We are very uncertain about the estimate.
- Low quality. Further research is very likely to have an important impact on our confidence in

Table 3. Effects of interventions.*

	Atovaquone-proguanil versus doxycycline	**Atovaquone-proguanil versus mefloquine**	**Doxycycline versus mefloquine**
(Number of trials making this comparison)	One.[27]	Three.[24,26,27]	Three.[17,21,27]
1. Clinical outcomes	No clinical outcomes were evaluated.	Clinical outcome was reported in one trial,[24] and there were no clinical cases of malaria in either group.	Clinical outcome was reported in two trials.[17,21] There was one case of clinical malaria in the doxycycline arm and none in the mefloquine arm (388 participants, two trials), so no difference was detected, due to small numbers.
2. 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 event (317 participants), dermatological adverse events (317 participants), gastrointestinal adverse events (317 participants), and neuropsychiatric adverse events (317 participants).	–	–
2a. Any adverse outcome	–	Adverse events and effects were common in both arms. We found no difference in effect between the drugs in the incidence 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.	No difference was detected in any adverse event between the drugs (441 participants, two trials).
2b. Dermatological adverse outcome	–	No difference was detected in dermatological adverse events (317 participants, one trial) or in dermatological adverse effects (976 participants, one trial).	No difference was detected in dermatological adverse events (441 participants, two trials).
2c. Gastrointestinal adverse outcome	–	No difference was detected in 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.	No difference was detected in gastrointestinal adverse events (441 participants, two trials) or in gastrointestinal adverse effects (253 participants, one trial).

(*Continued*)

Table 3. (*Continued*)

	Atovaquone-proguanil versus doxycycline	Atovaquone-proguanil versus mefloquine	Doxycycline versus mefloquine
2d. Neuropsychiatric adverse outcome	–	**[Fig. 1]** 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. One trial measured total mood disturbance scores.[26] The scores clearly favoured participants taking atovaquone-proguanil compared to mefloquine (MD –7.20, 95% CI –10.79 to –3.61; 119 participants).	**[Fig. 2]** 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 difference in effect between the drugs in the incidence of neuropsychiatric adverse effects (253 participants, one trial).
3. Serious adverse events (AEs):	No serious AE was reported.	No difference in effect between the drugs in the incidence of any serious AE (1293 participants, two trials).	No serious AE was reported.

the estimate of effect, and is likely to change the estimate.
- Moderate quality. Further research is likely to have an important impact on our confidence in the estimate of effect, and may change the estimate.

The two main reasons for the very low or low quality of the evidence in this review were:

- Indirectness, due to the fact that data for children and adults were not reported separately.
- Imprecision in the effect estimates (i.e. wide 95% confidence intervals), which was due to the small number of studies per comparison and/or to the limited number of participants/events per study.

All studies in this review 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.[61] 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.

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. Adverse effects by definition include "any event for which the causal relation between the intervention and the event is at least a reasonable possibility."[13] 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

when 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.

Also amongst the limitations of this review were the pre-defined selection criteria which excluded placebo-controlled trials, and also excluded studies conducted on semi-immune populations. This had the beneficial effect of limiting heterogeneity across studies and enhancing the generalizability of the findings to our target population of non-immune travellers, but it 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.

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.

Conclusions

National policies on malaria prevention have historically been led by expert opinion, rather than by critical review of the evidence.[9,10] However the available 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 for travellers will therefore continue to depend on non-experimental data, including knowledge of regional and local drug sensitivities, which may be incomplete or biased.

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. The poor tolerability of mefloquine in travellers, especially in female travellers, in now a clinical commonplace, even though until recently it was widely argued that mefloquine was "well tolerated" in travellers and that consumer concerns about its safety were due to "media hype".

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, including:

- Relative cost of the available drugs.[42]
- Concurrent protection afforded by any of the available drugs against other diseases, besides malaria.
- Patient contraindications (e.g. pregnancy, breastfeeding, age, occupation) to any of the available drugs.
- Possible drug-drug interactions.
- Previous patient experience of any of the available drugs.
- Relative ease of administration of the available drugs.
- Known rare serious adverse events associated with the available drugs.
- Travel itinerary, and season of travel.

Doxycycline, especially in its monohydrate (not its hyclate) formulation, appears to be exceptionally useful as malaria prophylaxis for international travellers. This is due to its good safety profile in adults, its low cost, and its protective efficacy against many travel-related infections, besides malaria. However the safety or otherwise of doxycycline in children aged $<$8 years needs to be more rigorously investigated.

Primaquine is recommended by some national authorities as first-line malaria chemoprophylaxis, but there is no evidence from head-to-head comparisons to support primaquine use as primary prophylaxis in travellers. Primaquine should be investigated for this indication in head-to-head comparisons with doxycycline, and with atovaquone-proguanil.

Competing Interests

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors report no conflicts of interest.

Authors' Contributions

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

developing the methodology for analysing adverse events and adverse effects separately, and also agreed the discussion and the conclusions.

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