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Mefloquine for preventing malaria during travel to endemic areas (Review)

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[Intervention Review]

Mefloquine for preventing malaria during travel to endemic areas

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ABSTRACT

Background

Mefloquine is one of four antimalarial agents commonly recommended for preventing malaria in travellers to malaria-endemic areas. Despite its high efficacy, there is controversy about its psychological side effects.

Objectives

To summarize the efficacy and safety of mefloquine used as prophylaxis for malaria in travellers.

Search methods

We searched the Cochrane Infectious Diseases Group Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL), published on the Cochrane Library; MEDLINE; Embase (OVID); TOXLINE (https://toxnet.nlm.nih.gov/newtoxnet/toxline.htm); and LILACS. We also searched the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; http://www.who.int/ictrp/en/) and ClinicalTrials.gov (https://clinicaltrials.gov/ct2/home) for trials in progress, using 'mefloquine', 'Lariam', and 'malaria' as search terms. The search date was 22 June 2017.

Selection criteria

We included randomized controlled trials (for efficacy and safety) and non-randomized cohort studies (for safety). We compared prophylactic mefloquine with placebo, no treatment, or an alternative recommended antimalarial agent. Our study populations included all adults and children, including pregnant women.

Data collection and analysis

Two review authors independently assessed the eligibility and risk of bias of trials, extracted and analysed data. We compared dichotomous outcomes using risk ratios (RR) with 95% confidence intervals (CI). Prespecified adverse outcomes are included in 'Summary of findings' tables, with the best available estimate of the absolute frequency of each outcome in short-term international travellers. We assessed the certainty of the evidence using the GRADE approach.

Main results

We included 20 RCTs (11,470 participants); 35 cohort studies (198,493 participants); and four large retrospective analyses of health records (800,652 participants). Nine RCTs explicitly excluded participants with a psychiatric history, and 25 cohort studies stated that the choice of antimalarial agent was based on medical history and personal preference. Most RCTs and cohort studies collected data on self-reported or clinician-assessed symptoms, rather than formal medical diagnoses.

Mefloquine efficacy

Of 12 trials comparing mefloquine and placebo, none were performed in short-term international travellers, and most populations had a degree of immunity to malaria. The percentage of people developing a malaria episode in the control arm varied from 1% to 82% (median 22%) and 0% to 13% in the mefloquine group (median 1%).

In four RCTs that directly compared mefloquine, atovaquone-proguanil and doxycycline in non-immune, short-term international travellers, only one clinical case of malaria occurred (4 trials, 1822 participants).

Mefloquine safety versus atovaquone-proguanil

Participants receiving mefloquine were more likely to discontinue their medication due to adverse effects than atovaquone-proguanil users (RR 2.86, 95% CI 1.53 to 5.31; 3 RCTs, 1438 participants; *high-certainty evidence*). There were few serious adverse effects reported with mefloquine (15/2651 travellers) and none with atovaquone-proguanil (940 travellers).

One RCT and six cohort studies reported on our prespecified adverse effects. In the RCT with short-term travellers, mefloquine users were more likely to report abnormal dreams (RR 2.04, 95% CI 1.37 to 3.04, *moderate-certainty evidence*), insomnia (RR 4.42, 95% CI 2.56 to 7.64, *moderate-certainty evidence*), anxiety (RR 6.12, 95% CI 1.82 to 20.66, *moderate-certainty evidence*), and depressed mood during travel (RR 5.78, 95% CI 1.71 to 19.61, *moderate-certainty evidence*). The cohort studies in longer-term travellers were consistent with this finding but most had larger effect sizes. Mefloquine users were also more likely to report nausea (*high-certainty evidence*) and dizziness (*high-certainty evidence*).

Based on the available evidence, our best estimates of absolute effect sizes for mefloquine versus atovaquone-proguanil are 6% versus 2% for discontinuation of the drug, 13% versus 3% for insomnia, 14% versus 7% for abnormal dreams, 6% versus 1% for anxiety, and 6% versus 1% for depressed mood.

Mefloquine safety versus doxycycline

No difference was found in numbers of serious adverse effects with mefloquine and doxycycline (*low-certainty evidence*) or numbers of discontinuations due to adverse effects (RR 1.08, 95% CI 0.41 to 2.87; 4 RCTs, 763 participants; *low-certainty evidence*).

Six cohort studies in longer-term occupational travellers reported our prespecified adverse effects; one RCT in military personnel and one cohort study in short-term travellers reported adverse events. Mefloquine users were more likely to report abnormal dreams (RR 10.49, 95% CI 3.79 to 29.10; 4 cohort studies, 2588 participants, *very low-certainty evidence*), insomnia (RR 4.14, 95% CI 1.19 to 14.44; 4 cohort studies, 3212 participants, *very low-certainty evidence*), anxiety (RR 18.04, 95% CI 9.32 to 34.93; 3 cohort studies, 2559 participants, *very low-certainty evidence*), and depressed mood (RR 11.43, 95% CI 5.21 to 25.07; 2 cohort studies, 2445 participants, *very low-certainty evidence*). The findings of the single cohort study reporting adverse events in short-term international travellers were consistent with this finding but the single RCT in military personnel did not demonstrate a difference between groups in frequencies of abnormal dreams or insomnia.

Mefloquine users were less likely to report dyspepsia (RR 0.26, 95% CI 0.09 to 0.74; 5 cohort studies, 5104 participants, *low certainty-evidence*), photosensitivity (RR 0.08, 95% CI 0.05 to 0.11; 2 cohort studies, 1875 participants, *very low-certainty evidence*), vomiting (RR 0.18, 95% CI 0.12 to 0.27; 4 cohort studies, 5071 participants, *very low-certainty evidence*), and vaginal thrush (RR 0.10, 95% CI 0.06 to 0.16; 1 cohort study, 1761 participants, *very low-certainty evidence*).

Based on the available evidence, our best estimates of absolute effect for mefloquine versus doxycyline were: 2% versus 2% for discontinuation, 12% versus 3% for insomnia, 31% versus 3% for abnormal dreams, 18% versus 1% for anxiety, 11% versus 1% for depressed mood, 4% versus 14% for dyspepsia, 2% versus 19% for photosensitivity, 1% versus 5% for vomiting, and 2% versus 16% for vaginal thrush.

Additional analyses, including comparisons of mefloquine with chloroquine, added no new information. Subgroup analysis by study design, duration of travel, and military versus non-military participants, provided no conclusive findings.

Authors' conclusions

The absolute risk of malaria during short-term travel appears low with all three established antimalarial agents (mefloquine, doxycycline, and atovaquone-proguanil).

The choice of antimalarial agent depends on how individual travellers assess the importance of specific adverse effects, pill burden, and cost. Some travellers will prefer mefloquine for its once-weekly regimen, but this should be balanced against the increased frequency of abnormal dreams, anxiety, insomnia, and depressed mood.

12 April 2019

Up to date

All studies incorporated from most recent search

All eligible published studies found in the last search (22 Jun, 2017) were included

PLAIN LANGUAGE SUMMARY

Can mefloquine prevent malaria during travel to areas where the disease is widespread?

We summarized trials that evaluated the effectiveness and safety of mefloquine when used to prevent malaria in people travelling to areas where the disease is widespread. We searched for relevant studies up to 22 June 2017 and included 20 randomized trials that involved 11,470 participants, 35 cohort studies (198,493 participants) and four large retrospective analyses of health records (800,652 participants).

What are the concerns about mefloquine and what are the alternatives?

Mefloquine is often prescribed to prevent malaria during travel to areas where the disease is widespread. However, there is controversy about the safety of mefloquine, especially when prescribed for military personnel in stressful situations, and there have been reports of depression and suicide.

The only commonly-used alternative drugs are doxycycline (which can cause skin problems and indigestion) and atovaquone-proguanil (which is often more expensive).

What the research says

Mefloquine appears to be a highly effective drug to reduce the risk of malaria (*low-certainty evidence*), however, evidence did not come from short-term international travellers.

Mefloquine has not been shown to have more frequent serious side effects than either atovaquone-proguanil (*low-certainty evidence*) or doxycycline (*very low-certainty evidence*).

People who take mefloquine are more likely to stop taking the drug due to side effects than people who take atovaquone-proguanil (*high-certainty evidence),* but may be equally as likely to stop as people who take doxycyline (*low-certainty evidence).*

People taking mefloquine are more likely to have abnormal dreams, insomnia, anxiety and depressed mood during travel than people who take atovaquone-proguanil (*moderate-certainty evidence*) or doxycyline (*very low-certainty evidence*). Doxycycline users are more likely to have dyspepsia, photosensitivity, vomiting, and vaginal thrush (*very low-certainty evidence*).

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Mefloquine versus atovaquone-proguanil for preventing malaria in travellers

Mefloquine compared with atovaquone-proguanil for preventing malaria in travellers

Population: non-immune adults and children travelling to or living in malaria-endemic settings

Intervention: mefloquine 250 mg weekly

Comparison: atovaquone-proguanil (250 mg atovaquone and 100 mg proguanil hydrochloride) daily

Outcome data collection: physicians performed blinded assessment of whether reported symptoms could be related to the study drug

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Studies contributing to effect estimate (participants)	Additional studies considered in GRADE assessment (participants)	Certainty of the evidence (GRADE)
	Atovaquone-proguanil	Mefloquine				
Clinical malaria	—	—	—	2 RCTs (1293)	—	⊕⊕⊖⊖ **low** [1,2,3]
Serious adverse effects	**0 per 100**	**1 in 100** (0 to 12)	**RR 1.40** (0.08 to 23.22)	4 cohort studies (3693)	1 RCT (976)	⊕⊕⊖⊖ **low** [1,2,4,5]
Discontinuation of drug due to adverse effects	**2 per 100**	**6 per 100** (3 to 11)	**RR 2.86** (1.53 to 5.31)	3 RCTs (1438)	7 cohort studies (4498)	⊕⊕⊕⊕ **high** [1,2,4,6]
Abnormal dreams	**7 per 100**	**14 per 100** (10 to 21)	**RR 2.04** (1.37 to 3.04)	1 RCT (976)	7 cohort studies (3848)	⊕⊕⊕⊕ **high** [1,2,4,6]
Insomnia	**3 per 100**	**13 per 100** (8 to 23)	**RR 4.42** (2.56 to 7.64)	1 RCT (976)	8 cohort studies (3986)	⊕⊕⊕⊕ **high** [1,2,4,6]
Anxiety	**1 per 100**	**6 per 100** (2 to 21)	**RR 6.12** (1.82 to 20.66)	1 RCT (976)	4 cohort studies (2664)	⊕⊕⊕⊖ **moderate** [1,2,4,7]

Depressed mood	**1 per 100**	**6 per 100** (2 to 20)	**RR 5.78** (1.71 to 19.61)	1 RCT (976)	6 cohort studies (3624)	⊕⊕⊕⊖ **moderate** [1,2,4,7]
Abnormal thoughts or perceptions	**0 per 100**	**1 per 100** (0 to 4)	**RR 1.50** (0.30 to 7.42)	3 cohort studies (2433)	—	⊕⊖⊖⊖ **very low** [1,2,8]
Nausea	**3 per 100**	**8 per 100** (5 to 15)	**RR 2.72** (1.52 to 4.86)	1 RCT (976)	7 cohort studies (3509)	⊕⊕⊕⊕ **high** [1,2,4,6]
Vomiting	**1 per 100**	**1 per 100** (0 to 4)	**RR 1.31** (0.49 to 3.50)	1 RCT (976)	3 cohort studies (2180)	⊕⊕⊕⊖ **moderate** [1,2,4,7]
Abdominal pain	**5 per 100**	**5 per 100** (3 to 8)	**RR 0.90** (0.52 to 1.56)	1 RCT (976)	7 cohort studies (3509)	⊕⊕⊖⊖ **moderate** [1,2,4,8]
Diarrhoea	**8 per 100**	**8 per 100** (5 to 12)	**RR 0.94** (0.60 to 1.47)	1 RCT (976)	7 cohort studies (3509)	⊕⊕⊕⊖ **moderate** [1,2,4,8]
Headache	**4 per 100**	**7 per 100** (4 to 12)	**RR 1.72** (0.99 to 2.99)	1 RCT (976)	8 cohort studies (4163)	⊕⊕⊕⊖ **moderate** [1,2,4,8]
Dizziness	**2 per 100**	**8 per 100** (4 to 15)	**RR 3.99** (2.08 to 7.64)	1 RCT (976)	8 cohort studies (3986)	⊕⊕⊕⊕ **high** [1,2,4,6]
Pruritis	**2 per 100**	**3 per 100** (1 to 5)	**RR 1.28** (0.60 to 2.70)	1 RCT (976)	3 cohort studies (1824)	⊕⊕⊕⊖ **moderate** [1,2,4,8]
Visual impairment	**2 per 100**	**4 per 100** (2 to 9)	**RR 2.04** (0.88 to 4.73)	1 RCT (976)	2 cohort studies (1956)	⊕⊕⊕⊖ **moderate** [1,2,4,8]
Mouth ulcers	**2 per 100**	**3 per 100** (1 to 6)	**RR 1.45** (0.70 to 3.00)	1 RCT (976)	2 cohort studies (783)	⊕⊕⊕⊖ **moderate** [1,2,4,8]

*The **assumed risk** is the median control group risk across studies unless stated 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). Where the control group risk was 0, we used a value of 0.5 to calculate the corresponding risk in the intervention group. Data from cohort studies were used when data from RCTs were unavailable.

Abbreviations: CI: confidence interval; RR: risk ratio

'Summary of findings' tables are usually limited to seven outcomes. For adverse effects this problematic, as there are many, and to include some and not others risks selective reporting. We have therefore included all prespecified outcomes in the table.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: 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 certainty: we are very uncertain about the estimate.

[1]No serious risk of bias: the RCTs were generally at low risk of bias but two of three were sponsored by the manufacturer of one of the study drugs. All cohort studies had methodological problems which could introduce confounding or bias. However, as the GRADE approach automatically downgrades certainty by two levels for non-randomized studies, we did not downgrade further.
[2]No serious indirectness: the RCTs were conducted in short-term international travellers to malaria-endemic areas in Africa or South America for less than 28 days. The cohort studies were from a variety of populations including short-term travellers (8 studies), longer-term occupational travellers (3 studies) and military personnel (1 study).
[3]Downgraded by two levels for serious imprecision: no episodes of malaria were recorded in either trial.
[4]No serious inconsistency: the findings of the cohort studies were consistent with the effects seen in the RCTs.
[5]No serious imprecision: serious adverse effects were rare in all studies.
[6]No serious imprecision. The effect was statistically significant and the overall data (RCTs and cohort studies) were adequately powered to detect this effect.
[7]Downgraded by one level for serious imprecision: although the direction of the effect was consistent across all trials, there was substantial heterogeneity in the size of the effect.
[8]Downgraded by one level for serious imprecision: the 95% CI is wide and includes important effects and no effect.

Summary of findings 2. Mefloquine versus doxycycline for preventing malaria in travellers

Mefloquine compared with doxycycline for preventing malaria in travellers

Population: Non-immune adults and children travelling to malaria-endemic settings

Intervention: Mefloquine 250 mg weekly

Comparison: Doxycycline 100 mg daily

Outcome data collection: Self-reported symptoms experienced whilst taking prophylaxis (adverse events)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Studies contributing to effect estimate (participants)	Additional studies considered in GRADE assessment (participants)	Certainty of the evidence (GRADE)
	Doxycycline	Mefloquine				
Clinical malaria	**1 per 100**	**1 per 100** (0 to 5)	**RR 1.35** (0.35 to 5.19)	4 RCTs (744)	—	⊕⊕⊖⊖ **low** [1,2,3,4]

Serious adverse effects	**6 per 1000** [5]	**9 per 1000** (1 to 61)	**RR 1.53** (0.23 to 10.24)	3 cohort studies (3722)	3 RCTs, 1 cohort study (682; 3772)	⊕⊝⊝⊝ **very low** [2,3,6,7]
Discontinuations due to adverse effects	**2 per 100**	**2 per 100** (1 to 6)	**RR 1.08** (0.41 to 2.87)	4 RCTs (763)	10 cohort studies (10,165)	⊕⊕⊝⊝ **low** [1,3,7,8]
Abnormal dreams	**3 per 100**	**31 per 100** (11 to 87)	**RR 10.49** (3.79 to 29.10)	4 cohort studies (2588)	1 RCT, 1 cohort study (123; 688)	⊕⊝⊝⊝ **very low** [2,6,9,10]
Insomnia	**3 per 100**	**12 per 100** (4 to 43)	**RR 4.14** (1.19 to 14.44)	4 cohort studies (3212)	1 RCT, 2 cohort studies (123; 355,627)	⊕⊝⊝⊝ **very low** [6,9,10,11]
Anxiety	**1 per 100**	**18 per 100** (9 to 35)	**RR 18.04** (9.32 to 34.93)	3 cohort studies (2559)	2 cohort studies (355,627)	⊕⊝⊝⊝ **very low** [6,9,10,11]
Depressed mood	**1 per 100**	**11 per 100** (5 to 25)	**RR 11.43** (5.21 to 25.07)	2 cohort studies (2445)	3 cohort studies (430,006)	⊕⊝⊝⊝ **very low** [6,9,10,11]
Abnormal thoughts or perceptions	**0 per 100**	**3 per 100** (0 to 24)	**RR 6.60** (0.92 to 47.20)	2 cohort studies (2445)	2 cohort studies (376,024)	⊕⊝⊝⊝ **very low** [6,9,10,11]
Nausea	**8 per 100**	**3 per 100** (2 to 4)	**RR 0.37** (0.30 to 0.45)	5 cohort studies (2683)	1 RCT, 1 cohort study (123; 668)	⊕⊝⊝⊝ **very low** [3,6,10,11]
Vomiting	**5 per 100**	**1 per 100** (1 to 1)	**RR 0.18** (0.12 to 0.27)	4 cohort studies (5071)	1 RCT (123)	⊕⊝⊝⊝ **very low** [3,6,10,11]
Abdominal pain	**15 per 100**	**5 per 100** (1 to 16)	**RR 0.30** (0.09 to 1.07)	3 cohort studies (2536)	1 RCT, 1 cohort (123; 668)	⊕⊝⊝⊝ **very low** [6,7,9,11]
Diarrhoea	**5 per 100**	**1 per 100** (1 to 4)	**RR 0.28** (0.11 to 0.73)	5 cohort studies (5104)	2 RCTs; 1 cohort study (376; 668)	⊕⊝⊝⊝ **very low** [3,6,10,11]

Dyspepsia	**14 per 100**	**4 per 100** (1 to 10)	**RR 0.26** (0.09 to 0.74)	5 cohort studies (5104)	—	⊕⊖⊖⊖ **low** [2,3,6,10]
Headache	**2 per 100**	**2 per 100** (1 to 6)	**RR 1.21** (0.50 to 2.92)	5 cohort studies (3320)	1 RCT, 1 cohort study (123; 688)	⊕⊖⊖⊖ **very low** [3,6,7,11]
Dizziness	**1 per 100**	**3 per 100** (1 to 14)	**RR 3.49** (0.88 to 13.75)	5 cohort studies (2633)	1 RCT, 2 cohort studies (123; 355,627)	⊕⊖⊖⊖ **very low** [3,6,7,11]
Visual impairment	**3 per 100**	**7 per 100** (4 to 12)	**RR 2.37** (1.41 to 3.99)	2 cohort studies (1875)	—	⊕⊖⊖⊖ **very low** [2,6,7,9]
Pruritis	**3 per 100**	**2 per 100** (1 to 3)	**RR 0.52** (0.30 to 0.91)	2 cohort studies (1794)	1 cohort study (688)	⊕⊖⊖⊖ **very low** [6,9,10,11]
Photosensitivity	**19 per 100**	**2 per 100** (1 to 2)	**RR 0.08** (0.05 to 0.11)	2 cohort studies (1875)	1 cohort study (688)	⊕⊖⊖⊖ **very low** [2,6,9,10]
Vaginal thrush	**16 per 100**	**2 per 100** (1 to 3)	**RR 0.10** (0.06 to 0.16)	1 cohort study (1761)	1 cohort study (354)	⊕⊖⊖⊖ **very low** [2,6,9,10]

*The **assumed risk** is the median control group risk across cohort studies unless stated 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). Where the control group risk was 0, we used a value of 0.5 to calculate the corresponding risk in the intervention group. Where no RCTs including short-term travellers reported on our prespecified adverse outcomes, we included information from cohort studies as our primary analysis.

'Summary of findings' tables are usually limited to seven outcomes. For adverse effects this problematic, as there are many, and to include some and not others risks selective reporting. We have therefore included all prespecified outcomes in the table.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: 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 certainty: we are very uncertain about the estimate.

[1]No serious risk of bias: none of the RCTs adequately described methods of random sequence generation or allocation concealment, However, given that so few events occurred in these trials, it is unlikely to have introduced bias.
[2]No serious inconsistency: the direction of the effect is consistent across study designs, or there in consistency in the finding of no effect.

[3]No serious indirectness: the primary analysis included studies in short-term international travellers, longer-term occupational travellers, and military personnel.

[4]Downgraded by two levels for imprecision: only seven episodes of clinical malaria occurred in the four trials, and consequently, the analysis was substantially underpowered to exclude important differences.

[5]For serious adverse outcomes we expressed the control group risk as the overall risk in the control group.

[6]No serious risk of bias: all cohort studies had methodological problems which could introduce confounding or bias. However, as the GRADE approach automatically downgrades certainty by two levels for non-randomized studies, we did not downgrade further.

[7]Downgraded by one level for serious imprecision: the 95% confidence interval includes both clinically important effects and no effect.

[8]Downgrade by one level for serious inconsistency: although there was no substantial difference between drugs in the cohort studies, the proportion of discontinuations was higher with both drugs: 14% for mefloquine and 9% for doxycycline.

[9]Downgraded by one level for indirectness: the primary analysis included only cohort studies in longer-term occupation travellers (USA Peace Corps volunteers) and military personnel. Adverse effects in shorter-term international travellers may be lower.

[10]No serious imprecision: the effect was statistically significant and the overall data (RCTs and cohort studies) were adequately powered to detect this effect.

[11]Downgraded by one level for serious inconsistency: there was heterogeneity between trials in the direction of effect.

BACKGROUND

Description of the condition

Malaria is a parasitic protozoal infection which is usually transmitted through the bite of female *Anopheles* mosquitoes (Warrell 2002). It is most common in tropical and subtropical regions. Clinical disease is caused by infection of red blood cells by one of four *Plasmodium* species: *P. falciparum*, *P. vivax*,*P. ovale*, and*P. malariae* (WHO 2017). Humans can also become infected by forms of malaria that usually infect animals, such as*P. knowlesi* (WHO 2017). Clinical presentation is nonspecific and varied; symptoms include fever, chills, headache, diarrhoea, muscle cramps, and abdominal pain (WHO 2015). Severe disease is usually caused by infection with *P. falciparum*, but can also occur following infection with *P. vivax* and *P. knowlesi.* Host factors determining severity include genetics, host immune status, and age (WHO 2015).

The true global incidence and prevalence of malaria is difficult to determine; the highest disease burden occurs in sub-Saharan Africa where vital registration and disease notification systems are weak (Murray 2014). However, the latest World Health Organization (WHO) figures estimate 212 million new cases of malaria in 2015 leading to 429,000 deaths (WHO 2016). Around 125 million travellers visit malaria-endemic areas annually, and all need to take steps to prevent infection with malaria (Croft 2005). Each year there are between 10,000 and 30,000 known cases of malaria in returned travellers, but the real figure is likely to be higher due to under-reporting (WHO 2017).

The individual risk of acquiring malaria is determined by the host immune status, the area travelled to, the duration of travel and season, and the use of prevention measures. Pregnant women, young children and non-immune travellers are particularly vulnerable to severe disease if they become infected (WHO 2015). In Europe, the incidence of malaria is higher in people who travel to their country of origin to visit friends and relatives than in tourists (Behrens 2015). However, mortality is higher in tourists (Behrens 2015).

The natural life cycle of malaria involves the consecutive infection of two hosts: female *Anopheles* mosquitoes and humans (CDC 2015a). The female mosquito acquires the disease when taking a blood meal from an infected human host. It will then become infectious over a period of 10 to 14 days depending on the region. Sporozoites are injected into the human host the next time the mosquito feeds. These travel via the blood stream to the liver and develop into schizonts which then rupture releasing merozoites. Merozoites invade erythrocytes and undergo asexual replication. Some of these develop through ring stage trophozoites into schizonts which rupture releasing further merozoites and thus perpetuate the infection. Others will develop into female and male gametocytes which are ingested by *Anopheles* mosquitoes during a blood meal leading to the spread of disease.

Description of the intervention

Mefloquine has been available for use in Europe since 1985 and the USA since 1990 (Schlagenhauf 1999). Alongside atovaquone-proguanil and doxycycline, it is considered standard chemoprophylaxis by many international health guidelines (CDC 2015b; PHAC 2014; PHE 2015; WHO 2017).

Mefloquine belongs to the aryl amino acid group of antimalarial agents. Mefloquine has a long half life and is given as a weekly dose of 250 mg when used for prophylaxis in adults (Schlagenhauf 2010). Mefloquine is effective against all five strains of malaria known to affect humans. Although guidelines vary, many state that mefloquine should be taken for two to three weeks before travel and continued for four weeks following return (WHO 2017).

There are several situations in which mefloquine is potentially advantageous. All guidelines recommend that where avoidable pregnant women should not travel to areas where malaria is endemic (WHO 2017). However, where travel is essential, mefloquine is often the preferred option. Mefloquine is widely considered to be safe within the second and third trimesters of pregnancy and guidelines increasingly recommend its use in the first trimester (CDC 2015b; Schlagenhauf 2010). Mefloquine is suitable for both children who weigh more than 5 kg and breastfeeding mothers (Schlagenhauf 2010).

Doxycycline has restrictions on its use during pregnancy due to effects on skeletal development found in animal studies. The use of atovaquone-proguanil is limited by a lack of evidence for safety (PHE 2015). Chloroquine-proguanil is considered safe for pregnant women, but its use is limited by widespread resistance (PHAC 2014).

The main side effects of mefloquine are gastrointestinal, neurological and psychological. Psychological side effects vary from those considered to be very common (including insomnia and abnormal dreaming) to those with unknown frequency (including psychosis and suicidal ideation) (eMC 2015a). Existing drug labels suggest that these side effects are both prodromal and dose related (eMC 2015a).

How the intervention might work

Malaria chemoprophylaxis is defined as the use of antimalarial medication to prevent the clinical symptoms of malaria (Schlagenhauf 2010). This is because no drugs are able to prevent the introduction of infection by destroying the sporozoites injected by the female *Anopheles* mosquito. Chemoprophylaxis is one of several tools used to prevent malaria; other recommended measures include sleeping under insecticide-treated bed nets, wearing insecticide-treated clothing, and applying chemical repellent sprays to the skin surface (WHO 2017). None of these methods provide complete protection and a combination of approaches is advised.

Chemoprophylaxis works by blocking the development or reproduction of the malaria parasite at various stages in its life cycle:

- doxycycline and mefloquine are examples of suppressive prophylactics and act in the blood stream as the schizonts invade erythrocytes. Doxycycline therefore needs to be taken for at least one month after returning from endemic areas (Shanks 2005);
- atovaquone-proguanil and primaquine have effects on the early liver stages of *Plasmodium* spp and prevent the progression to blood stage parasites which cause clinical illness. These agents therefore only need to be taken for one week after leaving the malaria-endemic area (Shanks 2005).

Currently, the baseline efficacy of doxycycline, atovaquone-proguanil and mefloquine when used as prophylaxis to prevent malaria is thought to be similar. Most guidelines therefore recommend selecting appropriate antimalarial prophylaxis based on individual choice, pre-existing conditions, side effect profile, and drug resistance patterns in the destination country (CDC 2015b; PHE 2015; WHO 2017). Drug resistance to all antimalarial agents is a growing concern, and mefloquine resistance has been reported in some areas of north-western Thailand (Treiber 2010; Treiber 2011).

In addition, the efficacy of all forms of malaria prevention is impeded by adherence. Nearly all cases of fatal malaria in travellers occur due to non-adherence with prophylactic measures (Schlagenhauf 2010). However, this needs to be balanced against the tolerability and safety of chemoprophylaxis; the frequency of mild to moderate adverse drug reactions varies from 32% to 45% (Schlagenhauf 2003). Both policy makers and individual travellers need to balance carefully the risk benefit profile of contracting malaria against using chemoprophylaxis.

Why it is important to do this review

Mefloquine has long been associated with neurological and psychological side effects which range from mild headaches and dizziness to reports of suicide and psychosis. The frequency and severity of these outcomes has been debated. In 2013 the USA Food and Drug Administration (FDA) released a safety communication regarding potential long-term and significant neurological and psychiatric side effects of mefloquine (FDA 2013). This included the addition of a boxed warning to the drug label, the most serious form of warning that can be issued. Similarly in Europe in 2014 the European Medicine Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) required a change to the summary of product characteristics noting that "...in a small number of patients it has been reported that neuropsychiatric reactions (for example, depression, dizziness or vertigo and loss of balance) may persist for months or longer, even after discontinuation of the drug" (EMA 2014). This has been incorporated into summaries of product characteristics throughout Europe. Most recently the UK Defence Committee has suggested mefloquine should only be used as a drug of last resort (UK Parliament 2016).

Previous reviews on this topic have limited analyses to randomized controlled trials (RCTs) (Jacquerioz 2009; Jacquerioz 2015). However, RCTs are not always the optimal study design to determine the type, prevalence or nature of adverse events and adverse effects, and many set inclusion criteria which exclude groups of people who are likely to be affected (Loke 2007). In addition, adverse effects are often the primary outcome measure of non-randomized trials, meaning that researchers may attempt to capture and define adverse events in a more rigorous manner than when they are a tertiary measure (Loke 2011).

This Cochrane Review update broadened study inclusion criteria to include non-randomized studies that provide useful information regarding the side effect profile of mefloquine.

This review did not address:

- the efficacy or safety of alternative forms of malaria chemoprophylaxis;
- the use by pregnant women of mefloquine as intermittent presumptive treatment of malaria, or;
- the use by travellers of emergency standby malaria treatment.

This new edition replaces the Cochrane Review on mefloquine for preventing malaria in non-immune adult travellers (Jacquerioz 2015). Malaria prophylaxis in children living in endemic areas, chemoprophylaxis in pregnant women, and malaria prevention in people with sickle cell disease have been assessed in other Cochrane Reviews (Meremikwu 2008; Oniyangi 2006; Radeva-Petrova 2014).

OBJECTIVES

To summarize the efficacy and safety of mefloquine used as prophylaxis for malaria in travellers.

METHODS

Criteria for considering studies for this review

Types of studies

For efficacy we included randomized and quasi-randomized controlled trials, including cluster-randomized trials.

For safety we also included non-randomized controlled trials/cohort studies. We included both prospective and retrospective cohort studies, but excluded studies where recruitment was linked to the occurrence of specific adverse events.

A list of study design features for all included studies is included in Appendix 1.

Types of participants

Adults and children, including pregnant women.

Types of interventions

Intervention

Mefloquine at a prophylactic dose (for example, 250 mg once weekly in adults and equivalent dosing for children).

Control

Placebo, no intervention or an alternative malaria chemoprophylaxis agent in current use.

Types of outcome measures

Efficacy

Clinical cases of malaria.

Safety

- Adverse effects of any severity: defined as "an adverse event for which the causal relation between the intervention and the event is at least a reasonable possibility" (Loke 2011);
- serious adverse effects are those "leading to death, [which] are life threatening, require inpatient hospitalization or prolongation of existing hospitalization, or result in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect" (ICH 1994);
- adverse events of any severity: defined as “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” (WHO-ART 2008);

- serious adverse events are those "leading to death, [which] are life threatening, require inpatient hospitalization or prolongation of existing hospitalization, or result in persistent or significant disability or incapacity, or is a congenital anomaly/ birth defect." (ICH 1994);
- discontinuations of study drug due to adverse effects;
- measures of adherence to the drug regimen.

Pregnancy-related outcomes:

- adverse pregnancy outcomes: spontaneous abortions, stillbirths, congenital malformations.

Study authors often use the terms 'adverse event', 'adverse effect' or 'side effect' interchangeably and loosely. Where possible, we used the definitions described above to distinguish adverse events and adverse effects. Adverse effects encompasses reporting by study authors of 'adverse effects', 'side effects', 'adverse events attributed to the study drug', 'adverse reactions', and 'symptoms related to the study drugs'.

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

We searched the following databases using the search terms and strategy described in Appendix 2:

- Cochrane Infectious Diseases Group Specialized Register to 22 June 2017;
- Central Register of Controlled Trials (CENTRAL), published on the Cochrane Library to 22 June 2017;
- MEDLINE (PubMed) from 1966 to 22 June 2017;
- Embase (Ovid) from 1974 to 22 June 2017; and
- LILACS (Bireme) from 1982 to 22 June 2017.

We also searched the WHO International Clinical Trials Registry Platform (WHO ICTRP) and ClinicalTrials.gov (https://clinicaltrials.gov/) for trials in progress, using 'mefloquine', 'Lariam', and 'malaria' as search terms (22 June 2017).

For the safety analysis we also searched MEDLINE (PubMed) (1966 to 22 June 2017), Embase (Ovid) (1974 to 22 June 2017), and TOXLINE (1980 to 22 June 2017) (https://toxnet.nlm.nih.gov/newtoxnet/toxline.htm). The following MEDLINE terms were adapted as needed: ("Mefloquine/adverse effects"[Mesh] OR "Mefloquine/poisoning"[Mesh] OR "Mefloquine/toxicity"[Mesh]); Mefloquine ti, ab AND (safety OR tolerability OR death*OR suicid* OR adverse OR reaction* OR “side effect*”) ti, ab.

Searching other resources

We checked the reference lists of included studies for any references not identified by our searches.

Data collection and analysis

Selection of studies

Two review authors independently screened the results of the literature search for potentially relevant trials using Covidence software (Covidence 2017), and looked for multiple publications from the same data set. Full text copies were retrieved for all trials deemed potentially relevant for inclusion.

Two review authors then independently assessed all identified trials for inclusion in the review using the prespecified inclusion criteria. Any disagreements were resolved through discussion.

Data extraction and management

Two review authors independently extracted data using a standardized and pre-piloted data collection form. When available we extracted data on:

- details of study: start and end dates, setting (country of recruitment and country of malaria exposure), study design, method of participant recruitment and selection, number of participants enrolled, number of participants for whom data was available, mean duration of exposure to malaria, antimalarial resistance pattern of mefloquine and the comparator;
- study participants: inclusion and exclusion criteria, age, gender, body mass index (BMI), pregnancy status, risk factors (for malaria and for adverse outcomes), immune or non-immune participants, military or non military;
- details of the intervention: drug dose during prophylaxis, use of a loading dose, duration of drug therapy before and after travel, frequency of drug administration and use of any co-interventions;
- outcomes measured and reported including definition, method of detection, timing in relation to treatment, duration and frequency of monitoring.

We resolved any disagreements through discussion, and where necessary we consulted a third review author. If clarification was necessary, we attempted to contact the trial authors for further information.

For dichotomous data, we recorded the number of participants experiencing the event and the number analysed in each group. For continuous outcome data, we extracted arithmetic means and standard deviations for each group together with the numbers analysed in each group. We also extract medians and ranges where provided.

We extracted details of all serious adverse events and effects. For non-serious adverse events and effects we sought information on the following specific symptoms and groups of symptoms which are frequently associated with mefloquine, doxycycline or atovaquone-proguanil:

- ear and labyrinth disorders: vertigo;
- eye disorders: visual impairment;
- gastrointestinal disorders: nausea, vomiting, abdominal pain, diarrhoea, dyspepsia;
- nervous system disorders: dizziness and headaches;
- psychiatric disorders: abnormal dreams, insomnia, anxiety, depression, psychosis; and
- skin and subcutaneous tissue disorders: pruritis, photosensitivity, vaginal candida.

We also reported data on all other very common (> 1/10) and common (> 1/100 to < 1/10) adverse events and adverse effects, as defined by the electronic Medicines Compendium (eMC 2015b).

Where possible we attempted to derive absolute estimates of adverse outcomes (events or effects). For all adverse outcomes, we included only the denominator trials that actively reported the presence or absence of each specific adverse event or effect.

Most RCTs and cohort studies collected data on self-reported or clinician-assessed symptoms rather than formal medical diagnoses. Therefore, we reported outcomes as symptoms. For example, we reported on 'depressed mood' rather than 'depression'.

When deciding which relative effect measure to present in 'Summary of findings' tables, we considered which meta-analysis most closely answered our PICO (population, intervention, comparator, outcome/s) question. We created a decision tree in advance to assess the directness of a group of studies in relation to: the population studied (short-term international travellers versus other populations), outcomes measured (adverse effects versus adverse events), and study design (RCTs versus cohort studies). The intervention and comparator were fixed in each drug-pair comparison. Other less direct meta-analyses were used in our appraisal of the certainty of the evidence. The decision tree used is provided in Appendix 3.

Conventionally, 'Summary of findings' tables include up to seven outcomes. However, the key questions for clinical decision making relate to adverse effects, and therefore limiting the number of outcomes a priori was problematic, as we could not know in advance which adverse effects mefloquine would have. To constrain the number of outcomes in the 'Summary of findings' tables to seven would mean only reporting outcomes where effects were shown, which would lead to selective reporting.

We included 'Summary of findings' tables for comparisons of mefloquine with doxycycline and atovaquone-proguanil. This decision was made because chloroquine is used less frequently than mefloquine, doxycyline and atovaquone-proguanil. As reported in Results, the adverse effect profile of mefloquine in comparison to chloroquine was consistent with comparisons with doxycycline and atovaquone-proguanil.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias of each included study. For randomized and quasi-randomized controlled trials we used Cochrane's 'Risk of bias' tool (Higgins 2011). 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; selective outcome reporting and other risk of bias. We categorized these judgements as low risk of bias, high risk of bias, or unclear risk of bias.

For non-randomized (cohort) studies we assessed the risk of bias using the Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (now referred to as ROBINS-I) (ACROBAT-NSRI tool). We followed the guidance for making judgements on the risk of bias in eight domains: confounding, selection of participants into the study, measurement of interventions, departures from intended interventions, missing data, selection of the reported result and other risk of bias. We categorized these judgements as low risk of bias, moderate risk of bias, serious risk of bias and critical risk of bias. Where no information was provided on a category, this was stated. The criteria we used to make specific judgements are provided in Table 1.

For adverse events and adverse effects, we assessed the risk of bias in the conduct of the study by examining whether harms were predefined using standardized or precise definitions, ascertainment methods were adequately described, monitoring was active or passive and data collection was prospective or retrospective (Table 2). For laboratory tests and other investigations we assessed whether the number and timing of the tests was adequate.

We resolved any disagreement through discussion, and where necessary, we consulted a third review author.

Measures of treatment effect

We analysed data using Review Manager 5 (RevMan 5) (RevMan 2014) and combined dichotomous data using risk ratios (RR). For continuous data summarized by arithmetic means and standard deviations, we combined data using mean differences (MD). We present RRs and MD with 95% confidence intervals (CI) and report medians and ranges in tables for non-RCTs.

Unit of analysis issues

When trials included more than two comparison groups, we split the trial for analysis as individual pair-wise comparisons. If more than one comparison group was included in a meta-analysis, we ensured that participants were only counted once by dividing the cases and participants evenly between the comparisons.

For clinical cases of malaria, we included participants as the unit of analysis, such that each participant was counted once in the intervention or placebo arm. Where study reporting was unclear regarding the unit of analysis (that is, total clinical cases of malaria rather than clinical cases in each participant) we noted this in footnotes and performed a sensitivity analysis excluding these results.

Dealing with missing data

If data from trial reports were insufficient, unclear, or missing, we attempted to contact the trial authors for additional information.

Our primary analysis was a complete-case analysis which excluded all participants without treatment outcomes. No imputation measures for missing data were applied.

Where studies had grouped symptoms together by body system when reporting safety outcomes, we contacted authors to obtain disaggregated data. We obtained two additional full data sets (Cunningham 2014; Korhonen 2007) and received further clarification from two study authors (Kato 2013; Sonmez 2005). The full details of subsequent analyses are provided in the characteristics of included studies tables.

Assessment of heterogeneity

We assessed heterogeneity among trials by inspecting forest plots for overlapping CIs, applying the Chi^2 test with a 10% level of

statistical significance, and using the I^2 statistic with a value of 50% to denote moderate levels of heterogeneity.

Assessment of reporting biases

We were unable to assess publication bias using funnel plots because there were too few trials reporting the same outcomes.

Data synthesis

We carried out statistical analyses using RevMan 5 (RevMan 2014). We analysed randomized controlled trials (RCTs) and non-RCTs separately, and compared interventions as individual pair-wise comparisons.

In the absence of heterogeneity, we used a fixed-effect model. Where we identified moderate heterogeneity, and it was appropriate to combine data, we used the random-effects model. When it was not appropriate to combine data in a meta-analysis, we tabulated data and reported outcomes as a narrative.

We report the term used for each adverse event in each trial. Where trials used different terminology for similar adverse events and adverse effects, we coded them using the preferred term based on Medical Dictionary for Regulatory Activities (MedDRA) terminology (for example, sleepiness, somnolence) and analysed these together (MedDRA 2016).

Subgroup analysis and investigation of heterogeneity

We explored possible sources of heterogeneity using subgroup analyses (study design, military versus non-military participants, short- versus long-duration of travel).

Sensitivity analysis

We conducted sensitivity analyses to evaluate the robustness of the results to the risk of bias components, by excluding studies at high or unclear risk of bias.

RESULTS

Description of studies

Results of the search

Searches (conducted 22 June 2017) identified 2155 records; we screened seven additional studies after reviewing reference lists. Of these, we excluded 1953 after assessing titles and abstracts. We retrieved 209 full text publications to assess for inclusion.

Included studies

We included 20 randomized controlled trials (RCTs) (11,470 participants), 35 cohort studies (190,286 participants) and four large retrospective analyses of health records (800,652 participants).

Efficacy outcomes were reported in 14 RCTs conducted between 1977 and 2003 in Thailand (four trials), Brazil, Cambodia, Ghana, Indonesia, Ivory Coast, Malawi, Nigeria, Kenya and two studies which included travellers to various destinations (10,710 participants). Two were conducted in short-term international travellers (Overbosch 2001; Schlagenhauf 2003); nine involved general populations living in endemic areas who are likely to have some immunity to malaria (Boudreau 1991; Bunnag 1992; Hale 2003; Nosten 1994; Pearlman 1980; Salako 1992; Sossouhounto 1995; Steketee 1996; Weiss 1995), two recruited non-immune military personnel (Arthur 1990; Ohrt 1997), and one recruited a mixed military and civilian semi-immune population (Santos 1993).

All 20 included RCTs and 35 cohort studies reported safety outcomes. Nine RCTs explicitly excluded participants with a psychiatric history, and 25 cohort studies stated that the choice of antimalarial agent was based on medical history and personal preference. Most RCTs and cohort studies collected data on self-reported or clinician-assessed 'symptoms', rather than formal medical diagnoses. Consequently, when describing these data we used non-medical descriptions such as 'depressed mood' rather than 'depression', even where the trial authors described the symptom as depression. However, four retrospective cohort studies analysed healthcare records (Eick-Cost 2017; Meier 2004; Schneider 2013; Wells 2006) and looked for people with formal mental health diagnoses. Where outcomes were presented grouped by organ system, we approached study authors for additional data and received full data sets for two studies (Cunningham 2014; Korhonen 2007) and additional information from another two (Kato 2013; Sonmez 2005).

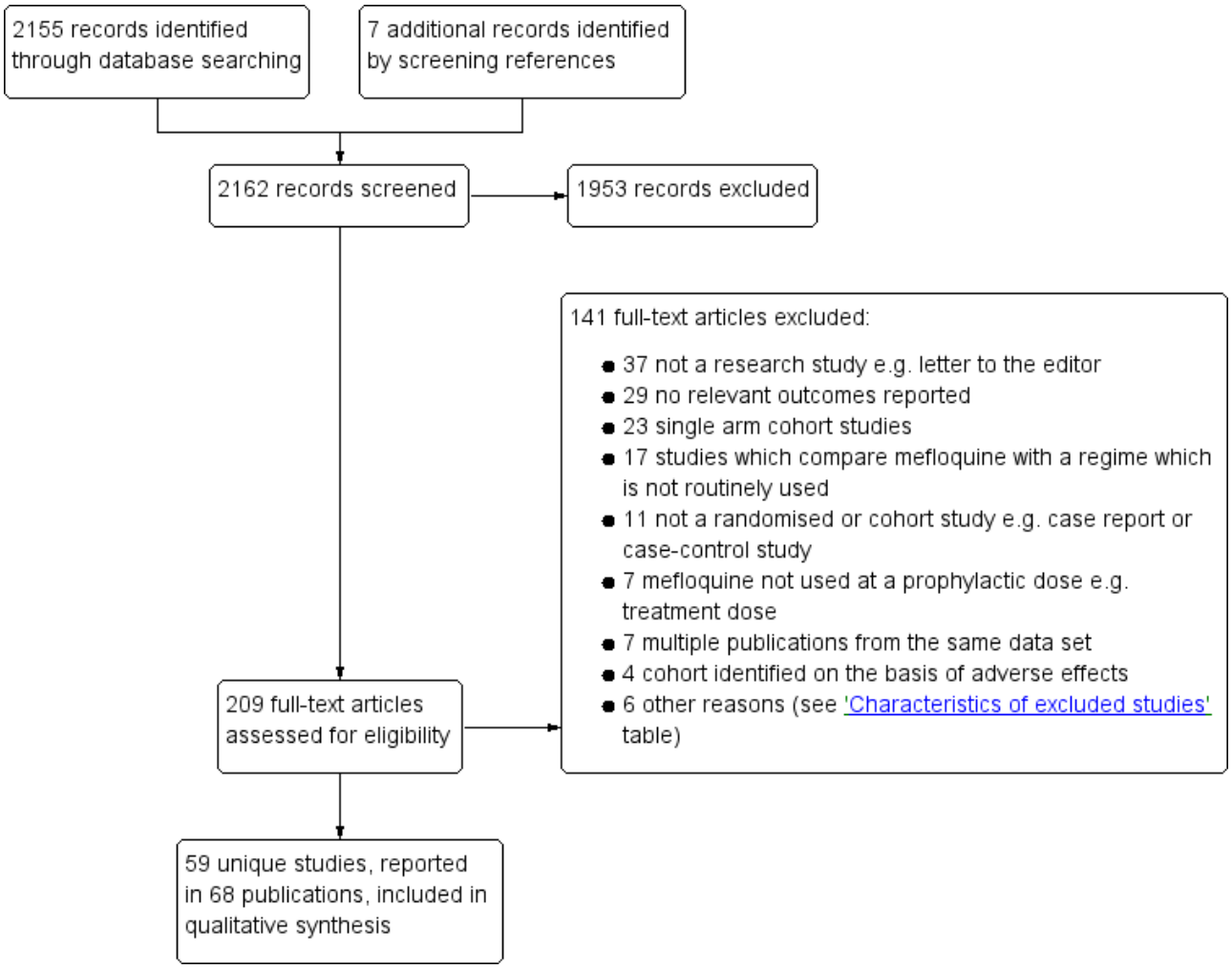
Three RCTs (1827 participants) and 24 cohort studies (170,487 participants) included short-term international travellers. Five cohort studies included long-term occupational travellers (UK Foreign and Commonwealth Office Staff and Peace Corps volunteers) (13,211 participants); four RCTs (961 participants) and six cohort studies (6588 participants) included military personnel (including 1 study with a mixed military and civilian population). Thirteen RCTs included local residents who did not travel outside their home countries: Australia (Davis 1996), Ghana (Hale 2003), Israel (Potasman 2002), Ivory Coast (Sossouhounto 1995), Kenya (Weiss 1995), Malawi (Steketee 1996), the Netherlands (Vuurman 1996), Nigeria (Salako 1992), Switzerland (Schlagenhauf 1997) and Thailand (Boudreau 1991, Bunnag 1992, Nosten 1994, Pearlman 1980).

Seven RCTs and three cohort studies were sponsored by Roche (manufacturer of mefloquine), three RCTs and one cohort study were sponsored by GlaxoSmithKline (manufacturer of atovaquone-proguanil), one RCT was sponsored by Pfizer (manufacturer of doxycycline), and one by Mepha Ltd (manufacturer of a film-coated form of mefloquine). Only one RCT and one cohort study reported whether the study sponsor had any influence over collecting, analysis or interpretation of study results or the decision to publish.

Excluded studies

We excluded 141 studies after full-text screening (Figure 1). We excluded 37 studies because they were not research studies; 29 studies reported no relevant outcomes; 23 studies were single arm cohort studies and did not meet our inclusion criteria; 17 studies compared mefloquine with a regime which is not routinely used; 11 studies were not a randomized or cohort study (for example, case report or case-control study); in seven studies mefloquine was not used at a prophylactic dose, for example, treatment dose; seven studies were multiple publications from the same data set as included studies; four cohort studies the population was identified on the basis of having experienced adverse effects and we excluded 6 studies for other reasons. We have provided full details in the 'Characteristics of excluded studies' tables.

Figure 1. Study flow diagram.



Risk of bias in included studies

We performed 'Risk of bias' assessments for the included RCTs using the Cochrane 'Risk of bias' assessment tool. We assessed the risk of bias in the cohort studies using the ACROBAT-NSRI tool (now referred to as ROBINS-I). For a summary of the 'Risk of bias' assessments for RCTs see Figure 2.

Figure 2. 'Risk of bias' summary for RCTs: review authors' judgements about each 'Risk of bias' item for each included study.

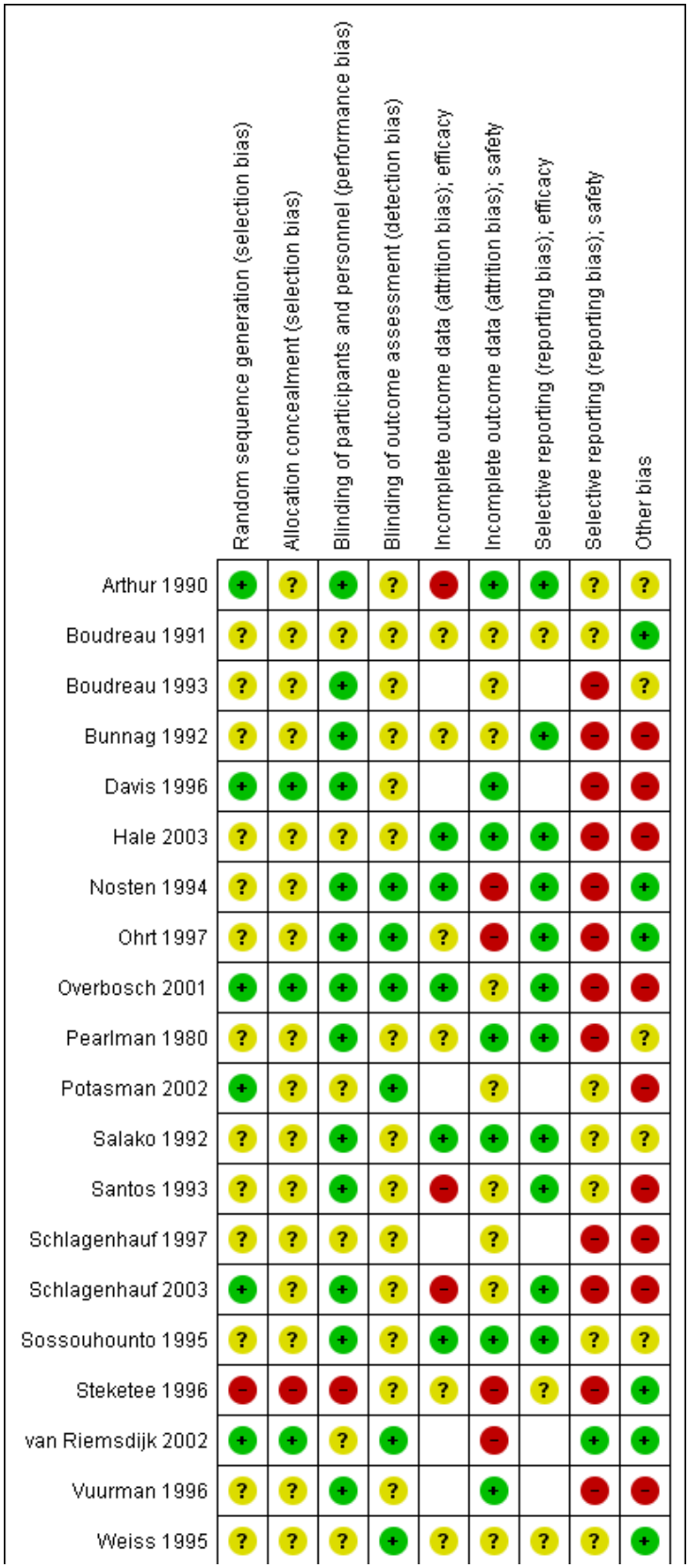


Figure 2. (Continued)

Allocation

Three trials were at low risk of selection bias, with adequate descriptions of generation of the random sequence and allocation concealment (Davis 1996; Overbosch 2001; van Riemsdijk 2002). A further 16 trials were at unclear risk of selection bias due to providing insufficient information regarding their methodology. One trial described sequential allocation of unblinded participants (Steketee 1996).

Blinding

Seven trials adequately described blinding of study personnel, including blinding of pathology technicians when detecting malaria, and blinding of outcome assessors when assessing safety outcomes (Nosten 1994; Ohrt 1997; Overbosch 2001; Potasman 2002; Schlagenhauf 2003; van Riemsdijk 2002; Weiss 1995). The remaining 13 trials did not adequately describe how outcome assessors were blinded.

Incomplete outcome data

Six trials had low and balanced losses to follow-up rates for efficacy outcomes (Hale 2003; Nosten 1994; Overbosch 2001; Salako 1992; Sossouhounto 1995; Weiss 1995). One trial was at high risk of bias because investigators did not follow up participants beyond the active phase of treatment for relapses (Santos 1993). Two studies did not make the method of detection of malaria, frequency or duration of follow up clear (Arthur 1990; Schlagenhauf 2003).

Seven trials had low losses to follow-up rates for adverse outcomes (Arthur 1990; Davis 1996; Hale 2003; Pearlman 1980; Salako 1992; Sossouhounto 1995; Weiss 1995). We judged four of the trials to be at high risk of bias because investigators did not provide numbers of participants lost to follow up across groups (Nosten 1994; Steketee 1996); did not assess all participants who received the study drug in the final analysis (Ohrt 1997); and because the proportion of participants who did not complete the study due to adverse outcomes varied significantly between groups (van Riemsdijk 2002).

Selective reporting

Fourteen trials reported on efficacy outcomes, and twelve of these appropriately reported all outcomes.

However, 21 trials reported on our safety outcomes and only nine of these appropriately reported on all pre-specified outcomes. Three of these trials only reported on statistically significant differences between groups (Boudreau 1993; Pearlman 1980; Schlagenhauf 1997), and another four did not report data from all time points (Bunnag 1992; Nosten 1994; Ohrt 1997; Overbosch 2001). Two trials reported aggregate data across multiple time points (Schlagenhauf 2003; Steketee 1996), one trial only reports symptoms which occurred in > 10% of participants in each study arm (Davis 1996). Vuurman 1996 only reported events which occurred more than once and Hale 2003 reports the total number of serious adverse events does not allocate them to a drug regimen.

Other potential sources of bias

Seven trials were sponsored by Roche (manufacturer of mefloquine) (Bunnag 1992; Davis 1996; Ohrt 1997; Santos 1993; Schlagenhauf 1997; Schlagenhauf 2003; Vuurman 1996), three were sponsored by GlaxoSmithKline (manufacturer of atovaquone-proguanil) (Hale 2003; Overbosch 2001; Schlagenhauf 2003), one by Pfizer (manufacturer of doxycycline) (Ohrt 1997), and one by Mepha Ltd (manufacturer of a film-coated form of mefloquine) (Potasman 2002). Only one made the role of the study sponsor clear (Ohrt 1997).

We have presented details of the risk of bias of cohort studies in the 'Effects of interventions' section.

Effects of interventions

See: **Summary of findings for the main comparison** Mefloquine versus atovaquone-proguanil for preventing malaria in travellers; **Summary of findings 2** Mefloquine versus doxycycline for preventing malaria in travellers

Comparison 1: Mefloquine versus placebo or no treatment

Description of studies

RCTs

Nine RCTs comparing prophylactic mefloquine with placebo reported efficacy (4032 participants, Table 3), and 13 reported safety outcomes (4293 participants, Table 4). The trials were conducted between 1977 and 2003, and none included participants travelling outside their home country. One trial conducted among soldiers in Indonesia described participants as non-immune (Ohrt 1997), but immunity is likely to be low in other trials from Asia (Bunnag 1992; Nosten 1994; Pearlman 1980). The participants in four trials from Africa were described as semi-immune (Hale 2003; Salako 1992; Sossouhounto 1995; Weiss 1995). Santos 1993 was conducted in an area of Brazil in which endemic transmission occurs.

Seven trials used mefloquine at a dose of 250 mg weekly (or equivalent doses for children), four at 250 mg weekly for the first four weeks and then 125 mg weekly for the remainder of the study, and one trial used mefloquine doses of 500 mg every four weeks and 250 mg every two weeks (Santos 1993). Pearlman 1980 used mefloquine doses of 180 mg weekly, 360 mg weekly and 360 mg fortnightly. Trial duration varied from 48 hours to 26 weeks.

For safety, nine trials used interviews with study personnel to elicit adverse events (Bunnag 1992; Hale 2003; Nosten 1994; Ohrt 1997; Salako 1992; Santos 1993; Schlagenhauf 1997; Vuurman 1996; Weiss 1995). Of these, six trials questioned participants about symptoms at least weekly (Hale 2003; Nosten 1994; Ohrt 1997; Salako 1992; Vuurman 1996; Weiss 1995). Two trials used participant self-reported diaries to record any adverse events (Davis 1996, Potasman 2002). Pearlman 1980 used a weekly 'sick call' by study personnel and Sossouhounto 1995 provided 'access

to the village health centre'. Only two trials used explicit definitions for adverse events and effects that allow for reproducible ascertainment (Davis 1996, Vuurman 1996). For safety outcomes, nine of the 13 trials adequately described how adverse events were ascertained. Eleven trials actively sought adverse events, and all 13 collected data prospectively (Table 5).

Eleven of thirteen which assessed safety outcomes trials did not adequately describe random sequence generation or allocation concealment, and eight did not adequately describe how outcome assessors and study personnel were blinded. We judged eight trials to be at high risk of selective outcome reporting with regard to safety outcomes. In two trials, this was because the overall number of adverse events in each study arm was reported, but not the type or severity (Bunnag 1992; Potasman 2002). Davis 1996 reported only adverse events that occurred in more than 10% of participants in both study arms; Vuurman 1996 reported only adverse events that occurred more than once; and Nosten 1994 only reported on adverse events in the second phase of the trial.

Five trials were funded by Roche (manufacturer of mefloquine) (Bunnag 1992; Davis 1996; Santos 1993; Schlagenhauf 1997; Vuurman 1996) and one by GlaxoSmithKline (manufacturer of atovaquone-proguanil) (Hale 2003) and one by Mepha Ltd (manufacturer of a film-coated form of mefloquine) (Potasman 2002).

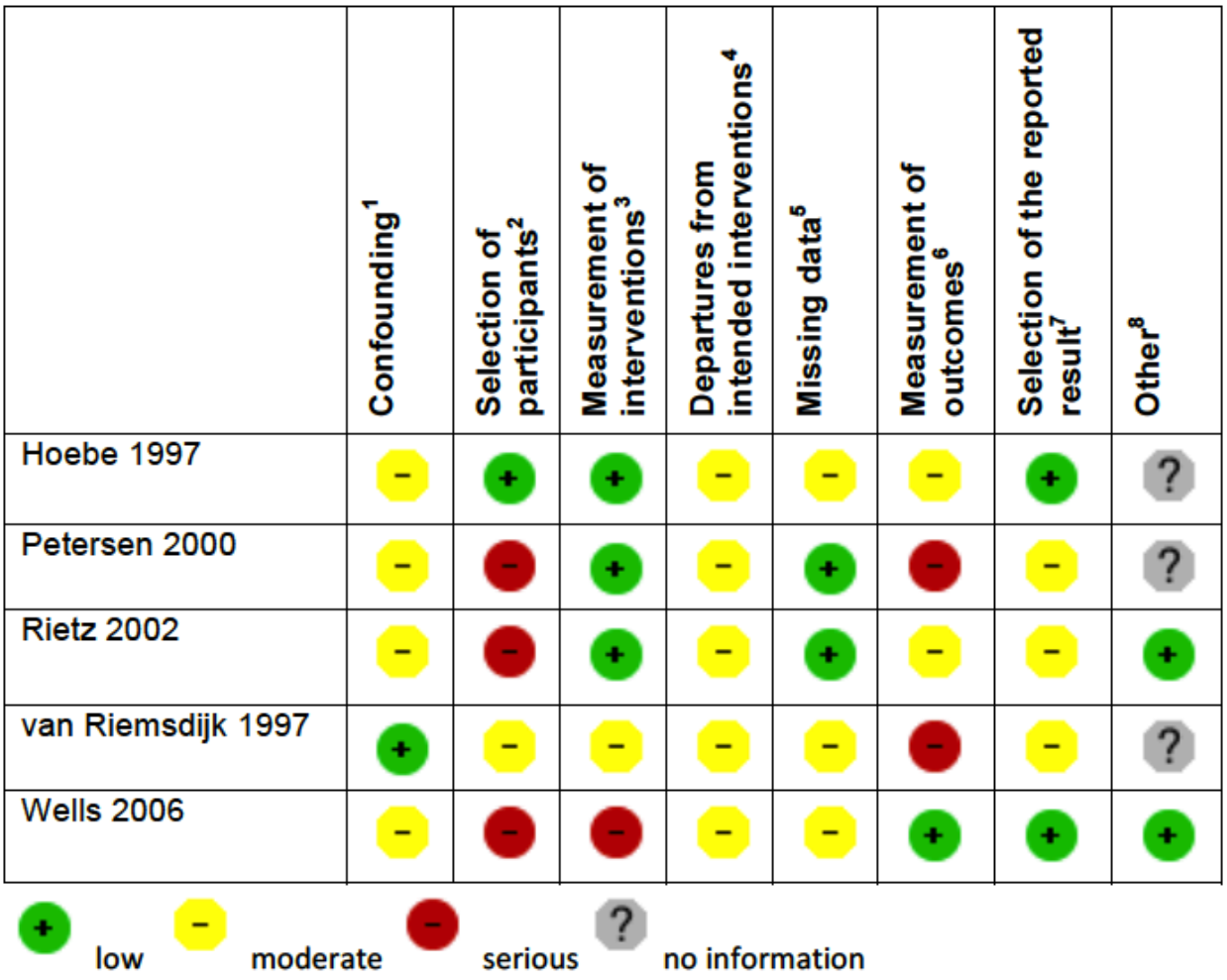
Cohort studies

Five cohort studies compared mefloquine users with participants who travelled but did not take antimalarial prophylaxis at all (Hoebe 1997; Petersen 2000; Rietz 2002; van Riemsdijk 1997; Wells 2006). Four of these were conducted in travellers, and one in military personnel (Table 4).

Two cohort studies included travellers who were prescribed an antimalarial agent but did not commence using (Hoebe 1997; Petersen 2000) and two asked travellers about an extensive list of general complaints which could have occurred during their journey (Rietz 2002; van Riemsdijk 1997). Wells 2006 was a retrospective healthcare record analysis looking at hospitalizations in active-duty USA military personnel (397, 442 participants).

Two cohort studies had non-response rates of over 20%. Wells 2006 was at serious risk for selection of participants and measurement of outcomes because start of follow up began after participants had finished taking mefloquine, authors used surrogate measures for mefloquine exposure and there was a possibility that some participants in the reference groups took mefloquine. Four cohort studies actively sought information from participants about adverse events and only one (van Riemsdijk 1997) obtained information prospectively (see Figure 3).

Figure 3. 'Risk of bias' summary in cohort studies: mefloquine versus placebo/no treatment [1]Assesses whether our pre-defined confounders were measured and balanced across groups.
[2]Assesses the non-response rate of prospective participants.
[3]Assesses the risk that participants labelled as taking mefloquine (or another antimalarial) actually took something else.
[4]Assesses the risk that participants whose adverse effects are attributed to mefloquine (or another antimalarial) actually took another drug as well.
[5]Assesses whether outcome data reasonably complete for most participants and whether intervention status reasonably complete for those in whom it was sought.
[6]Assesses whether the outcome measure was subjective, and whether participants and outcome assessors were blinded.
[7]Assesses whether it is clear that all information collected within the study has been reported.
[8]Assess the risk of bias due to influence by a corporate study sponsor.



Efficacy

Mefloquine is highly efficacious in reducing clinical cases of malaria compared to placebo, although there were important differences among trials, particularly regarding the dose of mefloquine used, populations studied and the risk of malaria in the control group (Analysis 1.1). The risk of malaria was highest in the trial in military personnel travelling to Indonesia, described as "largely non-immune", where 53/65 (81%) of those in the placebo group had an episode of malaria compared to 0/67 (0%) with mefloquine (RR 0.01, 95% CI 0.00 to 0.16; Ohrt 1997, 126 participants). In the remaining trials the risk of malaria with placebo ranged from 1% to 59% (Bunnag 1992; Hale 2003; Nosten 1994; Pearlman 1980; Salako 1992; Santos 1993; Sossouhounto 1995; Weiss 1995).

Although quantitative heterogeneity was high, the direction of the effect was consistent across all trials. We performed a series of subgroup analyses by dose and immune status of participants, but this did not explain the heterogeneity or provide a reliable point estimate of efficacy with subgroups.

Five trials also reported the effect on parasitaemia (which was much more common than clinical malaria) (Hale 2003; Nosten 1994; Salako 1992; Sossouhounto 1995; Weiss 1995). Overall, mefloquine reduced numbers of participants who developed parasitaemia by around 80% (RR 0.18, 95% CI 0.06 to 0.55; 3 trials, 414 participants, Analysis 1.2), and substantially reduced the number of episodes of parasitaemia (RR 0.05, 95% CI 0.00 to 5.25; 2 trials, 510 participants, Analysis 1.2).

Safety

Serious adverse events or effects

Only three serious adverse events were reported from six RCTs, none of which were attributed to the drug regimen (1/592 mefloquine users versus 2/629 placebo; 6 trials; 1221 participants, Analysis 1.3). The serious event in the mefloquine user was the death of a pregnant woman who received mefloquine (septic shock after an emergency caesarean section for obstructed labour) (Nosten 1994). For serious pregnancy-related outcomes, Nosten 1994 reported four congenital malformations in the mefloquine group: limb dysplasia (1 case), ventricular septal defect (2 cases), amniotic bands (1 case) and one in the placebo group: anencephaly. All were considered unrelated to the drug regimen (Table 6).

By comparison in cohort studies, seven serious adverse effects (all attributed by study authors to the drug regimen) were reported among 913 mefloquine users, compared to none in 254 travellers who did not use antimalarials (RR 3.08, 95% CI 0.39 to 24.11; 2 studies, 1167 participants; Analysis 1.3; Table 7). Five of these were psychological (depression) and two were neurological adverse effects (dizziness).

Wells 2006 was a retrospective healthcare record analysis that reported adverse events. It compared numbers of hospitalizations in military personnel who had been prescribed mefloquine and were deployed to active duty in malarial areas, with those who had been deployed to non-malarial areas, and with military personnel with duty zip codes for Europe or Japan, who had not been deployed to active duty. Mefloquine users were less likely to be hospitalized (after deployment) with mood disorders (RR 0.38, 95% CI 0.17 to 0.86; 241,239 participants) or for any cause (RR 0.60, 95% CI 0.51 to 0.71; 241,239 participants) than military personnel who did not receive any antimalarial agents (but who were deployed to a war zone).

Discontinuations due to adverse effects

Within RCTs the number of people who discontinued the study drug due to adverse effects was low in both groups: 6/541 (1.1%) with mefloquine versus 4/583 (0.7%) with placebo (RR 1.64, 95% CI 0.55 to 4.88; 7 trials, 1124 participants, Analysis 1.4). No comparative data were available on this outcome from cohort studies because the comparison was with no treatment.

Prespecified adverse events or effects

None of the RCTs or cohort studies for this comparison reported on adverse effects (symptoms attributed by researchers or participants to the drug regimen). All comparisons were for adverse events (all symptoms that occurred while taking the study drug).

Gastrointestinal symptoms

Within RCTs, participants who received mefloquine were more likely to experience nausea than those who took placebo (RR 1.35, 95% CI 1.05 to 1.73; 2 trials, 244 participants, Analysis 1.5), but there was no difference between groups for vomiting, abdominal pain or diarrhoea (Analysis 1.6; Analysis 1.7; Analysis 1.8). The results from cohort studies were consistent with this finding, with more mefloquine users experiencing nausea (RR 1.85, 95% CI 1.42 to 2.43; 3 studies, 1901 participants, Analysis 1.5).

One RCT in pregnant women (Nosten 1994) reported on both upper and lower abdominal pain. Inclusion of both groups of results in sensitivity analyses had no impact on the results.

Neurological symptoms

Mefloquine users in RCTs were no more likely that recipients who took placebo to experience headache (RR 0.84, 95% CI 0.71 to 0.99; 5 trials, 791 participants, Analysis 1.9) or dizziness (RR 1.03, 95% CI 0.90 to 1.17; 3 trials, 452 participants, Analysis 1.10). This is in contrast to cohort studies, in which participants who took mefloquine were significantly more likely to experience dizziness than participants who travelled but took no prophylaxis (RR 1.80, 95% CI 1.29 to 2.49; 3 studies, 1901 participants, Analysis 1.10).

Psychological symptoms

None of the RCTs included in the analysis reported on any of our prespecified psychological symptoms. Participants in cohort studies who received mefloquine were more likely than participants who did not take prophylaxis to experience abnormal dreams (RR 2.35, 95% CI 1.15 to 4.80; 2 cohort studies, 931 participants, Analysis 1.11), and insomnia (RR 1.46, 95% CI 1.06 to 2.02; 2 cohort studies, 931 participants, Analysis 1.12). Effects on anxiety (RR 1.21, 95% CI 0.67 to 2.21; 2 cohort studies, 931 participants; I^2 statistic = 48%; Analysis 1.13), depressed mood (RR 2.43, 95% CI 0.65 to 9.07; 3 cohort studies, 1901 participants, I^2 statistic = 72%, Analysis 1.14) and abnormal thoughts or perceptions (RR 5.77, 95% CI 0.79 to 42.06; 1 cohort study, 970 participants, Analysis 1.15), were not consistent across studies, and overall, did not reach standard levels of statistical significance.

Other symptoms

Mefloquine users in cohort studies were more likely to experience pruritis (RR 6.71, 95% CI 1.58 to 28.55; 1 cohort study, 197 participants, Analysis 1.16). However, this finding was not replicated in RCTs (RR 0.86, 95% CI 0.60 to 1.24; 3 RCTs, 609 participants, Analysis 1.16). There was no difference between groups for visual impairment and vertigo in either RCTs nor cohort studies (Analysis 1.17; Analysis 1.18).

Other adverse events reported in more than 1% of study participants (in either study arm) in RCTs and cohort studies are presented in Analysis 1.19 and Analysis 1.20. Only respiratory tract infection reached statistical significance between groups; data were from a single trial with few events (RR 2.63, 95% CI 1.04 to 6.61; 1 trial, 140 participants).

Studies reporting groups of symptoms or other outcomes which could be used as proxy markers of psychological or neurological adverse effects are reported in Appendix 4.

Pregnancy outcomes

Nosten 1994 conducted an RCT in pregnant women over 20 weeks gestation. There was no reported difference between mefloquine and placebo for spontaneous abortions (RR 0.48, 95% CI 0.04 to 5.22; 311 participants), still births (RR 2.63, 95% CI 0.86 to 8.08; 311

participants) or congenital malformations (RR 3.82, 95% CI 0.43 to 33.83; 311 pregnant women). However, the trial was significantly underpowered to evaluate these outcomes.

Adherence

In their RCT, Davis 1996 reported on any measure of adherence to the drug regimen assessed by pill count and direct questioning. Reported adherence was 100% in both arms.

Comparison 2: Mefloquine versus doxycycline

Description of studies

RCTs

Four RCTs, enrolling 1317 participants, reported on both efficacy and safety (Table 8). One was conducted in short-term travellers (Schlagenhauf 2003), two in military personnel (Arthur 1990; Ohrt 1997) and one in Kenyan children (Weiss 1995). The populations were described as non-immune (Arthur 1990; Schlagenhauf 2003), "largely" non-immune (Ohrt 1997) and semi-immune (Weiss 1995). Trial duration varied from four weeks to four months. The method for detecting malaria was unclear in two trials (Arthur 1990; Schlagenhauf 2003). Three studies conducted daily interviews with participants to monitor for adverse events (Arthur 1990; Ohrt 1997; Weiss 1995) and one used a participant self-reporting questionnaire (Schlagenhauf 2003).

None of the RCTs adequately described allocation concealment. Blinding of participants was adequately described in all but Weiss 1995; two trials did not adequately describe how outcome assessors were blinded (Arthur 1990; Schlagenhauf 2003). We also considered Ohrt 1997 and Schlagenhauf 2003 to be at high risk of selective outcome reporting because they did not report all collected data: Ohrt 1997 completed an exit questionnaire within the last month of the study, but did not report all results; Schlagenhauf 2003 collected data at baseline, twice before travel and once on return, but only presented data for participants "who completed questionnaires at recruitment and at least one of the follow up periods". All four studies collected information on adverse events actively and prospectively (Table 9). Schlagenhauf 2003 was funded by GlaxoSmithKline (manufacturer of atovaquone-proguanil) and Roche (manufacturer of mefloquine) and Ohrt 1997 was funded by Roche and Pfizer (manufacturers of doxycycline) but specified that "neither of the pharmaceutical companies that provided support played any role in the gathering, analysing or interpreting the data".

Cohort studies

We included 20 cohort studies that assessed and reported safety outcomes, in a total of 435,209 participants. Of these, 10 were conducted in short-term travellers (Goodyer 2011; Laver 2001; Lobel 2001; Meier 2004; Napoletano 2007; Philips 1996; Schwartz 1999; Sharafeldin 2010; Stoney 2016; Waner 1999), four in longer-term occupational travellers (Cunningham 2014; Korhonen 2007; Landman 2015; Tan 2017) and six in military personnel (Eick-Cost 2017; Saunders 2015; Shamiss 1996; Sonmez 2005; Terrell 2015; Tuck 2016); none included pregnant women. Most (17 cohort studies) used participant self-reported questionnaires to monitor adverse events.

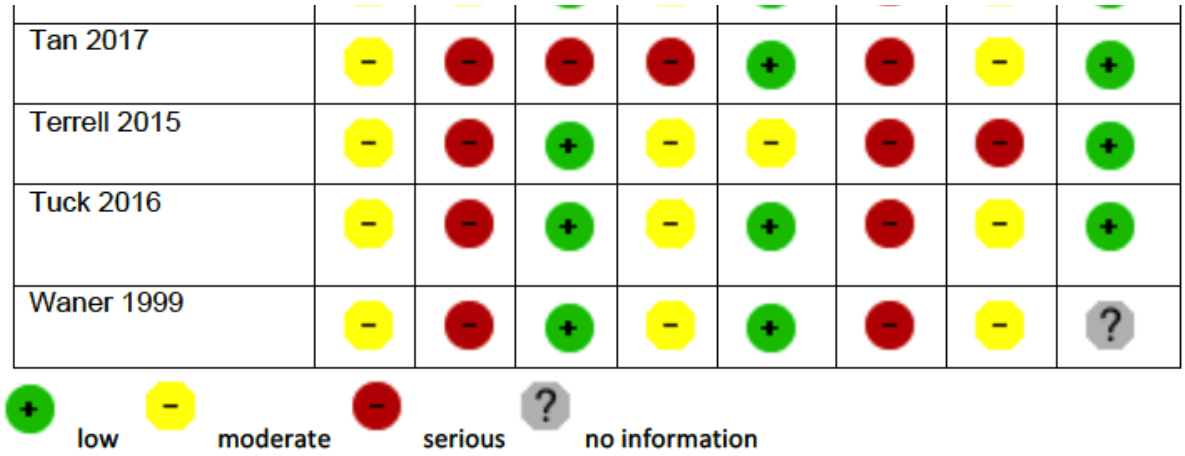
Ten cohort studies had non-response rates of over 20% (Cunningham 2014; Korhonen 2007; Landman 2015; Lobel 2001; Philips 1996; Sharafeldin 2010; Tan 2017; Terrell 2015; Tuck 2016; Waner 1999), (Figure 4). We judged two to be at high risk of missing data; Goodyer 2011 included pre- and post-travel questionnaires, with an interim loss to follow-up rate of 27%, and Terrell 2015 excluded participants from the analysis if they reported an adverse effect but did not record its impact on their ability to work. None of these studies blinded participants or mentioned outcome assessors being blinded to intervention status. Seven studies collected data retrospectively, and eight collected information at an unclear or variable time point during treatment (Table 9). One study (Goodyer 2011) was funded by GlaxoSmithKline (manufacturer of atovaquone-proguanil), one (Meier 2004) by Roche (manufacturer of mefloquine), and one (Philips 1996) by Roche and Pfizer (manufacturers of doxycycline) (see Figure 4).

Figure 4. 'Risk of bias' summary in cohort studies: mefloquine versus doxycycline [1]Assesses whether our pre-defined confounders are measured and balanced across groups.
[2]Assesses the non-response rate of prospective participants.
[3]Assesses the risk that participants labelled as taking mefloquine (or another antimalarial) actually took something else.
[4]Assesses the risk that participants whose adverse effects are attributed to mefloquine (or another antimalarial) actually took another drug as well.
[5]Assesses whether outcome data reasonably complete for most participants and whether intervention status reasonably complete for those in whom it was sought.
[6]Assesses whether the outcome measure was subjective, and whether participants and outcome assessors were blinded.
[7]Assesses whether it is clear that all information collected within the study has been reported.

[8]Assesses the risk of bias due to influence by a corporate study sponsor.

	Confounding[1]	Selection of participants[2]	Measurement of interventions[3]	Departures from intended interventions[4]	Missing data[5]	Measurement of outcomes[6]	Selection of the reported result[7]	Other[8]
Cunningham 2014	−	−	−	−	+	−	+	?
Eick-Cost 2017	−	+	−	−	+	−	+	?
Goodyer 2011	−	−	+	−	−	−	−	−
Korhonen 2007	−	−	−	−	+	−	+	+
Landman 2015	−	−	−	−	+	−	+	?
Laver 2001	−	−	+	−	+	−	−	+
Lobel 2001	−	−	+	−	+	−	−	?
Meier 2004	−	+	−	−	+	−	+	−
Napoletano 2007	−	−	−	+	+	−	+	?
Philips 1996	−	−	+	−	+	−	−	−
Saunders 2015	−	+	−	−	+	−	−	?
Schwartz 1999	−	−	−	+	−	−	−	?
Shamiss 1996	−	+	+	+	+	−	−	?
Sharafeldin 2010	−	−	−	−	+	−	−	+
Stoney 2016	−	−	+	−	+	−	−	+
Tan 2017	−	−	−	−	+	−	−	+

Figure 4. (Continued)



Efficacy

Only seven episodes of malaria were reported while participants were receiving prophylaxis; similar numbers of participants were infected in both arms (4 episodes in 378 mefloquine users versus 3 episodes in 366 doxycycline users: RR 1.35, 95% CI 0.35 to 5.19; 4 trials, 744 participants, Analysis 2.1).

Weiss 1995 reported on episodes of parasitaemia in the semi-immune population. There was no clear difference between groups (RR 1.47, 95% CI 0.68 to 3.14; 62 participants).

Safety

Serious adverse events or effects

Only Ohrt 1997 described an adverse event as "serious" (acute hysteria) in a doxycycline user, but did not provide sufficient detail to meet our definition. No other serious adverse outcomes were described in RCTs including 348 mefloquine users and 334 doxycycline users (Analysis 2.2; Table 6).

In comparison, three cohort studies reported a total of 29 serious adverse effects (attributed to the study drug by users): 19 in 2125 mefloquine users, and 10 in 1597 doxycycline users (RR 1.53, 95% CI 0.23 to 10.24; 3 cohort studies, 3722 participants; Analysis 2.2, Table 7).

Serious adverse effects in mefloquine users were psychological (4 cases) or due to dizziness (3), heart palpitations (2), limb numbness (1), abdominal pain (1), visual disturbance (1), yeast infection (1), passing out (2), seizure (1) and three hospitalizations with "either gastrointestinal or neurologic symptoms". In contrast, serious adverse effects in doxycycline users were due to gastrointestinal disturbance (6), anaemia (1), photosensitivity (1), oesophagitis (1) and cough (1).

In addition, a cohort study (Lobel 2001) reported on hospitalizations in users of mefloquine and doxycycline which were not necessarily attributed to the drug regimen (adverse events). There were eight hospitalizations in 3703 mefloquine users, and none in 69 doxycycline users, with no statistically significant difference between groups (RR 0.32, 95% CI 0.02 to 5.51; 3772 participants, Table 6).

Discontinuations due to adverse effects

There were no overall differences between groups in numbers of discontinuations due to adverse effects in the RCTs (8/391 mefloquine users, 8/382 doxycycline users, RR 1.08, 95% CI 0.41 to 2.87; 4 RCTs, 773 participants, Analysis 2.3) or cohort studies (852/6116 mefloquine users, 378/4049 doxycycline users, RR 0.92, 95% CI 0.54 to 1.55; 10 cohort studies, 10,165 participants, Analysis 2.3). However, heterogeneity among cohort studies was high (I^2 statistic = 85%).

Prespecified adverse outcomes

Prespecified adverse effects (attributed to the study drug) were only reported by cohort studies conducted in long-term occupational travellers (3 studies) and military personnel (3 studies). These form our primary analysis (see Appendix 3 for decision tree).

One RCT in military personnel (Ohrt 1997) and one cohort study in short-term international travellers (Philips 1996) reported on all symptoms experienced by participants while taking the study drug (adverse events). Two large retrospective analyses of health records in general practice (Meier 2004) and USA military personnel (Eick-Cost 2017) databases compared rates of incident neurological or psychological diagnoses in participants who had received a prescription for mefloquine or doxycycline (adverse events).

Gastrointestinal symptoms

Across the cohort studies reporting adverse effects, mefloquine users were less likely to report nausea (RR 0.37, 95% CI 0.30 to 0.45; 5 cohort studies, 2683 participants, Analysis 2.4), vomiting (RR 0.18, 95% CI 0.12 to 0.27; 4 cohort studies, 5071 participants, Analysis 2.5), abdominal pain (RR 0.30, 95% CI 0.09 to 1.07; 4 cohort studies, 2569 participants, Analysis 2.6) and diarrhoea (RR 0.28, 95% CI 0.11 to 0.73; 5 cohort studies, 5104 participants, Analysis 2.7).

However, this finding was not consistent across study types. In the single RCT in military personnel that reported adverse events, no differences were demonstrated for nausea, vomiting, abdominal pain or diarrhoea. In the single cohort study in short-term international travellers reporting adverse events, mefloquine users were more likely to report nausea and diarrhoea; there was

no difference between groups for abdominal pain (Analysis 2.4; Analysis 2.5; Analysis 2.6; Analysis 2.7).

Dyspepsia was consistently more common in doxycycline users but there was substantial heterogeneity in the size of this effect (RR 0.26, 95% CI 0.09 to 0.74; 5 cohort studies, 5104 participants, I^2 statistic = 77%, Analysis 2.8)

Neurological symptoms

In the cohort studies reporting adverse effects, no difference was demonstrated for headache (RR 1.21, 95% CI 0.50 to 2.92; 5 cohort studies, 3322 participants, Analysis 2.9) or dizziness (RR 3.49, 95% CI 0.88 to 13.75; 5 cohort studies, 2633 participants, Analysis 2.10).

In the RCT in military personnel (Ohrt 1997) and a cohort study in short-term international travellers (Philips 1996) both headache and dizziness were more common in mefloquine users. However, a large retrospective analysis of health records in military personnel (Eick-Cost 2017) found higher rates of dizziness in doxycycline users (Analysis 2.9; Analysis 2.10).

Psychological symptoms

In the cohort studies reporting adverse effects, mefloquine users were more likely to report abnormal dreams (RR 10.49, 95% CI 3.79 to 29.10; 4 cohort studies, 2588 participants, Analysis 2.11), insomnia (RR 4.14, 95% CI 1.19 to 14.44; 4 cohort studies, 3212 participants, Analysis 2.12), anxiety (RR 18.04, 95% CI 9.32 to 34.93; 3 cohort studies, 2559 participants, Analysis 2.13) and depressed mood (RR 11.43, 95% CI 5.21 to 25.07; 2 cohort studies, 2445 participants, Analysis 2.14). There were 15 episodes of abnormal thoughts and perceptions with mefloquine and none with doxycyline in cohort studies reporting adverse effects (RR 6.60, 95% CI 0.92 to 47.20; 2 cohort studies, 2445 participants, Analysis 2.15).

The findings of the single cohort study in short-term international travellers reporting adverse events (Philips 1996) were consistent with this. However in the single RCT (Ohrt 1997) and the large retrospective healthcare record analyses, there were either no differences between groups, or doxycycline users were more likely to experience psychological symptoms (Analysis 2.11; Analysis 2.12; Analysis 2.13; Analysis 2.14; Analysis 2.15).

Other prespecified symptoms

Pruritis was more common in doxycycline users in cohort studies reporting adverse effects (RR 0.52, 95% CI 0.30 to 0.91; 2 cohort studies, 1794 participants, Analysis 2.16), but more common with mefloquine in the single cohort in short-term travellers reporting adverse events (RR 2.69, 95% CI 0.93 to 7.78; 1 cohort study, 668 participants).

In cohort studies reporting adverse effects, photosensitivity was more common in doxycycline users (RR 0.08, 95% CI 0.05 to 0.11; 2 cohort studies, 1875 participants, Analysis 2.17), as was vaginal yeast infection in female participants (RR 0.10, 95% CI 0.06 to 0.16; 1 cohort study, 1761 participants, Analysis 2.18). The findings of the single cohort study in short-term travellers reporting adverse events were consistent with this finding (Analysis 2.17; Analysis 2.18).

Visual impairment was more commonly reported among mefloquine users (RR 2.37, 95% CI 1.41 to 3.99; 2 cohort studies, 1875 participants; Analysis 2.19).

Other adverse events and effects

A range of other adverse effects were reported by the cohort studies. These included alopecia (hair loss), asthenia (physical weakness), balance disorder, decreased appetite, fatigue, hypoaesthesia (numbness), malaise, mouth ulcers, palpitations and tinnitus (Analysis 2.20). Mefloquine users were more likely to report alopecia (RR 3.44, 95% CI 1.96 to 6.03; 2 cohort studies, 1875 participants), unsteadiness (RR 2.87, 95% CI 1.48 to 5.59; 1 cohort study, 1761 participants) and limb numbness (RR 11.48, 95% CI 3.01 to 43.70; 2 cohort studies, 2445 participants), but were less likely to report malaise (RR 0.28, 95% CI 0.11 to 0.71; 1 cohort study, 734 participants).

Additional adverse events reported in the RCT and cohort studies are presented in Analysis 2.21 and Analysis 2.22 respectively. In Eick-Cost 2017, a large retrospective healthcare record analysis in USA military personnel that reported adverse events, mefloquine users were less likely than doxycycline users to receive formal medical diagnoses of adjustment disorder (RR 0.43, 95% CI 0.40 to 0.45; 354,959 participants), convulsions (RR 0.58, 95% CI 0.45 to 0.75), hallucinations (RR 0.18, 95% CI 0.08 to 0.45), post-traumatic stress disorder (PTSD) (RR 0.58, 95% CI 0.53 to 0.64), suicidal ideation (RR 0.38, 95% CI 0.31 to 0.47), and tinnitus (RR 0.65, 95% CI 0.61 to 0.71). There were no differences in overall rates of suicide in the large retrospective healthcare record analyses (4/53,029 mefloquine users and 15/322,995 doxycycline users; RR 1.21, 95% CI 0.32 to 4.56, Analysis 2.22).

Studies reporting groups of symptoms or other outcomes that could be used as proxy markers of psychological or neurological adverse effects are reported in Appendix 5.

Adherence

Arthur 1990, an RCT, performed serological assays to assess adherence. Arthur 1990 reported measurable serum drug levels at the end of the trial in 87% of 119 military personnel prescribed doxycycline and 92% of 134 who were prescribed mefloquine. However, medication was administered under the supervision of each participant's squad leader.

Thirteen cohort studies compared the proportion of participants with 100% self-reported adherence and found higher rates of adherence during travel in mefloquine users (RR 1.15, 95% CI 1.12 to 1.18; 13 cohort studies, 15,583 participants, Analysis 2.23), but no differences between groups in the post-travel period (RR 1.08, 95% CI 0.95 to 1.22; 4 cohort studies, 840 participants, Analysis 2.23). Most (77%) mefloquine users described themselves as adherent during travel (range 24% to 100%), compared to 63% of doxycycline users (range 37% to 92%). In the post-travel period this dropped to 55% of mefloquine users (range 50% to 87%) and 51% of doxycycline users (range 27% to 75%). There was no difference in the results when the analysis was limited to short-term international travellers (RR 1.11, 95% CI 1.06 to 1.17; 4 cohort studies; 8390 participants).

Comparison 3: Mefloquine versus atovaquone-proguanil

Description of studies

RCTs

Two RCTs in non-immune travellers reported efficacy, with most participants visiting sub-Saharan Africa for fewer than three weeks (Overbosch 2001; Schlagenhauf 2003). Efficacy was assessed by testing for antibodies to a circumsporozoite protein four weeks after travel in the study by Overbosch 2001, and the method was unclear in Schlagenhauf 2003.

Three RCTs (Overbosch 2001; Schlagenhauf 2003; van Riemsdijk 2002), and 16 cohort studies (Andersson 2008; Belderok 2013; Cunningham 2014; Eick-Cost 2017; Goodyer 2011; Kato 2013; Korhonen 2007; Kuhner 2005; Landman 2015; Laverone 2006; Napoletano 2007; Schneider 2013; Sharafeldin 2010; Stoney 2016; Tan 2017; Tuck 2016) assessed and reported safety outcomes (Table 10).

Two RCTs included adults and children aged ≥ 3 years (Overbosch 2001; van Riemsdijk 2002); all other studies were restricted to adults. The RCTs described participants as non-immune travellers, and most participants visited sub-Saharan Africa for fewer than three weeks. The cohort studies included short-term travellers (Belderok 2013; Goodyer 2011; Kato 2013; Kuhner 2005; Laverone 2006; Napoletano 2007; Schneider 2013; Sharafeldin 2010; Stoney 2016), longer-term occupational travellers (Cunningham 2014; Korhonen 2007; Landman 2015; Tan 2017) and military personnel (Andersson 2008; Eick-Cost 2017; Tuck 2016).

All three RCTs that assessed and reported safety outcomes collected information on adverse events actively and prospectively, and predefined harms using standardized and precise definitions (Overbosch 2001; Schlagenhauf 2003; van Riemsdijk 2002; Table 11). Only Overbosch 2001 performed a blinded assessment of whether there was a reasonable possibility that each adverse event was caused by the study drug (adverse effects). Overbosch 2001 was funded by GlaxoSmithKline (manufacturer of atovaquone-proguanil) and Schlagenhauf 2003 received funding from both GlaxoSmithKline and Roche (manufacturers of mefloquine).

Cohort studies

In the cohort studies, safety was assessed by self-reported questionnaires (Andersson 2008; Belderok 2013; Cunningham 2014; Goodyer 2011; Kato 2013; Korhonen 2007; Kuhner 2005; Landman 2015; Laverone 2006; Sharafeldin 2010; Stoney 2016; Tan 2017; Tuck 2016), telephone interview (Napoletano 2007), and retrospective analysis of a healthcare records (Eick-Cost 2017; Schneider 2013). Seven studies collected adverse event data retrospectively and six collected these data at an unclear or variable time point during treatment (Table 11). One study (Goodyer 2011) was funded by GlaxoSmithKline (manufacturer of atovaquone-proguanil) and one (Schneider 2013) was funded by Roche (manufacturer of mefloquine) (Figure 5).

Figure 5. 'Risk of bias' summary in cohort studies: mefloquine versus atovaquone-proguanil [1]Assesses whether our pre-defined confounders are measured and balanced across groups.
[2]Assesses the non-response rate of prospective participants.
[3]Assesses the risk that participants labelled as taking mefloquine (or another antimalarial) actually took something else.
[4]Assesses the risk that participants whose adverse effects are attributed to mefloquine (or another antimalarial) actually took another drug as well.
[5]Assesses whether outcome data reasonably complete for most participants and whether intervention status reasonably complete for those in whom it was sought.
[6]Assesses whether the outcome measure was subjective, and whether participants and outcome assessors were blinded.
[7]Assesses whether it is clear that all information collected within the study has been reported.

[8]Assesses the risk of bias due to influence by a corporate study sponsor.

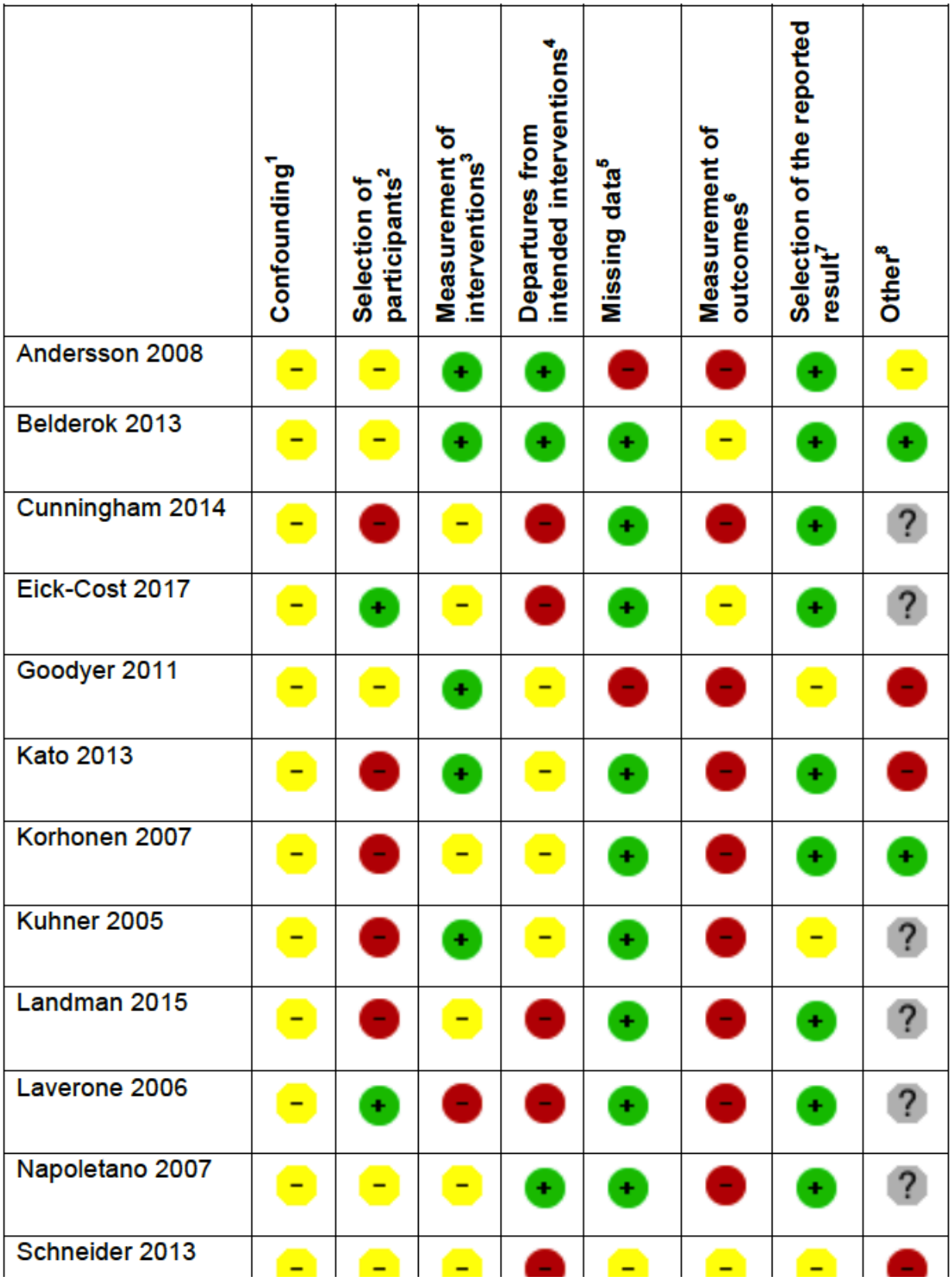
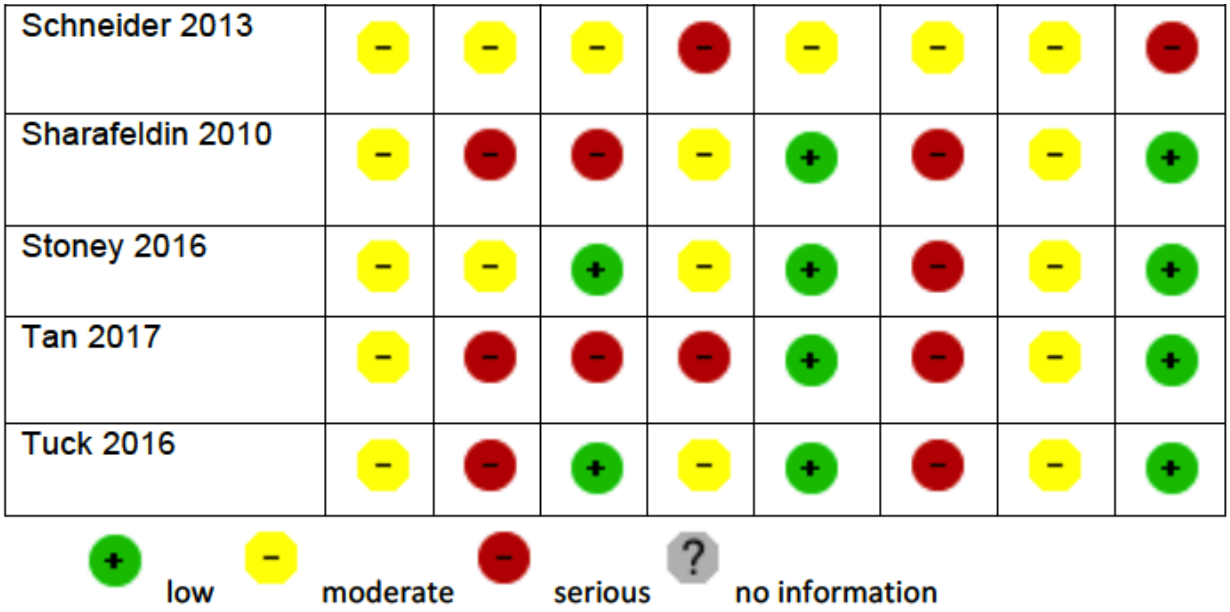


Figure 5. (Continued)



Efficacy

No clinical cases of malaria were recorded (2 RCTs, 636 mefloquine users; 657 atovaquone-proguanil users).

Safety

Serious adverse events or effects

Overbosch 2001, an RCT, reported 10 serious adverse events in 483 participants who received mefloquine and four in 493 participants who received atovaquone-proguanil. None were considered attributable to the drug regimen (Table 6).

Three cohort studies reported a total of 15 serious adverse effects (attributed by participants to the study drug) in 2651 mefloquine users (Table 7). There were no serious adverse effects reported in participants who received atovaquone-proguanil (940 users). The difference between groups was not statistically significant (RR 1.40, 95% CI 0.08 to 23.22; 3 cohort studies, 3591 participants, Analysis 3.2).

The serious adverse effects in mefloquine users were: psychological (4 cases), dizziness (3), heart palpitations (2), limb numbness (1), abdominal pain (1), visual disturbance (1), yeast infection (1), and passing out (2).

Discontinuations due to adverse effects

In the RCTs, participants who received mefloquine were more likely to discontinue their medication due to adverse effects than participants who took atovaquone-proguanil (39/714 mefloquine versus 13/724 atovaquone-proguanil; RR 2.86, 95% CI 1.53 to 5.31; 3 RCTs, 1438 participants, Analysis 3.3).

The overall effect size was similar in the cohort studies (RR 2.73, 95% CI 1.83 to 4.08; 9 cohort studies, 7785 participants, Analysis 3.3).

Prespecified adverse effects

Gastrointestinal symptoms

Mefloquine users were more likely to report nausea than atovaquone-proguanil users with similar effect sizes in the RCT (RR 2.72, 95% CI 1.52 to 4.86; 976 participants) and overall in the cohort studies (RR 2.50, 95% CI 1.54 to 4.06; 7 cohort studies, 3509 participants, Analysis 3.4). There were no consistent differences in the frequency of reported vomiting (Analysis 3.5), abdominal pain (Analysis 3.6) or diarrhoea (Analysis 3.7). Mouth ulcers were less commonly reported with mefloquine in cohort studies (RR 0.12, 95% CI 0.04 to 0.37; 2 cohort studies, 783 participants), but not in the RCT (RR 1.45, 95% CI 0.70 to 3.00; 976 participants; Analysis 3.8).

Neurological symptoms

Mefloquine users were more likely to report headache although this did not reach standard levels of statistical significance in the RCT (RR 1.72, 95% CI 0.99 to 2.99; 976 participants). The effect was larger and consistent across the cohort studies (RR 3.42, 95% CI 1.71 to 6.82; 8 cohort studies, 4163 participants, I^2 statistic = 0%, Analysis 3.9). Similarly, dizziness was more common in mefloquine users in the RCT (RR 3.99, 95% CI 2.08 to 7.64) and consistently more common in the cohort studies (RR 3.83, 95% CI 2.23 to 6.58; 8 cohort studies, 3986 participants, Analysis 3.10). The same trend was seen in the retrospective healthcare record analyses, although the effect size was smaller (RR 1.23, 95% CI 1.04 to 1.46; 49,419 participants).

Psychological symptoms

In the RCT, mefloquine users were more likely than atovaquone-proguanil users to report abnormal dreams (RR 2.04, 95% CI 1.37 to 3.04), insomnia (RR 4.42, 95% CI 2.56 to 7.64), anxiety (RR 6.12, 95% CI 1.82 to 20.66) and depressed mood (RR 5.78, 95% CI 1.71 to 19.61; 976 participants) (Overbosch 2001). Consistent, larger effects were seen in the cohort studies: abnormal dreams (RR 6.81, 95% CI 1.65 to 28.15; 7 cohort studies, 3848 participants, Analysis 3.11), insomnia (RR 7.29, 95% CI 4.37 to 12.16; 8 cohort studies, 3986 participants, Analysis 3.12), anxiety (RR 10.10, 95% CI 3.48 to 29.32;

4 cohort studies, 2664 participants, Analysis 3.13) and depressed mood (RR 8.02, 95% CI 3.56 to 18.07; 6 cohort studies, 3624 participants, Analysis 3.14). In addition, 21 mefloquine users and no atovaquone-proguanil users reported abnormal thoughts or perceptions, but the difference between groups was not statistically significant (RR 1.50, 95% CI 0.30 to 7.42; 3 cohort studies, 2441 participants, Analysis 3.15).

Consistent effects were seen in the retrospective healthcare record analysis (adverse events, Eick-Cost 2017) although the effect size was smaller.

Other prespecified adverse symptoms

No differences were demonstrated for pruritis (1 RCT, 3 cohort studies; Analysis 3.16); or visual impairment (1 RCT, 2 cohort studies; Analysis 3.17).

Other adverse outcomes

Other adverse effects reported in more than 1% of study participants in cohort studies (in either study arm) included: allergic reaction, alopecia (hair loss), asthenia (weakness), balance disorder, cough, disturbance in attention, dyspepsia, fatigue, hypoaesthesia, loss of appetite, muscle pain, palpitation, photosensitization, pyrexia, rash, restlessness, slight illness, somnolence, tinnitus and circulatory disorders (Analysis 3.18). Mefloquine users were more likely to report concentration difficulties (RR 4.45, 95% CI 1.84 to 10.77; 3 cohort studies, 1363 participants).

In the large retrospective healthcare record analyses which reported adverse events, mefloquine users were more likely to receive formal medical diagnoses of adjustment disorder (RR 1.76, 95% CI 1.54 to 2.02; 49,419 participants, Analysis 3.19), PTSD (RR 2.51, 95% CI 1.93 to 3.26; Analysis 3.19), suicidal ideation (RR 1.69, 95% CI 1.03 to 2.77; Analysis 3.19) and tinnitus (RR 1.42, 95% CI 1.21 to 1.68; Analysis 3.19). However, users were less likely to experience hallucinations (RR 0.25, 95% CI 0.08 to 0.79; Analysis 3.19).

Studies reporting groups of symptoms, or other outcomes which could be used as proxy markers of psychological or neurological adverse effects, are reported in Appendix 6.

Adherence

van Riemsdijk 2002 monitored adherence through reference to the participants' diary cards and counts of returned study medication. It was found that 93% of mefloquine users were completely adherent, compared to 98.3% of atovaquone-proguanil users (RR 0.95, 95% CI 0.88 to 1.02; 1 RCT, 119 participants, Analysis 3.20).

Overbosch 2001 defined participants as adherent if they took at least 80% of prescribed doses. Overbosch 2001 also found no difference between the groups during travel (RR 0.98, 95% CI 0.95 to 1.01; 966 participants; Analysis 3.20). However, analysis in the post-travel period found that mefloquine users were less likely to complete the regimen (RR 0.80, 95% CI 0.74 to 0.85; 966 participants); 93% of mefloquine users were adherent during travel, dropping to 70% in the post-travel period, compared to 95% and 88% for atovaquone-proguanil.

Six cohort studies compared the proportion of participants with 100% self-reported adherence and found no difference during travel (RR 1.08, 95% CI 0.86 to 1.34; 6 cohort studies, 5577 participants, Analysis 3.21) or in the post-travel period (RR 0.89, 95% CI 0.64 to 1.23; 2 cohort studies, 422 participants, Analysis 3.21). In these studies, 60% of mefloquine users described themselves as adherent during travel, dropping to 51% in the post-travel period, compared to 53% and 62% respectively for people who took atovaquone-proguanil.

Belderok 2013 categorized travellers as adherent if they took at least 75% of prescribed doses. Belderok 2013 reported higher rates of adherence in participants who took mefloquine both during and after travel. Meta-analysis of these results did not result in a significant difference (during travel: RR 1.04, 95% CI 0.77 to 1.40; 5 cohort studies, 2810 participants, post-travel: RR 1.07, 95% CI 0.72 to 1.59; 3 cohort studies, 941 participants).

Pregnancy outcomes

One cohort study included respondents who were pregnant (Cunningham 2014) but did not report which prophylaxis the women took or on any outcomes related to pregnancy.

Mefloquine versus chloroquine

Description

RCTs

We included five RCTs comparing mefloquine with chloroquine that reported on efficacy and six on safety (Table 12). Trials were conducted in immune or semi-immune adult populations in the Ivory Coast (Sossouhounto 1995), Malawi (Steketee 1996), Nigeria (Salako 1992) Thailand (Boudreau 1991; Bunnag 1992) and the USA. (Boudreau 1993). The Malawi trial by Steketee 1996 was limited to pregnant women. None included non-immune travellers or children. All six trials used interview with study personnel to obtain information about adverse events. Boudreau 1993 excluded participants with a history of psychiatric or neurological problems.

None of the trials adequately described random sequence generation or allocation concealment. Participants were adequately blinded in four trials (Boudreau 1993; Bunnag 1992; Salako 1992; Sossouhounto 1995), the trial in pregnant women did not blind participants or outcome assessors (Steketee 1996). We judged three of the trials to be at high risk of selective reporting of safety outcomes. Bunnag 1992 was funded by Roche (manufacturer of mefloquine). Five trials actively sought information on adverse events (Boudreau 1991; Boudreau 1993; Bunnag 1992; Salako 1992; Steketee 1996) and all collected information prospectively (Table 13).

Cohort studies

We included 15 cohort studies in this comparison; 12 included short-term travellers (Albright 2002; Corominas 1997; Hill 2000; Laver 2001; Laverone 2006; Lobel 2001; Napoletano 2007; Petersen 2000; Rietz 2002; Steffen 1993; Stoney 2016; Waner 1999) and three longer-term occupational travellers (Cunningham 2014; Korhonen 2007; Tan 2017) (Table 12). Albright 2002 included only children. Twelve studies used participant-self reported questionnaires to collect information about adverse events; three of these, including the largest study (Steffen 1993, 145,003 participants), collected information from travellers flying back to Europe from Africa. The remaining three studies collected information through interviews with study personnel (Albright 2002; Hill 2000; Napoletano 2007)

Eight of the cohort studies had non-response rates of over 20% (Figure 6). We judged 14 cohort studies to be at low risk of missing data, the largest study (Steffen 1993) was at moderate risk due to a 15% loss to follow-up between the first and second questionnaire in the second phase of the study. Steffen 1993 did not report on non-serious adverse effects from the first phase of the study (44,677 participants) and was funded by Roche (manufacturer of mefloquine). Six studies collected information about adverse events at set time points (Corominas 1997; Hill 2000; Napoletano 2007; Petersen 2000; Rietz 2002; Stoney 2016; Tan 2017), and one collected information prospectively (Stoney 2016) (Table 13; Figure 6).

Figure 6. 'Risk of bias' summary in cohort studies: mefloquine versus chloroquine [1]Assesses whether our pre-defined confounders are measured and balanced across groups.
[2]Assesses the non-response rate of prospective participants.
[3]Assesses the risk that participants labelled as taking mefloquine (or another antimalarial) actually took something else.
[4]Assesses the risk that participants whose adverse effects are attributed to mefloquine (or another antimalarial) actually took another drug as well.
[5]Assesses whether outcome data reasonably complete for most participants and whether intervention status reasonably complete for those in whom it was sought.
[6]Assesses whether the outcome measure was subjective, and whether participants and outcome assessors were blinded.
[7]Assesses whether it is clear that all information collected within the study has been reported.

[8]Assesses the risk of bias due to influence by a corporate study sponsor.

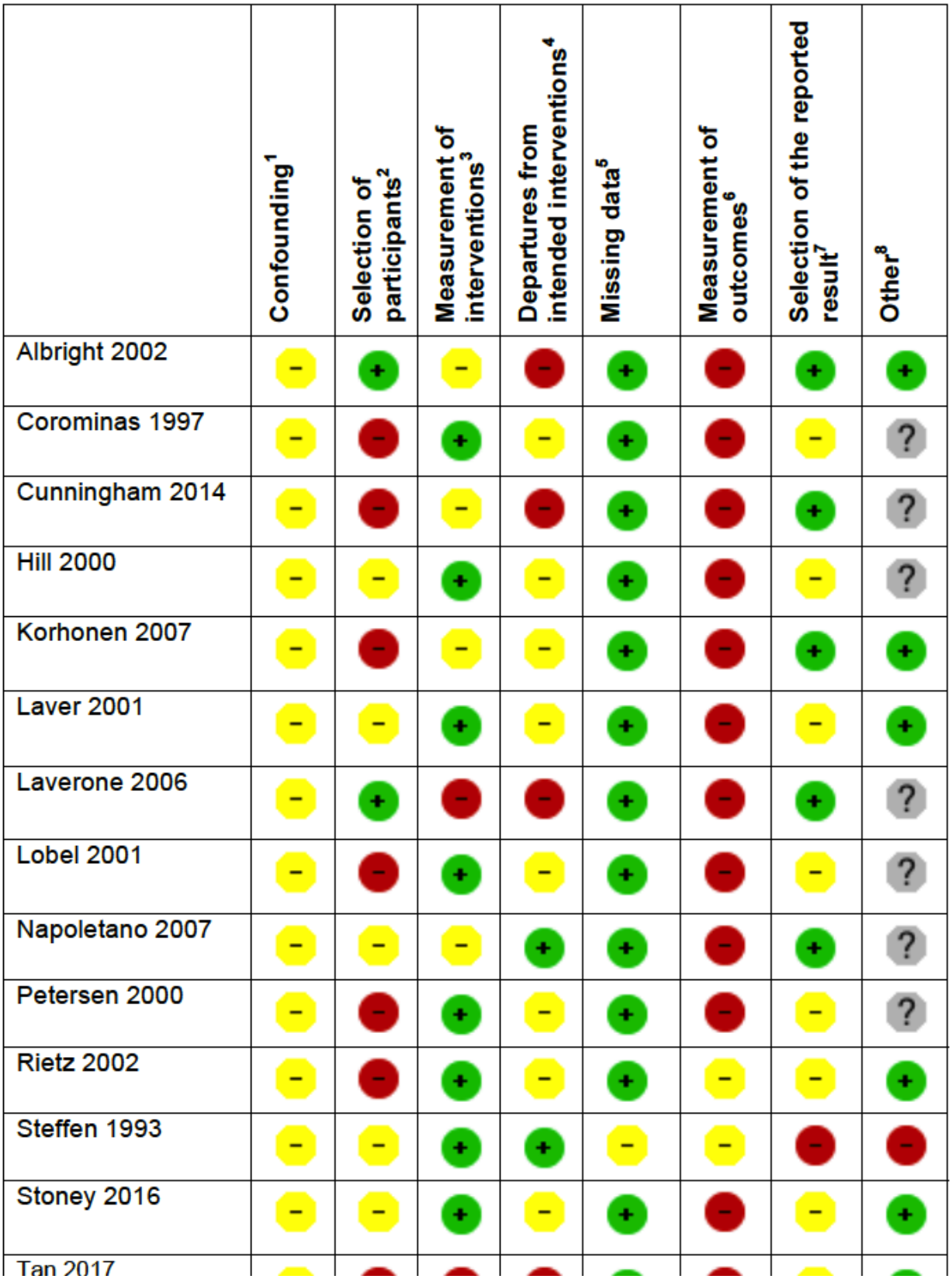
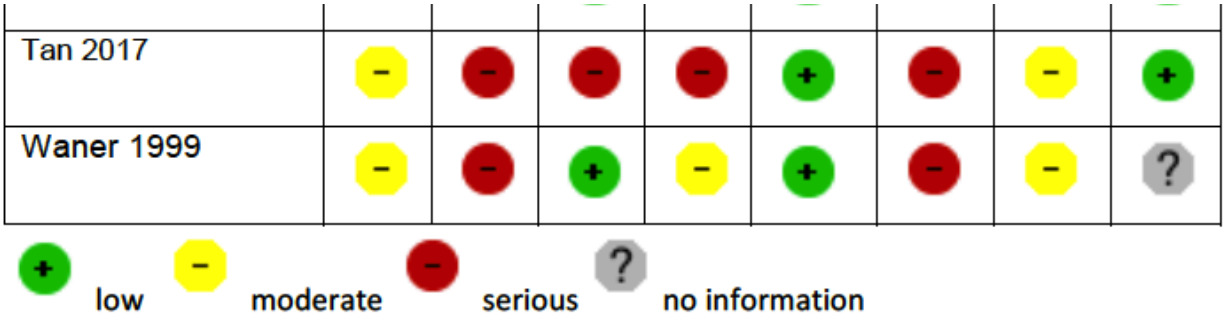


Figure 6. (Continued)



Efficacy

Participants who took mefloquine were less likely to experience malaria than participants who took chloroquine (RR 0.38, 95% CI 0.28 to 0.52; 4 RCTs, 877 participants, Analysis 4.1). However, two RCTs were conducted in settings with known chloroquine resistance at the study sites, and the other two reported no episodes of malaria in either study arm. All RCTs included semi-immune populations, and were conducted over 20 years ago.

Safety

Serious adverse events or effects

Across four RCTs, two serious adverse events were reported in 529 mefloquine users and none in 471 chloroquine users; the difference between groups was not significant (RR 2.77, 95% CI 0.32 to 23.85; 5 RCTs, 1000 participants, Analysis 4.2, Table 6). Both events were psychiatric admissions due to depression and suicidal thoughts; both study participants had previous psychiatric histories. In one case, the participant's psychiatrist did not think the event was drug-related, and in the other "felt this individual's current depression was not drug related, unless it was aggravated by inability to sleep". Additionally, Steketee 1996 described one withdrawal due to a "neuropsychiatric side effect" (disorientation to time and place) but did not provide enough detail to meet our definition of serious adverse event or effect.

Four cohort studies reported a total of 29 serious adverse effects (attributed by users to the study drug) in 56,674 mefloquine users, and 13 serious adverse effects in 22,583 chloroquine users. The difference between groups was not statistically significant (RR 1.14, 95% CI 0.62 to 2.07; 6 cohort studies; 79,257 participants; Analysis 4.2). Serious side effects in mefloquine users were psychological (11 cases), dizziness (5), seizures (3), heart palpitations (2), abdominal pain (1), blackout (2), visual disturbance (1), limb numbness (1), yeast infection (1), and two which were not described (Table 7). Those in chloroquine users were psychological (4 cases), seizures (3), abdominal pain (1) and visual disturbance (1).

Discontinuations of the study drug due to adverse effects

There was no differences between groups in the number of discontinuations due to adverse effects in the RCTs (RR 1.60, 95% CI 0.61 to 4.18; 3 RCTs, 815 participants, Analysis 4.3) or cohort studies in short-term international travellers (RR 0.99, 95% CI 0.78 to 1.26; 6 cohort studies, 55,397 participants, Analysis 4.3). However, in the two cohort studies in longer-term occupational travellers, mefloquine users were significantly more likely to stop taking medication (RR 2.97, 95% CI 2.41 to 3.66; 2 cohort studies; 6085 participants; Analysis 4.3).

Prespecified adverse effects

The RCTs only reported adverse events (all symptoms without assessing whether they might be related to the study drug). Our primary analysis was therefore taken from the six cohort studies reporting adverse effects.

Gastrointestinal symptoms

There were no consistent differences between groups for nausea (RR 1.23, 95% CI 0.89 to 1.68; I^2 statistic = 78%, 6 cohort studies, 58,984 participants, Analysis 4.4), vomiting (RR 1.05, 95% CI 0.78 to 1.40; 5 cohort studies, 5577 participants, Analysis 4.5) or abdominal pain (RR 0.99, 95% CI 0.80 to 1.22; 4 cohort studies, 5440 participants; Analysis 4.6). This was consistent with adverse events reported by RCTs (Analysis 4.4; Analysis 4.5; Analysis 4.6)

Overall, mefloquine users were less likely to report diarrhoea but this finding was from a single cohort study with over 90% of the weight in the meta-analysis (RR 0.84, 95% CI 0.74 to 0.95; 5 cohort studies, 5577 participants; Analysis 4.7). No difference was seen in the RCTs (Analysis 4.7).

Neurological symptoms

In the cohort studies, there was no substantial difference between groups in the proportion of participants reporting headache (RR 0.84, 95% CI 0.53 to 1.34; 6 cohort studies, 56,998 participants, Analysis 4.8), but mefloquine users reported more dizziness (RR 1.51, 95% CI 1.34 to 1.70; 5 cohort studies, 56,710 participants; Analysis 4.9). The RCTs reporting adverse events did not demonstrate a difference between groups (Analysis 4.8; Analysis 4.9).

Psychological symptoms

Across the cohort studies, mefloquine users were more likely to report abnormal dreams (RR 1.21, 95% CI 1.10 to 1.33; 4 cohort studies, 2845 participants, Analysis 4.10), anxiety (RR 6.30, 95% CI 4.37 to 9.09; 3 cohort studies, 3408 participants, Analysis 4.12), depressed mood (RR 3.14, 95% CI 1.15 to 8.57; I^2 statistic = 90%; 5 cohort studies, 58,855 participants, Analysis 4.13) and abnormal thoughts or behaviour (RR 5.49, 95% CI 2.65 to 11.35; 4 cohort studies, 4831 participants, Analysis 4.14). Of these outcomes only abnormal dreams was reported by RCTs and the result was consistent with the cohort studies (Analysis 4.10). Insomnia was reported by five cohort studies (RR 1.81, 95% CI 0.73 to 4.51; 5 cohort studies, 56952 participants) and two RCTs (RR 1.19, 95% CI

0.76 to 1.84; 2 RCTs, 359 participants), and no consistent differences were seen between groups (Analysis 4.11).

Other prespecified adverse symptoms

There were no consistent differences demonstrated in reported pruritis between groups in cohort studies (RR 1.13, 95% CI 0.92 to 1.40; 2 cohort studies; 55,544 participants) or RCTs (RR 0.28, 95% CI 0.03 to 2.93; 2 RCTs, 413 participants; Analysis 4.15). There were no differences in visual impairment in cohort studies (RR 1.10, 95% CI 0.50 to 2.44; I^2 statistic = 90%, 5 cohort studies, 58,847 participants), or in the single RCT (RR 0.14, 95% CI 0.01 to 2.63; 210 participants, Analysis 4.16).

Prespecified adverse symptoms restricted to cohort studies in short-term travellers

Analysis 4.18 presents the pre-specified adverse symptoms restricted to the cohort studies in short-term travellers.

Other adverse outcomes

Other adverse effects reported by cohort studies were alopecia (hair loss), asthenia, altered spatial perception, balance disorder, confusion, decreased appetite, fatigue, hypoaesthesia, irritability, mouth ulcers, paraesthesia, palpitation, photosensitization, restlessness, slight illness, somnolence and yeast infection (Analysis 4.19). Of note, single cohort studies found that mefloquine users were more likely to report altered spatial perception (RR 3.16, 95% CI 1.55 to 6.45; 2032 participants), unsteadiness (RR 3.59, 95% CI 2.15 to 6.00; 2137 participants), alopecia (RR 1.69, 95% CI 1.27 to 2.25; 2137 participants), limb numbness (RR 20.26, 95% CI 1.23 to 333.93; 2137 participants) and tingling (RR 2.22, 95% CI 1.27 to 3.89; 2 cohort studies, 2778 participants).

Other adverse events reported by RCTs were abdominal distension, anger, disturbance in attention, irritability, loss of appetite, malaise and altered mood (Analysis 4.20). No statistically significant differences were noted.

Pregnancy-related outcomes

One quasi-randomized trial (Steketee 1996) was conducted in pregnant Malawian women and reported no difference between mefloquine and chloroquine for spontaneous abortions (RR 0.80, 95% CI 0.36 to 1.79; 2334 participants), still births (RR 1.01, 95% CI 0.67 to 1.52; 2334 participants) or congenital malformations (0 events in either study arm, 2334 participants, Analysis 4.21). Steketee 1996 sequentially allocated participants to each drug regimen, and did not blind participants or study personnel.

Adherence

Three cohort studies in short-term travellers (Hill 2000; Laver 2001; Rietz 2002) compared the proportion of participants with 100% self-reported adherence and found no difference overall (RR 1.00, 95% CI 0.90 to 1.13; 3 cohort studies, 852 participants, Analysis 4.22). Among participants in these studies, 84% of mefloquine users described themselves as adherent during travel (range 71% to 88%) compared to 82% of chloroquine users (range 82% to 85%). In the two studies in longer-term occupational travellers, self-reported adherence was higher in mefloquine users (RR 2.02, 95% CI 1.80 to 2.26; 2 cohort studies, 5777 participants).

One study (Stoney 2016) measured adherence in the post-travel period and found no difference (RR 1.00, 95% CI 0.54 to 1.87; 46 participants, Analysis 4.22). However, rates of completion were low in both groups (56% in mefloquine users and 54% in chloroquine users).

Subgroup analyses

Given the similarity in adverse effect profiles for mefloquine compared to the two main alternatives (doxycycline and atovaquone-proguanil), we combined findings from the two comparisons and performed a series of subgroup analyses to explore the effects of study design, duration of travel, and military versus non-military participants.

Prespecified adverse effects

Study design

Only one RCT performed a blinded assessment of whether there was a reasonable possibility that any reported symptoms could be related to the study drug (Overbosch 2001). We compared this with participants self-reporting of adverse effects in cohort studies. The findings were largely consistent across study designs with mefloquine users experiencing higher rates of headache (Analysis 5.4), dizziness (Analysis 5.5), abnormal dreams (Analysis 5.6), insomnia (Analysis 5.7), anxiety (Analysis 5.8) and depressed mood (Analysis 5.9). Although the relative risk of psychiatric side effects was consistently slightly higher in cohort studies, in only one case was the test for subgroup differences statistically significant (abnormal dreams: RCT: RR 2.04, 95% CI 1.37 to 3.04; 976 participants, cohort studies: RR 7.30, 95% CI 2.51 to 21.18; 7 cohort studies, 4543 participants, test for subgroup differences P = 0.03).

Duration of travel

The relative risk of all psychological adverse effects was higher with longer-term travel than in short-term travel; insomnia (short-term RR 3.09 versus longer-term RR 8.67), anxiety (short-term RR 3.26 versus longer-term RR 18.05), depressed mood (short-term RR 2.52 versus longer-term RR 12.59) and abnormal thoughts and perceptions (short-term RR 1.29 versus longer-term RR 7.78) (Table 14). However, in only one case was the test for subgroup differences statistically significant (P range 0.02 to 0.40). This same effect was not observed with gastrointestinal symptoms (nausea, abdominal pain, diarrhoea) or neurological symptoms (headache, dizziness).

Military versus non-military participants

There were no significant differences in the relative risk of adverse effects between military and non-military participants (Table 15). Very few cohort studies in military personnel reported on our prespecified symptoms. In one of these in which military personnel who took mefloquine for 6 months or longer (Andersson 2008), the rates of psychological side effects were significantly higher than in short-term travellers, but not significantly different from other trials in longer-term travellers.

Adherence

Study design

Across cohort studies, self-reported complete adherence was slightly higher in participants who took mefloquine than in users of other antimalarial agents (RR 1.16, 95% CI 1.03 to 1.30; 11 cohort studies, 12131 participants, Analysis 5.13). However, there was no difference in self-reported completion of the treatment after return (RR 1.04, 95% CI 0.92 to 1.17; 4 cohort studies, 1221 participants, Analysis 5.14).

Duration of travel

Self-reported complete adherence was slightly higher in short-term travellers who took mefloquine than users of other antimalarial agents (RR 1.10, 95% CI 1.03 to 1.18; 7 cohort studies, 7241 participants). However, the same effect was not seen in longer-term travellers (RR 1.20, 95% CI 0.88 to 1.62; 4 cohort studies, 4890 participants, test for subgroup differences P = 0.61, Table 14).

There was no overall difference in rates of completing the treatment regimen after return in short-term travellers who took mefloquine than in those who received other antimalarial agents (RR 1.04, 95% CI 0.92 to 1.17; 4 cohort studies, 1221 participants). No studies in longer-term travellers monitored adherence after return.

Military versus non-military participants

There were no differences in self-reported complete adherence when comparing military versus non-military participants, either during travel or after return (Table 15).

DISCUSSION

Summary of main results

Mefloquine efficacy

We included 12 randomized controlled trials (RCTs) that compared mefloquine with placebo; none were performed in short-term international travellers, and most populations had a degree of immunity to malaria. The percentage of people developing a malaria episode in the control arm varied from 1% to 82% (median 22%) and in the mefloquine group 0% to 13% (median 1%).

In four other RCTs that directly compared mefloquine, atovaquone-proguanil and doxycycline in non-immune, short-term international travellers, only one clinical case of malaria occurred (*low certainty evidence*).

Mefloquine safety versus currently used alternatives

Serious adverse effects have been reported for mefloquine and doxycyline, but not for atovaquone-proguanil. Serious adverse effects are uncommon, and on statistical testing, no difference was detected between mefloquine and atovaquone-proguanil (*low-certainty evidence*), or between mefloquine and doxycycline (*very low-certainty evidence*).

Participants who received mefloquine were more likely to discontinue their medication due to adverse effects than participants who received atovaquone-proguanil (*high-certainty evidence*), but there was no difference in comparisons with doxycycline (*low-certainty evidence*).

We included one RCT and six cohort studies that reported our prespecified adverse effects that compared mefloquine and atovaquone-proguanil. In the RCT in short-term travellers, mefloquine users were more likely to report abnormal dreams (*moderate-certainty evidence*), insomnia (*moderate-certainty evidence*), anxiety (*moderate-certainty evidence*), and depressed mood during travel (*moderate-certainty evidence*). The cohort studies in longer-term travellers were consistent with these findings but most had larger effect sizes. Mefloquine users were also more likely to report nausea (*high-certainty evidence*) and dizziness (*high-certainty evidence*).

We included six cohort studies in longer-term occupational travellers that compared mefloquine with doxycycline which reported our prespecified adverse effects. We also included one RCT in military personnel and one cohort in short-term travellers that reported adverse events. Mefloquine users were more likely to report abnormal dreams (*very low-certainty evidence*), insomnia (*very low-certainty evidence*), anxiety (*very low-certainty evidence*) and depressed mood (*very low-certainty evidence*). The findings of the single cohort study reporting adverse events in short-term international travellers were consistent with these findings but the single RCT in military personnel did not demonstrate a difference between groups in the frequency of abnormal dreams or insomnia. Doxycycline users were more likely to report dyspepsia (*very low-certainty evidence*), photosensitivity (*very low-certainty evidence*), vomiting (*very low-certainty evidence)* and vaginal thrush (*very low-certainty evidence*).

Comparisons with chloroquine showed a broadly consistent pattern with these results.

Overall completeness and applicability of evidence

Mefloquine has been licensed for prevention of malaria in travellers since the late 1980s, and as such, it is perhaps surprising how few well-conducted RCTs were available. However, because we were mainly interested in the adverse effect profiles of different antimalarial agents, cohort studies (of which there are many) are probably the most appropriate study design despite their inherent limitations. Most RCTs excluded people with a previous history of mental health problems, precluding an analysis of whether psychological side effects are more common in this group. Conversely, many of the cohort studies explicitly stated that the choice of antimalarial agent was influenced by both past medical history and personal preference. While this undoubtedly introduces some confounding between study groups, we consider this confounding to be appropriate and directly applicable to clinical practice. Similarly, we would normally be cautious about interpreting unblinded self-reported assessments of adverse effects and causality. In this scenario, self-reported adverse effects provide useful and relevant information for travellers, who would also be unblinded. It should be noted that the reported adverse effects are largely self-reported psychiatric symptoms and not formal psychiatric diagnoses.

Given the heterogeneity in trial design, mefloquine doses used, and the study population, we were unable to derive a reliable estimate for mefloquine efficacy. However, the evidence suggests that mefloquine is likely to be highly effective in reducing clinical episodes of malaria. Comparative trials found no difference in efficacy between mefloquine and atovaquone-proguanil or doxycycline for preventing clinical malaria, but the number of malaria episodes was very low, and consequently, much larger trials would be needed to exclude clinically important differences. As a consequence, knowledge about antimalarial resistance patterns in the country of travel seems an appropriate approach to decision making rather than further RCTs.

The choice between antimalarial agents will therefore depend on how individual travellers rate the relative importance of specific adverse effects, pill burden and cost. Prophylactic mefloquine is widely acknowledged to cause abnormal dreams and psychological adverse effects and we found consistent evidence for these effects across comparisons with atovaquone-

proguanil, doxycycline and chloroquine (the most commonly used alternatives). Doxycycline does not have the same risk of psychological adverse effects, but is associated with increased risk of photosensitivity, dyspepsia, and vaginal thrush, which some travellers will undoubtedly consider important. In line with this, participants who received mefloquine were more likely to discontinue treatment due to adverse effects than participants who received atovaquone-proguanil, but there was no difference in comparisons with doxycycline.

We found estimating the risk of serious psychological adverse effects from the studies was not straightforward. Study authors used the term 'serious' loosely, and often did not provide us with the detail required to determine whether these events met standardized definitions. Furthermore, the estimates of the absolute risk in both mefloquine and comparator arm varied considerably between trials, which may be related to data collection methods and the cut-offs used rather than true differences among populations. Overall, we did not identify large differences in the risk of serious adverse effects among antimalarial agents; but what we did find was that the nature of these serious adverse effects corresponded with the known side effect profile of each drug.

The findings of our related systematic review which analysed deaths and parasuicides associated with mefloquine prophylaxis, and included case reports, had findings consistent with this (Tickell-Painter 2017). This systematic review reports that there were no suicides we could reliably attribute to mefloquine prophylaxis, and one para-suicide with a possible causal association. In the analysed reports, we identified two deaths with a probable association that appeared to be idiosyncratic drug reactions; the remaining eight deaths we categorised as “unlikely” to be related to mefloquine, or “unclassifiable”.

We believe it is important that the large retrospective healthcare record analyses did not demonstrate a clear quantitative association between mefloquine use and formal mental health disorders. This may reflect the inadequacy of the study methods to detect this outcome, but may also reflect the transient nature of the mood disturbance, with resolution once mefloquine is discontinued. We were unable to comment on the severity or duration of the reported adverse effects based on the available data.

The data on mefloquine at a prophylactic dose during pregnancy were limited (2 RCTs; no comparative cohort studies). Both RCTs included semi-immune populations who did not travel.

Mefloquine has an advantage as the only malaria prophylaxis with a once weekly regimen. Many have cited this as a mechanism to improve adherence, which is notoriously low in all users of antimalarial prophylaxis. However, the evidence base for this assertion is weak, with almost all data originating from cohort studies which reported a variety of measures of self-reported complete adherence.

We were unable to perform some prespecified subgroup analyses including children versus adults, female versus male travellers and pregnant versus non-pregnant women. This meant we were unable to test whether women were more likely to experience adverse effects from mefloquine use (which has been widely reported in the literature).

We appreciate that the distinction between adverse events (all events regardless of relationship to the study drug) and adverse effects (events attributed by study authors or participants to the study drug) can seem arbitrary and cause confusion. However, we consulted extensively with methodologists who advised that both outcomes are useful to decision makers, and there is no overall gold standard. For example, reporting only the adverse effects (for example, hospitalizations, psychiatric side effects) thought to be attributed to the drug regimen can introduce selective bias by the study authors. For controversial or pharmaceutical company-funded studies this can distort the outcomes. By comparing all events across both groups any difference in the relative risk can be compared without the potential for selective bias. However, this does have its own limitations, such as if the two groups were not comparable at baseline or if the sample size is not big enough to exclude differences due to chance. We therefore chose to include both options (events and effects) to give readers and decision makers the complete picture.

Quality of the evidence

In the 'Summary of findings' tables we present what we consider to be the best estimate of effect for each outcome, within each comparison. Where possible we chose the estimate from RCTs reporting adverse effects, but where this was not available we used estimates from cohort studies. However, when making judgements about the certainty of evidence we considered all the evidence available, as well as the consistency of the effect across different population groups and study designs.

For the comparison of mefloquine with atovaquone-proguanil, the best estimates of effect came from a single, well-conducted RCT in short-term travellers, recording participant-reported adverse effects. The findings of this study were supported by seven cohort studies in long-term occupational travellers and military personnel. We considered the evidence of increased risk of abnormal dreams and insomnia to be high certainty because the effects were consistent across all population groups. However, we downgraded the effect estimate on anxiety and depressed mood for inconsistency to moderate certainty because there was substantial variation in the effect size across populations, with much larger effects in long-term travellers and military personnel.

For the comparison of mefloquine with doxycycline, the only available RCT was very small, and reported adverse events rather than adverse effects. Consequently, we considered the effect estimates from cohort studies to be more reliable. Evidence from cohort studies was automatically downgraded to low based on the inherent bias in the study design. We further downgraded almost all estimates of effect for indirectness, because most data were from long-term travellers and military personnel, and may therefore over estimate the effect in short-term travel. The evidence is therefore considered to be very low-certainty with little confidence in the size of the effect. It is important to note however, that the pattern of adverse effects with mefloquine in these cohort studies is entirely consistent with the pattern seen in comparisons of mefloquine with atovaquone-proguanil and chloroquine.

Potential biases in the review process

During the course of this review we made changes to the protocol. Two changes were made to shorten the overall length of the review:

- we excluded comparisons of mefloquine with primaquine and tafenoquine because these are planned for assessment in another Cochrane Review (Rodrigo 2016);
- we excluded single-arm cohort studies because there were sufficient data from comparative studies to reach reasonable conclusions. These studies have been analysed for the very rare outcomes of death or attempted suicide in another systematic review (Tickell-Painter 2017).

We do not think these decisions biased the review.

Agreements and disagreements with other studies or reviews

Several recently published reviews regarding the safety of mefloquine have been narrative, and included little or no description of methods applied and a lack of clearly defined and prespecified outcomes (McCarthy 2015; Nevin 2015; Schlagenhauf 2010). McCarthy 2015 and Nevin 2015 discuss the policy implications of mefloquine use by the military which was beyond the scope of this Cochrane Review.

Schlagenhauf 2010 highlighted several areas in which mefloquine prophylaxis may be considered advantageous (during pregnancy and while breastfeeding, in long-term travellers, travellers who are visiting friends and relatives and families with small children). The main disagreement with our review was in regard to safety in long-term travellers, in whom the review authors refer to mefloquine as "a good option if well tolerated". This is based on a narrative analysis of a single cohort study which compared mefloquine users with users of chloroquine-proguanil, which was not included in this review (Lobel 1993).

Our review added data from several additional studies evaluating longer-term use (Andersson 2008; Cunningham 2014; Korhonen 2007; Landman 2015), and we found some observational evidence that risk of adverse effects was higher than with short-term travel.

Our findings are broadly consistent with the previous version of this Cochrane Review, which was withdrawn (Jacquerioz 2015). Jacquerioz 2015 found higher rates of neuropsychiatric adverse events in mefloquine users compared with users of both atovaquone-proguanil and doxycycline. We expanded on this finding by providing estimated risks for specific neurological and psychiatric symptoms, and by including additional data from cohort studies. Jacquerioz 2015 included a brief analysis of case reports of deaths associated with mefloquine in the Discussion. We excluded this analysis from this update, but this aspect has been addressed in a separate review of single-arm cohort studies and case reports (Tickell-Painter 2017).

Two recent reviews included evaluations of mefloquine efficacy and safety during pregnancy. González 2014 concluded there were no indications that mefloquine use during pregnancy carries an increased risk for the foetus. González 2014 included additional studies to those we included in this Cochrane Review, including mefloquine when used at treatment dose, or as intermittent presumptive treatment in pregnancy. Muanda 2015 also included mefloquine when used as intermittent presumptive treatment in pregnancy. Muanda 2015 reported findings from two trials in which the number of adverse events (Briand 2009), and number of serious adverse events (González 2014a) was higher in participants who received mefloquine as intermittent presumptive treatment in pregnancy than in those who received sulphadoxine-pyrimethamine.

AUTHORS' CONCLUSIONS

Implications for practice

The absolute risk of malaria during short-term travel appears to be very low with all three established antimalarial agents (mefloquine, doxycycline and atovaquone-proguanil).

The choice of antimalarial agent will therefore depend on how individual travellers rate the relative importance of specific adverse effects, pill burden and cost. Some will prefer mefloquine for its once-weekly regimen, but this should be balanced against the increased frequency of abnormal dreams, anxiety, insomnia, and depressed mood during travel.

Implications for research

Given the low absolute risk of malaria in travellers, very large trials would be necessary to exclude clinically important differences among antimalarial agents. As a consequence, knowledge about antimalarial resistance patterns in the country of travel seems an appropriate approach to decision making rather than further RCTs.

Although a large number of RCTs evaluating mefloquine prophylaxis have been performed, very few could be included in our analyses. Many RCTs chose to report proxy measures of psychiatric outcomes, such as Profile of Mood States questionnaires and Environmental Symptoms Questionnaires, which are difficult for clinicians and participants to interpret. Furthermore, many studies grouped symptoms together when reporting outcomes. 'Neuropsychiatric' or 'neuropsychologic' were commonly used terms, although the symptoms included varied from headaches to psychosis, making them of limited value in clinical decision making.

Even though we found moderate- and high-certainty evidence that mefloquine use is associated with a range of psychological adverse effects, further RCTs could increase confidence in the size of the effect. The relative risk of psychological side effects was higher with long-term use of mefloquine, although this finding was only statistically significant in one comparison. An alternative explanation is the possibility of an interaction between mefloquine and level of psychological stress given the occupation of participants surveyed (Foreign and Commonwealth Office workers, Peace Corps volunteers and military personnel). Further research should examine these potential interactions.

Furthermore, well-designed trials could test hypotheses regarding male versus female users, whether mefloquine users with a previous history of mental health problems are more likely to experience psychological adverse effects, and the severity or duration of the reported adverse effects.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Albright 2002

Methods	Design: retrospective cohort study. Study dates: November 1997 to January 2000 Malaria transmission pattern and local antimalarial drug resistance: various destinations, not specified. Adverse event monitoring: one off telephone interview with parents whose children had previously been prescribed antimalarial prophylaxis.
Participants	Number enrolled: 177 fit inclusion criteria and interviewed, 190 contacted Inclusion criteria: children aged ≤ 13 years who visited the travel clinic at the Children's Memorial Hospital in Chicago within the study dates. Subjects who were not on other medications. Exclusion criteria: "...data were only included if the child was living with the interviewed parent while taking the antimalarial". "Unwillingness to participate in the study and language barriers". Factors influencing drug allocation: "children... instructed to take mefloquine or chloroquine for malaria prophylaxis". Country of recruitment: USA. Country of malaria exposure: various; Africa 58%, Central or South America 21%, India 12% or Eastern Asia 9%. Duration of exposure to malaria: various, not specified. Type of participants: travellers
Interventions	1. Mefloquine* 2. Chloroquine* **dosing regimen not specified*
Outcomes	1. Adverse effects; any, nausea, vomiting, diarrhoea, headache, insomnia, abnormal dreams

Albright 2002 *(Continued)*

	2. Serious adverse effects 3. Discontinuations of study drug due to adverse effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** Age, sex and destination of travel were recorded, but were not reported across prophylactic regimens **2. Selection of participants into the study: low** Non-response rate 1.6% **3. Measurement of interventions: moderate** The prescription was provided by a travel clinic, but participants were asked to recall if they discontinued their medication 2.8 to 28 months after visiting **4. Departures from intended interventions: serious** Information was collected up to 2 years after taking the drug. No information was captured on switches. **5. Missing data: low** All information was collected at one time point, there were no losses to follow-up. **6. Measurement of outcomes: serious** The outcome measure was subjective, participants and personnel were not blinded. **7. Selection of the reported results: low** All outcomes included in the introduction were reported in the results **8. Other: low** "The authors had no financial or other conflicts of interest to disclose"

Andersson 2008

Methods	Design: prospective cohort study Study dates: March 2004 to November 2006 Malaria transmission pattern and local antimalarial drug resistance: malaria attack rate of 44% with *P falciparum* in another similar study at the time Adverse event monitoring: patient self-reported questionnaire
Participants	Number enrolled: 690 soldiers sent questionnaire, 609 respondents Inclusion criteria: all Swedish soldiers deployed to Liberia within the study dates

Andersson 2008 *(Continued)*

	Exclusion criteria: none stated. Factors influencing drug allocation: "...mefloquine was prescribed to almost all soldiers in the first two contingents and to about two-thirds in the last three contingents. The remaining soldiers were recommended atovaquone/ proguanil. The latter group consisted mainly of those with body weight < 70 kg and those who had already experienced adverse events with mefloquine. No other drug regimes were used". Country of recruitment: Sweden Country of malaria exposure: Liberia Duration of exposure to malaria: 6 months Type of participants: military
Interventions	1. Mefloquine* 2. Atovaquone-proguanil* **dosing regimen not specified*
Outcomes	*Included in the review:* 1. Adverse events; any, nausea, vomiting, abdominal pain, diarrhoea, headache, dizziness, abnormal dreams nightmares, insomnia sleep disturbance, depression 2. Serious adverse events; serious 3. Adverse events; other (concentration difficulties, mouth ulcers, fever, muscle pain) 4. Discontinuations of study drug due to adverse effects *Outcomes assessed not included in the review:* 5. Clinical cases of malaria 6. Overall satisfaction with the drug 7. Whether they would take the drug again 8. Measures of adherence to the drug regimen (data provided on aggregate)
Notes	Funding sources: Not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** Information on potential confounders is not provided across prophylactic groups **2. Selection of participants into the study: moderate** 609/690 (88%) response rate **3. Measurement of interventions: low** All participants were issued with the study drug. **4. Departures from intended interventions: low** Switches were recorded and reported

Andersson 2008 *(Continued)*

5. Missing data: serious

Outcomes were reported from 3 of 5 cohorts. No information was provided for 2 remaining cohorts.

6. Measurement of outcomes: serious

The outcome measure was subjective, participants and personnel were not blinded.

7. Selection of the reported results: low

All outcomes prespecified in the introduction were reported.

8. Other: moderate

Study sponsor not mentioned, but 2 study authors worked for GlaxoSmithKline

Arthur 1990

Methods	Design: RCT Study dates: June to August 1988 Malaria transmission pattern and local drug resistance: local chloroquine resistance Adverse event monitoring: blood taken at induction and at days 57 and 70 of treatment. Interviews regarding side effects when sera taken. Stool sample at induction, at end of exercise and at any time participants sought medical care.
Participants	Number enrolled: 270 Inclusion criteria: soldiers (aged 18 to 40 years), awaiting deployment to Thailand Exclusion criteria: previous history of gastrointestinal illness Country of recruitment: USA Country of malaria exposure: Thailand Duration of exposure to malaria: 5 weeks Type of participants: soldiers, non-immune
Interventions	1. Mefloquine (1 x 250 mg tablet) once weekly, starting 1 week before travel and continuing throughout the period of deployment.* 2. Doxycycline (1 capsule containing doxycycline hyclate 100 mg) once daily, starting 1 week before travel and continuing throughout the period of deployment* Co-interventions: Both groups given doxycycline 100mg daily for suppression of *P falciparum* and primaquine 45 mg weekly for elimination of liver hypnozoites for 6 weeks on return to the USA. **matched placebo for each treatment arm*
Outcomes	*Included in the review:* 1. Clinical cases of malaria 2. Serious adverse event

Arthur 1990 *(Continued)*

	3. Adverse events; diarrhoea 4. Discontinuation of study drug due to adverse effects 5. Measures of adherence to the drug regimen *Outcomes assessed not included in the review:* 6. Laboratory tests; enteric pathogens 7. Adverse events; nausea, vomiting, headache, dizziness (data provided on aggregate)
Notes	Funding sources: Pfizer Inc supplied active and placebo doxycycline; Hoffman-La Roche Inc supplied active and placebo mefloquine

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Volunteers were assigned from a computer generated random number list to receive daily doxycycline or weekly mefloquine"
Allocation concealment (selection bias)	Unclear risk	Comment: Unclear how the tablets were labelled and whether allocation concealment occurred
Blinding of participants and personnel (performance bias) Adverse effects/events	Low risk	"Soldiers receiving mefloquine also received identical appearing doxycycline placebo capsules daily, and those receiving daily doxycycline received weekly mefloquine placebo tablets"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: described as double blind but no explanation of how this was achieved for researchers and outcome assessors
Incomplete outcome data (attrition bias); efficacy	High risk	"Of the 270 volunteers who were deployed, 253 were correctly taking the assigned study malaria prophylaxis on arrival in Korat" Comment: Reasons for not taking medication were not reported. Method of detection for malaria, frequency and duration of follow-up were not reported
Incomplete outcome data (attrition bias); safety	Low risk	Comment: 17 participants (6%) were not "correctly taking the prophylaxis on arrival to Korat" and were excluded from the analysis. Data were not stratified by time point
Selective reporting (reporting bias); efficacy	Low risk	"None of the soldiers developed malaria"
Selective reporting (reporting bias); safety	Unclear risk	Comment: data for general side effects (e.g. headaches) were presented for the study population but not for each group
Other bias	Unclear risk	Comment: study sponsor not mentioned

Belderok 2013

Methods	Design: prospective cohort study Study dates: October 2006 to October 2007

Belderok 2013 *(Continued)*

	Malaria transmission pattern and local antimalarial drug resistance: various destinations, not specified Adverse event monitoring: not performed
Participants	Number enrolled: 945 Inclusion criteria: People aged ≥ 18 years were eligible if they were planning to travel for 1 to 13 weeks to one or more malaria-endemic countries. Exclusion criteria: None stated Factors influencing drug allocation: "Dutch national guidelines for travelers' health advice" Country of recruitment: Netherlands Regions of malaria exposure: various; Asia 48%, Africa 30% and Latin America 22% Duration of exposure to malaria: various; 49% ≤ 13 days, 35% 14 to 28 days and 9% ≥ 29 days Type of participants: travellers
Interventions	1. Mefloquine: taken 3 weeks prior to arrival, during trip and for 4 weeks after return, dose and frequency of dose not specified 2. Atovaquone-proguanil: 1 day prior to arrival, during trip and for 7 days after return, dose and frequency of dose not specified 3. Proguanil: On day of arrival, during trip and for 4 weeks after return, dose and frequency of dose not specified
Outcomes	*Included in the review:* 1. Measures of adherence to the drug regime *Outcomes assessed not included in the review:* 2. Clinical cases of malaria 3. Predictors of adherence to malaria prophylaxis 4. Use of antimosquito preventive measures
Notes	Funding sources: The Amsterdam Academic Collaborative Center on Public Health is financially supported by the Netherlands Organization for Health Research and Development (ZonMw; grant number 7115 0001, http://www.zonmw.nl/nl/)

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** Length of stay, travel destination, age and sex were not reported across groups **2. Selection of participants into the study: moderate** Non-response rates were not reported **3. Measurement of interventions: low** Participants made daily diary entries during travel **4. Departures from intended interventions: low**

Belderok 2013 *(Continued)*

	Participants made daily diary entries during travel **5. Missing data: low** Information was collected at one time point **6. Measurement of outcomes: moderate** Outcome assessors were not blinded, methods were comparable across groups **7. Selection of the reported results: low** Outcomes were reported for 610/620 participants **8. Other: low** Government funding

Boudreau 1991

Methods	Design: RCT Study dates: July 1983 to March 1984 Malaria transmission pattern and local antimalarial drug resistance: "in this area we believe the efficacy of chloroquine prophylaxis at the time of the study was negligible" Adverse event monitoring: "at each 2 week visit… history of symptoms over the previous fortnight was obtained. Patients were asked about fever, chills, headache, nausea, vomiting, diarrhoea, anorexia, rash, myalgia and dysuria or abnormally coloured urine". Laboratory studies were performed at baseline and at 6 weeks in participants who had not developed malaria
Participants	Number enrolled: 501 Inclusion criteria: "Only males 21 years of age or over were accepted" Exclusion criteria: "All participants were required to have a negative malaria smear (after examination of 200 fields on thick smear) on entry into the study". "...the use of other antimalarials or antibiotics" Country of recruitment: Cambodia Country of malaria exposure: Cambodia Duration of exposure to malaria: ongoing in semi immune population, 14 week study period Type of participants: Thai gem miners with a degree of immunity
Interventions	*Included in review comparisons:* 1. Mefloquine (2 x 250 mg tablet) fortnightly for 14 weeks* 2. Chloroquine (1 x 300 mg tablet) weekly* *Not included in review comparisons:* 3. Fansidar (2 x 500 mg sufadoxine and 25 mg pyrimethamine) fortnightly and chloroquine (1 x 300 mg tablet) weekly* **matched placebo for each treatment arm*
Outcomes	*Included in the review:*

Boudreau 1991 *(Continued)*

	1. Clinical cases of malaria 2. Adverse events; other (myalgias, rash) *Outcomes assessed not included in the review:* 3. Laboratory tests; haematocrit, complete blood count, transaminase levels, total and direct bilirubin, alkaline phosphatase, blood urea nitrogen 4. Adverse events; headache, anorexia, fever, chills, nausea, diarrhoea or vomiting (data provided on aggregate)
Notes	Funding sources: Support for this study was from the USA Army Medical Research and Development Command

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Assignment… is a 4:3:2 ratio" Comment: method of sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Comment: no details of allocation concealment were reported
Blinding of participants and personnel (performance bias) Adverse effects/events	Unclear risk	"Every two weeks in a double blind fashion one of the investigators administered five tablets to each subject" Comment: not mentioned whether placebo tablets had an identical appearance
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: described as double blind but no mention of how this was achieved for researchers and outcome assessors
Incomplete outcome data (attrition bias); efficacy	Unclear risk	"Only 194 patients completed the study until positivity or end of the 14 weeks observation period". "Therefore of the original 501 enrollees, 63 were discarded due to positivity at week 0 and 104 were discarded since they never returned beyond week 0". Comment: Losses to follow-up during the study was not reported across groups
Incomplete outcome data (attrition bias); safety	Unclear risk	"Only 194 patients completed the study until positivity or end of the 14 weeks observation period...Any subject missing one appointment was excluded from the study though each subject's records up to the time of exclusion were entered into the survival analysis...After 3 weeks post treatment and a negative malaria smear some patients wishing to continue were reentered under a new study number and were assigned a double blind randomized treatment"
Selective reporting (reporting bias); efficacy	Unclear risk	Comment: number of people contracting malaria in each group and person-weeks in the study were reported
Selective reporting (reporting bias); safety	Unclear risk	"There were no significant differences in frequency of complaints among the study groups for headache, anorexia, fever, chills, nausea, diarrhoea, or vomiting".

Boudreau 1991 *(Continued)*

		Comment: Data for specific adverse events not reported. Methods section states participants were asked about dysuria and abnormally coloured urine, but this was not reported in the results
Other bias	Low risk	Support for this study was from the USA Army Medical Research and Development Command

Boudreau 1993

Methods	Design: RCT Study dates: not mentioned Malaria transmission pattern and local antimalarial drug resistance: not applicable Adverse event monitoring: "At each visit, the subject answered two computerised questionnaires (the Environmental Symptoms Questionnaire and the Profile of Mood States) [and] a physician interview was performed"
Participants	Number enrolled: 359 Inclusion criteria: "males at least 18 years old, met military weight standards, were available for weekly administration of medications and monitoring during the 13 week study period, and were willing to give informed consent" Exclusion criteria: "treatment with beta-blocking agents or other cardiotropic drugs, underlying chronic disease, history of cardiac arrhythmia, medical history of psychiatric or neurological problems within the last 5 years, anaemia or impaired hepatic or renal function. Women were excluded from participation in the study due to the risk of teratogenicity involved when the drug is used in early pregnancy" Country of recruitment: USA Country of malaria exposure: not applicable Duration of exposure to malaria: not applicable Type of participants: military, non-travellers
Interventions	1. Mefloquine (1 x 250 mg tablet), larium 228 mg base (F Hoffman La Roche) weekly for 11 weeks 2. Mefloquine (1 x 250 mg tablet), larium 228 mg base (F Hoffman La Roche) weekly for 11 weeks, with loading dose of 1 x 250 mg tablet daily for 3 days during the first week 3. Chloroquine (1 x 300 mg tablet), 300 mg base (F Hoffman La Roche) weekly for 11 weeks
Outcomes	*Included in the review:* 1. Adverse events; nausea, vomiting, abdominal pain, diarrhoea, headache, dizziness, abnormal dreams, insomnia 2. Adverse events; other (irritability, poor concentration, anger, moodiness, abdominal distension, anorexia, environmental symptoms questionnaire (ESQ), sleep assessment, Profile of Mood States questionnaire) *Outcomes assessed not included in the review:* 3. Laboratory tests: haemoglobin, haematocrit, platelets, white blood cell count, alanine aminotransferase, blood urea nitrogen and creatinine 4. Analysis of the dizziness index on the ESQ

Boudreau 1993 *(Continued)*

	5. Spontaneous comments on the ESQ (data provided on aggregate)
Notes	Funding sources: Not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...military personnel were assigned to drug groups in a ratio of approximately 3:3:1…stratification was performed by major subordinate command so that equal proportions of each study group would be represented in each MSC" Comment: not mentioned how the randomisation code was generated
Allocation concealment (selection bias)	Unclear risk	Comment: method allocation concealment not mentioned
Blinding of participants and personnel (performance bias) Adverse effects/events	Low risk	"...the 'double dummy' method of blinding was employed with either chloroquine or mefloquine placebos administered with active drug… In addition, during the first week of the study, on days two and three, a single mefloquine tablet or placebo was administered. Both drugs and placebos had an extremely bitter taste... identical placebo tablets"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: described as double blind but no description provided of how this was achieved for researchers and outcome assessors
Incomplete outcome data (attrition bias); efficacy	Unclear risk	N/A
Incomplete outcome data (attrition bias); safety	Unclear risk	Comment: 15 medical withdrawals are reported within the study. It is unclear whether these are the only losses to follow up which occurred, or whether they occurred in the mefloquine loading dose group or weekly administration group.
Selective reporting (reporting bias); efficacy	Unclear risk	N/A
Selective reporting (reporting bias); safety	High risk	'table 5 outlines the percent of the group with symptoms only when significance was demonstrated' 'selected haematology and biochemistry tests were performed… no significant differences were noted among the three drugs when comparing the mean values' Comment: data is not fully reported for 'other symptoms'; only significant results are reported for the ESQ, and data for spontaneous comments on the ESQ are not reported; data is not fully reported for the POMS.
Other bias	Unclear risk	Comment: study sponsor not mentioned, but the lead author is attributed to 'Pharmaceutical Systems Incorporated'

Bunnag 1992

Methods	Design: RCT Study dates: July 1987 to January 1988

Bunnag 1992 *(Continued)*

	Malaria transmission pattern and local antimalarial drug resistance: "a malaria endemic area". Reports chloroquine, sulfadoxine-pyrimethamine and quinine resistance within Thailand at the time of the study. Adverse event monitoring: "volunteers asked about adverse events at each visit (weeks 4, 9, 14, 19, 24, 28)...starting week 14, volunteers reporting adverse events were interviewed by members of the hospital team; most of them were also seen by principal investigators"
Participants	Number enrolled: 605 randomized, 3 excluded because of baseline parasitaemia Inclusion criteria: "...healthy male volunteers, aged between 16 and 60, living in this area, were recruited" Exclusion criteria: "persons with a known history of allergy against sulphonamides, with an evidence illness of fever, or which a positive blood film (with or without symptomatic malaria) were excluded" Country of recruitment: Thailand Country of malaria exposure: Thailand Duration of exposure to malaria: trial duration 24 weeks Type of participants: Thai residents in a malaria-endemic area (presumed semi-immune)
Interventions	*Included in the review:* 1. Mefloquine (1 tablet containing 125 mg mefloquine) once weekly, double dose during first 4 weeks* 2. Chloroquine (1 tablet containing 300 mg chloroquine) once weekly* 3. Placebo *Not included in the review:* 4. Fansifem (1 tablet containing 125 mg mefloquine, 250 mg sulfadoxine, 12.5 mg pyrimethamine) once weekly, double dose during first 2 weeks* 5. Fansidar (1 tablet containing 500 mg sulfadoxine, 25 mg pyrimethamine) once weekly* **matched placebo for each treatment arm*
Outcomes	*Included in the review:* 1. Clinical cases of malaria 2. Adverse events; any 3. Discontinuations of study drug due to adverse effects *Outcomes assessed not included in the review:* 4. Laboratory tests; haematocrit, white blood cell count and neutrophil count
Notes	Funding sources: "The project was jointly organized and conducted by the Malaria Division, Department of Communicable Disease, Ministry of Public Health; the Hoffman-La Roche company, Basel, Switzerland; and The Faculty of Tropical Medicines, Mahidol University, Bangkok"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Eligible volunteers were randomly assigned to treatment groups"

Bunnag 1992 *(Continued)*

		Comment: method of random sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	"The tablets were identical in appearance; they were packed in numbered blister packs and were in addition labelled weeks 1-24... the coded test drugs for weeks 1-4 were given to every subject" Comment: no mention of concealed opaque envelopes or central allocation
Blinding of participants and personnel (performance bias) Adverse effects/events	Low risk	"A randomised double blind trial…the tablets were identical in appearance; they were packed in numbered blister packs"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: described as double blind but no explanation provided of how this was achieved for researchers and outcome assessors
Incomplete outcome data (attrition bias); efficacy	Unclear risk	"Of the 605 subjects originally randomised, 3 were excluded because of baseline parasitaemia... Although some of the volunteers left the study for personal reasons (moving away from the area)" Comment: numbers lost to follow up have not been reported
Incomplete outcome data (attrition bias); safety	Unclear risk	"94% (116/123) in the mefloquine group and 98% (119/121) in the placebo group were included for adverse event reporting" "Although some of the volunteers left the study for personal reasons (moving away from the area)" Comment: numbers lost to follow-up were not reported
Selective reporting (reporting bias); efficacy	Low risk	Comment: Malaria cases were fully reported
Selective reporting (reporting bias); safety	High risk	Comment: Data were collected but not reported for adherence to drug regimen. Data were provided on aggregate across all time points. The number of adverse events were reported but not types or severity
Other bias	High risk	"The project was jointly organized and conducted by the Malaria Division, Department of Communicable Disease, Ministry of Public Health; the Hoffman-La Roche company, Basel, Switzerland; and The Faculty of Tropical Medicines, Mahidol University, Bangkok"

Corominas 1997

Methods	Design: retrospective cohort study Study dates: June 1992 to July 1994 Malaria transmission pattern and local antimalarial drug resistance: various, not specified Adverse event monitoring: patient self-reported questionnaire
Participants	Number enrolled: 1511 questionnaires distributed, 1054 respondents Inclusion criteria: travellers who visited areas with a risk of malaria infection who were travelling on short trips < 6 weeks duration Exclusion criteria: none mentioned

Corominas 1997 *(Continued)*

	Factors influencing drug allocation: *The fact of participating in this study did not change at all the typical prophylaxis when performing, which followed the usual criteria* (Google Translate = "El hecho de participar en este estudio no cambio en absoluto el tipico de profilaxis al realizar, que siguio los criterios habituales" Country of recruitment: Spain Country of malaria exposure: various, not specified Duration of exposure to malaria: various, not specified Type of participants: travellers
Interventions	*Included in the review:* 1. Mefloquine (1 x 250 mg tablet) weekly, starting 1 week prior to travel, during the trip and 4 weeks following return from the malaria-endemic area 2. Chloroquine (5 mg/kg) weekly, starting 1 week prior to travel, during the trip and 4 weeks following return from the malaria-endemic area *Outcomes assessed not included in the review:* 3. Chloroquine and proguanil (chloroquine base 5 mg/kg, once weekly plus proguanil 100 mg daily, if weight < 55 kg and 200 mg daily if weight > 55 kg) starting 1 week prior to travel, during the trip and 4 weeks following return from the malaria-endemic area
Outcomes	*Included in the review:* 1. Adverse effects; any, vertigo, visual impairment, nausea, vomiting, abdominal pain, diarrhoea, insomnia, anxiety, depression, pruritis 2. Adverse effects; other (irritability) 3. Discontinuations of study drugs due to adverse effects *Outcomes assessed not included in the review:* 4. Mean number of symptoms reported per traveller 5. Adverse effects; other, incidence < 1% (amnesia, tremor, paraesthesia, seizures, hyper-reflexia, drowsiness, asthenia, nervousness, difficulty concentrating, mouth ulcers, acne, cardiac rhythm disturbance)
Notes	Funding sources: Not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** Sex was reported across groups. No other confounders were reported **2. Selection of participants into the study: serious** 1054/1511 (70%) response rate **3. Measurement of interventions: low** The antimalarial prescription was provided by a travel clinic which also performed the study **4. Departures from intended interventions: moderate**

Corominas 1997 *(Continued)*

	Discontinuations were reported across groups. It is unclear if information regarding switches was obtained **5. Missing data: low** All participants were included in the analysis. All information was included at one time point **6. Measurement of outcomes: serious** Comment: the outcome measure was subjective, participants and personnel were not blinded **7. Selection of the reported results: moderate** The analysis of the relationship of symptoms by weight was reported only for mefloquine **8. Other: no information** No information was provided regarding the study sponsor

Cunningham 2014

Methods	Design: cross-sectional cohort study Study dates: questionnaire emailed July 2012, reminder emails were circulated at 8 and 12 weeks Malaria transmission pattern and local antimalarial drug resistance: various destinations, not specified Adverse event monitoring: patient self-reported questionnaire
Participants	Number enrolled: 579 questionnaires emailed, 327 responses Inclusion criteria: all Foreign and Commonwealth Office staff posted to a malaria-endemic area Exclusion criteria: none stated Factors influencing drug allocation: "prophylaxis based on the Advisory Committee on Malaria Prevention in UK Travellers (ACMP) guidelines" Country of recruitment: various, not specified Country of malaria exposure: various, not specified Duration of exposure to malaria: 0 to 3 months N = 16 (4.9%), 4 to 6 months N = 26 (8.0%), 7 to 12 months N = 46 (14.1%), 13 to 36 months N = 75 (22.9%), > 36 months N = 167 (51.1%) Type of participants: UK Foreign and Commonwealth Office staff
Interventions	1. Mefloquine* 2. Atovaquone-proguanil* 3. Doxycycline* 4. Chloroquine* **dosing regimen not specified*
Outcomes	*Included in the review:* 1. Adverse effects; psychiatric disorders (abnormal dreams)

Cunningham 2014 *(Continued)*

	2. Adverse effects; other (skin sensitivity, indigestion, other psychological) *Outcomes assessed not included in the review:* 3. Clinical cases of malaria 4. Background knowledge of malaria 5. Attitudes regarding malaria prophylaxis 6. Use of personal protective measures 7. Impact of pregnancy on malaria prevention 8. Measures of adherence to drug regimen (data provided on aggregate)
Notes	Funding sources: not mentioned Communications with study authors: the study authors provided us with access to the full original data set. Thedata set differed from findings in the published version of the paper, and we were unable to determine the cause for differences. The included figures were from the full data set

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** No information on confounders was provided across prophylaxis groups **2. Selection of participants into the study: serious** Response rate for the survey was 56.5% **3. Measurement of interventions: moderate** Participants were asked to self-report which medications they were prescribed. Compliance rate was 25% **4. Departures from intended interventions: serious** No questions were included in the questionnaire regarding switches between chemoprophylactic regimens **5. Missing data: low** All participants were included in the analysis **6. Measurement of outcomes: serious** Comment: the outcome measure was subjective; participants and personnel were not blinded **7. Selection of the reported results: low** The entire questionnaire was provided in full, all outcomes included were reported **8. Other: no information** Study sponsor not mentioned

Davis 1996

Methods	Design: RCT Study dates: not mentioned Malaria transmission pattern and local antimalarial drug resistance: not applicable Adverse event monitoring: daily self-reported diary. Three medical check ups for laboratory and other tests
Participants	Number enrolled: 106 randomized, 95 completed all study procedures Inclusion criteria: "healthy adult staff and students at teaching hospitals in Perth, Western Australia" Exclusion criteria: "Those with a past history of psychiatric conditions, or neurological, cardiac, hepatic or renal disease were excluded, as were pregnant or breastfeeding females and those with a known allergy to, or taking medication known to interact with quinolone drugs. None of the subjects had taken mefloquine in the 3 months before the study" Country of recruitment: Australia Country of malaria exposure: not applicable Duration of follow up: 7 weeks Type of participants: non-immune non-travellers
Interventions	1. Mefloquine (1 x 250 mg tablet), with placebo dose followed 1 week later by 250 mg mefloquine weekly, active treatment duration 4 weeks 2. Placebo, 1 tablet weekly, duration 5 weeks
Outcomes	*Included in the review:* 1. Measure of adherence to the drug regimen 2. Adverse events: other outcome measures (symbol digit modalities test, digit span forwards and backwards test, ECG, hearing loss at 6kHz) *Outcomes assessed not included in the review:* 3. Laboratory tests: serum glucose, insulin, ionized calcium, phosphate, magnesium and albumin concentrations 4. Adverse events: headache, lethargy, abdominal pain, diarrhoea, cough, nausea; study reports events occurring in the first week (after both groups had received placebo) and the relative risk of symptoms worsening over time
Notes	Funding sources: "We thank… F. Hoffman La Roche & Co. for financial support"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...allocation… was by a random number code generated by independent Fremantle Hospital Pharmacy staff"
Allocation concealment (selection bias)	Low risk	"...who kept the code strictly confidential until the last volunteer had completed the protocol"
Blinding of participants and personnel (performance bias)	Low risk	"Tablets were prepared in individually numbered but otherwise unlabelled containers... identical placebo tablets…"

Davis 1996 *(Continued)*

Adverse effects/events		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Allocation of active or placebo formulation was by a random number code generated by independent Freemantle hospital staff who kept the code strictly confidential" Comment: not mentioned whether outcomes assessors were blinded
Incomplete outcome data (attrition bias); efficacy	Unclear risk	N/A
Incomplete outcome data (attrition bias); safety	Low risk	"Of 106 randomised volunteers, 95 (90%) completed all study procedures... eight subjects withdrew after initial assessment and three after the second. Follow-up of these individuals revealed no toxicity in those allocated mefloquine"
Selective reporting (reporting bias); efficacy	Unclear risk	N/A
Selective reporting (reporting bias); safety	High risk	Comment: not all symptoms were reported, only those occurring in > 10% of participants in both groups. Absolute numbers of participants experiencing each symptom after mefloquine/placebo commenced not provided, only relative risk of symptoms worsening over time
Other bias	High risk	"We thank… F. Hoffman La Roche & Co. for financial support"

Eick-Cost 2017

Methods	Design: Retrospective cohort study Study dates: 1 January 2008 to 30 June 2013 Malaria transmission pattern and local antimalarial drug resistance: Various, not specified Adverse event monitoring: Data collected retrospectively from the Defense Medical Surveillance System, the Pharmacy Data Transaction Service and the Theater Medical Data Store
Participants	Number enrolled: 367,840 Inclusion criteria: Active component service members who filled a prescription for mefloquine, doxycycline or atovaquone-proguanil Exclusion criteria: Doxycycline and atovaquone-proguanil prescriptions were excluded if the service member previously or concurrently received mefloquine. Doxycycline prescriptions were restricted to 100 mg, once daily, tabular form, minimum 30 day prescription Factors influencing drug allocation: Not specified Country of recruitment: USA Country of malaria exposure: Various, not specified Duration of exposure to malaria: Various, not specified Type of participants: Military
Interventions	1. Mefloquine (250 mg weekly) 2. Atovaquone- proguanil*

Eick-Cost 2017 *(Continued)*

	3. Doxycycline (100 mg, tabular form, daily dose, 30 day minimum prescription) **dosing regimen not specified*
Outcomes	1. Adverse events (anxiety disorders, depressive disorders, psychoses, insomnia, vertigo) 2. Adverse events; other (adjustment disorders, post-traumatic stress disorder, tinnitus, suicidal ideation, convulsions, hallucinations, paranoia, confusion)
Notes	Funding source: not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** Identified confounders were measured and not balanced across groups **2. Selection of participants into the study: low** Start of intervention and start of follow-up coincided for most participants. Retrospective medical records were used, therefore there were no non-responders **3. Measurement of interventions: moderate** Information regarding drug prescriptions were obtained from a medical database, without any verification that users took the prescription **4. Departures from intended interventions: serious** Discontinuations and switches between prophylactic regimes were not recorded in the database **5. Missing data: low** All records in the research database were included in the analysis **6. Measurement of outcomes: moderate** Participants and outcome assessors (physicians) were not blinded. However, information was collected anonymously and on aggregate. Participants were unaware of their participation at the time of seeking healthcare **7. Selection of the reported results: low** Outcome data were reported for all outcomes prespecified for analysis **8. Other: no information** No information was available regarding the study sponsor.

Goodyer 2011

Methods	Design: prospective cohort study Study dates: December 2004 to April 2006 Malaria transmission pattern and local antimalarial drug resistance: various destinations, not specified

Goodyer 2011 *(Continued)*

	Adverse event monitoring: "a post travel questionnaire… approximately 1 week after they were due to complete their course of medication"
Participants	Number enrolled: 252 recruited, 185 completed pre- and post-travel questionnaires Inclusion criteria: "...to be eligible, travelers had to be at least 18 years of age and to have been prescribed or supplied... an antimalarial medication as a result of planned travel for a duration of 28 days or less." Exclusion criteria: "travelers participating in other prospective clinical research or observational studies, pregnant travelers or travelers planning to get pregnant during the study were excluded" Factors influencing drug allocation: "Treatment choice was solely at the discretion of the traveler and practitioner" Country of recruitment: UK Country of malaria exposure: various, not reported Duration of exposure to malaria: various, median 14 days (interquartile range 9 to 20) Type of participants: travellers
Interventions	1. Mefloquine* 2. Atovaquone-proguanil* 3. Doxycycline* **dosing regimen not specified*
Outcomes	*Included in the review:* 1. Any adverse effects 2. Measures of adherence to the drug regimen *Outcomes assessed not included in the review:* 3. Relative importance of factors in choice of antimalarial drugs, for both healthcare professionals and travellers
Notes	Funding sources: "The study was commissioned and paid for by GlaxoSmithKline"

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** "There were statistically significant differences in mean age" Several other confounders were not reported across groups **2. Selection of participants into the study: moderate** No information is provided regarding people who did not wish to participate **3. Measurement of interventions: low** The antimalarial prescription was provided by a travel clinic which also performed the study **4. Departures from intended interventions: moderate**

Goodyer 2011 *(Continued)*

	No information was captured regarding switches between interventions of interest **5. Missing data: serious** 185/252 participants completed the pre- and post-travel questionnaire. Interim loss to follow up 27% **6. Measurement of outcomes: serious** Comment: the outcome measure was subjective; participants and personnel were not blinded **7. Selection of the reported results: moderate** The number of reported side effects was reported, but not the types or severity **8. Other: serious** Funded by GlaxoSmithKline; the role of the study sponsor was not made clear

Hale 2003

Methods	Design: RCT Study dates: not mentioned Malaria transmission pattern and local antimalarial drug resistance: "the 20-week cumulative incidence of reinfection by *P. falciparum* to be nearly 100%". No mention of local drug resistance patterns Adverse event monitoring: "...during the prophylaxis and follow-up phases, health workers visited the subjects 3 times weekly. Subjects with physical complaints were examined by a study physician the next day or on an emergent basis, as needed. Hematologic analysis was done on days 4 and 10 after starting the loading dose phase and during weeks 4, 8, 12, and 15. Biochemical analysis was done during weeks 4, 8, 12, and 15"
Participants	Number enrolled: 530 enrolled and completed radical cure regimen. 509 participants took at least 1 dose of the weekly study drug or placebo and comprised the full intention-to-treat data set Inclusion criteria: "Inclusion criteria included the following: age of 18–60 years (men) or 50–60 years (women); lack of significant systemic illness as determined by history, physical examination, and clinical laboratory test results (including negative results of a urine pregnancy test for women); and absence of seizures or other neuropsychiatric illness (past or present)" Exclusion criteria: "The high rate of pregnancy and breast-feeding in women aged 18–49 years precluded their enrollment... G6PD deficiency accounted for 179 of 338 exclusions" Country of recruitment: Ghana Country of malaria exposure: Ghana Duration of exposure to malaria: trial duration 12 weeks Type of participants: Ghanain residents, semi-immune
Interventions	*Included in the review:* 1. Mefloquine (1 x 250 mg tablet, salt), weekly, with supervised 3 day loading dose* 2. Placebo, with supervised 3 day loading dose* *Not included in the review:*

Hale 2003 *(Continued)*

	3. Tafenoquine (1 x 25 mg tablet, base), weekly, with supervised 3 day loading dose* 4. Tafenoquine (1 x 50 mg tablet, base), weekly, with supervised 3 day loading dose* 5. Tafenoquine (1 x 100 mg tablet, base), weekly, with supervised 3 day loading dose* 6. Tafenoquine (1 x 200 mg tablet, base), weekly, with supervised 3 day loading dose* **matched placebo for each treatment arm*
Outcomes	*Included in the review:* 1.Clinical cases of malaria 2. Adverse events; any, abdominal pain, diarrhoea, headache 3. Adverse events; other (gastritis, back pain, myalgia, polyarthralgia/arthralgia, respiratory tract infection, sore throat, rash) 4. Discontinuation of study drug due to adverse effects *Outcomes assessed not included in the review:* 5. Laboratory tests; haematological and biochemical analyses
Notes	Funding sources: USA Army Medical Materiel Development

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The randomization code was generated in blocks of 11 numbers" Comment: not mentioned how randomization code was produced
Allocation concealment (selection bias)	Unclear risk	"Code numbers were assigned according to the chronological order of appearance of the subjects at screening. Study drugs were prepackaged and prelabeled with a unique study number according to the randomization code" Comment: no mention of opaque sealed envelopes
Blinding of participants and personnel (performance bias) Adverse effects/events	Unclear risk	"A 'double-dummy' design allowed double-blind administration of tafenoquine and mefloquine active drugs and their corresponding placebos" "A placebo (tafenoquine placebo, GlaxoSmith-Kline; mefloquine placebo, Hoffmann-La Roche) served as the negative comparator" Comment: does not report that the tablets were identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"All slides positive for the presence of malaria causing parasites, and an equal number of randomly selected slides with negative results were reevaluated by a second (blinded) microscopist." Comment: no other mention of outcome assessors being blinded and does not report that the researchers were blinded
Incomplete outcome data (attrition bias); efficacy	Low risk	"Data analysis for efficacy used 2 data sets: the 'full, intent-to-treat' data set (n=509), comprising all subjects who took at least 1 dose of the weekly study drug or placebo, and the 'per-protocol' data set (n=428), comprising those subjects who strictly fulfilled the protocol criteria"

Hale 2003 *(Continued)*

Incomplete outcome data (attrition bias); safety	Low risk	Comment: The safety and tolerability analyses included data for all participants who received at least 1 dose of the study drug or placebo (N = 513)
Selective reporting (reporting bias); efficacy	Low risk	Comment: total number of participants with positive blood smear result at any time during prophylaxis was reported. Clinical cases of malaria were reported
Selective reporting (reporting bias); safety	High risk	"There were 9 serious adverse events in the study... No serious adverse events were considered by study physicians to be related to the study drug, and no deaths occurred" Comment: Data for serious adverse events were not attributed to the drug regimen. No information was provided on how causality was assessed
Other bias	High risk	Acknowledgement of "Philip Pickford and Rachel Moate (GlaxoSmithKline), for statistical and editorial advisement"

Hill 2000

Methods	Design: retrospective cohort study Study dates: June 1989 to May 1991 Malaria transmission pattern and local antimalarial drug resistance: various, not specified Adverse event monitoring: patient self-reported questionnaire. "Any reported illness was followed up by telephone interview about the nature of the illness, during which time more complete information was obtained using standardized questions"
Participants	Number enrolled: 869 participants enrolled, 822 completed follow-up Inclusion criteria: all individuals attending the International Traveler's Medical Service at the University of Connecticut Health Center and traveling for ≤ 90 days Exclusion criteria: none mentioned Factors influencing drug allocation: "prior to travel each person was given extensive counseling and written material on the prevention of malaria and traveler's diarrhea. They were given prescriptions for prophylactic antimalarials" Country of recruitment: USA Country of malaria exposure: Various: Indian subcontinent 21%, central and east Africa 20%, South America 16%, Southeast Asia 14%, West Africa 10%, Central America and Mexico 10%, North Africa 65, East Asia 6%, Carribean 5%, Southern Africa 5%, Middle East 3% Duration of exposure to malaria: median 19 days (up to 90 days) Type of participants: travellers
Interventions	*Included in the review*: 1. Mefloquine* 2. Chloroquine* *Not included in the review*: 2. Chloroquine-proguanil* **dosing regimen not specified*

Hill 2000 *(Continued)*

Outcomes	*Included in the review:* 1. Any adverse effects 2. Discontinuations of study drug due to adverse effects 3. Measures of adherence to the drug regime *Outcomes assessed not included in the review:* 4. Clinical cases of malaria 5. Adverse events (provided for entire cohort, not by type of malaria prophylaxis) 6. Adverse effects; other (all gastrointestinal disorders, all nervous system disorders - no comparative data provided) 7. Illness during and following travel
Notes	Funding sources: Not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** Age, sex, destination and duration of travel were measured but not reported across groups **2. Selection of participants into the study: moderate** Non-response rate was not reported. **3. Measurement of interventions: low** The antimalarial prescription was provided by a travel clinic which also performed the study **4. Departures from intended interventions: moderate** Information was provided on discontinuations, but no information was captured on switches between interventions **5. Missing data: low** Information on adverse effects was available for all participants who ever filled the prescription for the study drug (571/612, 93%) **6. Measurement of outcomes: serious** Comment: the outcome measure was subjective; participants and personnel were not blinded **7. Selection of the reported results: moderate** It is unclear which questions were included in the questionnaire. Information was provided on aggregate **8. Other: no information** No information provided on study sponsor

Hoebe 1997

Methods	Design: retrospective cohort study Study dates: January to June 1995 Malaria transmission pattern and local antimalarial drug resistance: various, not specified Adverse event monitoring: one-off telephone interview between 4 and 20 weeks post-travell
Participants	Number enrolled: 454 eligible travellers, 300 successfully contacted and agreed to participate Inclusion criteria: subjects who visited the travel vaccination service of the regional public health institute in Maastricht if they had returned from their journey to tropical countries between 4 and 20 weeks previously. The group of non-users was formed by people who travelled either to tropical countries without malaria risk or to cities in malarious areas, and by travellers who were prescribed an antimalarial drug but did not commence use Exclusion criteria: participants who had a serious adverse reaction to mefloquine in the first week Country of recruitment: Netherlands Region of malaria exposure: various; Asia, Africa, South America Duration of exposure to malaria: mean ˜3 weeks (range 1 to 9 weeks) Type of participants: travellers
Interventions	*Included in the review:* 1. Mefloquine (1 x 250 mg tablet) weekly, taken 1 week prior to leaving, during travel and 4 weeks after departure 2. Non-users of antimalarials *Not included in the review:* 3. Proguanil (1 x 100 mg tablet) twice daily, taken during travel and 4 weeks after departure
Outcomes	1. Adverse events; any, nausea, vomiting, abdominal pain, diarrhoea, headache, dizziness, abnormal dreams, insomnia, anxiety, depression, pruritis 2. Adverse events; other (palpitations, severity of symptoms, time point of symptoms in relation to drug taking) 3. Discontinuations of study drug due to adverse effects 4. Measure of adherence to the drug regimen
Notes	Funding sources: Not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** Travel destination varies significantly between users of mefloquine and non-users of prophylaxis (6.7% America mefloquine versus 29.0% non-users) **2. Selection of participants into the study: low** 13/454 (2.8%) of travellers successfully contacted refused to participate

Hoebe 1997 *(Continued)*

3. Measurement of interventions: low

Prescription was provided by a travel clinic which also performed the study, and discontinuations were reported

4. Departures from intended interventions: moderate

No information regarding switches been interventions of interest was reported

5. Missing data: moderate

"If somebody discontinued drug use within a certain period, symptoms that occurred in the following period were not counted"

Comment: Mefloquine has a half life of 17 to 21 days

6. Measurement of outcomes: moderate

"The participants were specifically asked about symptoms instead of adverse effects...To hide our focus on symptoms as adverse effects of the drugs, participants were informed that the aim of the study was to investigate symptoms during travelling. We structured the questionnaire so that the interviewers asked about symptoms first and drug use last, in order to blind them to the drug used when addressing symptoms"

7. Selection of the reported results: low

All prespecified outcomes were reported.

8. Other: no information

Funding source was not mentioned

Jute 2007

Methods	Design: cross-sectional cohort study Study dates: 2003 Malaria transmission pattern and local antimalarial drug resistance: during the dry season (considered a low risk malaria season). Local chloroquine/proguanil resistance Adverse event monitoring: Patient self-reported questionnaire
Participants	Number enrolled: 90 questionnaires distributed, 68 responses Inclusion criteria: "all expatriate employees at the mine" Exclusion criteria: non mentioned Country of recruitment: Mali Country of malaria exposure: Mali Duration of exposure to malaria: various, not specified Type of participants: long-term expatriates
Interventions	*Included in the review:* 1. Mefloquine 2. Doxycycline

Jute 2007 *(Continued)*

	3. Atovaquone-proguanil *Not included in the review:* 4. Chloroquine-proguanil
Outcomes	1. Adverse effects; any
Notes	Study sponsor not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** Sex was recorded but not reported across chemoprophylaxis groups. Duration of travel was not reported. Destination of travel was set by the study design. **2. Selection of participants into the study: serious** 68/90 response rate (76%) **3. Measurement of interventions: no information** It was unclear whether information on participants chemoprophylaxis was taken from medical records or patient self-reporting **4. Departures from intended interventions: moderate** No information regarding switches between interventions of interest were reported. Discontinuations were reported **5. Missing data: low** All information was collected at one time point **6. Measurement of outcomes: serious** The outcome measure was subjective. There was no mention of participants or outcome assessors being blinded. **7. Selection of the reported results: no information** No information was provided regarding which topics were included within the questionnaire **8. Other: no information** Funding source was not mentioned

Kato 2013

Methods	Design: cross-sectional cohort study Study dates: June 2009 to June 2011 Malaria transmission pattern and local antimalarial drug resistance: various, not specified Adverse event monitoring: patient self-reported questionnaire
Participants	Number enrolled: 1119 eligible travellers, 316 enrolled

Kato 2013 *(Continued)*

	Inclusion criteria: "travelers who visited Hibiya Clinic, and requested antimalarial drugs for malaria chemoprophylaxis from June 2009 to June 2011" Exclusion criteria: none mentioned Factors influencing drug allocation: "The choice of anti-malarial drug was supported by sufficient explanation about the advantages and disadvantages (efficacy, method, duration, side effect, cost and approval) of each drug" Country of recruitment: Japan Region of malaria exposure: various (n): East Africa 76, West Africa 63, South Africa 50, Southeast Asia 36, Central Africa 36, South Pacific 21, South America 16, India 8, North Africa 5, Central America 1 Duration of exposure to malaria: mean 20.0 ± 9.6 days in the atovaquone-proguanil group and 59.0 ± 15.9 days in the mefloquine group Type of participants: travellers
Interventions	1. Mefloquine (1 x 250 mg tablet, Mephaquin; Mepha) weekly, starting 1 week prior to arrival, during the stay, and continuing for 4 weeks after leaving the endemic area 2. Atovaquone-proguanil (1 tablet containing 250 mg atovaquone and 100 mg proguanil, Malarone; GlaxoSmithKline) daily, starting 2 days prior to arrival, during the stay, and for 1 week after leaving the endemic area
Outcomes	1. Adverse effects (any vertigo/dizziness, nausea, abdominal pain, diarrhoea, headache, insomnia, depression, any cardiovascular, any gastrointestinal, any psychoneurotic, allergic reaction) 2. Discontinuations of study drug due to adverse effects
Notes	Funding sources: not mentioned Communications with the study authors: the study authors provided us with disaggregated study data for the following outcomes: vertigo/dizziness, nausea, abdominal pain, diarrhoea, headache, insomnia, depression. Because we did not get receive the full disaggregated data set, we also retained this study in the analysis of groups of symptoms

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** PTravellers in the mefloquine group were significantly younger than travellers in the A/P group (p=0.01)" **2. Selection of participants into the study: serious** "316 of 1119 travelers (28.2 %) were enrolled" **3. Measurement of interventions: low** The prescription has been provided by travel clinic which also performed the study and discontinuations have been reported **4. Departures from intended interventions: moderate** No information was available regarding switches between interventions of interest **5. Missing data: low**

Kato 2013 *(Continued)*

	One participant in the mefloquine group appears to be missing from the adverse events analysis. No reason was given **6. Measurement of outcomes: serious** Comment: the outcome measure was subjective; participants and personnel were not blinded **7. Selection of the reported results: low** Study authors provided us with disaggregated study data for individual outcomes **8. Other: serious** "The authors wish to acknowledge that Makoto Ono and Tomoko Kawamura of GlaxoSmithKline are highly appreciated for conducting Data Management and Statistics Analysis of this study"

Korhonen 2007

Methods	Design: prospective cohort study Study dates: 1 August 2005 to 31 July 2006. Malaria transmission pattern and local antimalarial drug resistance: various, chloroquine resistance specified by country of destination Adverse event monitoring: "Peace Corps medical staff in these countries were provided surveys for distribution during mandatory in-country volunteer training sessions"
Participants	Number enrolled: 2701 (6216 Peace Corps volunteers during the time period) Inclusion criteria: "all Peace Corps countries with malaria risk" Exclusion criteria: none mentioned Factors influencing drug allocation: "Volunteers are provided chemoprophylaxis (either chloroquine, mefloquine, doxycycline, or atovaquone/proguanil)... medical officers can provide alternative chemoprophylaxis regimens for volunteers when adverse events or other factors require the cessation of any medication" Country of recruitment: various Country of malaria exposure: various Duration of exposure to malaria: "6 months or longer" Type of participants: Peace Corps volunteers
Interventions	*Included in the review:* 1. Mefloquine* 2. Chloroquine* 3. Doxycycline* 4. Atovaquone-proguanil* **dosing regimen not specified*

Korhonen 2007 *(Continued)*

Outcomes	1. Adverse effects; any (mild, moderate, severe, sought medical advice), nausea, vomiting, abdominal pain, diarrhoea, headache, dizziness, abnormal dreams, insomnia, depression, anxiety, visual disturbance 2. Adverse effects; other (unsteadiness, hair loss, weakness, itchy skin, photosensitivity, yeast infection) 3. Serious adverse effects 4. Discontinuations of study drug due to adverse effects
Notes	Funding sources: "CK and PJ are employed by the Peace Corps, which has a significant number of volunteers taking anti-malarial medications. There were no other financial disclosures" Communications with study authors: The study authors provided us with access to the disaggregated study data for the specific symptoms mentioned above. The questionnaire in the paper allowed participants to describe side effects from the antimalarial they were currently taking, and any regimen they had previously used. For non-serious side effects, in line with the original paper, we only included side effects for the subject's original regimen. Where subjects had previously taken more than one regimen, we only include side effects for whichever regimen to which the participant attributed the greater number of side effects; this affected 70/2701 participants. This analysis resulted in a decrease in the effect size for side effects attributed to mefloquine. For serious side effects (hospitalizations) and discontinuations we included all participants entries for all regimens. In addition, our denominator differed from the original paper because we did not exclude participants who had been in post for fewer than six months

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** "The questionnaire did not collect demographic information because of privacy concerns" Comment: destination has been reported, but not by type of antimalarial chemoprophylaxis. Duration was set by the study design **2. Selection of participants into the study: serious** "A total of 2701 surveys were received yielding a response rate of 43%" **3. Measurement of interventions: moderate** Participants were asked to self-report which prophylaxis they were currently taking and had previously taken **4. Departures from intended interventions: moderate** Switches between interventions of interest were reported. Approximately 1/3 of study participants had switched prophylactic regimens **5. Missing data: low** We were able to include all participants in the study analysis because we had access to the original data set **6. Measurement of outcomes: serious** "If respondents identified any adverse event, the survey instructed them to self-report which drug they believed caused the adverse event"

Korhonen 2007 *(Continued)*

	Comment: the outcome measure was subjective; participants and personnel were not blinded **7. Selection of the reported results: low** We were able to include all results in the analysis because we had access to the original data set **8. Other: low** No evidence of pharmaceutical company funding

Kuhner 2005

Methods	Design: prospective cohort study Study dates: 2000 to 2003 Malaria transmission pattern and local antimalarial drug resistance: various, not specified Adverse event monitoring: retrospective patient self-reporting questionnaire
Participants	Number enrolled: 495 enrolled, 284 response rate Inclusion criteria: unclear. Users of the travel medicine department of the lower Saxony regional health office in Hanover, Germany Exclusion criteria: None mentioned Factors influencing drug allocation: "the prescriptions of medications followed individual consultation" Country of recruitment: Germany Country of malaria exposure: various, not specified Duration of exposure to drug: atovaquone-proguanil mean 2.6 weeks, mefloquine mean 7 weeks Type of participants: short-term travellers
Interventions	*Included in the review:* 1. Mefloquine* 2. Atovaquone-proguanil* *Not included in the review:* 3. Chloroquine-proguanil* 4. Chloroquine (not included in the study analysis) **dosing regimen not specified*
Outcomes	1. Adverse effects; any, nausea, vomiting, abdominal pain, diarrhoea, headache, dizziness, abnormal dreams, insomnia, pruritis 2. Adverse effects; other (concentration difficulties, palpitations, circulation disorders, rash) 3. Discontinuations of study drug due to adverse effects
Notes	Funding sources: not mentioned

Kuhner 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** Sex, age and duration of travel were reported but not balanced across groups **2. Selection of participants into the study: serious** 284/495 (59.8%) response rate **3. Measurement of interventions: low** The prescription was provided by a travel clinic which also performed the study; switches and discontinuations were recorded and reported. **4. Departures from intended interventions: moderate** No information was provided regarding switches between prophylactic regimens **5. Missing data: low** All information was collected at one time point **6. Measurement of outcomes: serious** The outcome measure was subjective. There was no mention of outcome assessors being blinded **7. Selection of the reported results: moderate** Insufficient information was provided regarding the questionnaire to know whether all outcomes were reported **8. Other: no information** Study sponsor not mentioned

Landman 2015

Methods	Design: prospective cohort study Study dates: 19 August to 30 September 2013 Malaria transmission pattern and local antimalarial drug resistance: various Adverse event monitoring: participant self-reported questionnaire
Participants	Number enrolled: 3207 emails sent, 1184 unique, valid responses received Inclusion criteria: "(volunteers in) Peace Corps offices of all 23 countries with active posts in the Africa region to all active Volunteers in-country" Exclusion criteria: Volunteers serving in Ethiopia, Kenya, Tanzania, Namibia, Botswana, South Africa Region of recruitment: African region except Ethiopia, Kenya, Tanzania, Namibia, Botswana, South Africa Factors influencing drug allocation: "all prophylaxis options (mefloquine, doxycycline, atovaquone-proguanil) [are] equally available... They are instructed to individualize their choice of agent

Landman 2015 *(Continued)*

	based on area-specific recommendations, drug contraindications and precautions, drug tolerance, and dosing schedule" Country of malaria exposure: various: Togo (3.7%), Sierra Leone (6.3%), Uganda (7.8%), Liberia (5.6%), Malawi (2.0%), Cameroon (11.4%), Benin (10.2%), Burkina Faso (1.9%), Zambia (6.0%), Mozambique (4.5%), Ghana (10.8%), Rwanda (5.4%), Gambia (4.4%), Madagascar (11.1%), Swaziland (2.3%) Duration of exposure to malaria: various, not specified Type of participants: Peace Corps volunteers
Interventions	1. Mefloquine* 2. Atovaquone-proguanil* 3. Doxycycline* **dosing regimen not specified*
Outcomes	*Included in the review:* 1. Adverse effects; any, vertigo, headache, abnormal dreams, insomnia, anxiety, depression, psychosis 2. Adverse effects; other (any neuropsychiatric disorder, any gastrointestinal disorder, any skin or subcutaneous disorder, limb numbness, tinnitus, 'constitutional', genitourinary) 3. Measures of adherence to the drug regimen *Outcomes assessed not included in the review:* 4. Reasons for non-adherence (not ascribed to prophylactic regimen, provided on aggregate), 5. Malaria knowledge 6. Health behaviours
Notes	Funding sources: not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** The age, sex and BMI of included participants was not recorded. The destination and duration of travel was not reported by prophylactic regimen **2. Selection of participants into the study: serious** 1184/3248 (36%) response rate **3. Measurement of interventions: moderate** Travellers were asked to self-report which prophylaxis they were taking at various time points during treatment **4. Departures from intended interventions: serious** "Two hundred seventy-six (35%) respondents reported having changed prophylaxis at some point during their service" Comment: this was not provided by prophylactic regimen **5. Missing data: low**

Landman 2015 *(Continued)*

	703/781 (90%) participants reported data for adherence; 733/781 (94%) participants reported data for adverse events. Data were only included from the 2015 version of the publication **6. Measurement of outcomes: serious** Comment: the outcome measure was subjective; participants and personnel were not blinded **7. Selection of the reported results: low** All outcomes prespecified in the methods section were reported **8. Other: no information** Study sponsor not mentioned

Laver 2001

Methods	Design: cross-sectional cohort study Study dates: February 2000 Malaria transmission pattern and local antimalarial drug resistance: "during February 2000, which was a peak period of malaria transmission in Zimbabwe" Adverse event monitoring: patient self-reported questionnaire
Participants	Number enrolled: 660 Inclusion criteria: Passengers in Harare and Victoria Falls international airport during February 2000 Exclusion criteria: "Children under the age of 18 were excluded on the assumption that parents probably influence their health seeking behavior... Excluded, were travelers from the African continent and VIP travelers who exited through special departure lounges" Factors influencing drug allocation: no infromation provided Country of recruitment: Zimbabwe Country of malaria exposure: Zimbabwe Duration of exposure to malaria: various: 1 week or less, N = 317; 8 days to 2 weeks, N = 144; 15 days to 4 weeks, N = 90; > 4 weeks, N = 41 Type of participants: travellers
Interventions	*Included in the review*: 1. Mefloquine* 2. Doxycycline* 3. Chloroquine* *Not included in the review:* 4. Proguanil* 5. Dapsone and pyrimethamine* 6. Chloroquine and proguanil*

Laver 2001 *(Continued)*

	**dosing regimen not specified*
Outcomes	*Included in the review:* 1. Measure of adherence to the drug regimen *Outcomes assessed not included in the review:* 2. Sources of pre-travel health advice 3. Knowledge about malaria transmission 4. Knowledge about malaria prevention 5. Threat and risk perception
Notes	Funding sources: not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** Sex (P < 0.008), education (P < 0.022), previous episodes of malaria (P < 0.001) and access to pre-travel advice (P < 0.001) were all significantly associated with reduced compliance at the significance value set by the study. None of these factors were adjusted for in the analysis **2. Selection of participants into the study: moderate** "The nonresponse rate was about 10% (n = 65), with the main reason being the short transit time" **3. Measurement of interventions: low** Participants were asked to self-report which prophylactic regimen they were taking while they were still taking it **4. Departures from intended interventions: moderate** No information was provided regarding switches between prophylactic regimens **5. Missing data: low** Adherence information was not available for 4/595 participants **6. Measurement of outcomes: serious** The outcome measure was based on participant self-reporting; participants and personnel were not blinded. **7. Selection of the reported results: moderate** There was insufficient information provided to know what questions were asked regarding adherence **8. Other: low** "The authors had no financial or other conflicts of interest to disclose"

Laverone 2006

Methods	Design: retrospective cohort study Study dates: 1 January 2003 to 31 December 2004 Malaria transmission pattern and local antimalarial drug resistance: various, not specified Adverse event monitoring: "An anonymous survey in a post-travel situation"
Participants	Number enrolled: 1176 agreed to participate, 1237 approached Inclusion criteria: "travellers who had already completed their journey for which they had undergone immunization prophylaxis and who had returned to complete their vaccination schedule" Exclusion criteria: none mentioned Factors influencing drug allocation: "offered health advice following the World Health Organization guidelines for international travel" Country of recruitment: Italy Regions of malaria exposure: 97 countries: 39 states in Africa, 25 in Asia, 16 in North and Central America, 8 in South America, 6 in Europe and 3 in Oceania Duration of exposure to malaria: 1 to 7 days, 8.9%; 8 to 14 days, 30.1%; 15 to 21 days, 34.6%; 22 to 30 days, 16.8%; > 30 days, 8.9%; not available 0.7% Type of participants: travellers
Interventions	*Included in the review:* 1. Mefloquine* 2. Atovaquone-proguanil* 3. Chloroquine* *Not included in the review:* 4.Chloroquine-proguanil* 5. Proguanil* **dosing regimen not specified*
Outcomes	*Included in the review:* 1. Adverse effects; any, visual impairment (blurred vision), nausea, vomiting, abdominal pain, diarrhoea, headache, dizziness, abnormal dreams (nightmares), insomnia, anxiety (anxiety disorder), depression, psychosis (hallucinations) 2. Adverse effects; other (slight illness, tiredness, restlessness, drowsiness, palpitations, weakness, photosensitization, mental confusion, rash) *Outcomes assessed not included in the review:* 3. Adverse effects; other, incidence < 1% (liver pain, aerophagy, rise in transaminase levels, gastrointestinal disturbance, epistaxis, fever) 4. Compliance with vaccinations 5. Side effects from vaccinations 6. Occurrence of health problems and unforeseen events during travel in the countries visited

Laverone 2006 *(Continued)*

	7. Attention to avoiding potentially risky food and drink
Notes	Funding sources: Not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** Demographic information was collected, but provided on aggregate for the entire cohort **2. Selection of participants into the study: low** 1176 of 1237 (95.1%) response rate **3. Measurement of interventions: serious** Participants were asked to self-report which prophylactic regimen they had used, up to over 12 months since travelling **4. Departures from intended interventions: serious** No switches were reported, and this information was not sought in the questionnaire **5. Missing data: low** 642/646 (99%) participants were included in the analysis **6. Measurement of outcomes: serious** Comment: the outcome measure was subjective; participants and personnel were not blinded **7. Selection of the reported results: low** The questionnaire was provided in full, and all outcomes were reported **8. Other: no information** No information was provided regarding the study sponsor

Lobel 2001

Methods	Design: cross-sectional cohort study Study dates: 13 July to 9 August 1997 Malaria transmission pattern and local antimalarial drug resistance: various, not specified Adverse event monitoring: patient self-reported questionnaire
Participants	Number enrolled: 6633 respondents, 5626 met inclusion criteria Inclusion criteria: "travelers departing Nairobi, or Mombasa, Kenya, from July 13 to August 9, 1997, on flights to Europe, including London, Paris, Frankfurt, Amsterdam, and Rome" Exclusion criteria: residents of African countries, individuals who had remained in Africa for more than 1 year, individuals who visited only non malarious areas, including Nairobi and Lesotho

Lobel 2001 *(Continued)*

	Factors influencing drug allocation: no information available Region of recruitment: Nairobi or Mombasa, Kenya Region of malaria exposure: Nairobi or Mombasa, Kenya Duration of exposure to malaria: < 5 weeks Type of participants: travellers
Interventions	*Included in the review:* 1. Mefloquine* 2. Doxycycline* 3. Chloroquine* *Not included in the review:* 4. Chloroquine-proguanil* 5. Proguanil* **dosing regimen not specified*
Outcomes	*Included in the review:* 1. Adverse effects; any, 2. Serious adverse outcomes 3. Adverse effects; other (neuropsychologic, gastrointestinal, respiratory) 4. Measure of adherence to the drug regimen *Outcomes assessed not included in the review:* 5. Pre-travel medical advice 6. Compliance with antimosquito measures 7. Self-treatment of presumed malaria
Notes	Funding sources: not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** The number of travellers and country of origin was reported, but was not adjusted for in the analysis. Sex, age and duration of stay were reported on aggregate. **2. Selection of participants into the study: serious** Response rate 6633/15,487 (43%) **3. Measurement of interventions: low** Participants were asked to provide information regarding their prophylactic regimen during their flight home, while they should have still been using it

Lobel 2001 *(Continued)*

4. Departures from intended interventions: moderate

No information was available regarding switches between alternative prophylactic regimens

5. Missing data: low

4934/4982 (99%) participants included in adverse event reporting

6. Measurement of outcomes: serious

Comment: the outcome measure was subjective; participants and personnel were not blinded

7. Selection of the reported results: moderate

There was insufficient information provided regarding the questions included in the questionnaire. Symptoms were grouped together to report outcomes

8. Other: low

"The authors had no financial or other conflicts of interest to disclose"

Mavrogordato 2012

Methods	Design: retrospective cohort study Study dates: October to December 2005, with a 2 year follow-up Malaria transmission pattern and local antimalarial drug resistance: "Malaria endemic area. Local chloroquine/proguanil resistance" Adverse event monitoring: Not clear
Participants	Number enrolled: 33 Inclusion criteria: not explicitly stated. Participants were travellers who took part in a scientific survey and rafting expedition in Ethiopia between October and December 2005 Exclusion criteria: none stated Country of recruitment: various, participants were from "a non-malarious area, mainly the UK" Country of malaria exposure: Ethiopia Duration of exposure to malaria: 3 months Type of participants: travellers
Interventions	*Included in the review:* 1. Mefloquine, dose not specified, during travel and 4 weeks after return 2. Atovaquone-proguanil, dose not specified, during travel and for 1 week after return 3. Doxycycline, dose not specified, during travel and 4 weeks after return *Not included in the review:* 4. Chloroquine-proguanil, dose not specified, during travel and 4 weeks after return
Outcomes	*Included in the review:*

Mavrogordato 2012 *(Continued)*

	1. Measures of adherence to the drug regimen *Outcomes assessed not included in the review:* 2. Clinical cases of malaria 3. Adverse effects (information not provided by drug class) 4. Factors influencing choice of prophylaxis
Notes	Funding sources: Work was supported by the Biomedical Research Centre (Grant RG561620 to AMLL)

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** Demographic information is provided for the entire cohort **2. Selection of participants into the study: low** No participants refused to participate in the study. Start of follow-up began at the start of travel and not at the start of treatment, but this was judged to have a low impact on monitoring self-reported adherence **3. Measurement of interventions: low** Intervention status was determined by one of the participants on the expedition **4. Departures from intended interventions: low** There are no documented switches between interventions of interest **5. Missing data: low** Two people (6%) were lost to follow-up in respect to data on efficacy. No participants were lost to follow-up when monitoring adherence **6. Measurement of outcomes: serious** Adherence was monitored by the medical officer on the trip, and reporting may have been influenced by social desirability bias **7. Selection of the reported results: low** All prespecified outcomes have been reported **8. Other: low** Government funding

Meier 2004

Methods	Design: retrospective cohort study Study dates: 1 January 1990 and 31 December 1999 Malaria transmission pattern and local antimalarial drug resistance: various, not specified

Meier 2004 *(Continued)*

	Adverse event monitoring: incident cases of depression, psychoses and panic attacks severe enough to require hospitalisation, referral to a specialist or specific pharmacological treatment within the UK general practice research database
Participants	Number enrolled: 35,370 Inclusion criteria: "men and women aged 17-79 years who received between one and four prescriptions for mefloquine, proguanil and/or chloroquine, or subjects who received one prescription only for doxycycline... we included only those subjects who medical record contained a code indicating that the person received the drug for malaria prophylaxis within 1 week of the prescription date e.g. 'travel advice' or 'prophylactic drug use'" Exclusion criteria: "participants who received the study drugs on a longer-term basis...subjects had to be enrolled in the database for at least 12 months before the date of the first prescription for a study drug and had to have had some recorded activity (diagnoses or drug prescriptions) after the prescription(s) for an antimalarial drug... subjects with a history of alcoholism" Country of recruitment: UK Country of malaria exposure: various, not specified Duration of exposure to malaria: various, not specified Type of participants: travellers
Interventions	*Included in the review:* 1. Mefloquine* 2. Doxycycline* *Not included in the review:* 3. Chloroquine-proguanil* 4. Proguanil* 5. Chloroquine* (data reported combined with proguanil and chloroquine-proguanil) **dosing regimen not specified*
Outcomes	1. Serious adverse events 2. Adverse events; psychiatric disorders (depression, psychosis) 3. Adverse events; other (panic attacks, suicide)
Notes	Funding sources: "This study was funded by an unconditional grant by F. Hoffmann-La Roche Ltd, Basel, Switzerland"

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** Women and those aged 40 to 49 years were at higher risk of depression but this was not adjusted for in the analysis. Risk ratio estimates for psychoses and panic attacks could not be adjusted for because numbers were too small for the multivariate model. Data on destination and duration of travel were not available **2. Selection of participants into the study: low**

Meier 2004 *(Continued)*

Recruitment onto the General Practice Research Database was unlikely to be related to exposure or outcome

3. Measurement of interventions: moderate

"Antimalarial drugs can be used for malaria prophylaxis, for treatment of an acute malaria infection, or as a reserve drug… In order to distinguish these options, we included only those subjects whose medical records contained a code indicating 'travel advice' or 'prophylactic drug use'"

4. Departures from intended interventions: serious

Discontinuations and switches between prophylactic regimens were not recorded in this database

5. Missing data: low

All participants in the research database were included in the analysis

6. Measurement of outcomes: moderate

"...we reviewed all computer records of potential cases and included or excluded cases on the available clinical information, blinded to exposure status"

Comment: general practitioners diagnosing patients would have been aware of their exposure status

7. Selection of the reported results: low

Information on all outcomes prespecified in the methods section were reported for all participants.

8. Other: serious

Funded by Roche pharmaceuticals

Napoletano 2007

Methods	Design: retrospective cohort study Study dates: 1 October 2005 to 30 June 2006 Malaria transmission pattern and local antimalarial drug resistance: various, not specified Adverse event monitoring: telephone questionnaire to all travellers to tropical countries for whom antimalarial chemoprophylaxis was prescribed
Participants	Number enrolled: 1906 questionnaires returned Inclusion criteria: participants staying in high risk malarial areas, aged between 18 and 65 years, with no severe underlying disease (e.g. heart disease, diabetes) with an available phone number Exclusion criteria: immigrants (due to potential difficulty in linguistic communication) Country of recruitment: Italy Country of malaria exposure: various: Kenya, Tanzania/Zanzibar, India, Madagascar, Brazil, other countries of South America, South Africa, Senegal, Mali, Myanmar, Ghana, Congo, and others Duration of exposure to malaria: mean stay 2 weeks Type of participants: Travellers

Napoletano 2007 *(Continued)*

Interventions	*Included in the review:* 1. Mefloquine* 2. Chloroquine* 3. Atovaquone + proguanil* 4. Doxycycline* *Not included in the review*: 5. Chloroquine + proguanil* **dosing regimen not specified*
Outcomes	*Included in the review:* 1. Adverse effects; any 2. Serious adverse effects 3. Adverse effects; other (any gastrointestinal, any neuropsychiatric) 4. Discontinuations of study drug due to adverse effects *Outcomes assessed not included in the review:* 5. Clinical cases of malaria 6. Eating habits during travel
Notes	Funding sources: Not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** Demographic information was provided on aggregate for the entire cohort **2. Selection of participants into the study: moderate** Non-response rates to the questionnaire were not reported **3. Measurement of interventions: moderate** The prescription was provided by several travel clinics which also performed the study. However, it was unclear whether this information was used to determine intervention status or relied on participant self-reporting **4. Departures from intended interventions: low** Discontinuations were reported, with detailed reasons for discontinuations. No switches to alternative regimens were reported **5. Missing data: low** All participants were included in the analysis **6. Measurement of outcomes: serious** Comment: the outcome measure was subjective; participants and personnel were not blinded

Napoletano 2007 *(Continued)*

	7. Selection of the reported results: low The methods section makes clear which outcomes were being assessed; all outcomes were reported **8. Other: no information** No information was provided regarding the study sponsor

Nosten 1994

Methods	Design: RCT Study dates: January 1987 to November 1990 Malaria transmission pattern and local antimalarial drug resistance: "in an area of seasonal malaria transmission... mefloquine and quinine resistance is increasing in this area, and the proportion of re-crudescent infections is rising" Adverse event monitoring: trial occurred over two phases. Phase 1: Weekly basic observations and simple symptom questionnaire. ECG, haematological and biochemical tests were done fortnightly. Children born to women in the trial were assessed at birth and at 3, 6, 12, and 24 months. Phase 2: weekly basic observations and expanded simple symptom questionnaire. ECG and blood tests were performed at baseline, at midstudy and at term. Each delivery was supervised. Additional assessments at 1 week and 2 and 9 months for children born to women in the trial
Participants	Number enrolled: 339 Inclusion criteria: "Women attending the weekly clinic were admitted to the study if they were at > 20 weeks of estimated gestation" Exclusion criteria: Not mentioned Region of recruitment: Thai-Burmese border Region of malaria exposure: Thai-Burmese border Duration of exposure to malaria: ongoing exposure in a semi-immune population, monitored until delivery Type of participants: Pregnant Thai residents in malaria-endemic area (presumed semi-immune)
Interventions	1. Mefloquine (1 x 250 mg tablet, Lariam; Hoffmann-La Roche) weekly for 4 weeks, then 125 mg weekly until delivery, with 500 mg base loading dose in phase 1 but not phase 2 2. Placebo (1 tablet) weekly until delivery
Outcomes	*Included in the review:* 1. Clinical cases of malaria 2. Episodes of parasitaemia 3. Serious adverse events (including childhood deaths) 4. Adverse events; vertigo, visual impairment (visual abnormalities), nausea, vomiting, abdominal pain, headache, dizziness, pruritis 5. Adverse events; other (weakness, anorexia, cough, falls, constipation, unsteadiness) 6. Discontinuation of study drug due to adverse effects

Nosten 1994 *(Continued)*

	7. Adverse pregnancy outcomes (spontaneous abortions, still births, congenital malformations) *Outcomes assessed not included in the review:* 8. Laboratory tests; haematologic (full blood count, haematocrit) and biochemical (creatinine, blood urea, transaminases, alkaline phosphatase, albumin, globulin) 9. Outcomes related to pregnancy; weight gain during follow-up, complications of labour, mean duration of labour, maternal anaemia 10. Fetal outcomes; mean birth weight, percent premature, fetal distress 11. Infant follow up; mean age at which children could crawl, sit, walk or talk, Romberg test
Notes	Funding sources: United Nations Development Programme/World Bank/World Health Organization Special Programme for Research and Training in Tropical Diseases; Wellcome Trust of Great Britain; Praevention Foundation. The Hague (to FLK)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...women were randomized to receive either mefloquine…or placebo" Comment: unclear what method of randomization was used
Allocation concealment (selection bias)	Unclear risk	"...the investigators were unaware of the randomisation" Comment: no mention of method used to conceal allocation
Blinding of participants and personnel (performance bias) Adverse effects/events	Low risk	"...double blind...women were randomised to receive either mefloquine…or identical placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"...the investigators were unaware of the randomisation"
Incomplete outcome data (attrition bias); efficacy	Low risk	Comment: total number of participants with positive blood smear result at any time during prophylaxis was reported. Clinical cases of malaria were reported"
Incomplete outcome data (attrition bias); safety	High risk	"Ten women (8%) in phase I (3 mefloquine, 7 placebo) and 18 (8%) in phase II (9 in each group) dropped out of the study. The main reason was the discomfort of blood sampling (26 cases) and, in 1 case, pruritus attributed to mefloquine" Comment: 28 women dropped out but reasons were provided for only 27 women; numbers were not provided across groups
Selective reporting (reporting bias); efficacy	Low risk	Comment: all episodes of parasitaemia and clinical cases of malaria were reported
Selective reporting (reporting bias); safety	High risk	Comment: Data on adverse effects were reported for only participants from phase 2 of the trial (220/339 women). Fifteen symptoms were listed in the comparative table, but the narrative states "twenty questions were asked". Romberg test results were not reported. Biochemical, haematological and ECG parameters were not reported other than "there were no differences"
Other bias	Low risk	Funding: United Nations Development Programme/World Bank/World Health Organization Special Programme for Research and Training in Tropical Dis-

Nosten 1994 *(Continued)*

	eases; Wellcome Trust of Great Britain; Praevention Foundation. The Hague (to FLK)

Ohrt 1997

Methods	Design: RCT Duration of study: May to July 1994 Malaria transmission pattern and local drug resistance: "*P. falciparum* resistant to sulfadoxine-pyrimethamine and both *P falciparum* and *P vivax* resistant to chloroquine" Adverse event monitoring: symptoms reported in the first week of the study, daily questioning about symptoms, exit questionnaire
Participants	Number enrolled: 204 Inclusion criteria: "All soldiers from military posts that were considered to have high malaria attack rates" Exclusion criteria: history of frequent travel, allergy to one of the study drugs, glucose-6-phosphate dehydrogenase deficiency, history of underlying illness Country of recruitment: Indonesia Country of malaria exposure: Indonesia Duration of exposure to malaria: Study duration was approximately 13 weeks Type of participants: military, semi-immune (60% of participants had prior exposure to malaria)
Interventions	1. Mefloquine (1 x 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).* 2. Doxycycline hyclate (1 x 100 mg capsule) once daily* 3. Placebo* Co-interventions: All soldiers were given doxycycline tablets for 4 to 6 weeks to enable clearance of sulfadoxine-pyrimethamine from the blood before study prophylaxis began. All participants received radical treatment for pre-existing malaria parasites in the blood and liver prior to beginning study prophylaxis. **matched placebo for each treatment arm*
Outcomes	*Included in the review:* 1. Clinical cases of malaria 2. Adverse events; any, nausea, vomiting, abdominal pain, diarrhoea, headache, dizziness, insomnia, abnormal dreams 3. Serious adverse events 4. Adverse events; other (all gastrointestinal, all neurologic, constipation, anorexia, fever, malaise, skin related, cough, somnolence, palpitations, sexual dysfunction) 5. Discontinuation of study drug due to adverse effect *Outcomes assessed not included in the review:*

Ohrt 1997 *(Continued)*

	6. Exit questionnaire (incomplete data reported)
Notes	Funding source: Pfizer Indonesia supplied active and placebo doxycycline; F. Hoffman-La Roche supplied active and placebo mefloquine, and gave financial support; USA Army Medical Research and Materiel Command gave financial support; USA Naval Medical Research and Development Command gave financial support

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Block randomization was used (block size, 15)" Comment: Used a randomization code, but it was not stated how it was generated
Allocation concealment (selection bias)	Unclear risk	"The randomization code was stored in individual envelopes in a locked box at the study site...Drugs were packaged into weekly ziplock plastic bags" Comment: Unclear whether the investigators or participants would foresee assignment. There was no mention of central allocation, sequentially numbered drug containers or sequentially numbers opaque sealed envelopes
Blinding of participants and personnel (performance bias) Adverse effects/events	Low risk	"Drugs were packaged into weekly zipper-lock plastic bags: each bag contained a mefloquine or mefloquine placebo tablet and a blister pack of seven doxycycline or doxycycline placebo capsules (double-dummy technique)" The placebo medication had an "identical appearance"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The randomisation code was stored in individual envelopes in a locked box at the study site. All investigators and study personnel did not have access to or know the randomisation code throughout the study"
Incomplete outcome data (attrition bias); efficacy	Unclear risk	"Sixteen of the 204 participants did not complete the study" Comment: It was unclear whether the duration of follow up included the post-prophylaxis period to monitor for relapses
Incomplete outcome data (attrition bias); safety	High risk	Exit questionnaire: "Only data from persons who were still receiving the study drug at the time of the questionnaire were included" Comment: numbers not reported
Selective reporting (reporting bias); efficacy	Low risk	"The primary end point for efficacy was the first occurrence of malaria, as documented by a positive malaria smear" Comment: all cases of malaria were reported.
Selective reporting (reporting bias); safety	High risk	Comment: Not all data were reported from the exit questionnaire; the study reports "...the only statistically significant finding". Data on adverse symptoms were not reported for the placebo group
Other bias	Low risk	"Neither of the pharmaceutical companies that provided support played any role in the gathering, analysing or interpreting the data"

Overbosch 2001

Methods	Design: RCT

Overbosch 2001 *(Continued)*

	Duration of study: April to October 1999 Malaria transmission pattern and local drug resistance: not mentioned Adverse event monitoring: "evaluated 7, 28 and 60 days after return to obtain information about a targeted list of adverse events"
Participants	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" Countries of recruitment: Canada, Germany, Netherlands, South Africa, UK Regions of malaria exposure: various malaria-endemic destinations (79% Africa, 6% South America) Mean duration of exposure to malaria: 2.5 weeks Type of participants: travellers, non-immune
Interventions	1. Mefloquine (1 x 250 mg tablet; or alternatively ¼, ½ or ¾ of a tablet, according to body weight) once weekly, starting 1 to 3 weeks before travel and continuing for 4 weeks after travel* 2. Atovaquone-proguanil (1 combined tablet containing 250 mg atovaquone and 100 mg proguanil hydrochloride; or alternatively 1 to 3 combined tablets for children 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* **matched placebo for each treatment arm*
Outcomes	*Included in the review:* 1. Clinical cases of malaria (antibody to blood-stage malaria parasites) 2. Adverse events; any 3. Serious adverse events 4. Adverse effects; any (moderate or severe), visual impairment, nausea, vomiting, abdominal pain, diarrhoea, headache, dizziness, abnormal dreams, insomnia, anxiety, depression, pruritis 5. Adverse effects; other (mouth ulcers) 6. Discontinuation of study drug due to adverse effects 7. Measures of adherence to the drug regimen *Outcomes assessed not included in the review:* 8. Laboratory tests; haematology (haemoglobin level, white blood cell count and platelet count) and chemistry (creatinine and alanine aminotransferase)
Notes	Funding source: GlaxoSmithKline "Subjects were enrolled in study MAL30010"- Enrollment criteria and study conduct were described in a separate publication (Høgh 2000) which refers to a different study population (atovaquone-proguanil versus chloroquine-proguanil).

Risk of bias

Overbosch 2001 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A computer-generated code was used to randomly assign a treatment number" (Høgh 2000)
Allocation concealment (selection bias)	Low risk	"Treatment codes were provided to investigators in opaque sealed envelopes, to be opened only if knowledge of study drug assignment was required for management of a medical emergency" (Høgh 2000)
Blinding of participants and personnel (performance bias) Adverse effects/events	Low risk	"For each active drug, capsules or film-coated tablets were identical in appearance to the matching placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All subjects and study personnel remained blinded to treatment assignment with 5 exceptions. Two subjects in the atovaquone-proguanil group and 3 in the mefloquine group lost their study drug during their return trip from a malaria-endemic area, and the investigator broke the blind to enable completion of postexposure prophylaxis with active drug"
Incomplete outcome data (attrition bias); efficacy	Low risk	"A total of 963 subjects completed the 60-day follow-up period and had efficacy information recorded. A total of 915 subjects had paired serum samples available for serological testing" Comment: 963/976 (randomized and received first dose of study drug) = 98.7%. 915/976 = 93.75%. Reasons for leaving the study early were reported and numbers were balanced across groups
Incomplete outcome data (attrition bias); safety	Unclear risk	Comment: 96.35% of randomized participants were included in adverse event reporting. Reasons for leaving the study early were reported and numbers were balanced across groups
Selective reporting (reporting bias); efficacy	Low risk	Comment: Full clinical details were provided for every episode in which an episode of malaria was considered (4 cases)
Selective reporting (reporting bias); safety	High risk	Comment: Data on adverse symptoms were not reported for the placebo group due to a shorter duration of follow-up. Data were collected 7, 28 and 60 days after travel. However, data were only presented for 7 days after return
Other bias	High risk	Funding: GlaxoSmithKline It was not made clear whether the interpretation of the study findings was independent of the study sponsor

Pearlman 1980

Methods	Design: RCT Study dates: unclear, during 1977 Malaria transmission pattern and local antimalarial drug resistance: "subjects were resident in an area highly endemic for *P. vivax* and chloroquine resistant *P. falciparum*" Adverse event monitoring: "a physician visited the study area each week and conducted a sick call for participating and nonparticipating villagers...Between physician visits, residents were taken to a nearby health centre for serious medical problems"

Pearlman 1980 *(Continued)*

Participants	Number enrolled: 990 Inclusion criteria: "All eligible and consenting villagers over 10 years of age were included in the study" Exclusion criteria: "Female villagers of childbearing age (15-44 years) were not considered for inclusion" Country of recruitment: The Bhu Phram Valley, Thailand Country of malaria exposure: The Bhu Phram Valley, Thailand Duration of exposure to malaria: study duration 26 weeks Type of participants: Thai residents, semi-immune
Interventions	1. Mefloquine (1 x 180 mg tablet, children 22 to 35 kg ½ dose) weekly 2. Mefloquine (1 x 360 mg tablet, children 22 to 35 kg ¼ dose) weekly 3. Mefloquine (1 x 360 mg tablet, children 22 to 35 kg ¼ dose) every 2 weeks 4. Placebo (1 x tablet) weekly Co-interventions: "Those who had experienced falciparum parasitemias were given a therapeutic dose of sulfadoxine (1,500 mg)-pyrimethamine (75 mg), and those with vivax or malariae parasitemias were treated with the standard regimen of chloroquine (1,500 mg over a 3-day period), followed by primaquine, 15 mg daily for 14 days, for those study subjects known to be G-6-PD normal"
Outcomes	*Included in the review:* 1. Clinical cases of malaria 2. Episodes of parasitaemia 3. Adverse events; any *Outcomes assessed not included in the review:* 4. Laboratory tests; haematocrit, white cell count, white cell differential, serum glutamic oxaloacetic transaminase, alkaline phosphatase and blood urea nitrogen
Notes	Funding sources: Not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Assignment to one of six treatment groups was made on a stratified random number basis" Comment: no details of how random numbers were generated
Allocation concealment (selection bias)	Unclear risk	"In the course of this visit, the technician opened a sealed, numbered envelope, gave the enclosed tablets, and observed the subject swallow them" Comment: no mention of the envelope being opaque
Blinding of participants and personnel (performance bias) Adverse effects/events	Low risk	"Each subject received two tablets each week (medication, placebo or a combination) in order to maintain the double blind nature of the study" "All tablets were identical in appearance"

Pearlman 1980 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: described as double blind but not clear how this was achieved
Incomplete outcome data (attrition bias); efficacy	Unclear risk	"Nine hundred and ninety nine subjects began the 25-week field trial and 856 completed it (86.5%). 160/189 (85%) of the mefloquine 180 mg weekly group, 169/191 (88%) of the mefloquine 360 mg weekly, 158/184 (86%) of the mefloquine 360 mg fortnightly and 36/44 (82%) of the placebo group completed the trial" Comment: reasons for losses to follow-up were not reported
Incomplete outcome data (attrition bias); safety	Low risk	"There was no clinical evidence of drug toxicity in the 990 study participants, nor were there significant changes in the biochemical parameters"
Selective reporting (reporting bias); efficacy	Low risk	"Table 2 shows the number of subjects in each group who completed the study, the number infected with P. falciparum, and the number of episodes of asexual parasitemia"
Selective reporting (reporting bias); safety	High risk	"There was no clinical evidence of drug toxicity in the 990 study participants" Comment: it was unclear whether all events that occurred during the 6 month trial period were included
Other bias	Unclear risk	Comment: study sponsor not reported

Petersen 2000

Methods	Design: retrospective cohort study Study dates: 1 May 1996 to 30 April 1998 Malaria transmission pattern and local antimalarial drug resistance: various, not specified Adverse event monitoring: patient self-reported questionnaire
Participants	Number enrolled: 5446 questionnaires mailed, 4158 respondents Inclusion criteria: "travellers 18 years old or older, who were not pregnant and had no previous adverse reactions to any of the prescribed drugs" Exclusion criteria: none mentioned Factors influencing drug allocation: "the standard recommendations to Danish travelers were followed" Country of recruitment: Denmark Country of malaria exposure: various, not specified Duration of exposure to malaria: various, not specified Type of participants: travellers
Interventions	*Included in the review:* 1. Mefloquine* 2. Chloroquine*

Petersen 2000 *(Continued)*

	Not included in the review: 3. Chloroquine + proguanil* **dosing regimen not specified*
Outcomes	*Included in the review:* 1. Adverse events; any 2. Serious adverse outcomes 3. Adverse effects; visual impairment (blurred vision), nausea, vomiting, abdominal pain, diarrhoea, dizziness, depression 4. Adverse effects; other (loss of appetite, strange thoughts, tingling, altered spatial perception, mouth ulcers) *Outcomes assessed not included in the review:* 5. Discontinuation of study drug due to adverse effects (data reported on aggregate) 6. Measure of adherence to the drug regimen (data reported on aggregate) 7. Duration in days of symptoms
Notes	Funding sources: Not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** The questionnaire collected information regarding age, body weight and gender, destination and duration of travel but these were not reported **2. Selection of participants into the study: serious** Response rate 4158/5446 (76.3%) **3. Measurement of interventions: low** The prescription was provided by a travel clinic which also performed the study, and switches and discontinuations have been recorded and reported **4. Departures from intended interventions: moderate** Discontinuations were reported. Although changes in prophylaxis were mentioned, it was unclear whether participants were analysed according to original or subsequent prophylactic grouping **5. Missing data: low** 4020/4158 (97%) of participants are included in the analysis for adverse events **6. Measurement of outcomes: serious** Comment: the outcome measure was subjective; participants and personnel were not blinded. It was unclear whether the questionnaire implied causality to the drug regimen **7. Selection of the reported results: moderate**

Petersen 2000 *(Continued)*

	The questionnaire included demographic information, but this was not reported. All results were reported according to short-term or long-term users of prophylaxis, which was not specified in the methods section **8. Other: no information** No information is provided regarding the study sponsor

Philips 1996

Methods	Design: cross-sectional cohort study Study dates: November 1993 to October 1994 Malaria transmission pattern and local antimalarial drug resistance: various, not specified Adverse event monitoring: patient questionnaire sent 2 weeks after travellers return
Participants	Number enrolled: 741 respondents, 918 questionnaires sent Inclusion criteria: "...travelers were asked to participate in the study when they attended TMVC clinics in Adelaide or Melbourne for pretravel consultation. If either doxycycline or mefloquine malaria chemoprophylaxis was recommended for part, or whole, of their itinerary, permission was sought to have them receive a mailed questionnaire" Exclusion criteria: "...under 18 years old, if doxycycline was recommended at doses other than 100mg daily, if other antimalarials were to be used during the intended journey, or if a traveller was not returning home in under 6 months" Factors influencing drug allocation: "Unless a contraindication existed for one or the other drug, the choice of which one to take was left to the traveler, the physician having already discussed, at some length, the different regimens, cost, and commonly reported adverse effects" Country of recruitment: Australia Region of malaria exposure: various (Southeast Asia, Africa, South Asia (India), Pacific) Duration of exposure to malaria: various, not specified Type of participants: travellers
Interventions	1. Mefloquine* 2. Doxycycline* **dosing regimen not specified*
Outcomes	*Included in the review:* 1. Adverse events; any, nausea/vomiting, abdominal pain, diarrhoea, headache, dizziness, abnormal dreams, insomnia, anxiety 2. Serious adverse events 3. Adverse events; other (mood change, palpitations, itching, rash, red skin, vaginal itch) 4. Adverse effects; any 5. Adverse effects; abdominal pain, diarrhoea 6. Discontinuation of study drug due to adverse effects

Philips 1996 *(Continued)*

	7. Measure of adherence to the drug regimen *Outcomes assessed not included in the review* 8. Reasons for choice of antimalarial drug regimen
Notes	Funding sources: "Thanks to Roche and Pfizer pharmaceutical companies for their financial support"

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** Identified confounders were measured and reported across groups. Mefloquine users were more likely to be female and had longer duration of treatment **2. Selection of participants into the study: serious** Response rate 668 of 918 (73%) **3. Measurement of interventions: low** The prescription was provided by a travel clinic which also performed the study; discontinuations were recorded and reported **4. Departures from intended interventions: moderate** Discontinuations were recorded. It was unclear whether information regarding switches was recorded **5. Missing data: low** All information was collected at one time point and all participants were included in the analysis **6. Measurement of outcomes: serious** Comment: The outcome measure was subjective; participants and personnel were not blinded **7. Selection of the reported results: serious** Information was reported for all adverse events recorded, but participants' assessment of causality to the study drug was only reported for two side effects **8. Other: serious** "Sponsored by Roche and Pfizer pharmaceuticals" The role of the study sponsor was not made clear

Potasman 2002

Methods	Design: RCT Study dates: unclear Malaria transmission pattern and local antimalarial drug resistance: not applicable

Potasman 2002 *(Continued)*

	Adverse event monitoring: "Two days after drug ingestion, a second EEG was performed, and a blood sample for mefloquine level was obtained...Travelers were given forms on which to record adverse effects that appeared within 48 hours after drug intake"
Participants	Number enrolled: 90 Inclusion criteria: not explicitly mentioned, included travellers from the Bnia Zion medical centre, Haifa, Israel Exclusion criteria: "Travelers younger than 18 years; with a history of epilepsy or depression, known allergy to mefloquine, cardiac conduction block; using beta-blockers; or who were pregnant...Travelers with an abnormal baseline EEG (unifocal or repetitive bursts)" Country of recruitment: Israel Country of malaria exposure: not applicable Duration of follow up: 48 hours Type of participants: non-travellers
Interventions	1. Mefloquine (1 x Mephaquine 250 mg tablet, Mepha, Aesch, Switzerland) one dose 2. Mefloquine (1 x Larium 250 mg tablet, Roche, Basel, Switzerland) one dose 3. Placebo
Outcomes	1. Adverse events; any 2. Adverse events; other (neuropsychiatric, abnormal EEG 48 hours after ingestion)
Notes	Funding sources: "Partially funded by Mepha Ltd, Aesch, Switzerland"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Eligible travelers were randomly assigned to one of three groups" "Randomization and statistical tests were carried out using Statmate and InStat"
Allocation concealment (selection bias)	Unclear risk	Comment: not mentioned
Blinding of participants and personnel (performance bias) Adverse effects/events	Unclear risk	"Participants were unaware of their group assignment until they completed their tests" Comment: methods used to blind participants not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"EEG pairs (pre- and post-mefloquine) were examined separately by two senior neurologists who were unaware of group allocation"
Incomplete outcome data (attrition bias); efficacy	Unclear risk	N/A
Incomplete outcome data (attrition bias); safety	Unclear risk	Comment: data were provided for all participants who were not excluded on the basis of abnormal baseline EEG
Selective reporting (reporting bias); efficacy	Unclear risk	N/A

Potasman 2002 *(Continued)*

Selective reporting (reporting bias); safety	Unclear risk	"Adverse effects, mainly gastrointestinal and neuropsychiatric were noted in 26 travellers" Comment: specific nature of each adverse effect is not noted per group
Other bias	High risk	Partially funded by Mepha Ltd, Aesch, Switzerland. Comment: the role of the study sponsor was not clear

Rack 2005

Methods	Design: retrospective cohort study Study dates: July 2003 to June 2004 Malaria transmission pattern and local antimalarial drug resistance: various, not specified Adverse event monitoring: patient self-reported questionnaire
Participants	Number enrolled: 794 Inclusion criteria: Travellers who were visiting five popular tropical regions or countries. Exclusion criteria: aged < 18 years, travelling for more than 2 months, and major acute or chronic diseases Country of recruitment: Germany Country of malaria exposure: Kenya/Tanzania, Senegal/Gambia, India/Nepal, Thailand, Brazil Duration of exposure to malaria: various, mean duration of travel 23.9 days Type of participants: travellers
Interventions	*Included in the review:* 1. Mefloquine* 2. Doxycycline* 3. Atovaquone-proguanil* 4. Chloroquine* *Not included in the review:* 5. Chloroquine-proguanil* **dosing regimen not specified*
Outcomes	*Included in the review:* 1. Narrative description of adverse effects *Outcomes assessed not included in the review:* 2. Risk behaviours during travel 3. Illness during travel 4. Seeking medical care owing to illness or accident

Rack 2005 *(Continued)*

	5. Accidents during travel
Notes	Funding sources: not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** Demographic information was provided for the entire cohort, not by prophylactic regimen **2. Selection of participants into the study: moderate** Numbers of participants choosing not to participate in the study were not reported **3. Measurement of interventions: serious** Participants were asked to self-report which prophylaxis they took after return. The time after return was not specified **4. Departures from intended interventions: no information** There was insufficient information provided to determine whether the questionnaire contained information regarding discontinuations or switches **5. Missing data: moderate** Follow up was obtained for 658 (83%) travellers **6. Measurement of outcomes: serious** There was insufficient information on the questionnaire about how adverse effects were sought and if outcome measures were objective. There was no mention of blinding of outcome assessors **7. Selection of the reported results: moderate** There was insufficient information provided regarding the questionnaire to determine if all questions were reported. Side effects were grouped to report symptoms **8. Other: no information** No information was provided regarding the study sponsor

Rieckmann 1993

Methods	Design: cohort study Study dates: 1989 Malaria transmission pattern and local antimalarial drug resistance: higher levels of *P falciparum* than *P vivax* locally. Local chloroquine and primaquine resistance Adverse event monitoring: unclear
Participants	Number enrolled: 349 Inclusion criteria: Unclear

Rieckmann 1993 *(Continued)*

	Exclusion criteria: Unclear Country of recruitment: Australia Country of malaria exposure: Papua New Guinea Duration of exposure to malaria: 3 to 13 week training exercises Type of participants: Soldiers
Interventions	*Included in the review:* 1. Mefloquine (1 x 250 mg weekly) 2. Doxycycline (1 x 100 mg tablet, daily, starting one day before deployment and continuing until 3 days after return) *Not included in the review:* 3. Doxycycline + primaquine 4. Doxycycline + chloroquine
Outcomes	*Included in the review:* 1. Narrative description of adverse effects *Outcomes assessed not included in the review:*: 2. Clinical cases of malaria
Notes	Funding sources: not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** No demographic information was provided **2. Selection of participants into the study: moderate** Numbers of participants choosing not to participate in the study not reported **3. Measurement of interventions: low** All participants were soldiers who were issued with medication **4. Departures from intended interventions: moderate** No information was provided regarding discontinuations or switches **5. Missing data: moderate** No losses to follow-up or treatment withdrawals were reported, but the paper does not clearly state that none occurred **6. Measurement of outcomes: serious** There was insufficient information on how adverse effects were sought and if outcome measures were objective. There was no mention of blinding outcome assessors **7. Selection of the reported results: moderate**

Rieckmann 1993 *(Continued)*

	There was insufficient information provided regarding the questionnaire to determine if all questions were reported. Side effects were grouped to report symptoms. **8. Other: no information** No information is provided regarding the study sponsor

Rietz 2002

Methods	Design: cross-sectional cohort study Study dates: June to December 2000 Malaria transmission pattern and local antimalarial drug resistance: various, not specified Adverse event monitoring: patient self-reported questionnaire
Participants	Number enrolled: 491 Inclusion criteria: "visitors over fifteen who were travelling to South or Central America, Africa, India or South-East Asia, including China, and who were not suffering from any chronic illness" Exclusion criteria: none mentioned Factors influencing drug allocation: "After talking to the doctor, the doctor wrote whether malaria prophylaxis had been decided on and if so which kind" Country of recruitment: Sweden Region of malaria exposure: various, including South or Central America, Africa, India or Southeast Asia, including China Duration of exposure to malaria: "most were abroad between two to four weeks" Type of participants: travellers
Interventions	*Included in the review:* 1. Mefloquine* 2. Chloroquine* 3. Non-users *Not included in the review:* 4. Chloroquine-proguanil* **dosing regimen not specified*
Outcomes	*Included in the review:* 1. Adverse events; any, seriously negative effect on the journey 2. Adverse effects; any 3. Adverse effects; other (neuropsychiatric, skin problems) *Outcomes assessed not included in the review:* 4. Importance attached to prophylaxis

Rietz 2002 *(Continued)*

	5. Whether travellers had any anxiety about side effects prior to taking prophylaxis
Notes	Funding sources: not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** Age, sex, destination and duration of travel data were collected but not reported across groups. BMI was not measured **2. Selection of participants into the study: serious** Response rate 62% **3. Measurement of interventions: low** The prescription was provided by a travel clinic which also performed the study **4. Departures from intended interventions: moderate** Discontinuations were reported, but not across groups. Switches were not recorded **5. Missing data: low** All participants who completed both questionnaires were included in the analysis **6. Measurement of outcomes: moderate** The outcome measure was subjective; participants and personnel were not blinded. Participants were asked to report all symptoms, and which they felt were due to prophylaxis **7. Selection of the reported results: moderate** Symptoms were grouped to report outcomes **8. Other: low** Source of funding not mentioned. "competing interests: none declared"

Salako 1992

Methods	Design: RCT Study dates: July 1987 to June 1988 Malaria transmission pattern and local antimalarial drug resistance: "holoendemic for malaria... at the time of the trial, chloroquine resistance was not a problem" Adverse event monitoring: "study participants were seen weekly up to week 28". Interview with study personnel for events such as "fever, chills, malaise, nausea and vomiting, rashes and other symptoms and signs that could be regarded as adverse events"
Participants	Number enrolled: 567

Salako 1992 *(Continued)*

	Inclusion criteria: "...adult males aged 16 to 60 years, judged healthy on clinical grounds (no history of any illness and physical examination revealed no evidence of an acute or chronic illness). The patients were not on any drugs" Exclusion criteria: "...known hypersensitivity to sulphonamides, antimalarial drug treatment in the preceeding four weeks, presence of chronic debilitating disease and inability to attend regularly for follow up" Country of recruitment: Nigeria Country of malaria exposure: Nigeria Duration of exposure to malaria: study duration 24 weeks Type of participants: Nigerian residents, semi-immune.
Interventions	1. Mefloquine (1 x 250 mg tablet, Hoffman-La Roche) weekly for 4 weeks followed by 1 x 125 mg tablet weekly for 20 weeks, total duration 24 weeks* 2. Chloroquine (1 x 300 mg base tablet, Hoffman-La Roche) weekly, total duration 24 weeks* 3. Placebo, 1 tablet (Hoffman-La Roche) weekly, total duration 24 weeks* **matched placebo for each treatment arm*
Outcomes	*Included in the review:* 1. Clinical cases of malaria 2. Episodes of parasitaemia 3. Adverse events; any, abdominal pain, diarrhoea, headache, dizziness, pruritis, visual impairment (blurred sight) 4. Serious adverse events 5. Discontinuations of study drug due to adverse effects *Outcomes assessed not included in the review:* 6. Laboratory tests; white blood cell counts, haematocrit, serum glutamic oxaloacetic transaminase and serum glutamic-pyruvic transaminase 7. Adverse events: rash, muscle stiffness (occurred in < 1% of study participants)
Notes	Funding sources: not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...subjects were allocated randomly into five groups on the basis of a pre-determined randomisation list" Comment: no mention of how the list was generated
Allocation concealment (selection bias)	Unclear risk	"...blister packs containing a total of 24 tablets were provided for each subject ...The packs and tablets were identical in appearance and were labelled with the appropriate double-blind number" Comment: no mention of opaque sealed envelopes or central allocation

Salako 1992 *(Continued)*

Blinding of participants and personnel (performance bias) Adverse effects/events	Low risk	"The packs and tablets were identical in appearance"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: described as double blind but no description provided of how this was achieved for researchers and outcome assessors
Incomplete outcome data (attrition bias); efficacy	Low risk	Comment: numbers lost to follow up were provided across groups, with reasons provided. 107/113 (95%) mefloquine recipients, 103/115 (90%) chloroquine recipients and 101/114 (89%) placebo recipients completed the trial
Incomplete outcome data (attrition bias); safety	Low risk	Comment: reports "number of individuals suffering adverse events during the trial". Numbers lost to follow up were provided across groups, with reasons provided. 107/113 (95%) mefloquine recipients, 103/115 (90%) chloroquine recipients and 101/114 (89%) placebo recipients completed the trial
Selective reporting (reporting bias); efficacy	Low risk	Comment: clinical cases of malaria and episodes of parasitaemia are reported for all participants
Selective reporting (reporting bias); safety	Unclear risk	"No change of clinical relevance occurred in any of the groups in the above laboratory tests" Comment: there was insufficient information available regarding the collection of adverse events to determine whether the reported list included all events or only a targeted list. Data not fully reported for blood tests
Other bias	Unclear risk	Comment: study sponsor not mentioned, but four of the authors are attributed to F Hoffman-La Roche

Santos 1993

Methods	Design: RCT Study dates: August 1982 to January 1983 Malaria transmission pattern and local antimalarial drug resistance: region considered hyperendemic. *P falciparum* resistant to chloroquine and “high prevalence of multiresistant *Plasmodium falciparum* transmission” Adverse event monitoring: during the initial screening visit, weekly visits, and a final visit at study end, participants were asked about illnesses, mainly about signs and symptoms compatible with malaria, and blood tests were done, including haematocrit and leucocyte count
Participants	Number enrolled: 122 Inclusion criteria: "volunteer soldiers and civilians aggregated to the 5th Battalion of Engineering and Construction in a community in Porto Velho" Exclusion criteria: aged < 12 years and > 55 years, pregnancy, people with debilitating disease, people who took antimalarial drugs in the previous four weeks and people with allergy to sulphonamides Country of recruitment: Brazil Country of malaria exposure: Brazil Duration of exposure to malaria: Mean duration within study (across groups) 16.9 weeks

Santos 1993 *(Continued)*

	Type of participants: Brazilian soldiers and civilians, semi-immune
Interventions	*Included in review comparisons:* 1. Mefloquine (2 x 250 mg tablets, Roche) every 4 weeks* 2. Mefloquine (1 x 250 mg tablet, Roche) every 2 weeks* 3. Placebo *Not included in review comparisons:* 4. Fansidar* **matched placebo for each treatment arm*
Outcomes	*Included in the review:* 1. Clinical cases of malaria 2. Adverse effects; any, anxiety *Outcomes assessed not included in the review:* 3. Laboratory tests; haematocrit, white blood cell counts, serum glutamic oxaloacetic transaminase and serum glutamic-pyruvic transaminase
Notes	Funding sources: Laboratory Roche provided mefloquine and "support" for conducting the study. Comando do 5o Batalhão de Engenharia e Construção, Porto Velho, RO, provided laboratory and field installations

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: described as a randomized controlled trial, but no details were given on the sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no description of allocation concealment provided
Blinding of participants and personnel (performance bias) Adverse effects/events	Low risk	"Each week... participants ingested 4 tablets of equal appearance, contained in sealed envelopes"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Each week... participants ingested 4 tablets of equal appearance, contained in sealed envelopes, with a code pre-determined for each individual and not opened after the completion of the study" Comment: no mention of blinding of outcome assessors
Incomplete outcome data (attrition bias); efficacy	High risk	"120 participants were initially recruited (30 in each group). Six of them were then excluded and were not included in the analysis. 8 participants left the area of study (one after the 10th week and 7 after the 11th week of exposure)" Outcomes were included in the analysis, and were substituted by eight new participants. With these six excluded participants and eight substituted participants, final sample size was 122.

Santos 1993 *(Continued)*

		Comment: participants were not followed up beyond the active phase of treatment for relapses
Incomplete outcome data (attrition bias); safety	Unclear risk	Comment: reasons for losses to follow-up were not reported
Selective reporting (reporting bias); efficacy	Low risk	Comment: all cases of malaria were reported
Selective reporting (reporting bias); safety	Unclear risk	Comment: there was insufficient information provided regarding the method of adverse effects monitoring to determine whether all outcomes had been reported
Other bias	High risk	Roche provided mefloquine and “support” for conducting the study

Saunders 2015

Methods	Design: retrospective cohort study Study dates: January to June 2007 Malaria transmission pattern and local antimalarial drug resistance: "malaria risk and transmission patterns have been known to shift rapidly in Afghanistan" Adverse event monitoring: "A retrospective, anonymous survey was completed by soldiers returning to Fort Drum, NY from Afghanistan"
Participants	Number enrolled: 2601 surveys distributed, 2351 (90%) returned Inclusion criteria: none mentioned Exclusion criteria: none mentioned Factors influencing drug allocation: "oral mefloquine 250 mg per week was the primary alternative to doxycycline... In some cases, mefloquine was chosen as the first-line therapy based on either perceived advantages in compliance, unit force protection, and/or operational concerns" Country of recruitment: USA Country of malaria exposure: Afghanistan Duration of exposure to malaria: various, not specified Type of participants: military
Interventions	Included in review comparisons: 1. Mefloquine* 2. Doxycycline* Not included in review comparisons: 3. Atovaquone-proguanil* (data on adverse events not collected; data on compliance not reported) **dosing regimen not specified*
Outcomes	*Included in the review:* 1. Adverse effects; any, vomiting, diarrhoea

Saunders 2015 *(Continued)*

	2. Adverse effects; other (heartburn/dyspepsia) 3. Discontinuations of study drug due to adverse effects 4. Measure of adherence to the drug regimen *Outcomes assessed not included in the review:* 5. Clinical cases of malaria 6. Adverse effects: numbers not reported in both groups (nausea, headache, dizziness, abnormal dreams, insomnia, depression, photosensitivity, rash, loss of appetite, pain and/or difficulty swallowing, vaginitis, lightheadedness, nervousness, ringing in ears, chills) 7. Use of personal protective measures to prevent mosquito bites
Notes	Funding sources: not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** Information was provided on duration of deployment, area of deployment, sex, age group and rank across regimens. Area deployed in Afghanistan and sex were different across groups. No adjustment for confounders was made in the analysis **2. Selection of participants into the study: low** Response rate 2351/2601 surveys (90%) **3. Measurement of interventions: moderate** Participants were asked to self-report which prophylaxis was used on return to the USA. It is unclear if participants were still receiving the intervention at this time **4. Departures from intended interventions: serious** "There were 520 respondents (25.2%) reporting more than one medication used to prevent malaria over the course of the deployment" **5. Missing data: low** Analysis included 1898/2011 (94.4%) respondents for doxycycline, 564/596 (94.6%) respondents for mefloquine **6. Measurement of outcomes: serious** Comment: the outcome measure was subjective; participants and personnel were not blinded. Different criteria were used to assess adverse effects related to mefloquine and doxycycline **7. Selection of the reported results: serious** There was insufficient information provided regarding the questionnaire to determine whether all included outcomes were reported. Data for doxycycline were provided by severity gradings but not for mefloquine **8. Other: no information** No information is provided regarding the study sponsor

Schlagenhauf 1997

Methods	Design: cross-over RCT Study dates: 1993 to 1994 Malaria transmission pattern and local antimalarial drug resistance: not applicable Adverse event monitoring: "Throughout dosing, the participants were monitored and questioned regarding their general well-being. The participants were seen 1) prior to taking any medication, 2) at the end of the first week (during which the loading dose was administered, 3) one week before testing, and 4) on the testing day itself when they were asked to report any changes from normal and questioned with regard to any symptoms experienced while taking the drug"
Participants	Number enrolled: 23 Inclusion criteria: "conducted with trainee pilots attending the Swiss Civil Aviation School during the classroom phases of their study" Exclusion criteria: "history of a seizure disorder; psychosis or severe depression; known allergy or sensitivity to mefloquine or related compounds; concurrent use of cardioactive medication; compromised renal or hepatic function; pregnancy or the intention to become pregnant within three months of mefloquine use; use of mefloquine in the preceding two months, and use of hypnotics or tranquillizers during the two weeks prior to testing and alcohol within 12 hr of testing" Country of recruitment: Switzerland Country of malaria exposure: not applicable Duration of follow up: 4 weeks Type of participants: Swissair trainee pilots, did not travel
Interventions	1. Mefloquine (1 x 250 mg tablet) given daily on 3 consecutive days followed from day 8 by once a week administration of 1 tablet for three consecutive weeks 2. Placebo (1 tablet) given daily on 3 consecutive days followed from day 8 by once a week administration of one tablet for 3 consecutive weeks
Outcomes	*Included in the review:* 1. Adverse events; any 2. Discontinuations of study drug due to adverse effects 3. Adverse events; other outcomes (instrument co-ordination analyser, sleep assessment, sway, neurobehavioural evaluation system, profile of mood states)
Notes	Funding sources: This study was sponsored by the F. Hoffmann La Roche Tropical Medicine Unit (Basel, Switzerland)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: method of randomization not reported
Allocation concealment (selection bias)	Unclear risk	Comment: no details of allocation concealment reported

Schlagenhauf 1997 *(Continued)*

Blinding of participants and personnel (performance bias) Adverse effects/events	Unclear risk	Comment: described as double blind but no mention of whether placebo was identical to the active formulation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: described as double blind but no description of who was blinded and how
Incomplete outcome data (attrition bias); efficacy	Unclear risk	N/A
Incomplete outcome data (attrition bias); safety	Unclear risk	"There was one withdrawal due to dizziness, diarrhea, and flu-like symptoms and three volunteers spontaneously reported minor sleep-related AEs (adverse events), including insomnia, unpleasant dreams, superficial sleep, and early awakening. These events all occurred in the mefloquine loading dose phase" Comment: not clear whether this withdrawal was included in the data analysis
Selective reporting (reporting bias); efficacy	Unclear risk	N/A
Selective reporting (reporting bias); safety	High risk	"The individual Environmental Symptom Questionnaire (ESQ) symptoms were also analyzed and items selected for their relevance to mefloquine administration were assessed by Cochran's Q test for related samples" Comment: intra-individual changes in scores were obtained during the study, but outcomes were presented as means across groups. Data from the ESQ were not reported, only "no significant differences". Data for the Profile of Mood States questionnaire was presented in a graph with no standard deviations
Other bias	High risk	This study was sponsored by the F. Hoffmann La Roche Tropical Medicine Unit (Basel, Switzerland). The role of the study sponsor was not clear

Schlagenhauf 2003

Methods	Design: RCT Study dates: 1998 to 2001 Malaria transmission pattern and local drug resistance: not mentioned Adverse event monitoring: patient self-reported questionnaire
Participants	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, history of severe adverse events with any of the four study drugs or a contra-indication for their use, pregnancy or unwillingness to adhere to reliable contraception, history of seizures, psychiatric disorders, severely impaired renal or hepatic function, concurrent or recent vaginal infections or bacterial enteric disorders, a history of photosensitivity, or unwillingness to adhere to the study protocol Countries of recruitment: Switzerland, Germany and Israel

Schlagenhauf 2003 *(Continued)*

	Region of malaria exposure: sub-Saharan Africa Duration of exposure to malaria: 1 to 3 weeks Type of participants: travellers
Interventions	1. Mefloquine (1 capsule containing mefloquine hydrochloride 274.09 mg, equivalent to mefloquine 250 mg base) once weekly, starting 17 days before travel and continuing for 4 weeks 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* 4. 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* **matched placebo for each treatment arm*
Outcomes	*Included in the review:* 1. Adverse events; any 2. Serious adverse events 3. Adverse events; other ('gastrointestinal', 'skin symptoms', 'neuropsychological') - any severity, mild, moderate, severe 4. Discontinuation of study drug due to adverse effects 5. Adverse events; other outcomes (profile of mood states, quality of life score)
Notes	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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was from a computer generated table of numbers in permuted blocks of five"
Allocation concealment (selection bias)	Unclear risk	"Participants were allocated treatment sequentially in order of study numbers. Allocation concealment was by sealed envelope" Comment: not reported whether envelopes were opaque
Blinding of participants and personnel (performance bias) Adverse effects/events	Low risk	"The drugs were provided as identical capsule blister packs in weekly cards"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: Described as double blind but no mention of how this was achieved for researchers and outcome assessors
Incomplete outcome data (attrition bias); efficacy	High risk	Comment: Method of detection for malaria, frequency and duration of follow up were not reported

Schlagenhauf 2003 *(Continued)*

Incomplete outcome data (attrition bias); safety	Unclear risk	"Adverse events were analysed in 623 participants who completed questionnaires at recruitment and at least one of the follow up periods" "Data was collected during recruitment and at follow up 13-11 days before departure, 6-4 days before departure and 7-14 days after departure" Comment: it was unclear how many participants provided data at each time point
Selective reporting (reporting bias); efficacy	Low risk	"No cases of malaria were reported for any study arm"
Selective reporting (reporting bias); safety	High risk	"Adverse events were analysed in 623 participants who completed questionnaires at recruitment and at least one of the follow up periods" "Data was collected during recruitment and at follow up 13-11 days before departure, 6-4 days before departure and 7-14 days after departure" Comment: Data were presented on aggregate across multiple time points
Other bias	High risk	Funding: Pfizer, GlaxoSmithKline, Roche, and Zeneca provided the drugs free of charge. GlaxoSmith Kline and Roche provided research grants. "Competing interests: PS has received speakers' honorariums and travel expenses from Roche and GlaxoSmithKline. She acted as a consultant to Roche in a drug safety database evaluation. RS has received speakers' honorariums and travel expenses from GlaxoSmithKline, Roche, and Pfizer. He is also a member of the advisory board of GlaxoSmithKline for malaria prophylaxis related questions. BB has received a speaker's honorarium and travel expenses from GlaxoSmithKline. HN has received speakers' honorariums and travel expenses from GlaxoSmithKline on different occasions. He has been principal or coinvestigator in several vaccine trials sponsored by GlaxoSmithKline"

Schneider 2013

Methods	Design: retrospective cohort study Study dates: 1 January 2001 and 1 October 2009 Malaria transmission pattern and local antimalarial drug resistance: various, not specified Adverse event monitoring: Incident cases of a neuropsychiatric disorder including anxiety, stress-related disorders or psychosis, depression, epilepsy or peripheral neuropathies during or after anti-malarial drug use within the UK general practice research database
Participants	Number enrolled: Not available Inclusion criteria: "We identified in the general practice research database all patients who had ≥ 1 prescription of mefloquine, chloroquine and/or proguanil or atovaquone/proguanil between January 1, 2001 and October 1, 2009, and who had a pre-travel consultation within 1 week of the prescription" Exclusion criteria: "We only included subjects who used anti-malarial drugs for malaria prophylaxis... Furthermore, individuals had at least 12 months of information on prescribed drugs and medical diagnoses before the first prescription date for a study drug. In addition, subjects had recorded activity (diagnoses or drug prescriptions) at any time after the prescription for an anti-malarial drug to include only subjects who returned to the UK. We excluded all patients with a diagnosis of malaria prior to the start of anti-malarial drug use, patients with a history of cancer, alcoholism, rheumatoid arthritis; or with an outcome of interest prior to using anti-malarial drugs. The date of the first neuropsychiatric disorder was the index date for each case"

Schneider 2013 *(Continued)*

	Country of recruitment: UK Country of malaria exposure: various, not specified Duration of exposure to malaria: various, not specified Type of participants: travellers
Interventions	*Included in review comparisons:* 1. Mefloquine* 2. Atovaquone-proguanil* *Not included in review comparisons:* 3. Chloroquine-proguanil* 4. Unexposed (case-control design) **dosing regimen not specified*
Outcomes	*Included in the review:* 1. Adverse events; psychiatric disorders (anxiety, depression, psychosis) 2. Adverse events; other ('anxiety or stress related disorders or psychosis', epilepsy, neuropathy, phobia, panic attack)
Notes	Funding sources: F. Hoffmann-La Roche Ltd., Basel, Switzerland

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** Age, sex and BMI were measured but only reported for people experiencing adverse events **2. Selection of participants into the study: moderate** "We excluded all patients with a personal history of recorded neuropsychiatric disorders from the study population, but family history is not consistently recorded in the database" **3. Measurement of interventions: moderate** "We only included subjects who used anti-malarial drugs for malaria prophylaxis. We identified prescriptions for which the GP recorded - within a week of the anti-malarial drug prescription - specific codes indicating that the person received the prescription for malaria prophylaxis, such as 'travel advice' or “prophylactic drug use” **4. Departures from intended interventions: serious** It is possible that participants discontinued or switched medication and this would not have been captured in the study **5. Missing data: moderate** The study did not report the total number of participants, only those who experienced adverse events

Schneider 2013 *(Continued)*

	6. Measurement of outcomes: moderate General practitioners diagnosing patients would have been aware of their exposure status **7. Selection of the reported results: moderate** Data for anxiety, stress-related disorders and psychosis were reported on aggregate **8. Other: serious** Study was sponsored by Roche. The role of the funding source was not made clear

Schwartz 1999

Methods	Design: cross-sectional cohort study Study dates: October 1995 to April 1998 Malaria transmission pattern and local antimalarial drug resistance: "both *P. falciparum* and *P. vivax* are hyperendemic" Adverse event monitoring: "...we directly contacted all travelers for complete follow-up and assessment of compliance. Fifty travelers taking primaquine completed a questionnaire regarding side effects"
Participants	Number enrolled: 158 Inclusion criteria: Israelis participating in rafting trips in Southern Ethiopia Exclusion criteria: none mentioned Country of recruitment: Israel Country of malaria exposure: Ethiopia Duration of exposure to malaria: 14 to 20 days Type of participants: travellers
Interventions	*Included in review comparisons:* 1. Mefloquine (1 x 250 mg tablet) weekly, Starting 1 week prior to departure, during travel and for 4 weeks after return 2. Doxycycline (1 x 100 mg tablet) daily *Not included in review comparisons:* 3. Primaquine 15 mg daily for travellers with body weight < 70 kg and 30 mg for those weighing > 70 kg, starting 1 day prior to departure and continuing for up to 2 days after departure 4. Hydroxychloroquine* **dosing regimen not specified*
Outcomes	*Included in the review:* 1. Discontinuations of study drug due to adverse effects

Schwartz 1999 *(Continued)*

	Outcomes assessed not included in the review: 2. Clinical cases of malaria 3. Measure of adherence to the drug regimen (not fully reported) 4. Adverse effects; any (methods of detection different for primaquine versus other regimens)
Notes	Funding sources: not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** Age, sex and BMI were not reported for any participants. Destination and duration of travel was roughly equivalent across all groups **2. Selection of participants into the study: moderate** Subjects were selected on the basis of their travel destination. Start of follow up and start of intervention coincide. No non-responses were reported **3. Measurement of interventions: moderate** "Prior to the trip, participants consulted one of a number of travel clinics in Israel, among them our clinic" Comment: it was unclear how intervention status was ascertained for participants who visited other clinics **4. Departures from intended interventions: low** Two discontinuations (158 participants) were reported **5. Missing data: serious** "In addition, we directly contacted all travelers for complete follow-up and assessment of compliance. Fifty travelers taking primaquine completed a questionnaire regarding side effects" It was unclear how information on discontinuations and side effects were obtained for participants who did not take primaquine" **6. Measurement of outcomes: serious** Comment: the outcome measure was subjective; participants and personnel were not blinded **7. Selection of the reported results: serious** "In addition, we directly contacted all travelers for complete follow-up and assessment of compliance. Fifty travelers taking primaquine completed a questionnaire regarding side effects" It was unclear how information on discontinuations and side effects was obtained for participants who did not take primaquine **8. Other: no information** No information was provided regarding the study sponsor

Shamiss 1996

Methods	Design: cross-sectional cohort study Study dates: not mentioned Malaria transmission pattern and local antimalarial drug resistance: not applicable Adverse event monitoring: patient self-reported questionnaire
Participants	Number enrolled: 45 Inclusion criteria: none mentioned Exclusion criteria: none mentioned Factors influencing drug allocation: "Prior knowledge about the side effect profile of mefloquine forced us to prescribe doxycycline 100 mg daily for aviators and mefloquine 250 mg weekly for non-aviator crew" Country of recruitment: Israel Country of malaria exposure: Rwanda and Zaire Duration of exposure to malaria: "biweekly flights to and from Rwanda to Zaire with an average of 4 hours stay in the field over a period of 2 months" Type of participants: military
Interventions	1. Mefloquine (1 x 250 mg tablet) weekly, starting on the day of travel (< 12 hours before the first flight) and continuing until 4 weeks after return 2. Doxycycline (1 x 100 mg tablet) daily, starting on the day of travel (< 12 hours before the first flight) and continuing until 4 weeks after return
Outcomes	*Included in the review:* 1. Adverse effects; any, nausea, abdominal pain, dizziness 2. Adverse effects; other (fatigue) 3. Discontinuations of study drug due to adverse effects 4. Measure of adherence to the drug regimen *Outcomes assessed not included in the review:* 5. Clinical cases of malaria
Notes	Funding sources: not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** Sex and BMI were not measured. Destination and duration of travel were set by the study design **2. Selection of participants into the study: low**

Shamiss 1996 *(Continued)*

"Prior knowledge about the side effects profile of mefloquine forced us to prescribe doxycycline 100 mg daily for aviators and mefloquine 250 mg weekly for non-aviator aircrew up to 1 mo after the last return"

All participants completed questionnaires.

3. Measurement of interventions: low

Type of prophylaxis used was set by the job of the included participants

4. Departures from intended interventions: low

"Two non-aviators were dropped from the study because of receiving the wrong prescription"

5. Missing data: low

"Two non-aviators were dropped from the study because of receiving the wrong prescription"

Information was provided for the remaining 43 participants.

6. Measurement of outcomes: serious

Comment: the outcome measure was subjective; participants and personnel were not blinded

7. Selection of the reported results: moderate

"...the questionnaire included questions about compliance, side effects attributed to chemoprophylaxis, and any illness after return"

No information was provided regarding illness after return.

8. Other: no information

No information is provided regarding the study sponsor

Sharafeldin 2010

Methods	Design: retrospective cohort study Study dates: July 2006 to December 2008 Malaria transmission pattern and local antimalarial drug resistance: various, not specified Adverse event monitoring: "Participants… were sent an informative email asking them to complete a web-based questionnaire"
Participants	Number enrolled: 242 students sent questionnaire, 180 respondents Inclusion criteria: "all medical students who had performed an elective abroad between July 2006 and December 2008, who had visited countries where hepatitis A is endemic, and who had notified the student registrar to obtain study credits" Exclusion criteria: none mentioned Factors influencing drug allocation: "...students are free to visit [our occupational health department] or any other travel clinic including the LUMC in-hospital travel clinic or their general practitioner" Country of recruitment: Netherlands Country of malaria exposure: none mentioned

Sharafeldin 2010 *(Continued)*

	Duration of exposure to malaria: mean duration of stay = 74 days (range 10 to 224 days) Type of participants: travellers
Interventions	*Included in review comparisons:* 1. Mefloquine* 2. Atovaquone-proguanil* 3. Doxycycline* *Not included in review comparisons:* 4. Primaquine* 5. Proguanil* 6. Chloroquine* (no data reported) **dosing regimen not specified*
Outcomes	*Included in the review:* 1. Adverse effects; any 2. Serious adverse outcomes 3. Discontinuations of study drug due to adverse effects *Outcomes assessed not included in the review:* 4. Clinical cases of malaria 5. Risk of infection with bloodborne viruses 6. Health risks while abroad 7. Health problems experienced whilst abroad 8. Health problems experienced on return
Notes	Funding sources: There was no dedicated funding for this project

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** Age, sex, destination and duration of travel were measured but information not provided across groups. BMI was not measured **2. Selection of participants into the study: serious** Response rate 180/242 (74.4%) **3. Measurement of interventions: serious** "...six students did not remember which prophylaxis had been prescribed" Students were asked to self-report which prophylaxis they took an average of 235 days after completing their trip **4. Departures from intended interventions: moderate**

Sharafeldin 2010 *(Continued)*

	"Eight students who used mefloquine (20%) stopped the drug prematurely as did ten students on atovaquone-proguanil (16%) and the student on doxycycline. Only two of these students switched to another prophylaxis"
	5. Missing data: low
	"none of the questionnaires was incomplete"
	All participants were included in the analysis
	6. Measurement of outcomes: serious
	The outcome measure was subjective; participants and personnel were not blinded
	7. Selection of the reported results: moderate
	Insufficient information was provided on how data on adverse effects were sought
	8. Other: low
	"There was no dedicated funding for this project"

Sonmez 2005

Methods	Design: prospective cohort study
	Study dates: April 2002 to October 2003
	Malaria transmission pattern and local antimalarial drug resistance: "20% of recent cases were due to *P. falciparum*' 'chloroquine resistant *P. falciparum"*
	Adverse event monitoring: "common questionnaires were used to investigate the compliance to and side effects of both regimes"
Participants	Number enrolled: 1400 soldiers worked in the region
	Inclusion criteria: "...all Turkish soldiers were examined in detail and serum samples were taken before heading for the region"
	Exclusion criteria: "...none of the participants had any chronic disease"
	Factors influencing drug allocation: "The preference of the preventive regime was related to the availability of the drugs... the prophylaxis was started with doxycycline, which was at hand in March 2002. Then again the soldiers who came after July 2002 were given mefloquine"
	Country of recruitment: Afghanistan
	Country of malaria exposure: Afghanistan
	Duration of exposure to malaria: "The average time of presence for a single soldier in Kabul region was approx. 6 month [sic]"
	Type of participants: military
Interventions	1. Mefloquine*
	2. Doxycycline*
	**dosing regimen not specified*

Sonmez 2005 *(Continued)*

Outcomes	*Included in the review:* 1. Serious adverse effects 2. Adverse effects; any, nausea, vomiting, abdominal pain, diarrhoea, headache, insomnia, dyspepsia, anorexia *Outcomes assessed not included in the review:* 3. Clinical cases of malaria
Notes	Funding sources: Not mentioned Communications with study author: Sonmez 2005 no longer had access to the original study data. However, the study authors confirmed that for table 1: "The comparisons of the number of side effects of both regimes" the number of side effects for specific symptoms e.g. nausea was equivalent to the number of soldiers reporting that side effect. In addition, the authors were able to clarify a discrepancy in the original text: the paper states "27 mefloquine takers (41.2%) reported 43 side effects at the 2nd week of prophylaxis". The total number of mefloquine participants was 228; 41.2% equates to 94 participants. The authors confirmed that the correct figure was 27 mefloquine users (11%).

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** Age of participants was balanced across groups. Destination and duration of travel were set by the study design. Sex and BMI were not reported **2. Selection of participants into the study: serious** 734 soldiers returned questionnaires (52.2%) **3. Measurement of interventions: low** All soldiers were issued with prophylaxis **4. Departures from intended interventions: low** Switches between prophylactic regimens were not possible **5. Missing data: low** The data were collected at 2 time points. The reported denominator for each time point was the same **6. Measurement of outcomes: serious** Comment: the outcome measure was subjective; participants and personnel were not blinded **7. Selection of the reported results: moderate** There was insufficient information provided to be sure that all outcomes included in the questionnaire were reported **8. Other: no information** No information was provided regarding the study sponsor

Sossouhounto 1995

Methods	Design: RCT Study dates: January 1989 to June 1989 Malaria transmission pattern and local antimalarial drug resistance: "region endemic for *P. falciparum* malaria" Adverse event monitoring: "participants had access to a village health center, where they could notify personnel of any malaise or side effects. Clinical examinations and parasitologic tests were performed every 4 weeks. Blood counts were carried out at the end of weeks 4, 19 and 24"
Participants	Number enrolled: 500 Inclusion criteria: "five-hundred male volunteers, aged 16-60 years, who were residents of a local village, were randomly assigned" Exclusion criteria: none mentioned Country of recruitment: Adzope region, Ivory Coast Country of malaria exposure: Adzope region, Ivory Coast Duration of exposure to malaria: study duration 20 weeks Type of participants: Ivory Coast residents, semi-immune
Interventions	*Included in review comparisons:* 1. Mefloquine (1 x 250 mg tablet) weekly in weeks 1 to 4, (1 x 125 mg tablet) weekly in weeks 5 to 20 2. Chloroquine (1 x 300 mg tablet) weekly for 20 weeks 3. Placebo (1 tablet) weekly for 20 weeks *Not included in review comparisons:* 4. Fansidar 5. Fansifem
Outcomes	*Included in the review:* 1. Clinical cases of malaria 2. Episodes of parasitaemia 3. Serious adverse events 4. Adverse events: any, diarrhoea, headache, pruritis *Outcomes assessed not included in the review:* 5. Laboratory tests; haematocrit and white blood cell count 6. Adverse events: other (leukopenia, malaise; did not occur in any study participants)
Notes	Funding sources: not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement

Sossouhounto 1995 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"Five-hundred male volunteers… were randomised" Comment: Method of randomization was not described
Allocation concealment (selection bias)	Unclear risk	Comment: no description of allocation concealment was provided
Blinding of participants and personnel (performance bias) Adverse effects/events	Low risk	"double blind". "The medications and placebo were identical in appearance"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: described as double blind but no information was provided on how this was achieved for researchers and outcome assessors
Incomplete outcome data (attrition bias); efficacy	Low risk	"Four hundred and ninety-nine subjects were evaluated for safety (at least one tablet taken and one visit) as well as for efficacy" Comment: 499/500 (99.8%) participants included in the analysis
Incomplete outcome data (attrition bias); safety	Low risk	"Four hundred and ninety-nine subjects were evaluated for safety (at least one tablet taken and one visit) as well as for efficacy" Comment: 499/500 (99.8%) participants included in the analysis
Selective reporting (reporting bias); efficacy	Low risk	Comment: all outcomes prespecified in the methods section were reported
Selective reporting (reporting bias); safety	Unclear risk	"Blood counts were carried out at the end of weeks 4, 19 and 24" Comment: blood counts were reported only for one participant who developed reversible leukopenia
Other bias	Unclear risk	Comment: no information provided regarding the study sponsor

Steffen 1993

Methods	Design: cohort study Study dates: Malpro 1- April 1985 to July 1988, Malpro 2- July 1988 to December 1991 Malaria transmission pattern and local antimalarial drug resistance: various, not stated Adverse event monitoring: self-completed questionnaires were distributed and collected by cabin crews to all passengers returning on charter planes
Participants	Number enrolled: 145,003 Inclusion criteria: not explicitly stated. This trial includes two publications, Steffen 1993 states "All passengers returning on charter planes from Mombasa, Kenya, to Europe", whereas Steffen 1990 states "all passengers flying back to Europe from East Africa (Kenya) or West Africa (9 countries)". Data have been included from Steffen 1993 Exclusion criteria: "All travellers who stayed longer than one year in tropical Africa were excluded, as were those who did not spend the main part of their visit in East Africa (Kenya, Tanzania and Uganda)" Country of recruitment: not applicable

Steffen 1993 *(Continued)*

	Region of malaria exposure: East Africa (Kenya, Tanzania, Uganda) Duration of exposure to malaria: various, not stated Type of participants: travellers
Interventions	*Included in review comparisons:* 1. Mefloquine* 2. Chloroquine (1 x 300 mg tablet) weekly *Not included in review comparisons:* 3. Chloroquine (1 x 600 mg tablet) weekly 4. Proguanil* 5. Chloroquine + proguanil* 6. Pyrimethamine + sulfadoxine* 7. Non-users (this population was asked about side effects (adverse effects) and instead answered regarding adverse events **dosing regimen not specified*
Outcomes	*Included in the review:* 1. Serious adverse effects 2. Adverse effects; any (mild, moderate or severe), visual impairment, nausea, headache, dizziness, insomnia, depression, pruritis 3. Adverse effects; other ('other skin', medical consultations due to side effects, incapacitation due to side effects, 'cutaneous', 'redness of the skin', consulted a doctor) 4. Discontinuations of study drug due to adverse effects *Outcomes assessed not included in the review:* 5. Clinical cases of malaria 6. Measures taken against mosquito bites 7. Sources of pre-travel health information 8. Places visited in tropical Africa
Notes	Funding sources: "This study was sponsored by F. Hoffman-La Roche Ltd, Basel, Switzerland"

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** Age, sex and BMI were not reported across different prophylactic groups **2. Selection of participants into the study: moderate** "In Malpro 1, 80.1% of all passengers completed the in-flight questionnaire… in Malpro 2 the response rate [was] 83.9%" **3. Measurement of interventions: low**

Steffen 1993 *(Continued)*

	Passengers were asked to self-report which malaria prophylaxis was used. Data were collected on the journey home, meaning it was likely that passengers were still taking this medication **4. Departures from intended interventions: low** Handschin 1997: "2.9% of passengers changed the prophylactic regimen during the observation period" **5. Missing data: moderate** Malpro 1 losses to follow-up 4.1%, Malpro 2 losses to follow-up 14.1% **6. Measurement of outcomes: moderate** The outcome measure was subjective; participants and personnel were not blinded. Serious adverse events were verified independently **7. Selection of the reported results: serious** Data on non-serious side effects were not included from Malpro 1- 31% of participants (44,667) were not included **8. Other: serious** The study was funded by Roche. The role of the study sponsor was not made clear

Steketee 1996

Methods	Design: quasi-RCT Study dates: September 1987 to June 1990 Malaria transmission pattern and local antimalarial drug resistance: "primarily *P falciparum* (> 90%), some *P malariae* and minimal *P ovale*... High levels of *Plasmodium falciparum* resistance to CQ... sensitivity of *P. falciparum* to mefloquine was documented" Adverse event monitoring: "At the time of each dose, a questionnaire was administered to record symptoms including fever and reported drug side effects since the last visit"
Participants	Number enrolled: 4220 Inclusion criteria: "...consecutive attenders at first antenatal clinic visit were enrolled at three sites… At a fourth side, consecutive attenders in their first and second pregnancy were enrolled" Exclusion criteria: "At this site [fourth site, government district hospital] women with two or more pregnancies were not enrolled because of the large number of patients attending the clinic and the limited number of study staff" Country of recruitment: Malawi Country of malaria exposure: Malawi Duration of exposure to malaria: Ongoing in semi-immune population - monitored from enrolment for various periods of time Type of participants: pregnant Malawian residents, semi-immune
Interventions	1. Mefloquine (1 x 250 mg tablet) weekly, with a single loading dose of 750 mg

Steketee 1996 *(Continued)*

	2. Chloroquine (1 x 300 mg tablet) weekly, with a loading dose 25 mg of base/kg given as a divided dose over 2 days 3. Chloroquine (1 x 300 mg tablet) weekly
Outcomes	*Included in the review:* 1. Episodes of parasitaemia 2. Adverse events; any 3. Serious adverse events 4. Discontinuations of study drug due to adverse effects 5. Adverse pregnancy outcomes; still births, abortions *Outcomes assessed not included in the review:* 6. Frequency of placental malarial infection 7. Frequency of prematurity or intra-uterine growth retardation 8. Frequency of maternal febrile illness or anaemia 9. Likelihood of infant acquisition of malarial infection
Notes	Funding sources: "This work was supported and made possible by the Africa Bureau, Office of Operations and New Initiatives and the Office of Analysis, Research and Technical Support, the USAID through the Africa Child Survival initiative… The Global Program on AIDS, World Health Organisation provided support for the HIV testing and evaluation portion of this study"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"Systematic assignment of regimens was done based on the clinic and day of enrolment… All women making their first antenatal clinic on a given day were assigned to the same regimen; the following day, enrolled women were assigned to the following regimen"
Allocation concealment (selection bias)	High risk	"Systematic assignment of regimens was done based on the clinic and day of enrolment… All women making their first antenatal clinic on a given day were assigned to the same regimen; the following day, enrolled women were assigned to the following regimen"
Blinding of participants and personnel (performance bias) Adverse effects/events	High risk	Comment: no mention of participants being blinded to which prophylactic regimen they were taking
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"All blood smear examinations were done with the microscopist blinded to the study subject's antimalarial regimen" Comment: No mention of outcome assessors being blinded to the treatment regimen used when assessing safety outcomes
Incomplete outcome data (attrition bias); efficacy	Unclear risk	"Among the 4187 enrolled women, 3380 (81%) [were analysed]… 94 did not have an initial blood smear result for comparison, 89 left the study area before follow up, 397 delivered before the follow up visit, 133 missed their appropriate follow up visit, and 94 did not have documented adherence to the drug regimen"

Steketee 1996 *(Continued)*

		Comment: numbers lost to follow up were not reported across groups
Incomplete outcome data (attrition bias); safety	High risk	"A total of 4101 women had information available after their first dose and 2976 women had information available after their dose at four weeks" Comment: reasons for missing data were not reported
Selective reporting (reporting bias); efficacy	Unclear risk	"Only *P falciparum* infections were of interest for this study… when *P malariae* alone was identified these infections were excluded from the analysis" "For the purposes of malaria prevention and infant outcome we analysed the group of women… only if they were enrolled in the study for six or more weeks and had received the appropriate amount of medication during their participation" "A total of 1,790 women delivered in study health facilities had received proper dosing on their antimalarial regimen, and had their peripheral blood examined" Comment: women who had reported fever during pregnancy, and during the 2 weeks prior to delivery was reported, but not reported across antimalarial drug regimens
Selective reporting (reporting bias); safety	High risk	"All other complaints e.g. weakness, heart palpitations accounted for less than 15% of reported symptoms" Comment: Data were collected weekly but only reported after the first and the fourth dose
Other bias	Low risk	"This work was supported and made possible by the Africa Bureau, Office of Operations and New Initiatives and the Office of Analysis, Research and Technical Support, the USAID through the Africa Child Survival initiative… The Global Program on AIDS, World Health Organisation provided support for the HIV testing and evaluation portion of this study"

Stoney 2016

Methods	Design: Prospective cohort study Study dates: 2009 to 2011 Malaria transmission pattern and local antimalarial drug resistance: various, not specified Adverse event monitoring: "...participants were asked to complete a survey each week during travel and a post-travel survey within 2–4 weeks after return"
Participants	Number enrolled: 628 participants completed all three surveys, 370 included in the analysis Inclusion criteria: "Travelers were included from among all those enrolled if they received a prescription for chemoprophylaxis, traveled to at least one malaria-endemic area, and completed pre- and post-travel surveys and at least one during-travel survey" Exclusion criteria: "To complete the study in a reasonable amount of time, only participants with shorter durations of travel (approximately 2 months) were included" Factors influencing drug allocation: "Several different medications are available for malaria chemoprophylaxis, depending on the traveler's destination and medical history" Country of recruitment: USA

Stoney 2016 *(Continued)*

	Country of malaria exposure: India (13%), Tanzania (8%), Kenya (7%), South Africa (7%), and Haiti (7%) Duration of exposure to malaria: median travel duration 13 days Type of participants: travellers
Interventions	*Included in the review:* 1. Mefloquine* 2. Doxycycline* 3. Atovaquone-proguanil* 4. Chloroquine* *Not included in the review:* 5. Primaquine* **dosing regimen not specified*
Outcomes	*Included in the review:* 1. Adverse effects; any, headache, abnormal dreams 'intense nightmares', any gastrointestinal 2. Discontinuations of study drug due to adverse effects 3. Measure of adherence to the drug regimen *Outcomes assessed not included in the review:* 4. Clinical cases of malaria 5. Reasons for non-compliance with chemoprophylaxis (data provided on aggregate), 6. Use of personal protective measures for malaria prevention
Notes	Funding sources: "This work was supported by a cooperative agreement [1 U19CI000508-01] between the Centers for Disease Control and Prevention and Boston Medical Center"

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** Age, sex, destination and duration of travel were recorded but figures were not reported across prophylactic regimens **2. Selection of participants into the study: moderate** No information was provided regarding travellers who did not wish to participate in the study **3. Measurement of interventions: low** "The type of chemoprophylaxis prescribed were collected from data entered by clinicians into patients' medical records" **4. Departures from intended interventions: moderate** No switches or discontinuations were reported. It was unclear whether this information was captured in the questionnaire

Stoney 2016 *(Continued)*

	5. Missing data: low 364/370 (98%) participants were included in the analysis **6. Measurement of outcomes: serious** Comment: the outcome measure was subjective, participants and personnel were not blinded **7. Selection of the reported results: moderate** Insufficient information provided on how data on adverse effects were obtained to determine whether all outcomes had been reported **8. Other: low** Government funding

Tan 2017

Methods	Design: retrospective cohort study Study dates: 18 July to 16 September 2016 Malaria transmission pattern and local antimalarial drug resistance: various, not specified Adverse event monitoring: patient self-reported questionnaire
Participants	Number enrolled: 8931 Inclusion criteria: Returned Peace Corps volunteers (RPCV) who served between 1995 and 2014 and had an e-mail address in Peace Corps' RPCV database Exclusion criteria: None mentioned Factors influencing drug allocation: none specified Country of recruitment: USA Country of malaria exposure: various, not specified Duration of exposure to malaria: various, not specified Type of participants: returned Peace Corps volunteers
Interventions	1. Mefloquine* 2. Doxycycline* 3. Atovaquone-proguanil* 4. Chloroquine* **dosing regimen not specified*
Outcomes	*Included in the review:* 1. Measure of adherence to the drug regimen *Outcomes assessed not included in the review:*

Tan 2017 *(Continued)*

	2. "Questions about medications before, during, or after Peace Corps, as well as habits such as drinking"
Notes	Funding source: "this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors"

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** Important confounders were measured but not been reported across groups. Duration and destination of travel were not measured **2. Selection of participants into the study: serious** 8931/47,238 potential respondents included (13% response rate) **3. Measurement of interventions: serious** Participants were asked to self-report which chemoprophylaxis they had taken at least 2 years after they had finished the course **4. Departures from intended interventions: serious** Limited information was provided regarding switches between interventions. Participants were asked to self-report this information at least 2 years after finishing treatment **5. Missing data: low** Information on adherence was reported for all participants who answered this question (5026 respondents/5055 who reported taking malaria prophylaxis) **6. Measurement of outcomes: serious** Comment: the outcome measure was subjective; participants and personnel were not blinded **7. Selection of the reported results: moderate** There was insufficient information provided to be sure that all outcomes included in the questionnaire were reported **8. Other: low** "This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors"

Terrell 2015

Methods	Design: cross-sectional cohort study Study dates: 2012 and 2013 Malaria transmission pattern and local antimalarial drug resistance: "...high risk of malaria (mainly *P. falciparum*) in Kenya, although the risk is assessed as very low in Nairobi and in the highlands above 2,500 m... widespread resistance to chloroquine" Adverse event monitoring: "...questionnaire-based, two-arm cohort study"

Terrell 2015 *(Continued)*

Participants	Number enrolled: 2032 completed questionnaires available, 220 failed to indicate which drug they were taking Inclusion criteria: all military personnel on deployment to Kenya who travelled on one of three main body flights on their return to the UK Exclusion criteria: none mentioned Factors influencing drug allocation: "...the choice of drugs considered in this study was limited to mefloquine or doxycycline... participants were free to use another drug should they experience unacceptable adverse effects or where there was an occupational reason" Country of recruitment: UK Country of malaria exposure: Kenya Duration of exposure to malaria: "The majority of participants spent approximately 6 weeks in Kenya with a small number spending a few weeks longer if they filled an administrative role" Type of participants: military
Interventions	*Included in review comparisons:* 1. Mefloquine* 2. Doxycycline* *Not included in review comparisons:* 3. Atovaquone-proguanil* (results not included in the analysis) **dosing regimen not specified*
Outcomes	*Included in the review :* 1. Adverse effects; any 2. Measure of adherence to the drug regimen *Outcomes assessed not included in the review:* 3. Clinical cases of malaria 4. Impact of adverse effects on self-reported ability to work
Notes	Funding sources: "The research was not sponsored by any external body" After we submitted the review for peer referee, the author sent us a spreadsheet containing numbers of events relating to a variety of symptoms after the review had been submitted for publication. These data are not included in the review and will require some clarification over how they were collected to allow us to assess risk of bias. This additional information will be considered in future updates.

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** "Although not formally recorded, each unit can be assumed to be composed of similar populations in terms of number, age, gender, occupation, and general health" **2. Selection of participants into the study: serious**

Terrell 2015 *(Continued)*

	"Completion rates were consistently poor throughout the study period with only 150 to 250 questionnaires returned per tranche of around 1,000 troops"
	3. Measurement of interventions: low
	Participants were asked to self-report which medication they were on while still taking the medication"
	4. Departures from intended interventions: moderate
	"...[participants] were invited to complete the questionnaire for whichever drug they took for the longer period"
	5. Missing data: moderate
	"2,032 completed questionnaires available for analysis of which 10.8% (220) failed to indicate which drug they were taking"
	6. Measurement of outcomes: serious
	The outcome measure was subjective; participants and personnel were not blinded
	7. Selection of the reported results: serious
	"In both arms, some participants indicated that they had experienced an adverse effect but did not report how it had impacted upon their ability to work. They were excluded from the final analysis"
	Mefloquine: 71 participants, doxycycline: 67 participants
	8. Other: low
	"The research was not sponsored by any external body"

Tuck 2016

Methods	Design: cohort study
	Study dates: 15 to 22 February 2015
	Malaria transmission pattern and local antimalarial drug resistance: not specified
	Adverse event monitoring: patient self-reported questionnaire
Participants	Number enrolled: 115 (337 eligible)
	Inclusion criteria: all land-based members of a UK military expedition to Sierra Leone
	Exclusion criteria: none specified
	Country of recruitment: Sierra Leone
	Country of malaria exposure: Sierra Leone
	Duration of exposure to malaria: not specified
	Type of participants: military
Interventions	1. Mefloquine
	2. Doxycycline

Tuck 2016 *(Continued)*

	3. Atovaquone-proguanil
Outcomes	*Included in the review:* 1. Adverse effects: any, nausea, abdominal pain, diarrhoea, dizziness, insomnia 'disturbed sleep', pruritis, indigestion, mouth ulcers, lethargy 2. Measure of adherence to the drug regime
Notes	Funding source: unfunded

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** Age, sex and BMI were not measured. Demographic information not reported across groups **2. Selection of participants into the study: serious** 151 (46.3%) returned survey forms **3. Measurement of interventions: low** Participants were asked to self-report which medication they were taking while taking it **4. Departures from intended interventions: moderate** Switches between groups were recorded. 8/151 recipients had medications switched due to unacceptable adverse effects. It was unclear to which drug adverse effects were attributed. **5. Missing data: low** Data were reported for all survey respondents. **6. Measurement of outcomes: serious** The outcome measure was subjective; participants and personnel were not blinded **7. Selection of the reported results: moderate** There was insufficient information provided to be sure that all outcomes included in the questionnaire were reported **8. Other: low** "This audit was unfunded"

van Riemsdijk 1997

Methods	Design: prospective cohort study Study dates: 24 February to 24 May 1994 Malaria transmission pattern and local antimalarial drug resistance: various, not stated

van Riemsdijk 1997 *(Continued)*

	Adverse event monitoring: participant self-reporting questionnaire
Participants	Number enrolled: 1791 eligible and willing to co-operate, data obtained from 1501 participants. Inclusion criteria: "...persons who visited the Travel Clinic in the period between 24 February and 24 May, 1994, and who had an anticipated date of return to the Netherlands before the end of the study period, and who had given informed consent" Exclusion criteria: none stated Country of recruitment: Rotterdam, Netherlands Region of malaria exposure: various; Africa, South America, Asia or the Middle East Duration of exposure to malaria: various, not specified Type of participants: travellers
Interventions	*Included in review comparisons:* 1. Mefloquine (1 x 250 mg tablet) weekly 2. Non-users of antimalarials *Not included in review comparisons:* 3. Proguanil (1 x 200 mg tablet) daily
Outcomes	*Included in the review:* 1. Adverse events; nausea, diarrhoea, dizziness, abnormal dreams, insomnia, anxiety, depression, visual impairment 2. Adverse events; other (agitation, confusion) *Outcomes assessed not included in the review:* 3. Profile of mood states (only reported in comparison with proguanil)
Notes	Funding sources: Not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Counfounding: low** Identified confounders were measured and balanced across groups **2. Selection of participants into the study: moderate** 1501/1791 (86% response rate) **3. Measurement of interventions: moderate** Comment: the prescription was provided by a travel clinic which also performed the study but no information regarding switches and discontinuations were recorded or reported **4. Departures from intended interventions: moderate** No information was provided on discontinuations or switches **5. Missing data: moderate**

van Riemsdijk 1997 *(Continued)*

	1227/1449 (85%) participants were included in the analysis; chloroquine-proguanil users were not included. The number of non-users decreased from 392 to 340 without explanation **6. Measurement of outcomes: serious** Comment: the outcome measure was subjective; participants and personnel were not blinded **7. Selection of the reported results: moderate** It was clear what was asked in the questionnaire. Information was sought on the severity of adverse events but this was not reported **8. Other: no information** No information was provided regarding the study sponsor

van Riemsdijk 2002

Methods	Design: RCT Malaria transmission pattern and local drug resistance: not mentioned Study dates: unclear Adverse event monitoring: baseline evaluation prior to travel, and follow up date 7 days after the participant left the endemic area and two scheduled telephone conversations
Participants	Number enrolled: 140 Inclusion criteria: travellers aged ≥ 3 years and weighing ≥ 11 kg with planned travel ≤ 28 days to a malaria-endemic area (Overbosch 2001) Exclusion criteria: In the published report "We excluded those who had risk factors for concentration impairment (e.g. use of opioids, hypnotics, or tranquillizers or use of alcohol 4 hours before testing)" Within Høgh 2000 (unclear if the same exclusion criteria were applied): 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) Country of recruitment: Rotterdam Travel Clinic, Netherlands Regions of malaria exposure: various malaria endemic destinations (66% in Africa, 13% South America, 24% other) Mean duration of exposure to malaria: 19 days Type of participants: travellers, non-immune
Interventions	1. Mefloquine (1 x 250 mg tablet; or ¼, ½ or ¾ of a tablet, according to body weight) once weekly, starting 7 days before travel and continuing for 4 weeks after travel* 2. Atovaquone-chloroguanil (1 combined tablet containing 250 mg atovaquone and 100 mg proguanil hydrochloride; or alternatively 1 to 3 combined children's 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*

van Riemsdijk 2002 *(Continued)*

**matched placebo for each treatment arm*

Outcomes	1. Adverse events; other outcomes (profile of mood states, neurobehavioural evaluation system) 2. Measures of adherence to the drug regimen 3. Discontinuations of the study drug due to adverse effects
Notes	Funding source: Netherlands Inspectorate for Healthcare gave financial support 'independently performed in a sample of patients from one center that participated in the MAL30010 multicenter clinical trial'- Enrollment criteria and study conduct were described in a separate publication (Høgh 2000) which refers to a different study population (atovaquone-proguanil versus chloroquine-proguanil). 'This study was planned and performed independently from the trial by other researchers and without knowledge of its results.' 'Subjects were separately recruited and asked for consent during the initial screening visit of the trial.'

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A computer-generated code was used to randomly assign a treatment number to the three bottles of study drug for every individual. At all sites consecutively enrolled individuals who satisfied all entry criteria received the next treatment number" (Høgh 2000)
Allocation concealment (selection bias)	Low risk	"Treatment codes were provided to investigators in opaque sealed envelopes, to be opened only if knowledge of study drug assignment was required for management of a medical emergency" (Høgh 2000)
Blinding of participants and personnel (performance bias) Adverse effects/events	Unclear risk	"To mask differences between the dosing regimes, placebo tablets were used... All placebo treatment regimens were identical to the aforementioned scheme for the active ingredient of mefloquine and atovaquone plus chloroguanide" Comment: did not mention whether the placebo and intervention tablets were identical in appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The assessments were made by researchers who were unaware of the treatment allocation"
Incomplete outcome data (attrition bias); efficacy	Unclear risk	N/A
Incomplete outcome data (attrition bias); safety	High risk	"We enrolled a total of 140 subjects in the cohort, 119 of whom completed the follow up" Comment: Those who did not complete follow up were not included in the subsequent statistical analysis. The proportion of participants who did not complete the study due to adverse outcomes varied significantly between groups (67% mefloquine and 33% atovaquone plus chloroguanide)
Selective reporting (reporting bias); efficacy	Unclear risk	N/A
Selective reporting (reporting bias); safety	Low risk	"Data were collected on concurrent medications, as well as subject's use of coffee, alcohol and illicit drugs"

van Riemsdijk 2002 *(Continued)*

		"stratification for sex and adjustment for potential confounders such as smoking and the use of coffee and tea did not affect the result" Comment: these data were not presented
Other bias	Low risk	Funding: "For this study came from the Inspectorate for Health Care. Glaxo Wellcome kindly provided us with the treatment allocation codes after completion of the study. No financial support, however, was received from any pharmaceutical company"

Vuurman 1996

Methods	Design: RCT Study dates: not mentioned Malaria transmission pattern and local antimalarial drug resistance: not applicable Adverse event monitoring: "After each driving test, subjects [described]... the presence and severity of adverse effects - drowsiness, weakness, headache, fatigue, nervousness, nausea, dizziness and memory disturbance"
Participants	Number enrolled: 42 Inclusion criteria: "...[volunteers] were medically screened by routine blood chemistry and haematology tests, a physical examination including an 12-lead ECG recording, and urine tests for pregnancy and drugs of abuse" Exclusion criteria: "...clinically relevant abnormalities in any blood test; far-field, binocular visual acuity that deviated by more than 0.65 dioptres from normal, corrected or uncorrected; known hypersensitivity to any drug; history of any serious gastrointestinal, hepatic, renal neurologic or psychiatric disorder; evidence of drug or alcohol abuse, excessive alcohol or nicotine use; blood donation or participation in a drug trial within the prior 2 months; and for premenopausal females, pregnancy, lactation or failure to exercise reliable birth control" Country of recruitment: Netherlands Country of malaria exposure: not applicable Duration of follow up: 30 days Type of participants: non-exposed Dutch nationals
Interventions	1. Mefloquine (1 x 250 mg tablet) weekly, with loading dose of one tablet daily for 3 days in week 1 2. Placebo (1 tablet) weekly, with identical loading regimen of placebo tablets
Outcomes	1. Adverse events; any, nausea, diarrhoea, headache, dizziness 2. Adverse events; other (fatigue) 3. Discontinuations of study drug due to adverse effects 4. Adverse events; other outcome measures (critical flicker/fusion frequency, critical instability tracking test, standardized stabilimetry method of the International Society of Posturography, tests of driving performance)
Notes	Funding sources: "The study was sponsored by F. Hoffmann-La Roche Ltd"

Risk of bias

Vuurman 1996 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The study followed a randomised, 2-arm, double-blind, parallel group design" Comment: method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	"The study followed a randomised, 2-arm, double-blind, parallel group design" Comment: method of allocation concealment not described
Blinding of participants and personnel (performance bias) Adverse effects/events	Low risk	"They received mefloquine 250 mg or placebo in identically appearing tablets"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: described as double blind but no description of how this was achieved for researchers and outcome assessors
Incomplete outcome data (attrition bias); efficacy	Unclear risk	N/A
Incomplete outcome data (attrition bias); safety	Low risk	Comment: dropouts were reported. 2/20 participants dropped out of the mefloquine group, one due to adverse effects related to the study drug
Selective reporting (reporting bias); efficacy	Unclear risk	N/A
Selective reporting (reporting bias); safety	High risk	"...subjects used 10 cm visual-analogue scales to describe their mood in three dimensions – 'Alertness', 'Contentedness', and 'Calmness'" Comment: outcomes relating to these descriptions were not reported. The study reports "events occurring more than once" in each group
Other bias	High risk	"The study was sponsored by F. Hoffmann-La Roche Ltd"

Waner 1999

Methods	Design: cross-sectional cohort study Study dates: April to May 1996 Malaria transmission pattern and local antimalarial drug resistance: "a high risk Malaria area... Chloroquine-resistant *P. falciparum* malaria" Adverse event monitoring: "In-flight self administered questionnaires were distributed and completed by travelers on flights returning to Johannesburg International Airport"
Participants	Number enrolled: 4035 questionnaires distributed, 3051 returned Inclusion criteria: All travelers boarding the only commercial airline serving this area during April and May 1996 were included in the survey Exclusion criteria: None mentioned Country of recruitment: South Africa

Waner 1999 *(Continued)*

	Country of malaria exposure: South Africa Duration of exposure to malaria: various, not specified Type of participants: travellers
Interventions	*Included in review comparisons:* 1. Mefloquine* 2. Doxycycline* 3. Chloroquine* *Not included in review comparisons:* 4. Chloroquine-proguanil* 5. Proguanil* **dosing regimen not specified*
Outcomes	*Included in review comparisons:* 1. Adverse effects; any *Outcomes assessed not included in the review:* 2. Sources of information on malaria prior to visit, 3. Use of personal protective measures against mosquitoes, 4. Measures of adherence to the drug regimen (information provided on aggregate), 5. Travellers knowledge of malaria symptoms
Notes	Funding sources: not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Confounding: moderate** Sex of travellers was not provided by prophylactic regimen. Destination of travel was set by the study design. BMI of travellers and duration of travel were not recorded **2. Selection of participants into the study: serious** Response rate 3051/4035 (75%) **3. Measurement of interventions: low** Travellers were asked to self-report which prophylactic regimen they were taking while still using the drug **4. Departures from intended interventions: moderate** No discontinuations or switches were reported. This information was not included in the questionnaire **5. Missing data: low**

Waner 1999 *(Continued)*

	Outcome data were available for 973/978 mefloquine recipients and 80/80 doxycycline recipients **6. Measurement of outcomes: serious** Comment: the outcome measure was subjective; participants and personnel were not blinded **7. Selection of the reported results: moderate** Insufficient information provided on how data on adverse effects were obtained to determine whether all outcomes were reported **8. Other: no information** No information was provided regarding the study sponsor.

Weiss 1995

Methods	Design: RCT Study dates: April to July 1993 Malaria transmission pattern and local antimalarial drug resistance: "Incidence of new cases of falciparum malaria during the rainy seasons has been measured at 90% in adults. *P. falciparum* accounts for > 95% of all malaria in Saradidi" Adverse event monitoring: "Each subject was visited daily at home by an assigned field worker, who asked about symptoms of malaria or drug side effects, obtained malaria smears, or administered drug doses if the subject was not at school"
Participants	Number enrolled: 169 Inclusion criteria: aged 9 to 14 years. "Screening consisted of a physical examination, a urine pregnancy test for girls, and blood tests for complete blood cell count; blood urea nitrogen, serum alanine aminotransferase, and glucose-6 phosphate dehydrogenase (G6PD) levels; and hemoglobin electrophoresis" Exclusion criteria: none mentioned Country of recruitment: Saradidi Rural Health Project, Nyanza province, Kenya on the shores of Lake Victoria Country of malaria exposure: Saradidi Rural Health Project, Nyanza province, Kenya on the shores of Lake Victoria Duration of exposure to malaria: study duration 4 months Type of participants: Kenyan residents, semi-immune
Interventions	1. Melfoquine (1 x 125 mg tablet) weekly, with a second dose given on the third day of the study, equal to their usual weekly medication. 2. Doxycycline (1 x 50 mg tablet) daily 3. Primaquine 4. Multivitamin (1 x tablet containing vitamin A, 2500 IU, thiamine, 1 mg, riboflavin, 0.5 mg, nicotinamide, 7.5 mg, ascorbic acid, 15 mg, vitamin 0 3, 250 IU) daily

Weiss 1995 *(Continued)*

	Co-interventions: After baseline malaria smears, all subjects received curative therapy for preexisting malaria: 7 days of quinine bisulfate, 300 mg three times daily, and doxycycline, 50 mg twice daily. The first dose of prophylactic drug was given starting the day after curative therapy finished
Outcomes	*Included in the review:* 1. Clinical cases of malaria 2. Episodes of parasitaemia 3. Discontinuations of study drug due to adverse effects *Outcomes assessed not included in the review:* 4. Laboratory tests; complete blood cell counts, blood urea nitrogen and serum alanine aminotransferase 5. Mean number of symptoms reported per subject: nausea, abdominal pain, diarrhoea, headache, fever
Notes	Funding sources: Financial support: USA Naval Medical Research and Development Command (work unit no. 623002A.81 0.00 J0 I.HFX. J433). Kenya Medical Research Institute. USA Army Medical Research and Materiel Command Provisional (contract no. DAMDI7-92-V-20J2)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Students from each village school were separately randomized, to control for geographic variation in malaria transmission" Comment: no description of how randomization was performed
Allocation concealment (selection bias)	Unclear risk	"All medications were in brown envelopes and were administered 7 days each week by I field worker at each school" Comment: no mention of whether envelopes were sealed or if field workers had access to their content
Blinding of participants and personnel (performance bias) Adverse effects/events	Unclear risk	Comment: no mention of whether participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"None of the malaria slide readers knew which drugs the subjects were taking. None of the field workers visiting the homes daily to ask about symptoms or clinical staff evaluating and treating subjects at the Saradidi Clinic knew which drugs the subjects were taking. If there was concern about a drug side effect, the clinical staff would consult the medical monitor, who would break the code for that subject. This occurred only four times during the studies"
Incomplete outcome data (attrition bias); efficacy	Unclear risk	N/A
Incomplete outcome data (attrition bias); safety	Unclear risk	Comment: number included in the safety analysis not reported
Selective reporting (reporting bias); efficacy	Unclear risk	N/A

Weiss 1995 *(Continued)*

Selective reporting (reporting bias); safety	Unclear risk	Comment: mean number of symptoms reported per subject during 11 weeks of the study were reported. A targeted list of symptoms was reported, with everything else included in 'all other'. It was unclear what this list included
Other bias	Low risk	Financial support: USA Naval Medical Research and Development Command (work unit no. 623002A.81 0.00 J0 I.HFX. J433). Kenya Medical Research Institute. USA Army Medical Research and Materiel Command Provisional (contract no. DAMDI7-92-V-20J2)

Wells 2006

Methods	Design: retrospective cohort study Study dates: January 2002 to December 31 2002 Malaria transmission pattern and local antimalarial drug resistance: various, not specified Adverse event monitoring: "The study cohort was electronically linked to the Standardized Inpatient Data Record (SIDR) and the Health Care Service Record (HCSR) to identify hospitalization... We analyzed any-cause hospitalization (excluding complications of pregnancy, childbirth, and the puerperium, congenital anomalies, and certain conditions originating in the perinatal period)"
Participants	Number enrolled: 397442 Inclusion criteria: "All active-duty US service members during the period January 1, 2002, and December 31, 2002, as reported by the Defense Manpower Data Center (DMDC), Monterey, CA. The mefloquine prescribed group was defined as service members who had been prescribed a minimum of seven mefloquine tablets beginning in 2002 and who were identified as having been deployed at some point during the same time period. We used two reference groups. The first reference group was comprised of service members who had duty zip codes for either Europe or Japan at some time during 2002 and had no evidence of having been deployed from October 1, 2001 through the individual's period of observation... The second reference group consisted of US service members who were identified as having been deployed for a minimum of 1 month during 2002" Exclusion criteria: "Both reference groups were restricted to individuals who had no evidence of having received a prescription for mefloquine or chloroquine or a doxycycline prescription for more than 14 tablets.' 'Individuals who could not be followed a minimum of 2 months were excluded from the study" Country of recruitment: USA Country of malaria exposure: various, not specified Duration of exposure to malaria: various, not specified Type of participants: military
Interventions	1. Mefloquine* 2. Non-users of antimalarials **dosing regimen not specified*
Outcomes	*Included in the review:* 1. Adverse events; serious (any hospitalization, hospitalizations due to vertiginous syndromes, migraine, dizziness and giddiness, anxiety disorders, somatoform disorders, mood disorders, PTSD, substance use disorders, personality disorders, nystagmus or adjustment reaction) *Outcomes assessed not included in the review:*

Wells 2006 *(Continued)*

	2. Hospitalizations coded according to classification system: infectious/parasitic, neoplasms, endocrine, nutritional, metabolic, blood and blood-forming organs, mental disorders, nervous system, circulatory system, respiratory system, digestive system, genitourinary system, skin and subcutaneous tissues, musculoskeletal and connective tissue, ill-defined conditions, injury and poisoning
Notes	Funding sources: "This represents report 05–05, supported by the Department of Defense, under work unit no. 60002"

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	**1. Counfounding: moderate** BMI, destination and duration of travel have not been recorded **2. Selection of participants into the study: serious** "Follow-up time began on return from deployment for mefloquine-prescribed members, and for the deployed reference group, on assignment to Europe or Japan, or January 1, 2002, whichever occurred last for the Europe/Japan reference group" Start of follow up began a long time after start of intervention **3. Measurement of interventions: serious** Surrogate measure used for mefloquine exposure. There was a possiblity that some participants in the second deployed reference group took mefloquine **4. Departures from intended interventions: moderate** "Both reference groups were restricted to individuals who had no evidence of having received a prescription for mefloquine or chloroquine or a doxycycline prescription for more than 14 tablets" **5. Missing data: moderate** "Individuals who could not be followed a minimum of 2 months were excluded from the study" Comment: number of participants in this group not reported **6. Measurement of outcomes: low** The outcome measure (hospitalizations) was objective **7. Selection of the reported results: low** All prespecified outcomes were reported **8. Other: low** Government funding

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

Study	Reason for exclusion
Abraham 1999	Cohort study. C ompared mefloquine with a regimen that is no longer used routinely

Study	Reason for exclusion
Adera 1995	Cohort study. R eported on efficacy but no other relevant outcomes
Adshead 2014	Single arm cohort study
Angelin 2014	No relevant outcomes reported
Anonymous 1991	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Anonymous 1998	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Anonymous 1998a	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Anonymous 2005	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Anonymous 2009	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Artaso 2004	Not a randomiz ed or cohort study e.g. case report or case control study
Arthur 1990a	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Banerjee 2001	No relevant outcomes reported
Barbero Gonzalez 2003	No relevant outcomes reported
Barrett 1996	Cohort study. C ompared mefloquine with a regimen that is no longer used routinely
Berger 1998	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Berman 2004	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Bernado 1994	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Bijker 2014	This trial evaluated chemoprophylaxis plus sporozoite immunization
Bjorkman 1991	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Black 2007	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Blanke 2003	Cohort study. R eported on efficacy but no other relevant outcomes
Botella de Maglia 1999	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Bourgeade 1990	Not a randomiz ed or cohort study e.g. case report or case control study
Brenier-Pinchart 2000	Not a randomiz ed or cohort study e.g. case report or case control study
Brisson 2012	No relevant outcomes reported
Bruguera 2007	Not a randomiz ed or cohort study e.g. case report or case control study
Burke 1993	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Caillon 1992	Not a randomiz ed or cohort study e.g. case report or case control study
Carme 1997	Cohort study. C ompared mefloquine with a regimen that is no longer used routinely

Study	Reason for exclusion
Castot 1988	Not a randomiz ed or cohort study e.g. case report or case control study
Cave 2003	No relevant outcomes reported
Charles 2007	No relevant outcomes reported
Chin 2016	No relevant outcomes reported
Clifford 2009	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Clift 1996	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Clyde 1976	Single-arm cohort study
Cobelens 1997	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Cohen 1997	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Conget 1993	Not a randomiz ed or cohort study e.g. case report or case control study
Conrad 1997	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Corbett 1996	Cohort study. C ompared mefloquine with a regimen that is no longer used routinely
Coulaud 1986	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Croft 1996	Not a randomiz ed or cohort study e.g. case report or case control study
Croft 1997	RCT. C ompared mefloquine with a regimen that is no longer used routinely
Del Cacho 2001	Cohort study. C ompared mefloquine with a regimen that is no longer used routinely
Dia 2010	No relevant outcomes reported
Durrheim 1999	Cohort study. Compare d mefloquine with a regimen that is no longer used routinely
Eamsila 1993	Cohort study. Compare d mefloquine with a regimen that is no longer used routinely
El Jaoudi 2010	Single arm cohort study
Fernando 2016	No relevant outcomes reported
Fujii 2007	Single arm cohort study
Hamer 2008	No relevant outcomes reported
Hellgren 1990	No relevant outcomes reported
Hopperus 1996	Single arm cohort study
Jaspers 1996	Single arm cohort study
Jensen 1998	Not a randomiz ed or cohort study e.g. case report or case control study

Study	Reason for exclusion
Karbwang 1991	Mefloquine not used at a prophylactic dose (e.g. treatment dose or i ntermittent preventive treatment of malaria in pregnancy dose)
Karbwang 1991a	Mefloquine was used as a combination regimen with sulph adoxine and pyrimethamine
Khaliq 2001	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Kimura 2006	No relevant outcomes reported
Kitchener 2003	No relevant outcomes reported
Kitchener 2005	Cohort study. A llocation to study drug was based on the occurrence of adverse effects
Kok 1997	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Kollaritsch 2000	Single arm cohort study
Kozarsky 1993	Single arm cohort study
Landry 2006	Single arm cohort study
Lapierre 1983	Single arm cohort study
Lim 2005	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Lobel 1993	Cohort study. C ompared mefloquine with a regimen that is no longer used routinely. C hloroquine users we re not clearly separated from users of chloroquine-proguanil
Looareesuwan 1987	No relevant outcomes reported
MacArthur 2002	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Malvy 2006	Cohort study. R eported on efficacy but no other relevant outcomes
Marcy 1996	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Massey 2007	No relevant outcomes reported
Matsumura 2005	Single arm cohort study
Meszaros 1996	Not a randomiz ed or cohort study e.g. case report or case control study
Michel 2007	Cohort study. R eported on efficacy but no other relevant outcomes
Mimica 1983	No relevant outcomes reported
Mizuno 2006	Single arm cohort study
Mizuno 2010	Single arm cohort study
Moon 2011	No relevant outcomes reported
Morales de Naime 1989	No relevant outcomes reported
Munawar 2012	Single arm cohort study

Study	Reason for exclusion
Mølle 2000	Cohort selected on basis of adverse events
Namikawa 2008	No relevant outcomes reported
Nasveld 2010	RCT. C ompared mefloquine with a regimen which is not used routinely
Nevin 2010	No relevant outcomes reported
Nevin 2012	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Nosten 1990	RCT. Did not include a comparator; compared alternate mefloquine doses
Nosten 1999	Mefloquine not used at a prophylactic dose (e.g. treatment dose or i ntermittent preventive treatment of malaria in pregnancy dose)
Nwokolo 2001	Cohort study. Compared mefloquine with a regimen that is no longer used routinely
Olanrewaju 2000	Single arm cohort study
Ollivier 2004	Single arm cohort study
Peetermans 2001	Cohort study. Compared mefloquine with a regimen that is no longer used routinely
Peragallo 1999	Cohort study. Compared mefloquine with a regimen that is no longer used routinely
Peragallo 2002	Single arm cohort study
Peragallo 2014	Single arm cohort study
Philips 1994	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Phillips 1996	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Phillips-Howard 1998	Cohort study. Compared mefloquine with a regimen that is no longer used routinely
Pistone 2007	No relevant outcomes reported
Port 2011	Mefloquine not used at a prophylactic dose (e.g. treatment dose or i ntermittent preventive treatment of malaria in pregnancy dose)
Potasman 2000	Cohort selected on basis of adverse events
Quinn 2016	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Reisinger 1989	RCT. C ompared mefloquine with a regimen that is no longer use d routinely
Rieckmann 1974	Mefloquine not used at a prophylactic dose (e.g. treatment dose or i ntermittent preventive treatment of malaria in pregnancy dose)
Rieke 1993	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Ries 1993	Not a randomiz ed or cohort study e.g. case report or case control study
Ringqvist 2015	Cohort selected on basis of adverse events

Study	Reason for exclusion
Rombo 1993	RCT. C ompared mefloquine with a regimen that is no longer used routinely
Rønn 1998	Mefloquine not used at a prophylactic dose (e.g. treatment dose or i ntermittent preventive treatment of malaria in pregnancy dose)
Sallent 1997	No relevant outcomes reported
Schlagenhauf 1996	Single arm cohort study
Scott 1993	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Smail 1991	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Smoak 1997	Single arm cohort study
Suriyamongkol 1991	Single arm cohort study
Tansley 2010	Mefloquine not used at a prophylactic dose (e.g. treatment dose or i ntermittent preventive treatment of malaria in pregnancy dose)
ter Kuile 1993	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Todd 1997	No relevant outcomes reported
Turner 2014	No relevant outcomes reported
Valerio 2005	No relevant outcomes reported
Van Genderen 2007	No participants received mefloquine prophylaxis
Van Grootheest 1999	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
van Riemsdijk 2004	Single arm cohort study
Venturini 2011	Single arm cohort study
Wagner 1986	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Wallace 1996	Field study in which troops switched extensively between mefloquine and doxycycline. Unable to attribute side effects to either prophylactic regimen
Weinke 1991	Cohort selected on basis of adverse events
White 2016	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Win 1985	Mefloquine not used at a prophylactic dose (e.g. treatment dose or i ntermittent preventive treatment of malaria in pregnancy dose)
Winstanley 1999	Not a research study of malaria prophylaxis e.g. letter to the editor or editorial
Wolters 1997	Cohort study. C ompared mefloquine with a regimen that is no longer used routinely

DATA AND ANALYSES

Comparison 1. Mefloquine versus placebo/non users

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical cases of malaria	9	1908	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.04, 0.19]
2 Malaria; episodes of parasitaemia in semi-immune populations	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Trials reporting number of participants with parasitaemia	3	414	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.06, 0.55]
2.2 Trials reporting number of episodes of parasitaemia	2	510	Risk Ratio (M-H, Random, 95% CI)	0.05 [0.00, 5.25]
3 Serious adverse events or effects (all studies)	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 RCTs (adverse events)	6	1221	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.14, 3.53]
3.2 Cohort studies (adverse effects)	2	1167	Risk Ratio (M-H, Fixed, 95% CI)	3.08 [0.39, 24.11]
4 Discontinuations due to adverse effects (all studies)	7	1130	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [0.55, 4.88]
4.1 RCTs (adverse effects)	7	1130	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [0.55, 4.88]
5 Nausea (all studies)	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 RCTs (adverse events)	2	244	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [1.05, 1.73]
5.2 Cohort studies (adverse events)	3	1901	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [1.42, 2.43]
6 Vomiting (all studies)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 RCTs (adverse events)	1	202	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.50, 1.19]
6.2 Cohort studies (adverse events)	2	1167	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.45, 1.21]
7 Abdominal pain (all studies)	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 RCTs (adverse events)	3	550	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.84, 1.40]
7.2 Cohort studies (adverse events)	2	1167	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.66, 1.42]
8 Diarrhoea (all studies)	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 RCTs (adverse events)	4	589	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.32, 1.62]

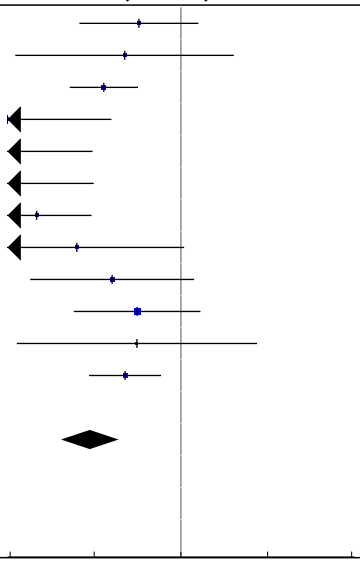
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.2 Cohort studies (adverse events)	3	1901	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.93, 1.68]
9 Headache (all studies)	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 RCTs (adverse events)	5	791	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.71, 0.99]
9.2 Cohort studies (adverse events)	1	197	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [0.63, 4.26]
10 Dizziness (all studies)	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 RCTs (adverse events)	3	452	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.90, 1.17]
10.2 Cohort studies (adverse events)	3	1901	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [1.29, 2.49]
11 Abnormal dreams (all studies)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 Cohort studies (adverse events)	2	931	Risk Ratio (M-H, Fixed, 95% CI)	2.35 [1.15, 4.80]
12 Insomnia (all studies)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Cohort studies (adverse events)	2	931	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [1.06, 2.02]
13 Anxiety (all studies)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 Cohort studies (adverse events)	2	931	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.67, 2.21]
14 Depressed mood (all studies)	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 Cohort studies (adverse events)	3	1901	Risk Ratio (M-H, Random, 95% CI)	2.43 [0.65, 9.07]
15 Abnormal thoughts and perceptions	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 Cohort studies (adverse events)	1	970	Risk Ratio (M-H, Fixed, 95% CI)	5.77 [0.79, 42.06]
16 Pruritis (all studies)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 RCTs (adverse events)	3	609	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.60, 1.24]
16.2 Cohort studies (adverse events)	1	197	Risk Ratio (M-H, Fixed, 95% CI)	6.71 [1.58, 28.55]
17 Visual impairment (all studies)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.1 RCTs (adverse events)	1	202	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.66, 1.46]
17.2 Cohort studies (adverse events)	1	970	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.27, 3.19]
18 Vertigo (all studies)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 RCTs (adverse events)	1	202	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.78, 1.34]
19 Other adverse events (RCTs)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 Arthralgia	1	140	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.02, 5.48]
19.2 Back pain	1	140	Risk Ratio (M-H, Fixed, 95% CI)	0.10 [0.01, 1.61]
19.3 Blurred vision	1	208	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.01, 3.89]
19.4 Cough	1	202	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.71, 1.14]
19.5 Constipation	1	202	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.53, 1.11]
19.6 Decreased appetite	1	202	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.95, 1.28]
19.7 Falls	1	202	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.82, 1.43]
19.8 Fatigue	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.14, 5.86]
19.9 Gastritis	1	140	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.10, 10.98]
19.10 Myalgia	1	140	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.36, 6.57]
19.11 Rash	1	140	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.04, 2.30]
19.12 Respiratory tract infection	1	140	Risk Ratio (M-H, Fixed, 95% CI)	2.63 [1.04, 6.61]
19.13 Sore throat	1	140	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.04, 2.75]
19.14 Unsteadiness	1	202	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.74, 1.52]
19.15 Weakness	1	202	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.96, 1.17]
20 Other adverse effects (cohort studies)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20.1 Agitation	1	734	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.61, 1.82]
20.2 Altered spatial perception	1	970	Risk Ratio (M-H, Fixed, 95% CI)	9.4 [0.57, 153.97]
20.3 Confusion	1	734	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.25, 1.78]
20.4 Loss of appetite	1	970	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.54, 1.50]
20.5 Mouth ulcers	1	970	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.39, 2.56]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.6 Palpitations	1	197	Risk Ratio (M-H, Fixed, 95% CI)	8.06 [0.44, 147.68]
20.7 Tingling	1	970	Risk Ratio (M-H, Fixed, 95% CI)	1.92 [0.59, 6.24]

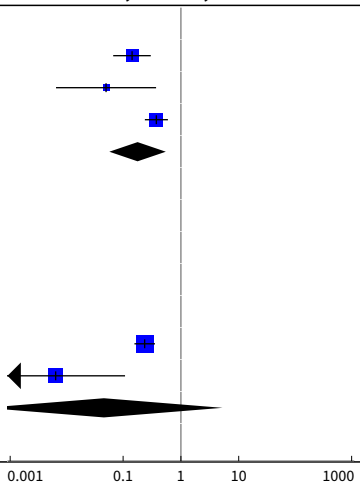
Analysis 1.1. Comparison 1 Mefloquine versus placebo/non users, Outcome 1 Clinical cases of malaria.

Study or subgroup	Mefloquine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bunnag 1992	2/123	6/121		10.24%	0.33[0.07,1.59]
Hale 2003	0/46	4/94		5.02%	0.22[0.01,4.08]
Nosten 1994	5/159	37/152		14.49%	0.13[0.05,0.32]
Ohrt 1997	0/61	53/65		5.39%	0.01[0,0.16]
Pearlman 1980	1/160	6/12		7.95%	0.01[0,0.1]
Pearlman 1980	0/169	6/12		5.23%	0.01[0,0.1]
Pearlman 1980	2/158	7/12		10.95%	0.02[0.01,0.09]
Salako 1992	0/107	7/101		5.15%	0.06[0,1.09]
Santos 1993	1/31	3/15		7.35%	0.16[0.02,1.42]
Santos 1993	2/32	3/15		9.68%	0.31[0.06,1.68]
Sossouhounto 1995	0/103	1/96		4.37%	0.31[0.01,7.54]
Weiss 1995	4/30	20/34		14.18%	0.23[0.09,0.59]
Total (95% CI)	**1179**	**729**		**100%**	**0.09[0.04,0.19]**
Total events: 17 (Mefloquine), 153 (Placebo)					
Heterogeneity: Tau^2=0.83; Chi^2=23.36, df=11(P=0.02); I^2=52.91%					
Test for overall effect: Z=6.21(P<0.0001)					



Analysis 1.2. Comparison 1 Mefloquine versus placebo/non users, Outcome 2 Malaria; episodes of parasitaemia in semi-immune populations.

Study or subgroup	Mefloquine n/N	n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Trials reporting number of participants with parasitaemia					
Hale 2003	6/46	86/94		38.31%	0.14[0.07,0.3]
Salako 1992	1/107	19/103		18.86%	0.05[0.01,0.37]
Weiss 1995	11/30	34/34		42.83%	0.38[0.24,0.6]
Subtotal (95% CI)	**183**	**231**		**100%**	**0.18[0.06,0.55]**
Total events: 18 (Mefloquine), 139 ()					
Heterogeneity: Tau^2=0.71; Chi^2=10.18, df=2(P=0.01); I^2=80.35%					
Test for overall effect: Z=3.01(P=0)					
1.2.2 Trials reporting number of episodes of parasitaemia					
Nosten 1994	22/159	89/152		54.16%	0.24[0.16,0.36]
Sossouhounto 1995	0/103	68/96		45.84%	0.01[0,0.11]
Subtotal (95% CI)	**262**	**248**		**100%**	**0.05[0,5.25]**
Total events: 22 (Mefloquine), 157 ()					



Study or subgroup	Mefloquine n/N	n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=10.69; Chi²=11.49, df=1(P=0); I²=91.3%					
Test for overall effect: Z=1.27(P=0.2)					

Favours mefloquine 0.001 0.1 1 10 1000 Favours placebo

Analysis 1.3. Comparison 1 Mefloquine versus placebo/non users, Outcome 3 Serious adverse events or effects (all studies).

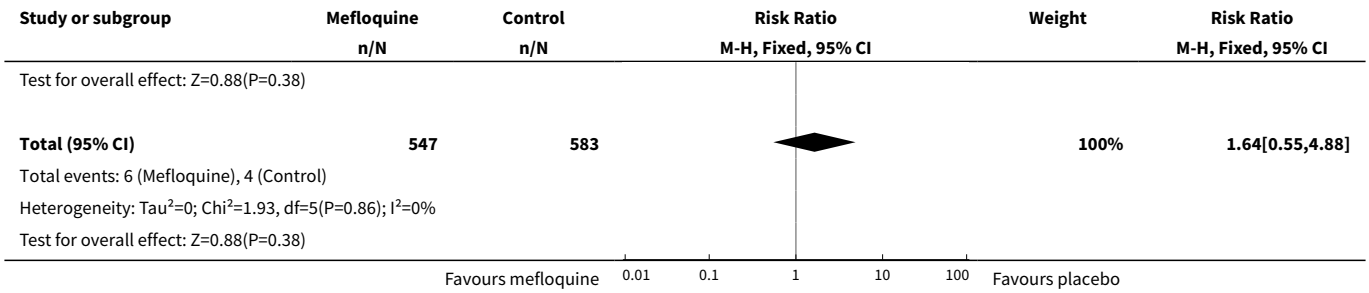
Study or subgroup	Mefloquine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 RCTs (adverse events)					
Bunnag 1992	0/116	1/121		41.58%	0.35[0.01,8.45]
Hale 2003	0/46	0/94			Not estimable
Nosten 1994	1/159	0/152		14.47%	2.87[0.12,69.88]
Ohrt 1997	0/61	0/65			Not estimable
Salako 1992	0/107	0/101			Not estimable
Sossouhounto 1995	0/103	1/96		43.95%	0.31[0.01,7.54]
Subtotal (95% CI)	**592**	**629**		**100%**	**0.7[0.14,3.53]**
Total events: 1 (Mefloquine), 2 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.18, df=2(P=0.55); I²=0%					
Test for overall effect: Z=0.44(P=0.66)					
1.3.2 Cohort studies (adverse effects)					
Hoebe 1997	2/104	0/93		38.77%	4.48[0.22,92.05]
Petersen 2000	5/809	0/161		61.23%	2.2[0.12,39.59]
Subtotal (95% CI)	**913**	**254**		**100%**	**3.08[0.39,24.11]**
Total events: 7 (Mefloquine), 0 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.11, df=1(P=0.74); I²=0%					
Test for overall effect: Z=1.07(P=0.28)					
Test for subgroup differences: Chi²=1.24, df=1 (P=0.27), I²=19.24%					

Favours mefloquine 0.005 0.1 1 10 200 Favours placebo

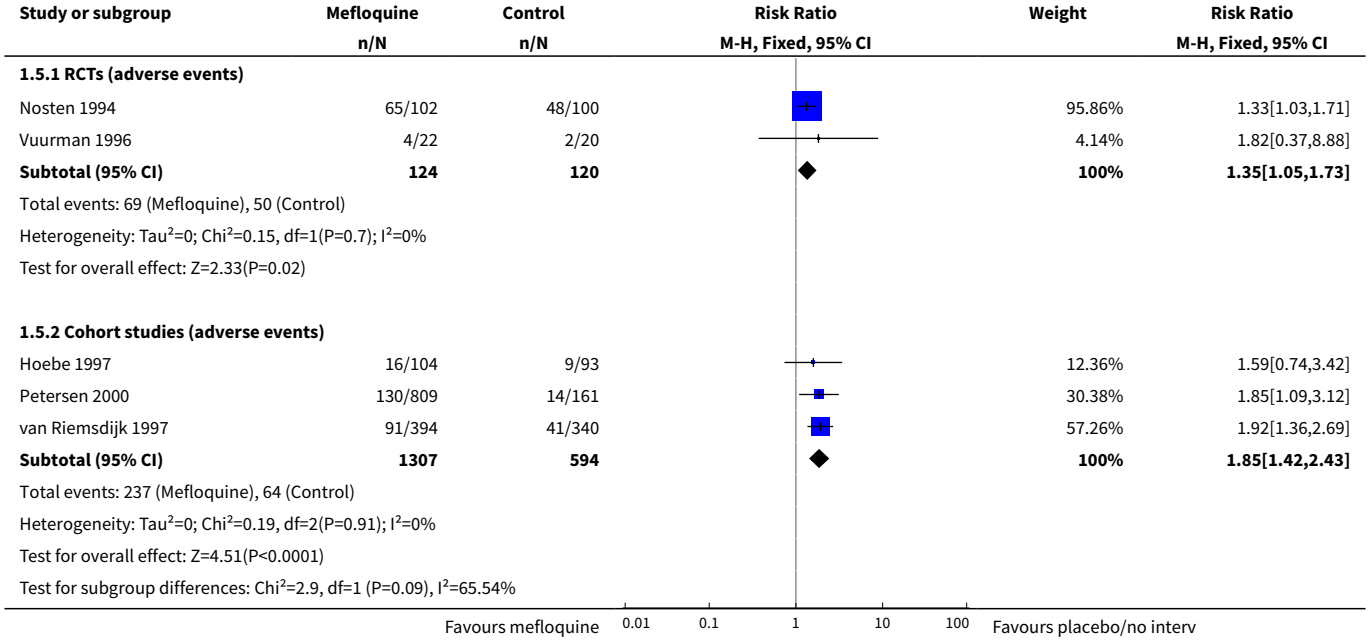
Analysis 1.4. Comparison 1 Mefloquine versus placebo/non users, Outcome 4 Discontinuations due to adverse effects (all studies).

Study or subgroup	Mefloquine n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 RCTs (adverse effects)					
Bunnag 1992	2/116	1/119		18.6%	2.05[0.19,22.32]
Hale 2003	0/46	3/94		43.66%	0.29[0.02,5.48]
Nosten 1994	1/159	0/152		9.63%	2.87[0.12,69.88]
Ohrt 1997	1/61	0/65		9.13%	3.19[0.13,76.93]
Salako 1992	0/113	0/101			Not estimable
Vuurman 1996	1/22	0/20		9.85%	2.74[0.12,63.63]
Weiss 1995	1/30	0/32		9.13%	3.19[0.14,75.49]
Subtotal (95% CI)	**547**	**583**		**100%**	**1.64[0.55,4.88]**
Total events: 6 (Mefloquine), 4 (Control)					
Heterogeneity: Tau²=0; Chi²=1.93, df=5(P=0.86); I²=0%					

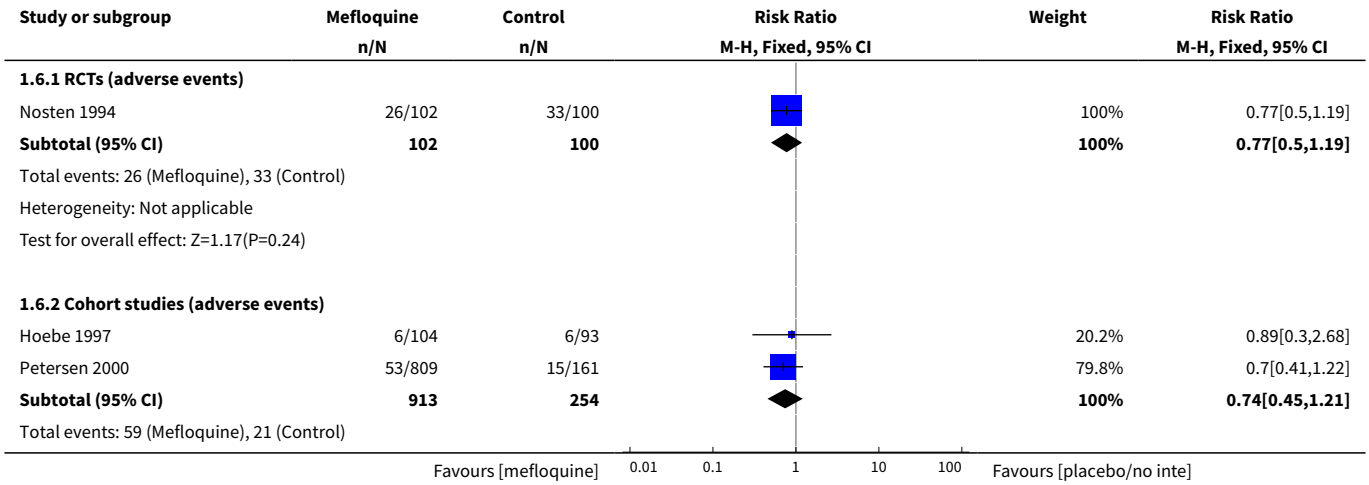
Favours mefloquine 0.01 0.1 1 10 100 Favours placebo



Analysis 1.5. Comparison 1 Mefloquine versus placebo/non users, Outcome 5 Nausea (all studies).



Analysis 1.6. Comparison 1 Mefloquine versus placebo/non users, Outcome 6 Vomiting (all studies).



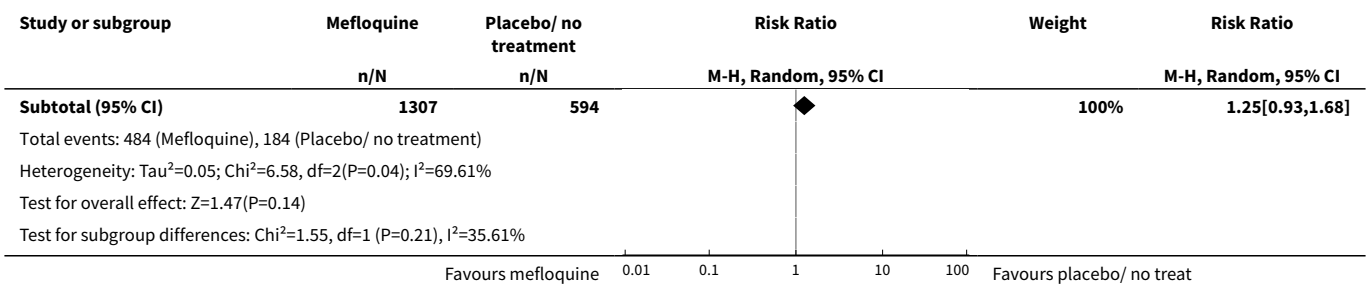
Study or subgroup	Mefloquine n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=0.15, df=1(P=0.7); I²=0%					
Test for overall effect: Z=1.19(P=0.23)					
Test for subgroup differences: Chi²=0.01, df=1 (P=0.9), I²=0%					

Analysis 1.7. Comparison 1 Mefloquine versus placebo/non users, Outcome 7 Abdominal pain (all studies).

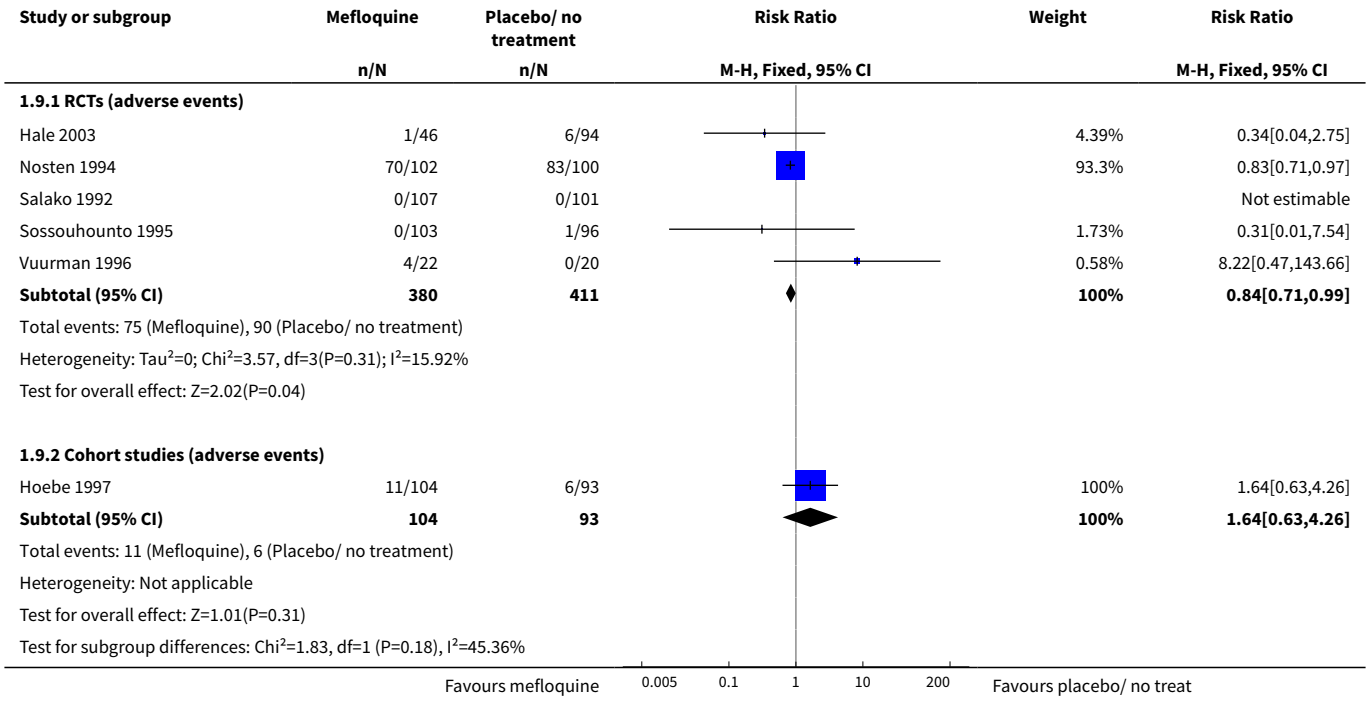
Study or subgroup	Mefloquine n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.7.1 RCTs (adverse events)					
Hale 2003	3/46	6/94		6.92%	1.02[0.27,3.9]
Nosten 1994	57/102	52/100		92.18%	1.07[0.83,1.39]
Salako 1992	1/107	0/101		0.9%	2.83[0.12,68.76]
Subtotal (95% CI)	**255**	**295**		**100%**	**1.09[0.84,1.4]**
Total events: 61 (Mefloquine), 58 (Control)					
Heterogeneity: Tau²=0; Chi²=0.36, df=2(P=0.83); I²=0%					
Test for overall effect: Z=0.64(P=0.52)					
1.7.2 Cohort studies (adverse events)					
Hoebe 1997	13/104	12/93		27.53%	0.97[0.47,2.02]
Petersen 2000	97/809	20/161		72.47%	0.97[0.62,1.51]
Subtotal (95% CI)	**913**	**254**		**100%**	**0.97[0.66,1.42]**
Total events: 110 (Mefloquine), 32 (Control)					
Heterogeneity: Tau²=0; Chi²=0, df=1(P=0.99); I²=0%					
Test for overall effect: Z=0.18(P=0.86)					
Test for subgroup differences: Chi²=0.25, df=1 (P=0.62), I²=0%					

Analysis 1.8. Comparison 1 Mefloquine versus placebo/non users, Outcome 8 Diarrhoea (all studies).

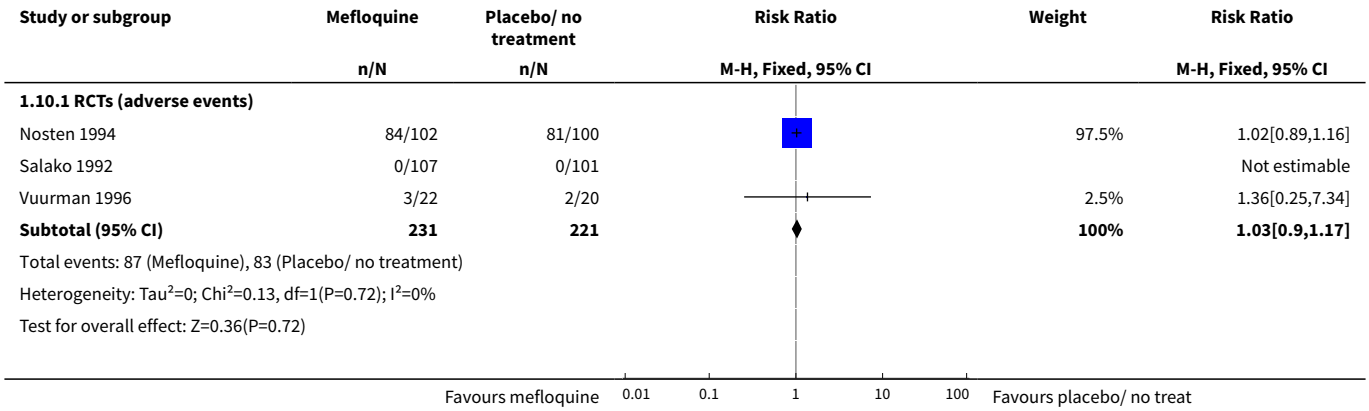
Study or subgroup	Mefloquine n/N	Placebo/ no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 RCTs (adverse events)					
Hale 2003	4/46	15/94		60.26%	0.54[0.19,1.55]
Salako 1992	1/107	0/101		6.47%	2.83[0.12,68.76]
Sossouhounto 1995	2/103	3/96		21.07%	0.62[0.11,3.64]
Vuurman 1996	2/22	1/20		12.2%	1.82[0.18,18.55]
Subtotal (95% CI)	**278**	**311**		**100%**	**0.72[0.32,1.62]**
Total events: 9 (Mefloquine), 19 (Placebo/ no treatment)					
Heterogeneity: Tau²=0; Chi²=1.62, df=3(P=0.65); I²=0%					
Test for overall effect: Z=0.79(P=0.43)					
1.8.2 Cohort studies (adverse events)					
Hoebe 1997	29/104	29/93		24.12%	0.89[0.58,1.38]
Petersen 2000	249/809	41/161		33.97%	1.21[0.91,1.61]
van Riemsdijk 1997	206/394	114/340		41.9%	1.56[1.31,1.86]

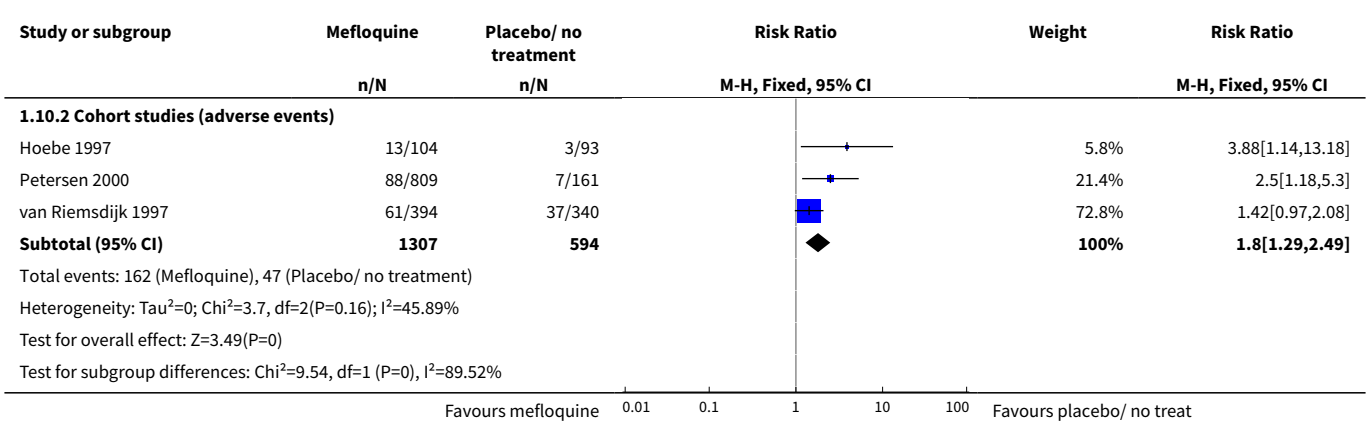


Analysis 1.9. Comparison 1 Mefloquine versus placebo/non users, Outcome 9 Headache (all studies).

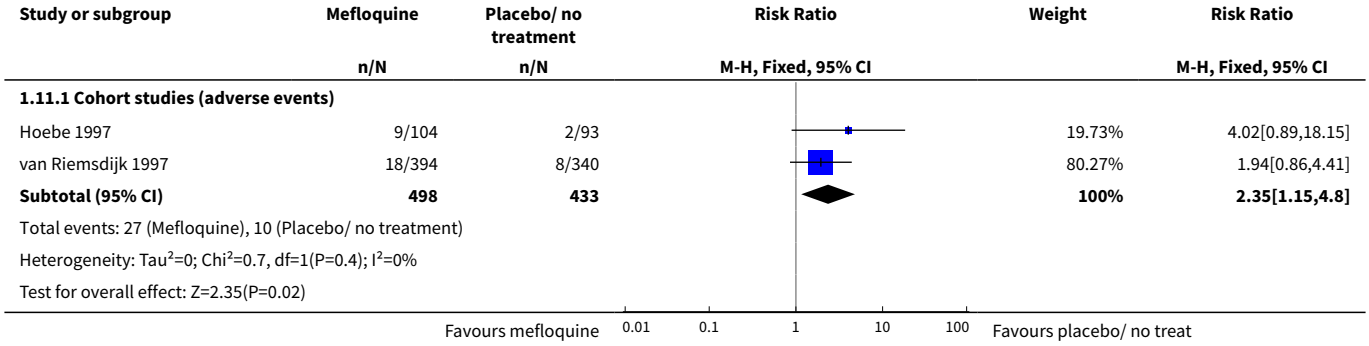


Analysis 1.10. Comparison 1 Mefloquine versus placebo/non users, Outcome 10 Dizziness (all studies).

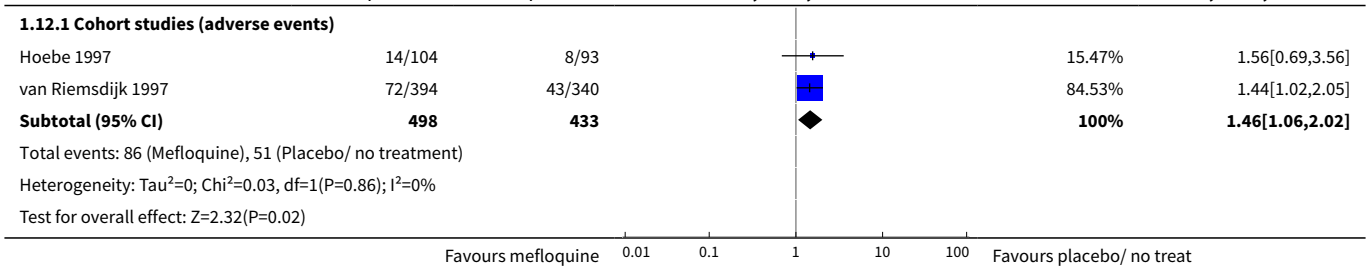




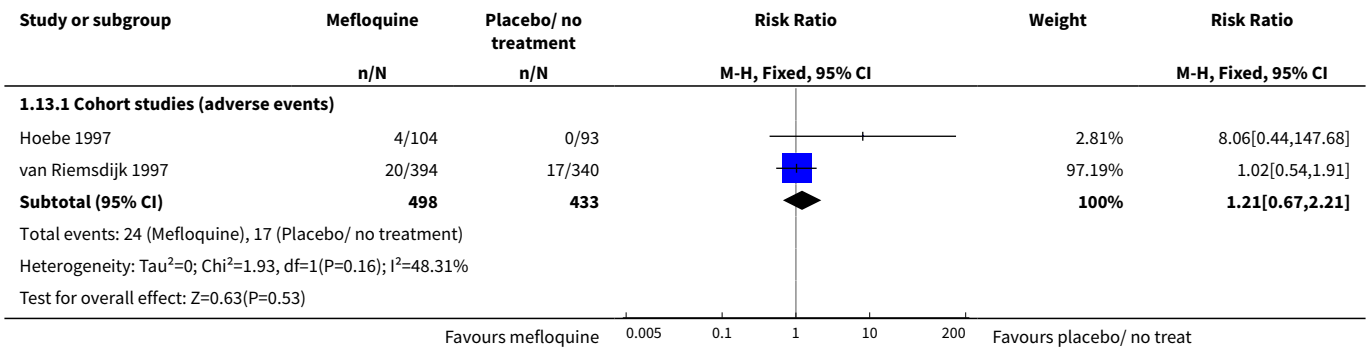
Analysis 1.11. Comparison 1 Mefloquine versus placebo/non users, Outcome 11 Abnormal dreams (all studies).



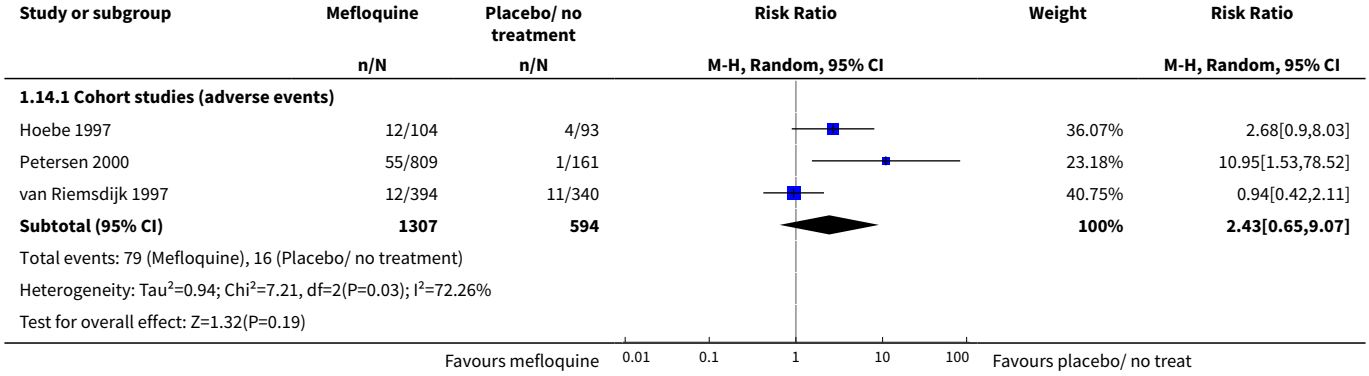
Analysis 1.12. Comparison 1 Mefloquine versus placebo/non users, Outcome 12 Insomnia (all studies).



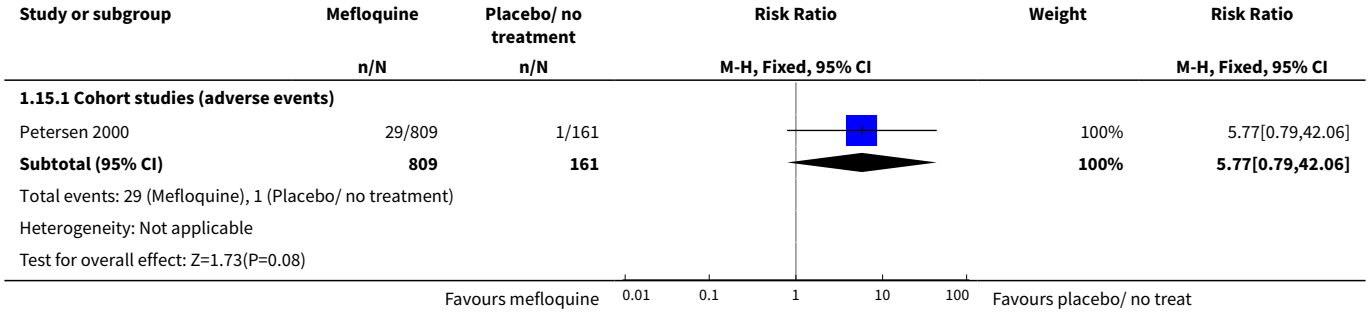
Analysis 1.13. Comparison 1 Mefloquine versus placebo/non users, Outcome 13 Anxiety (all studies).



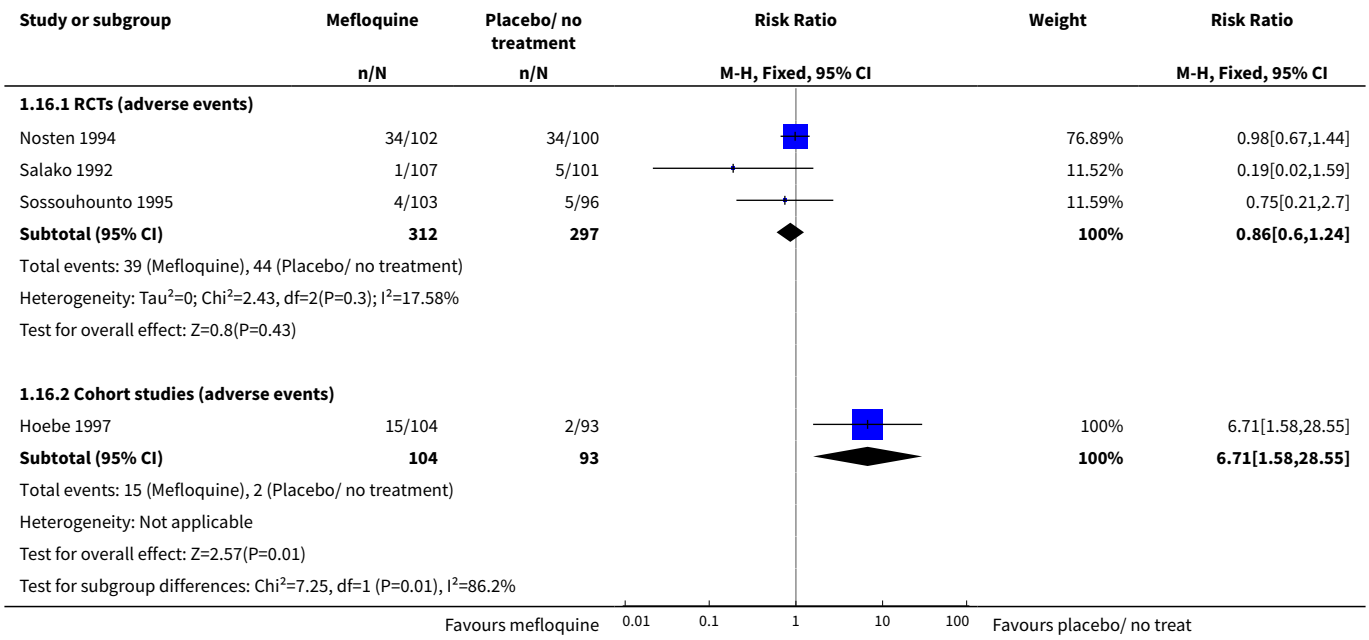
Analysis 1.14. Comparison 1 Mefloquine versus placebo/non users, Outcome 14 Depressed mood (all studies).



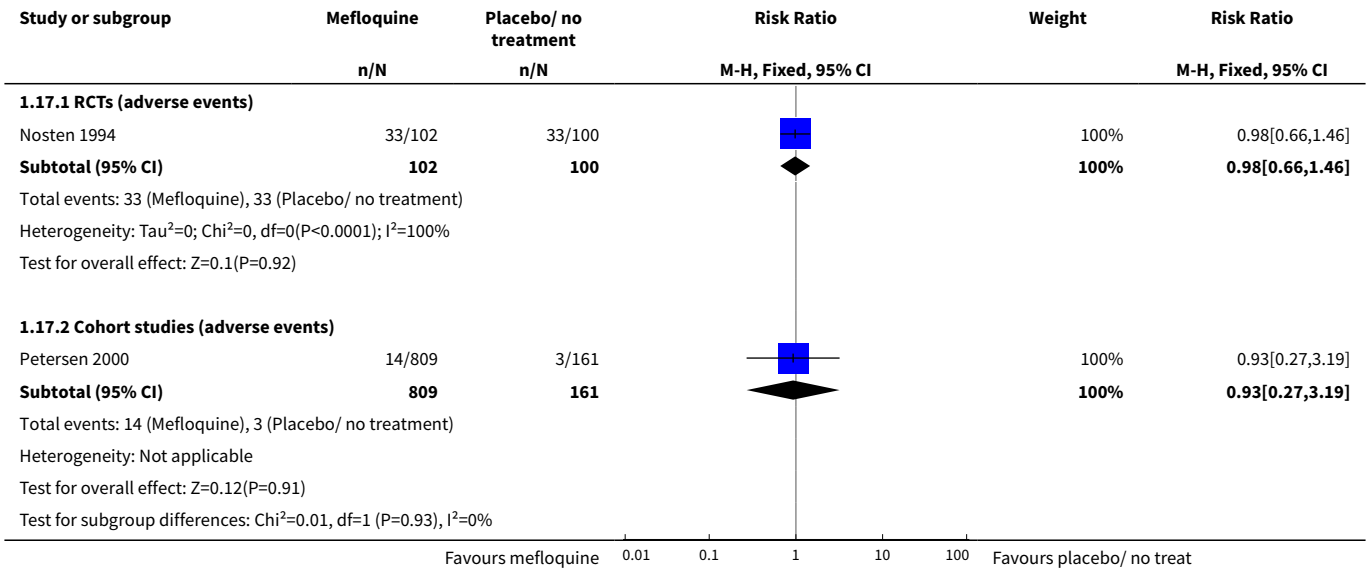
Analysis 1.15. Comparison 1 Mefloquine versus placebo/ non users, Outcome 15 Abnormal thoughts and perceptions.



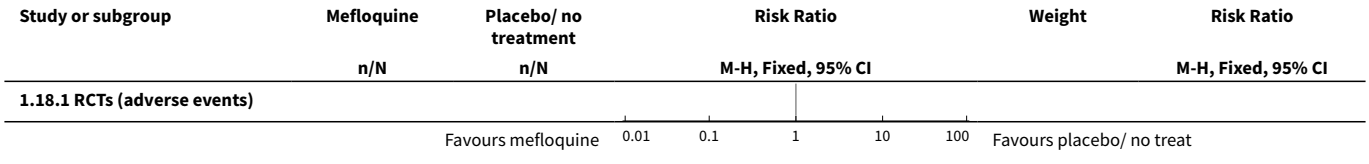
Analysis 1.16. Comparison 1 Mefloquine versus placebo/non users, Outcome 16 Pruritis (all studies).

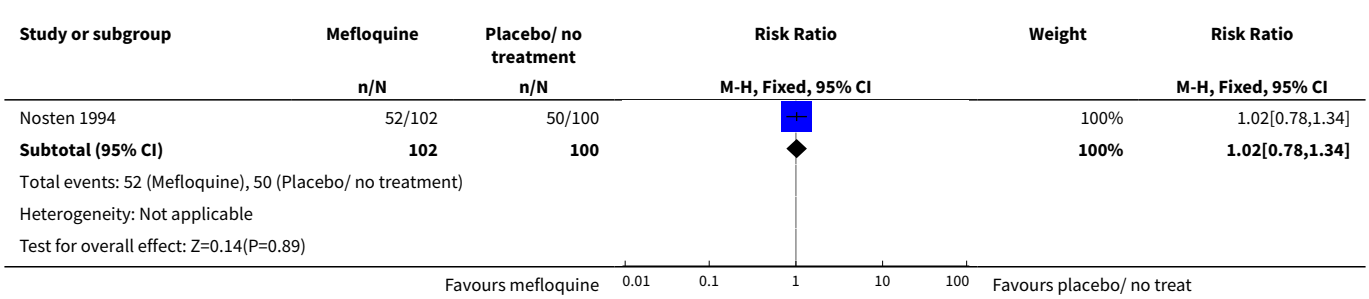


Analysis 1.17. Comparison 1 Mefloquine versus placebo/non users, Outcome 17 Visual impairment (all studies).

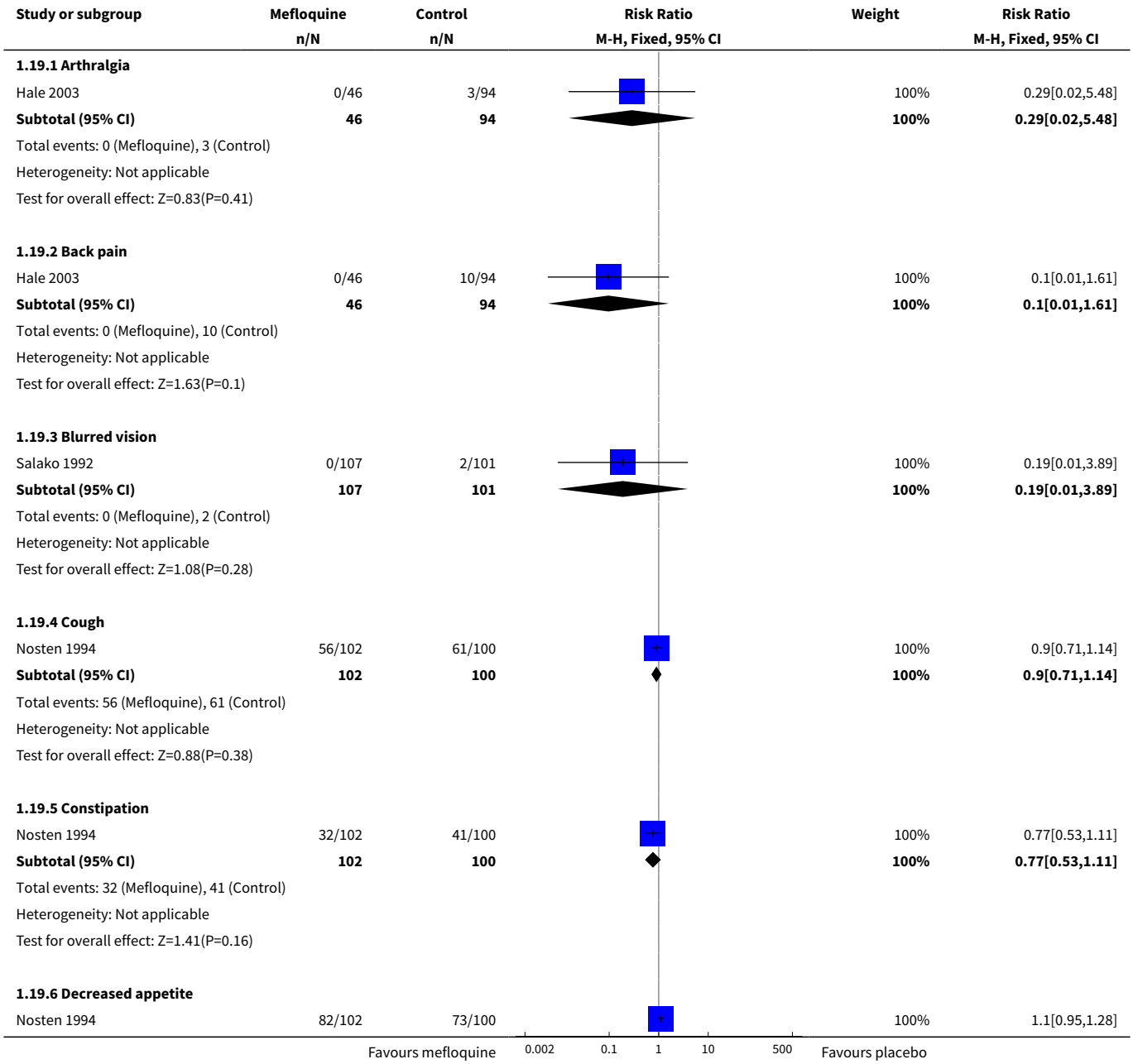


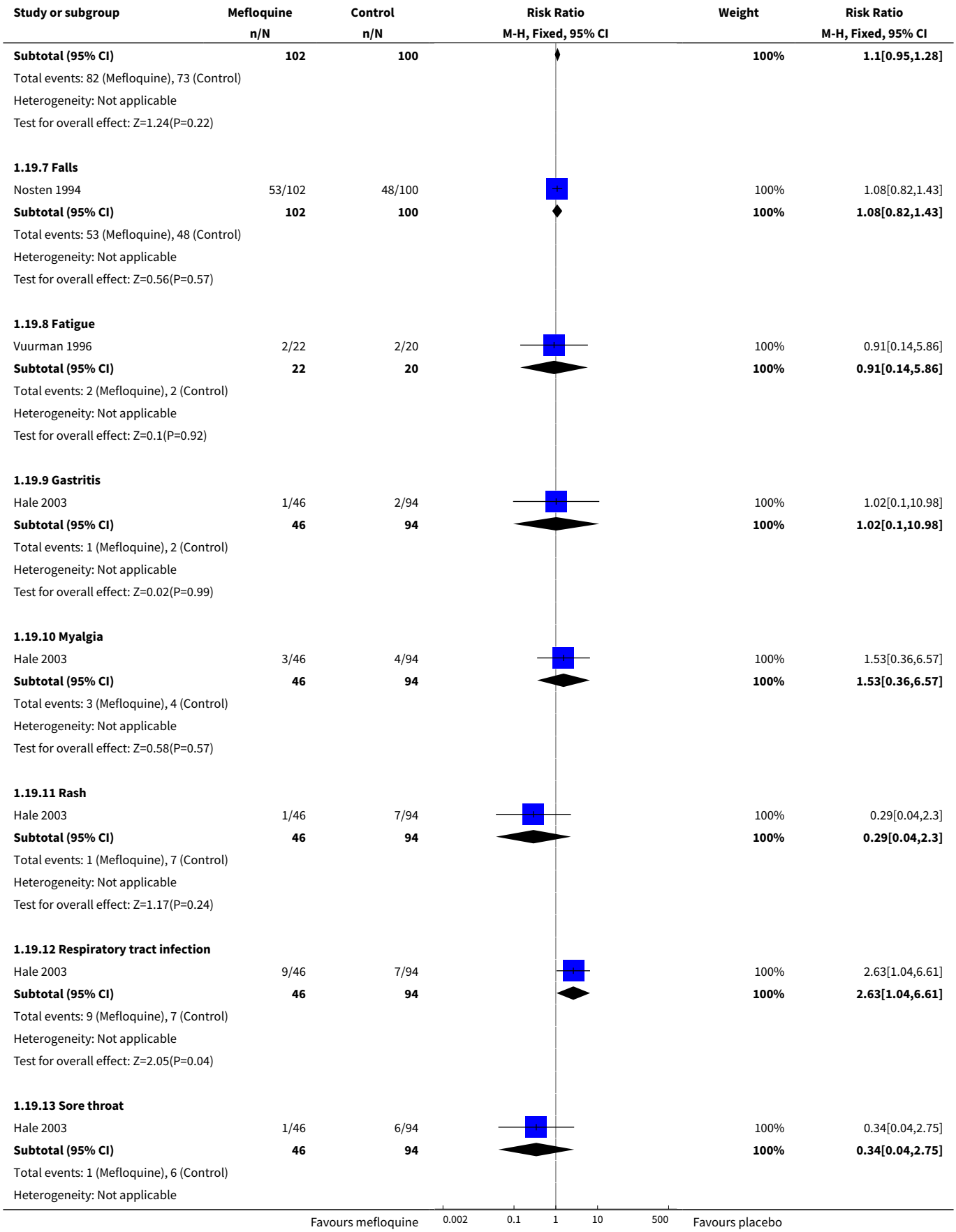
Analysis 1.18. Comparison 1 Mefloquine versus placebo/non users, Outcome 18 Vertigo (all studies).

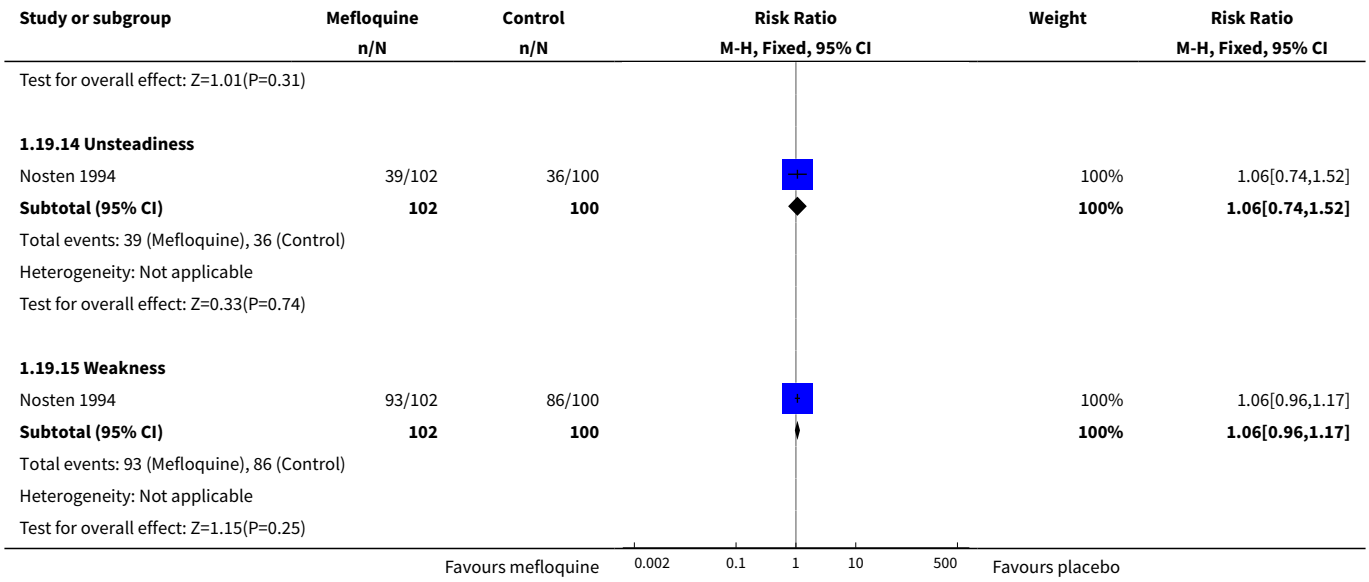




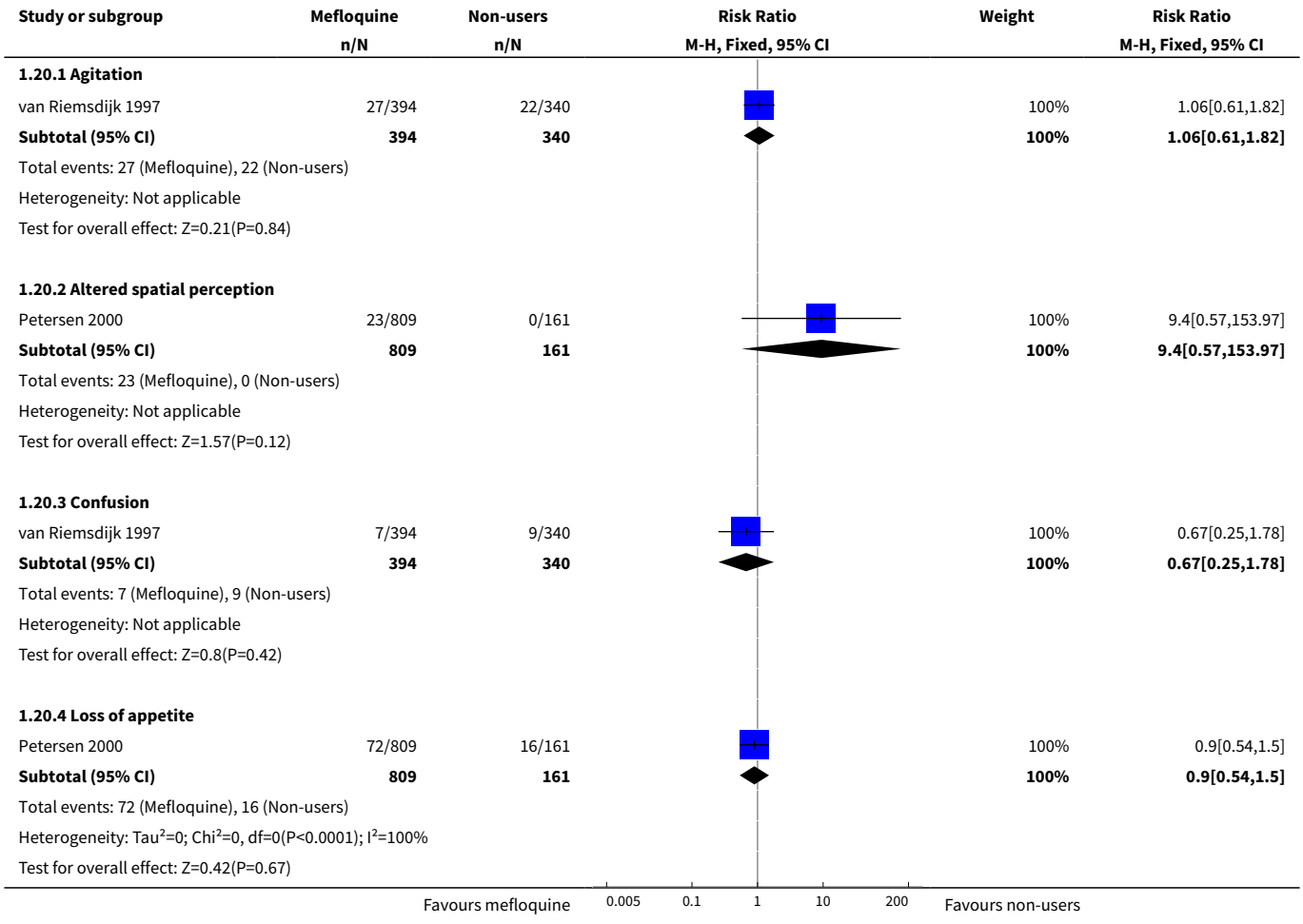
Analysis 1.19. Comparison 1 Mefloquine versus placebo/non users, Outcome 19 Other adverse events (RCTs).

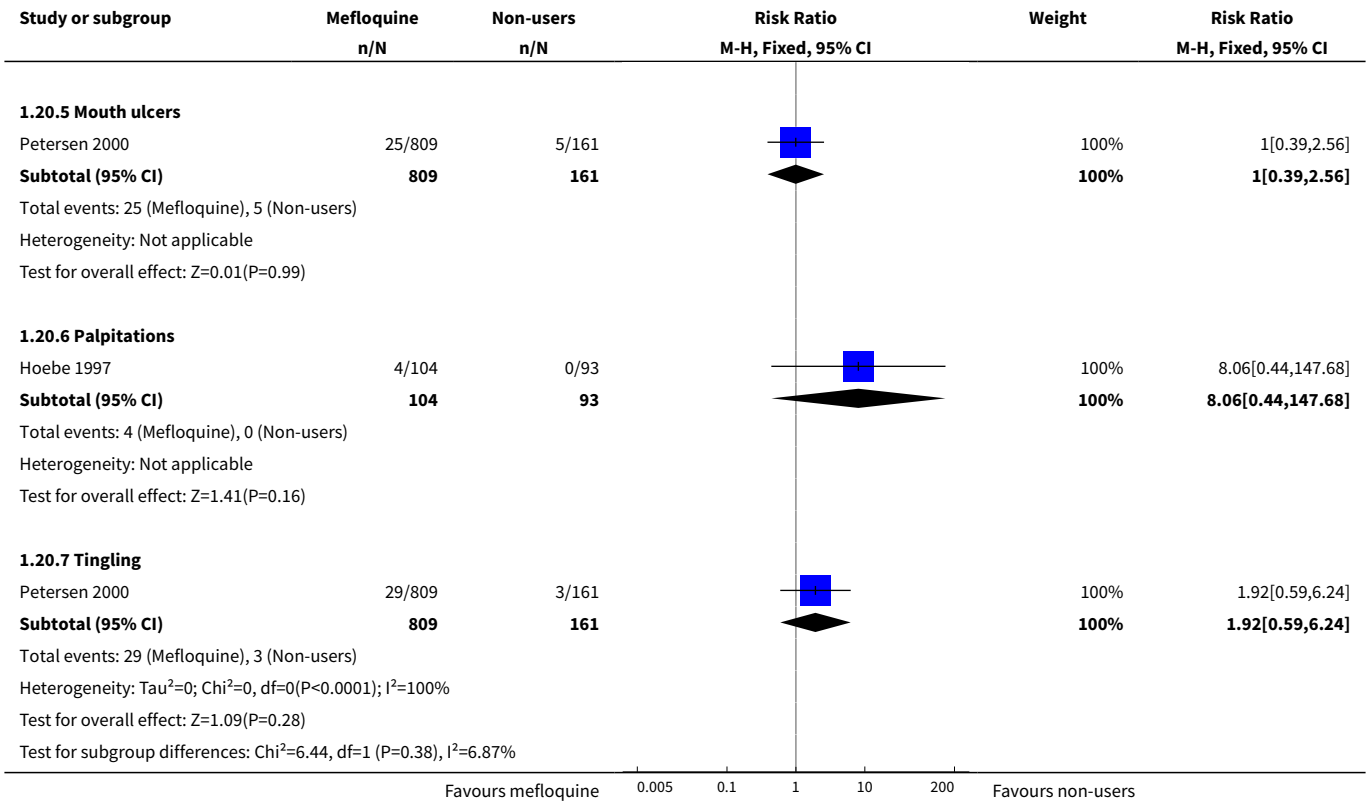






Analysis 1.20. Comparison 1 Mefloquine versus placebo/ non users, Outcome 20 Other adverse effects (cohort studies).





Comparison 2. Mefloquine versus doxycycline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical cases of malaria (RCTs)	4	744	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.35, 5.19]
2 Serious adverse events or effects (all studies)	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 RCTs (adverse events)	3	682	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.16]
2.2 Cohort studies (adverse effects)	3	3722	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.23, 10.24]
3 Discontinuations due to adverse effects (all studies)	14		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 RCTs	4	763	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.41, 2.87]
3.2 Cohort studies	10	10165	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.54, 1.55]
4 Nausea (all studies)	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Cohort studies (adverse effects)	5	2683	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.30, 0.45]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 RCTs (adverse events)	1	123	Risk Ratio (M-H, Fixed, 95% CI)	2.71 [0.75, 9.74]
4.3 Cohort studies (adverse events)	1	668	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [1.06, 2.43]
5 Vomiting (all studies)	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Cohort studies (adverse effects)	4	5071	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.12, 0.27]
5.2 RCTs (adverse events)	1	123	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [0.19, 21.84]
6 Abdominal pain (all studies)	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Cohort studies (adverse effects)	4	2569	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.09, 1.07]
6.2 RCTs (adverse events)	1	123	Risk Ratio (M-H, Random, 95% CI)	1.65 [0.74, 3.70]
6.3 Cohort studies (adverse events)	1	668	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.83, 2.18]
7 Diarrhoea (all studies)	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Cohort studies (adverse effects)	5	5104	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.11, 0.73]
7.2 RCTs (adverse events)	2	376	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.78, 1.29]
7.3 Cohort studies (adverse events)	1	668	Risk Ratio (M-H, Random, 95% CI)	3.58 [1.69, 7.59]
8 Dyspepsia (all studies)	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Cohort studies (adverse effects)	5	5104	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.09, 0.74]
9 Headache (all studies)	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 Cohort studies (adverse effects)	5	3322	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.50, 2.92]
9.2 RCTs (adverse events)	1	123	Risk Ratio (M-H, Random, 95% CI)	2.31 [1.25, 4.27]
9.3 Cohort studies (adverse events)	1	668	Risk Ratio (M-H, Random, 95% CI)	2.45 [1.38, 4.34]
10 Dizziness (all studies)	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Cohort studies (adverse effects)	5	2633	Risk Ratio (M-H, Random, 95% CI)	3.49 [0.88, 13.75]
10.2 RCTs (adverse events)	1	123	Risk Ratio (M-H, Random, 95% CI)	3.05 [1.30, 7.16]

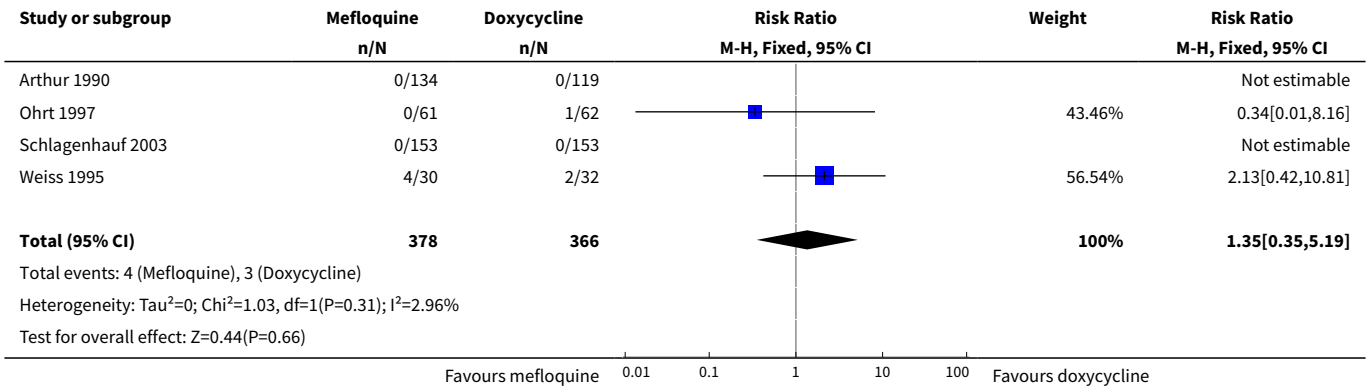
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.3 Cohort studies (adverse events)	1	668	Risk Ratio (M-H, Random, 95% CI)	2.40 [1.47, 3.90]
10.4 Retrospective health-care record analysis (adverse events)	1	354959	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.62, 0.73]
11 Abnormal dreams (all studies)	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Cohort studies (adverse effects)	4	2588	Risk Ratio (M-H, Random, 95% CI)	10.49 [3.79, 29.10]
11.2 RCTs (adverse events)	1	123	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.07, 15.89]
11.3 Cohort studies (adverse events)	1	668	Risk Ratio (M-H, Random, 95% CI)	4.33 [2.08, 9.00]
12 Insomnia (all studies)	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 Cohort studies (adverse effects)	4	3212	Risk Ratio (M-H, Random, 95% CI)	4.14 [1.19, 14.44]
12.2 RCTs (adverse events)	1	123	Risk Ratio (M-H, Random, 95% CI)	2.03 [0.65, 6.40]
12.3 Cohort studies (adverse events)	1	668	Risk Ratio (M-H, Random, 95% CI)	4.54 [2.09, 9.83]
12.4 Retrospective health-care record analysis (adverse events)	1	354959	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.43, 0.49]
13 Anxiety (all studies)	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 Cohort studies (adverse effects)	3	2559	Risk Ratio (M-H, Fixed, 95% CI)	18.04 [9.32, 34.93]
13.2 Cohort studies (adverse events)	1	668	Risk Ratio (M-H, Fixed, 95% CI)	8.74 [1.99, 38.40]
13.3 Retrospective health-care record analysis (adverse events)	1	354959	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.47, 0.56]
14 Depressed mood (all studies)	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 Cohort studies (adverse effects)	2	2445	Risk Ratio (M-H, Fixed, 95% CI)	11.43 [5.21, 25.07]
14.2 Cohort studies (adverse events)	1	668	Risk Ratio (M-H, Fixed, 95% CI)	6.27 [1.82, 21.62]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.3 Retrospective health-care record analysis (adverse events)	2	376024	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.51, 0.60]
15 Abnormal thoughts and perceptions	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 Cohort studies (adverse effects)	2	2445	Risk Ratio (M-H, Fixed, 95% CI)	6.60 [0.92, 47.20]
15.2 Retrospective health-care record analyses (adverse events)	2	376024	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.26, 0.66]
16 Pruritis (all studies)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 Cohort studies (adverse effects)	2	1794	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.30, 0.91]
16.2 Cohort studies (adverse events)	1	668	Risk Ratio (M-H, Fixed, 95% CI)	2.69 [0.93, 7.78]
17 Photosensitivity (all studies)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 Cohort studies (adverse effects)	2	1875	Risk Ratio (M-H, Fixed, 95% CI)	0.08 [0.05, 0.11]
17.2 Cohort studies (adverse events)	1	668	Risk Ratio (M-H, Fixed, 95% CI)	0.03 [0.00, 0.49]
18 Yeast infection (all studies)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 Cohort studies (adverse effects)	1	1761	Risk Ratio (M-H, Fixed, 95% CI)	0.10 [0.06, 0.16]
18.2 Cohort studies (adverse events)	1	354	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.06, 0.63]
19 Visual impairment (all studies)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 Cohort studies (adverse effects)	2	1875	Risk Ratio (M-H, Fixed, 95% CI)	2.37 [1.41, 3.99]
20 Other adverse effects (cohort studies)	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20.1 Alopecia	2	1875	Risk Ratio (M-H, Fixed, 95% CI)	3.44 [1.96, 6.03]
20.2 Asthenia	1	1761	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [0.89, 3.76]
20.3 Balance disorder	1	1761	Risk Ratio (M-H, Fixed, 95% CI)	2.87 [1.48, 5.59]
20.4 Decreased appetite	1	734	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.42, 3.64]

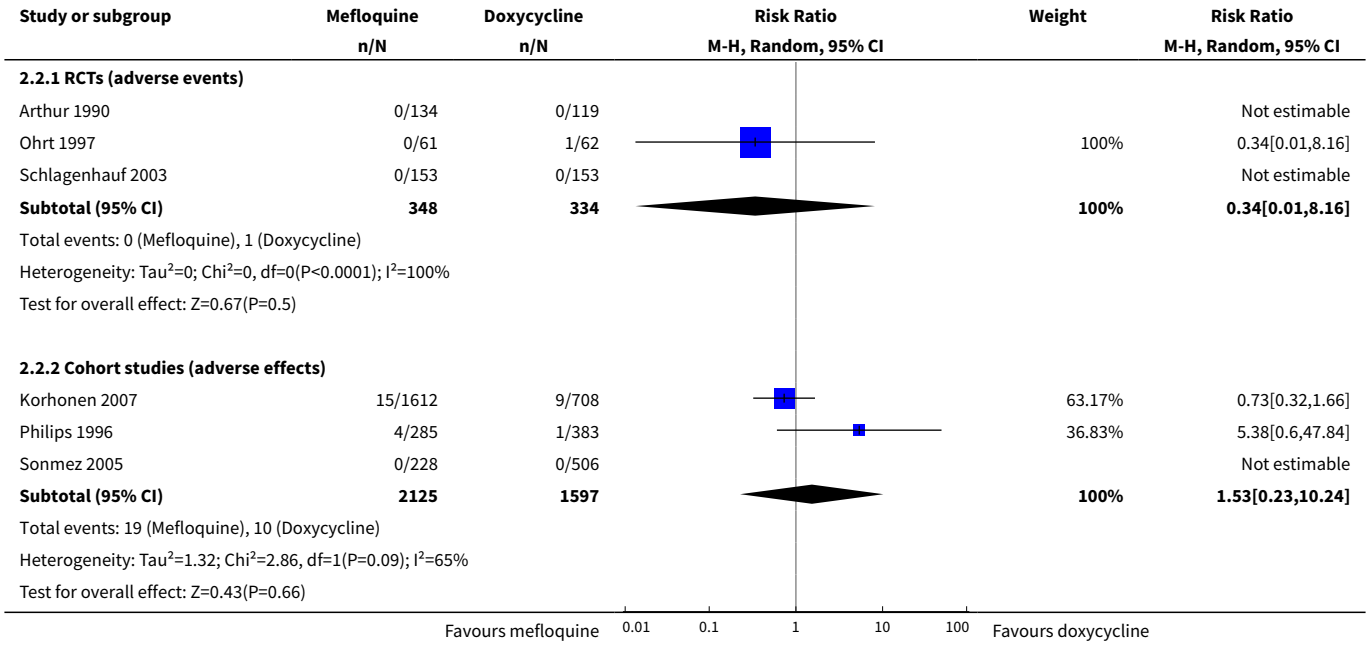
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.5 Fatigue	2	74	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.03, 1.77]
20.6 Hypoaesthesia	2	2445	Risk Ratio (M-H, Fixed, 95% CI)	11.48 [3.01, 43.70]
20.7 Malaise	1	734	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.11, 0.71]
20.8 Mouth ulcers	1	33	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.02, 11.42]
20.9 Palpitations	1	1761	Risk Ratio (M-H, Fixed, 95% CI)	2.76 [0.16, 48.91]
20.10 Tinnitus	1	684	Risk Ratio (M-H, Fixed, 95% CI)	7.20 [0.39, 133.30]
21 Other adverse events (RCTs)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
21.1 Constipation	1	123	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [0.19, 21.84]
21.2 Cough	1	123	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.28, 1.01]
21.3 Decreased appetite	1	123	Risk Ratio (M-H, Fixed, 95% CI)	3.56 [1.24, 10.20]
21.4 Malaise	1	123	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [0.88, 4.69]
21.5 Palpitations	1	123	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [0.19, 21.84]
21.6 Pyrexia	1	123	Risk Ratio (M-H, Fixed, 95% CI)	2.85 [1.09, 7.42]
21.7 Sexual dysfunction	1	123	Risk Ratio (M-H, Fixed, 95% CI)	3.05 [0.33, 28.51]
21.8 Somnolence	1	123	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [0.19, 21.84]
22 Other adverse events (cohort studies)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
22.1 Adjustment disorder	1	354959	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.40, 0.45]
22.2 Confusion	1	354959	Risk Ratio (M-H, Fixed, 95% CI)	2.18 [0.24, 19.49]
22.3 Convulsions	1	354959	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.45, 0.75]
22.4 Hallucinations	1	354959	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.08, 0.45]
22.5 Paranoia	1	354959	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.10, 1.63]
22.6 Palpitations	1	668	Risk Ratio (M-H, Fixed, 95% CI)	13.44 [1.73, 104.38]
22.7 Panic attacks	1	21065	Risk Ratio (M-H, Fixed, 95% CI)	4.16 [0.55, 31.49]
22.8 PTSD	1	354959	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.53, 0.64]
22.9 Rash	1	668	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.50, 2.94]
22.10 Suicidal ideation	1	354959	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.31, 0.47]
22.11 Suicide	2	376024	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.32, 4.56]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.12 Tinnitus	1	354959	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.61, 0.71]
23 Adherence (cohort studies)	14		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
23.1 Adherence during travel	13	15583	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [1.12, 1.18]
23.2 Adherence in the post-travel period	4	840	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.95, 1.22]

Analysis 2.1. Comparison 2 Mefloquine versus doxycycline, Outcome 1 Clinical cases of malaria (RCTs).



Analysis 2.2. Comparison 2 Mefloquine versus doxycycline, Outcome 2 Serious adverse events or effects (all studies).



Study or subgroup	Mefloquine n/N	Doxycycline n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for subgroup differences: Chi²=0.63, df=1 (P=0.43), I²=0%					

Favours mefloquine 0.01 0.1 1 10 100 Favours doxycycline

Analysis 2.3. Comparison 2 Mefloquine versus doxycycline, Outcome 3 Discontinuations due to adverse effects (all studies).

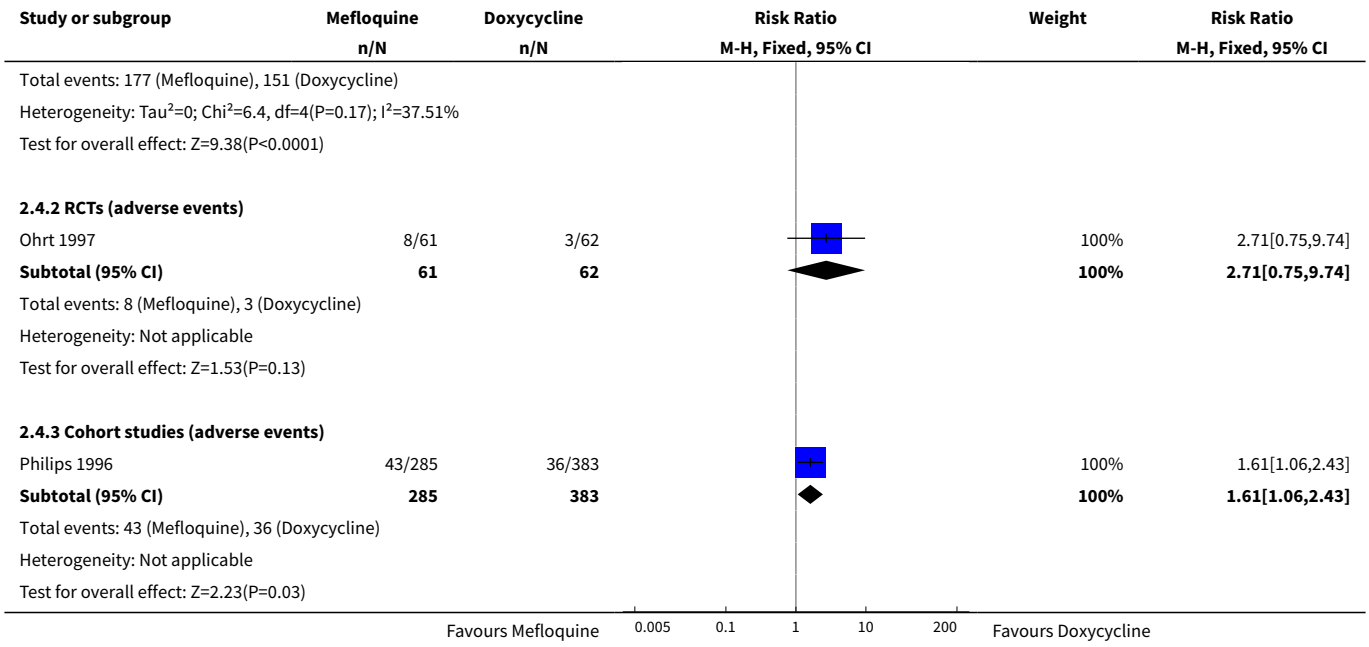
Study or subgroup	Mefloquine n/N	Doxycycline n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 RCTs					
Arthur 1990	0/134	0/119			Not estimable
Ohrt 1997	1/61	1/62		12.62%	1.02[0.07,15.89]
Schlagenhauf 2003	6/156	5/169		70.08%	1.3[0.4,4.17]
Weiss 1995	1/30	2/32		17.3%	0.53[0.05,5.58]
Subtotal (95% CI)	**381**	**382**		**100%**	**1.08[0.41,2.87]**
Total events: 8 (Mefloquine), 8 (Doxycycline)					
Heterogeneity: Tau²=0; Chi²=0.45, df=2(P=0.8); I²=0%					
Test for overall effect: Z=0.15(P=0.88)					
2.3.2 Cohort studies					
Korhonen 2007	370/1612	88/708		18.32%	1.85[1.49,2.29]
Napoletano 2007	66/548	4/33		11.65%	0.99[0.39,2.56]
Philips 1996	18/285	22/383		15.09%	1.1[0.6,2.01]
Saunders 2015	23/596	196/2011		16.82%	0.4[0.26,0.6]
Schwartz 1999	0/25	1/19		2.4%	0.26[0.01,5.97]
Shamiss 1996	0/13	1/28		2.41%	0.69[0.03,15.9]
Sharafeldin 2010	8/40	1/1		11.16%	0.28[0.1,0.75]
Stoney 2016	0/11	0/18			Not estimable
Tan 2017	365/2973	64/828		18.1%	1.59[1.23,2.05]
Tuck 2016	2/13	1/20		4.05%	3.08[0.31,30.59]
Subtotal (95% CI)	**6116**	**4049**		**100%**	**0.92[0.54,1.55]**
Total events: 852 (Mefloquine), 378 (Doxycycline)					
Heterogeneity: Tau²=0.37; Chi²=54.51, df=8(P<0.0001); I²=85.33%					
Test for overall effect: Z=0.32(P=0.75)					
Test for subgroup differences: Chi²=0.08, df=1 (P=0.77), I²=0%					

Favours mefloquine 0.01 0.1 1 10 100 Favours doxycycline

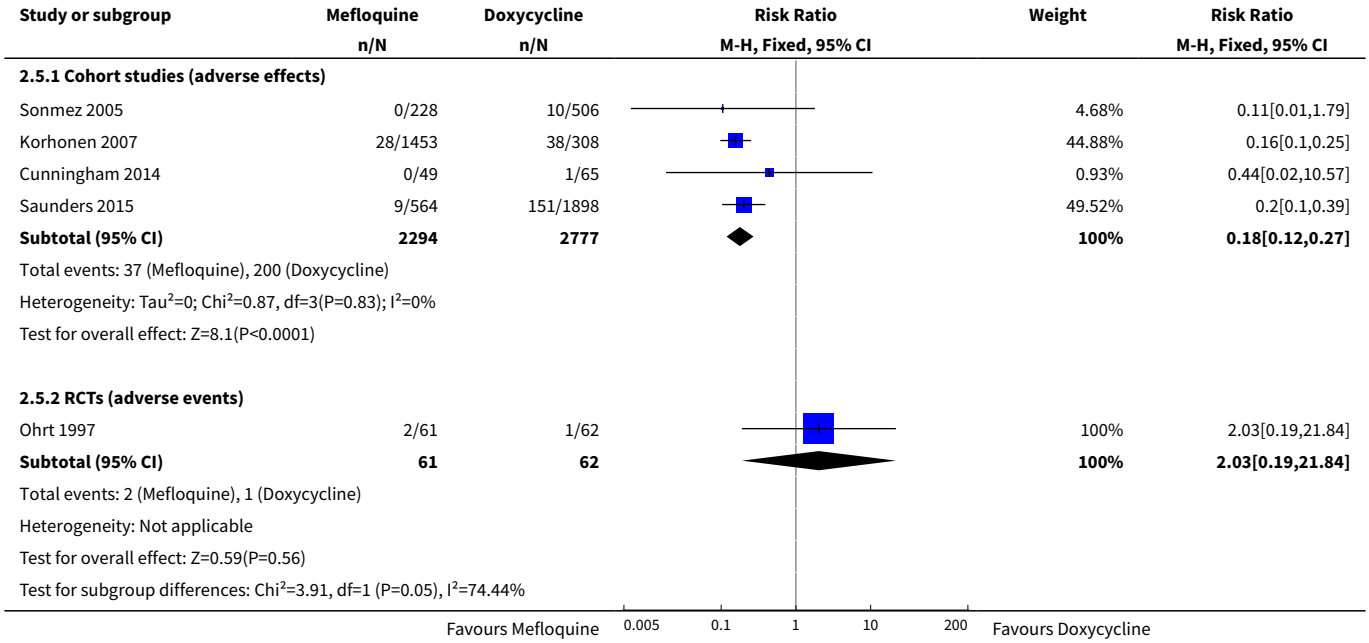
Analysis 2.4. Comparison 2 Mefloquine versus doxycycline, Outcome 4 Nausea (all studies).

Study or subgroup	Mefloquine n/N	Doxycycline n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.4.1 Cohort studies (adverse effects)					
Shamiss 1996	2/13	0/28		0.16%	10.36[0.53,201.6]
Sonmez 2005	7/228	41/506		12.68%	0.38[0.17,0.83]
Korhonen 2007	165/1453	102/308		83.77%	0.34[0.28,0.42]
Cunningham 2014	2/49	7/65		2.99%	0.38[0.08,1.75]
Tuck 2016	1/13	1/20		0.39%	1.54[0.11,22.49]
Subtotal (95% CI)	**1756**	**927**		**100%**	**0.37[0.3,0.45]**

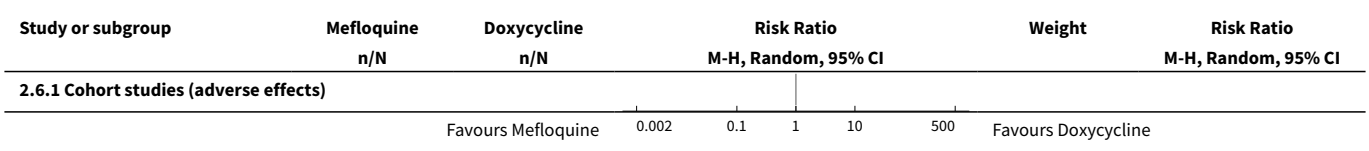
Favours Mefloquine 0.005 0.1 1 10 200 Favours Doxycycline

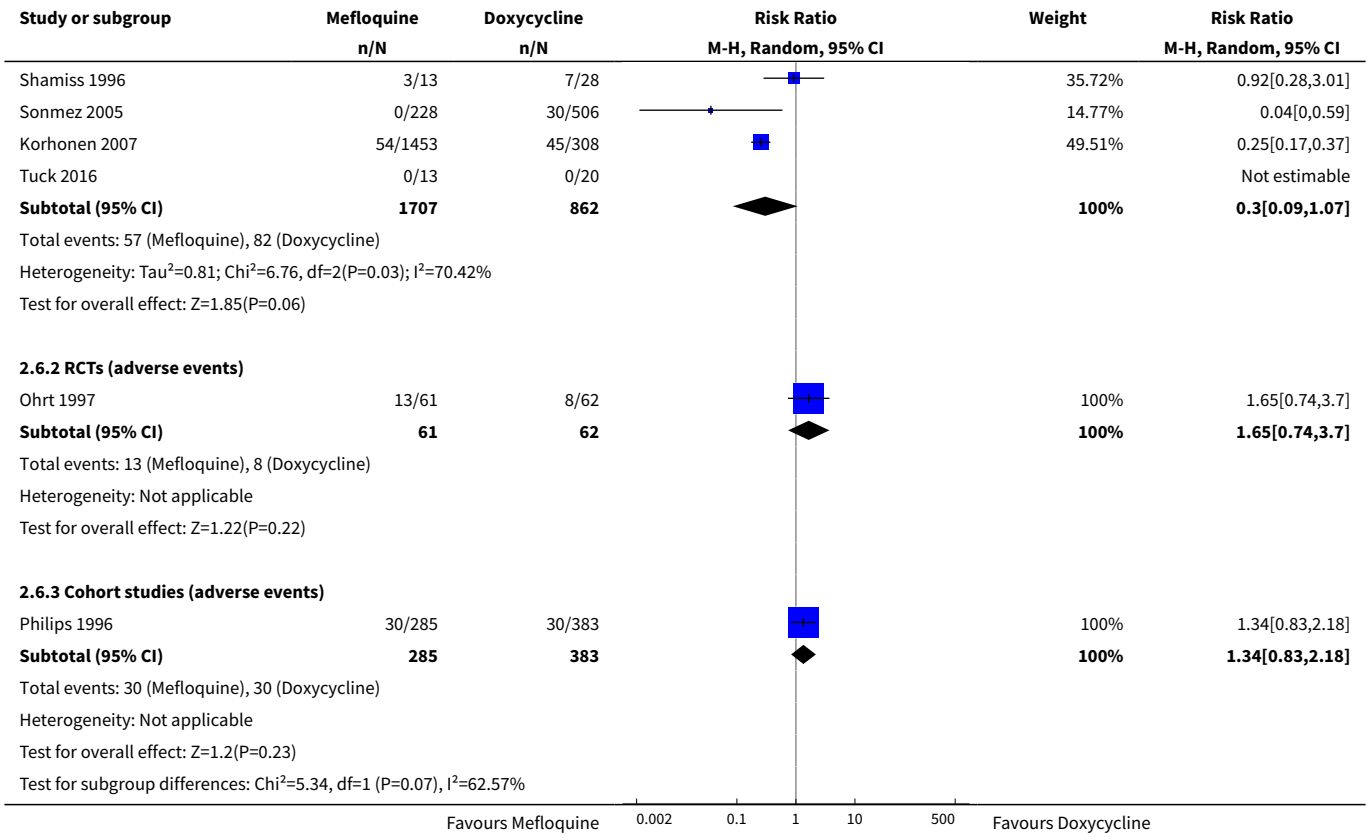


Analysis 2.5. Comparison 2 Mefloquine versus doxycycline, Outcome 5 Vomiting (all studies).

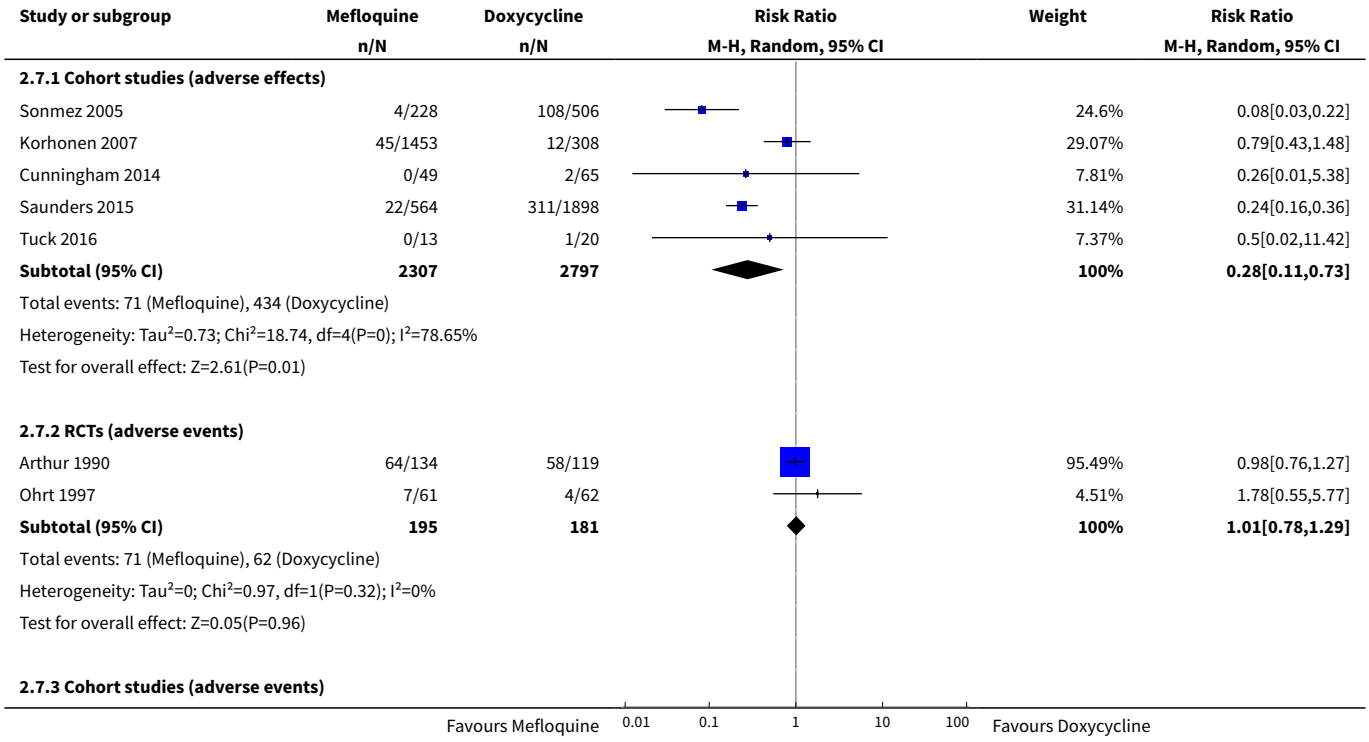


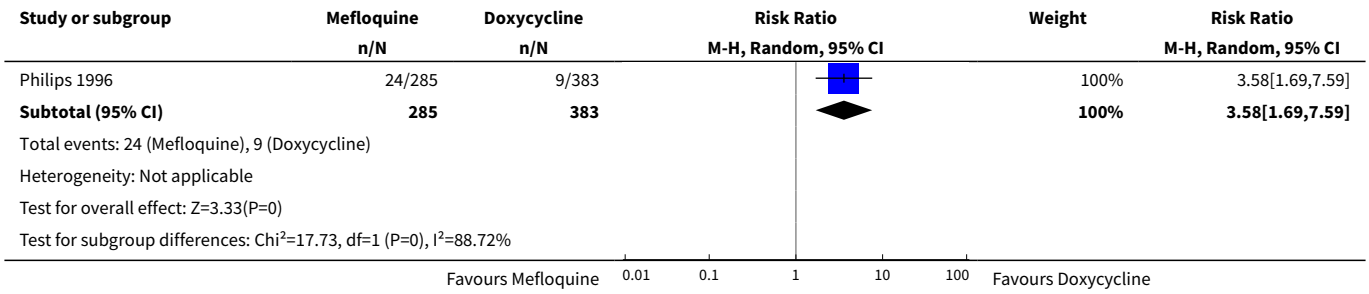
Analysis 2.6. Comparison 2 Mefloquine versus doxycycline, Outcome 6 Abdominal pain (all studies).



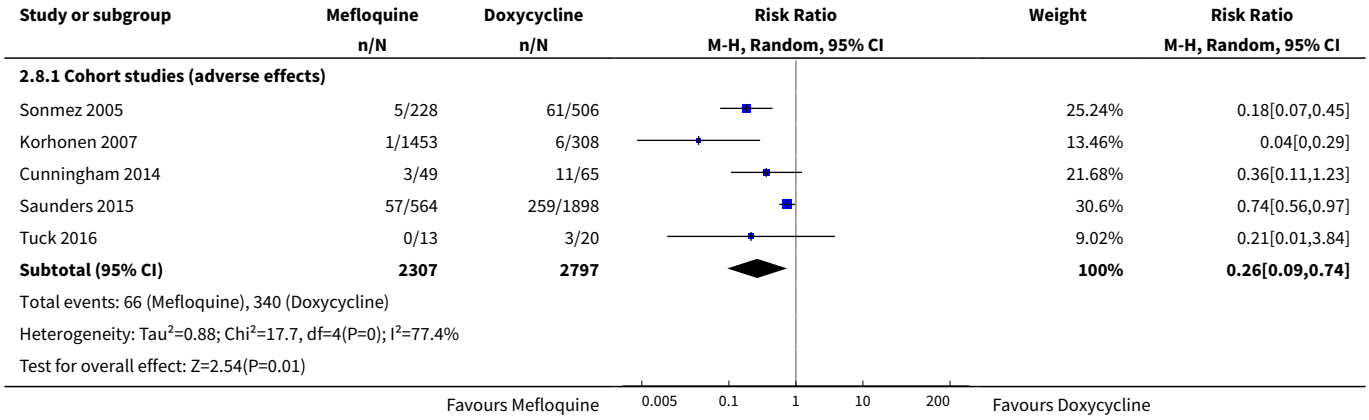


Analysis 2.7. Comparison 2 Mefloquine versus doxycycline, Outcome 7 Diarrhoea (all studies).

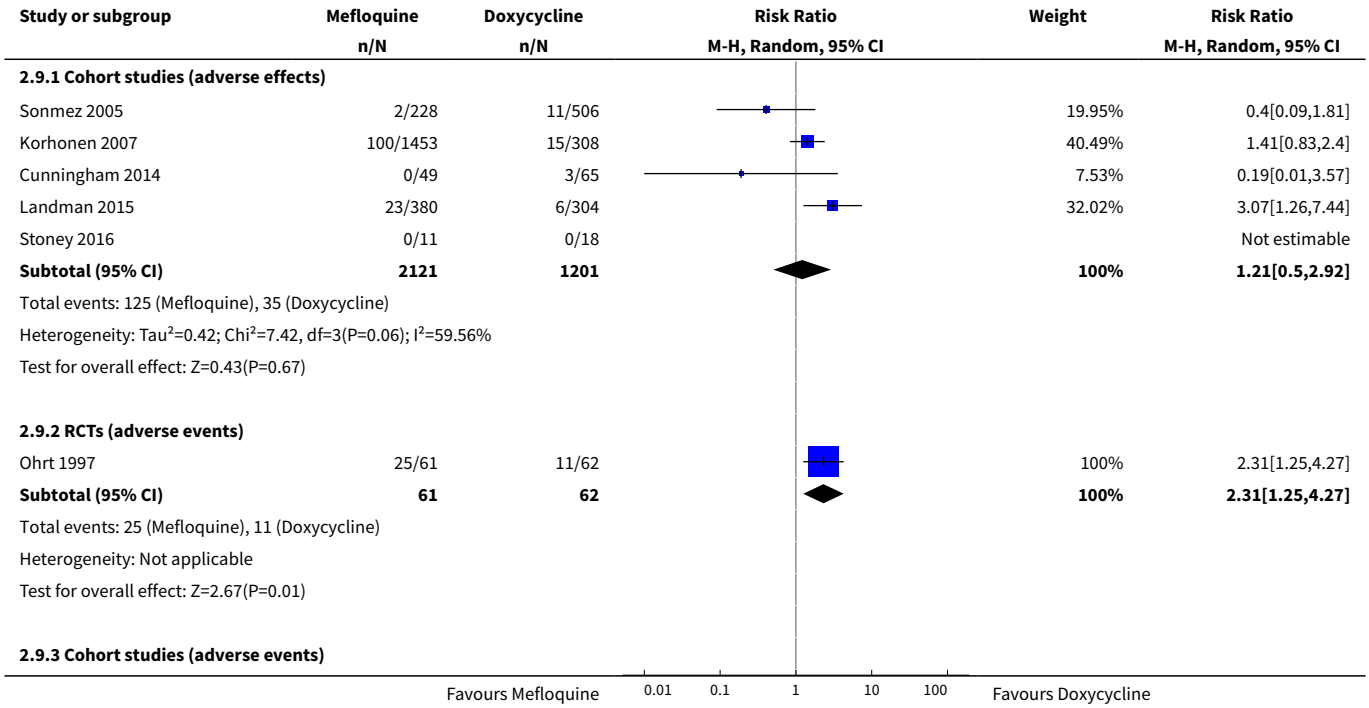


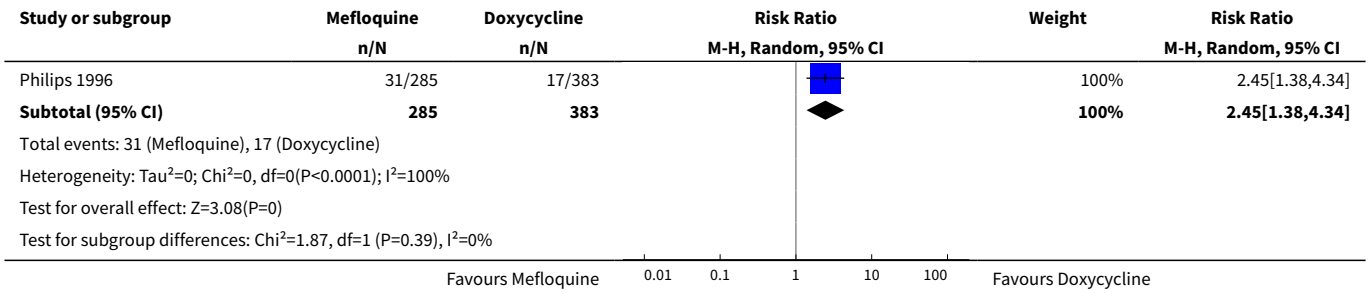


Analysis 2.8. Comparison 2 Mefloquine versus doxycycline, Outcome 8 Dyspepsia (all studies).

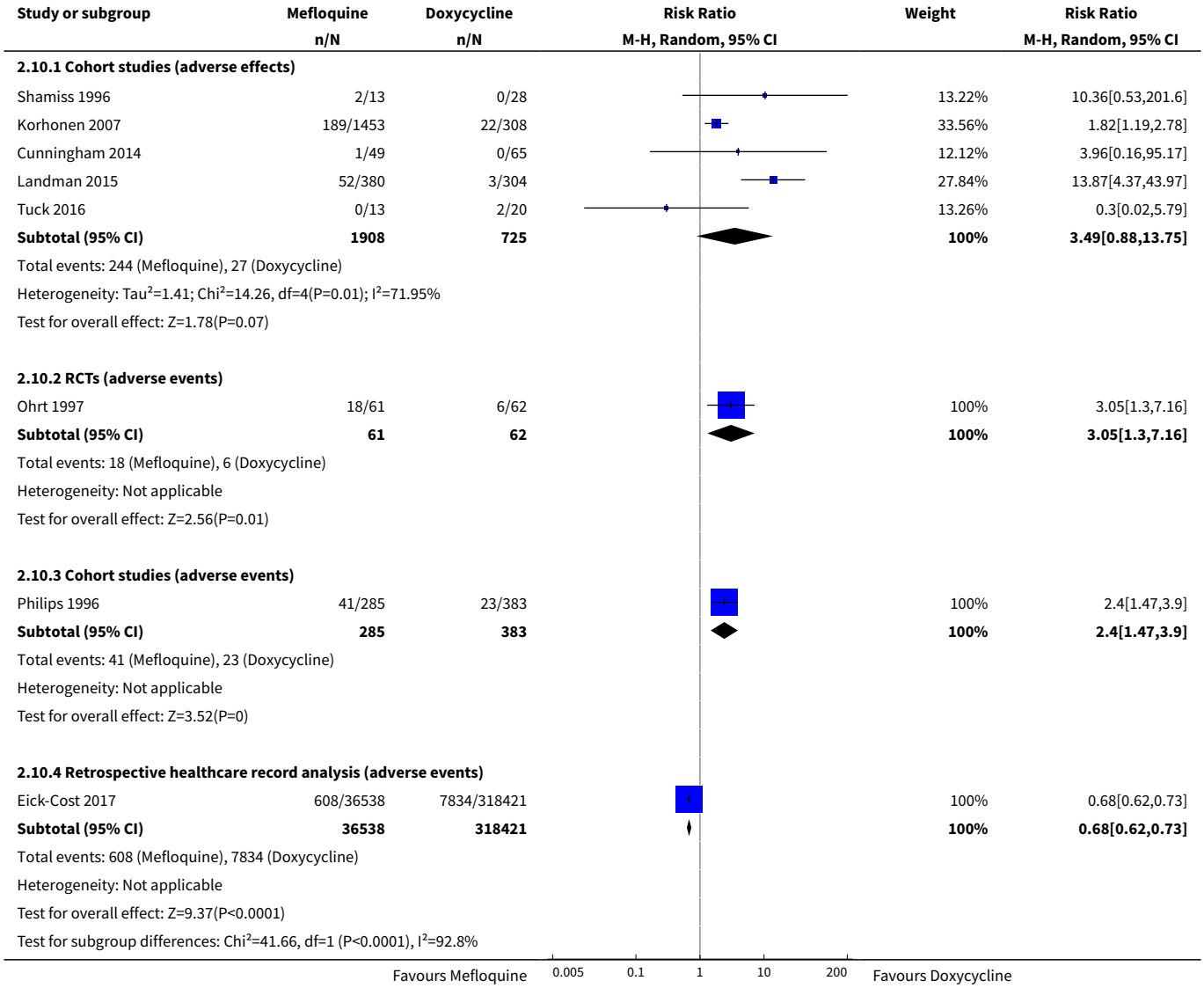


Analysis 2.9. Comparison 2 Mefloquine versus doxycycline, Outcome 9 Headache (all studies).



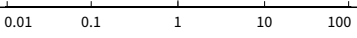


Analysis 2.10. Comparison 2 Mefloquine versus doxycycline, Outcome 10 Dizziness (all studies).



Analysis 2.11. Comparison 2 Mefloquine versus doxycycline, Outcome 11 Abnormal dreams (all studies).

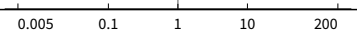
Study or subgroup	Mefloquine n/N	Doxycycline n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.11.1 Cohort studies (adverse effects)					
Korhonen 2007	775/1453	12/308		39.88%	13.69[7.85,23.89]
Cunningham 2014	5/49	3/65		24.71%	2.21[0.55,8.81]
Landman 2015	173/380	6/304		35.41%	23.07[10.37,51.33]
Stoney 2016	0/11	0/18			Not estimable
Subtotal (95% CI)	**1893**	**695**		**100%**	**10.49[3.79,29.1]**
Total events: 953 (Mefloquine), 21 (Doxycycline)					
Heterogeneity: Tau^2=0.6; Chi^2=8.53, df=2(P=0.01); I^2=76.55%					
Test for overall effect: Z=4.52(P<0.0001)					
2.11.2 RCTs (adverse events)					
Ohrt 1997	1/61	1/62		100%	1.02[0.07,15.89]
Subtotal (95% CI)	**61**	**62**		**100%**	**1.02[0.07,15.89]**
Total events: 1 (Mefloquine), 1 (Doxycycline)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.01(P=0.99)					
2.11.3 Cohort studies (adverse events)					
Philips 1996	29/285	9/383		100%	4.33[2.08,9]
Subtotal (95% CI)	**285**	**383**		**100%**	**4.33[2.08,9]**
Total events: 29 (Mefloquine), 9 (Doxycycline)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.92(P<0.0001)					
Test for subgroup differences: Chi^2=3.4, df=1 (P=0.18), I^2=41.14%					



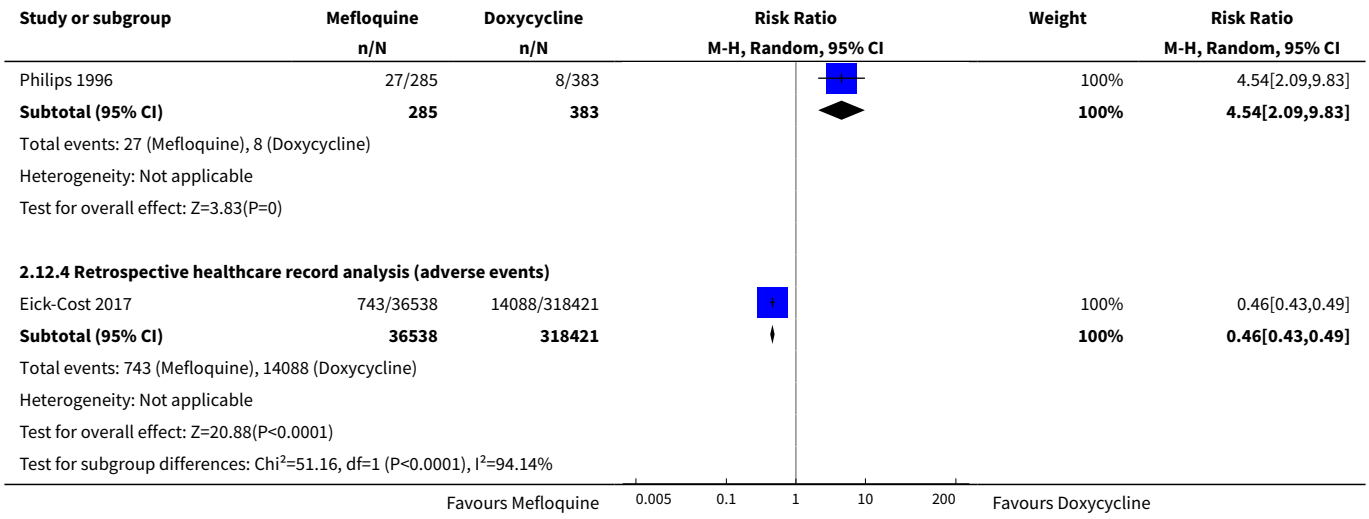
Favours Mefloquine — Favours Doxycycline

Analysis 2.12. Comparison 2 Mefloquine versus doxycycline, Outcome 12 Insomnia (all studies).

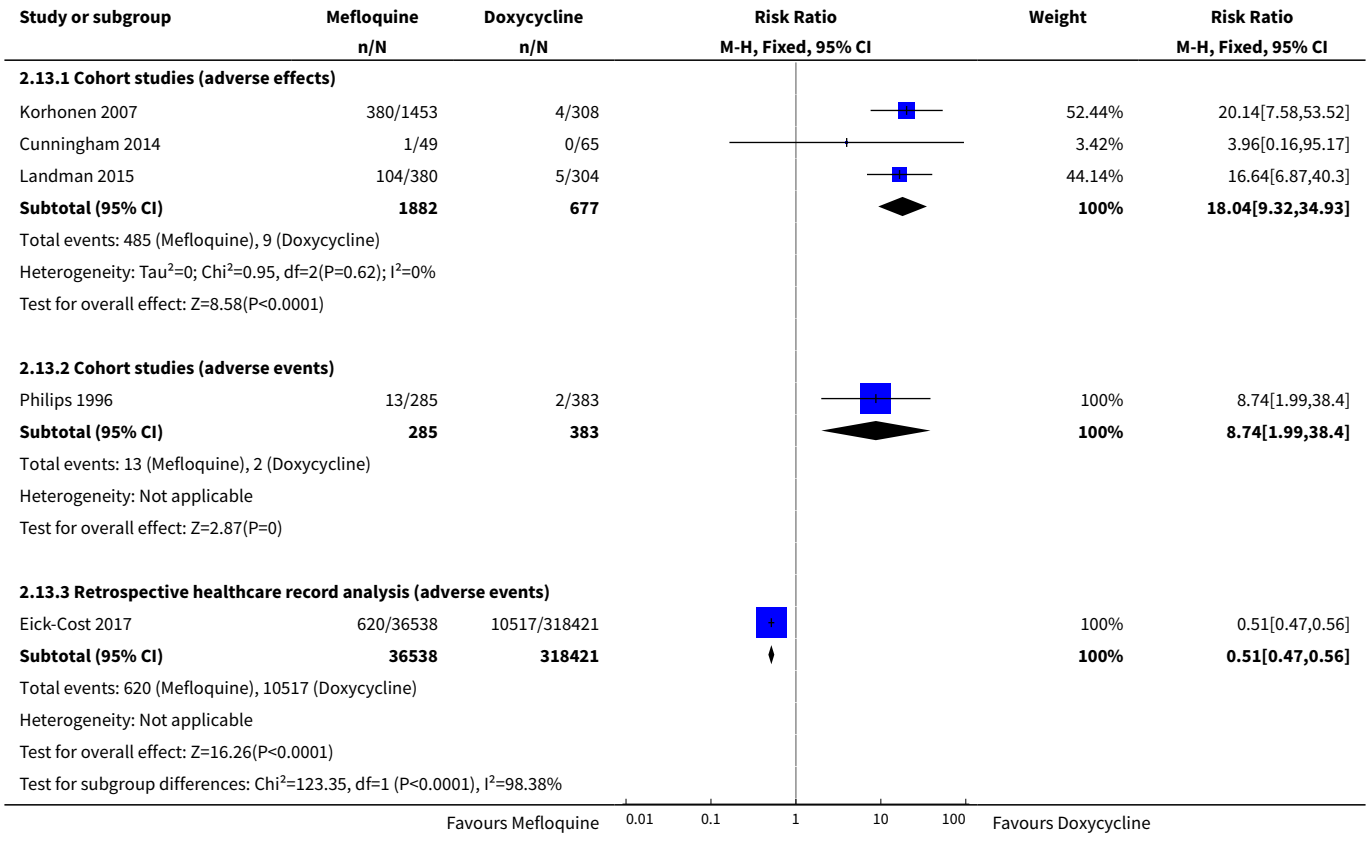
Study or subgroup	Mefloquine n/N	Doxycycline n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.12.1 Cohort studies (adverse effects)					
Sonmez 2005	0/228	14/506		12.75%	0.08[0,1.27]
Korhonen 2007	491/1453	8/308		32.61%	13.01[6.54,25.88]
Landman 2015	94/380	8/304		32.44%	9.4[4.64,19.04]
Tuck 2016	3/13	2/20		22.21%	2.31[0.44,11.98]
Subtotal (95% CI)	**2074**	**1138**		**100%**	**4.14[1.19,14.44]**
Total events: 588 (Mefloquine), 32 (Doxycycline)					
Heterogeneity: Tau^2=1.12; Chi^2=14.82, df=3(P=0); I^2=79.76%					
Test for overall effect: Z=2.23(P=0.03)					
2.12.2 RCTs (adverse events)					
Ohrt 1997	8/61	4/62		100%	2.03[0.65,6.4]
Subtotal (95% CI)	**61**	**62**		**100%**	**2.03[0.65,6.4]**
Total events: 8 (Mefloquine), 4 (Doxycycline)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.21(P=0.23)					
2.12.3 Cohort studies (adverse events)					



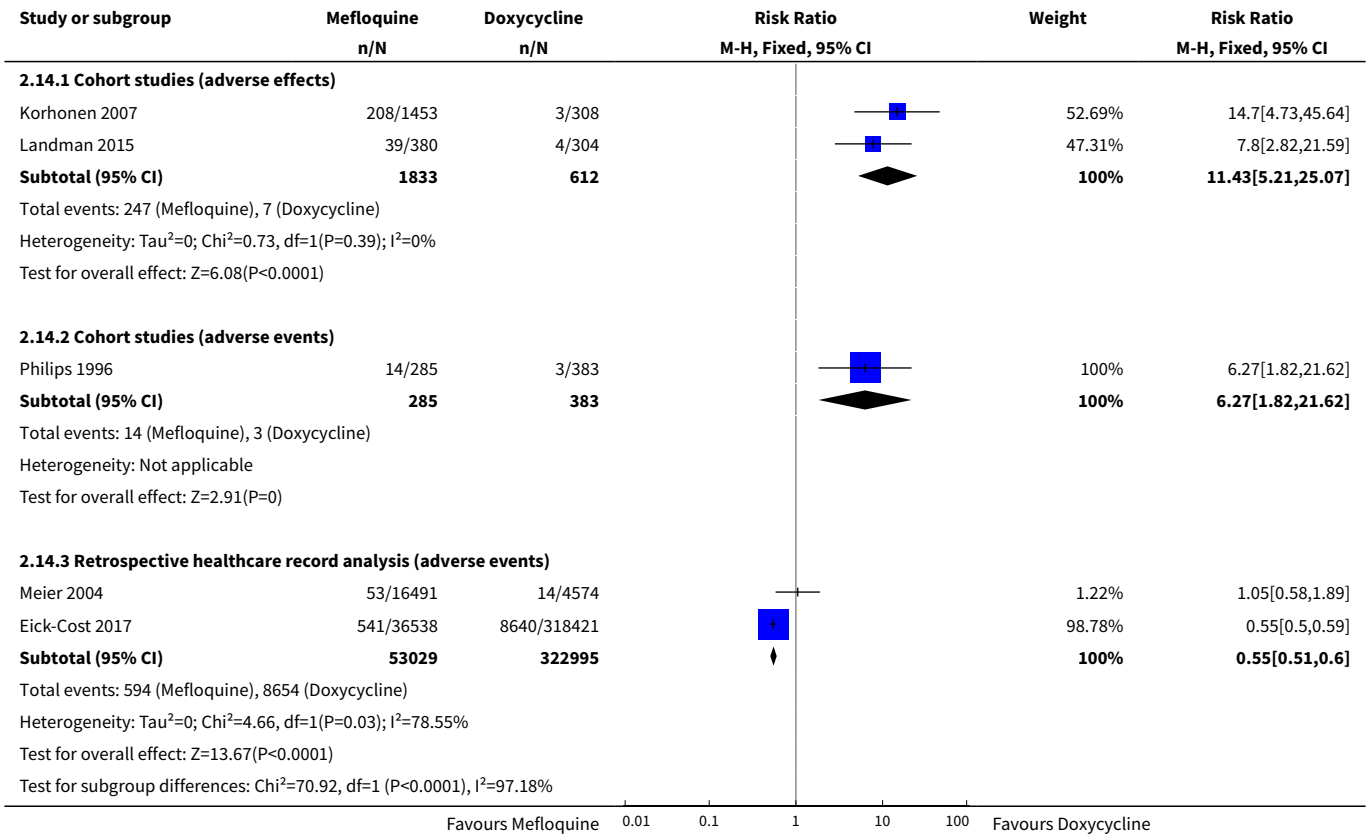
Favours Mefloquine — Favours Doxycycline



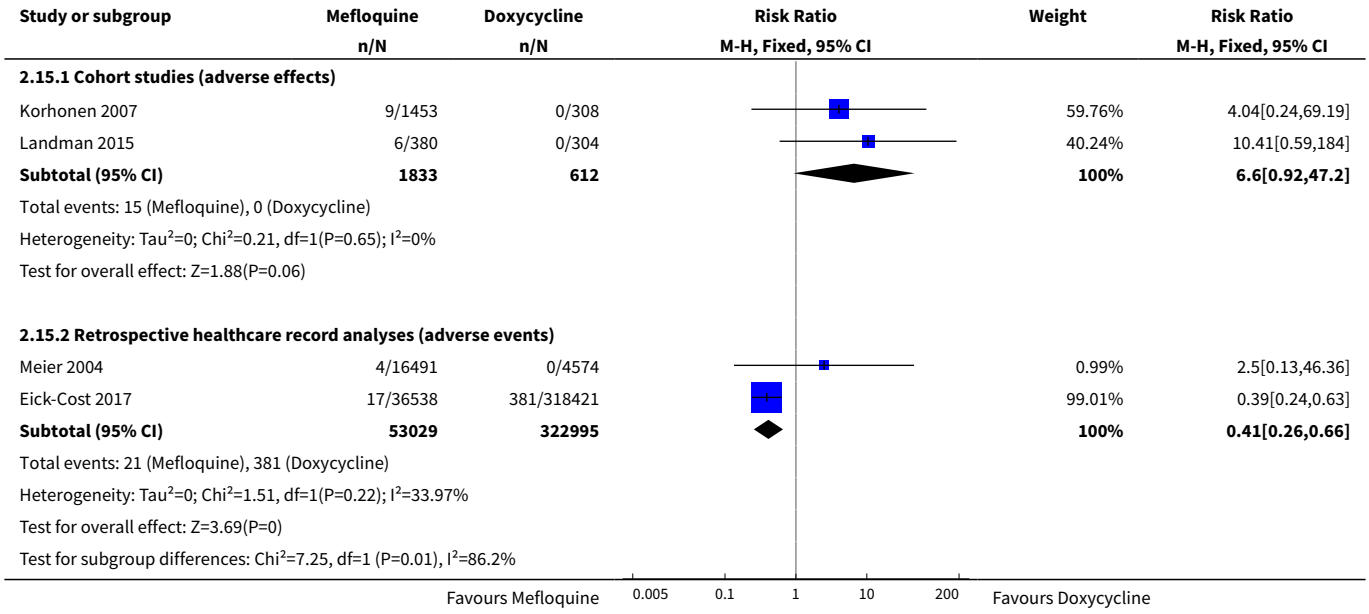
Analysis 2.13. Comparison 2 Mefloquine versus doxycycline, Outcome 13 Anxiety (all studies).



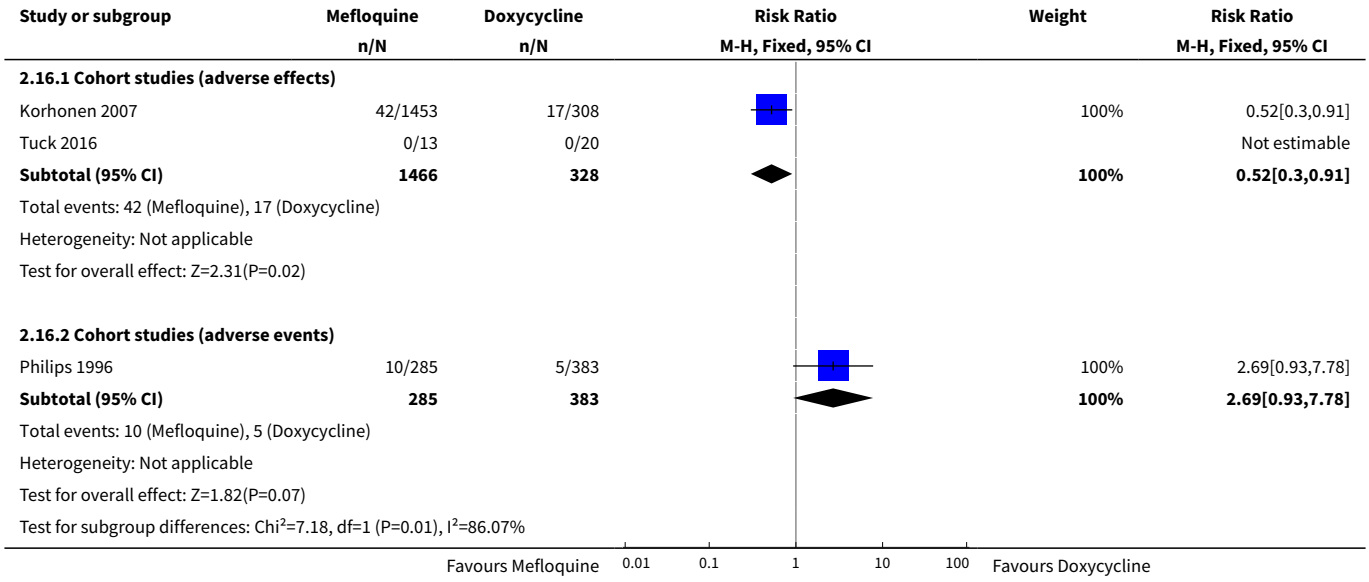
Analysis 2.14. Comparison 2 Mefloquine versus doxycycline, Outcome 14 Depressed mood (all studies).



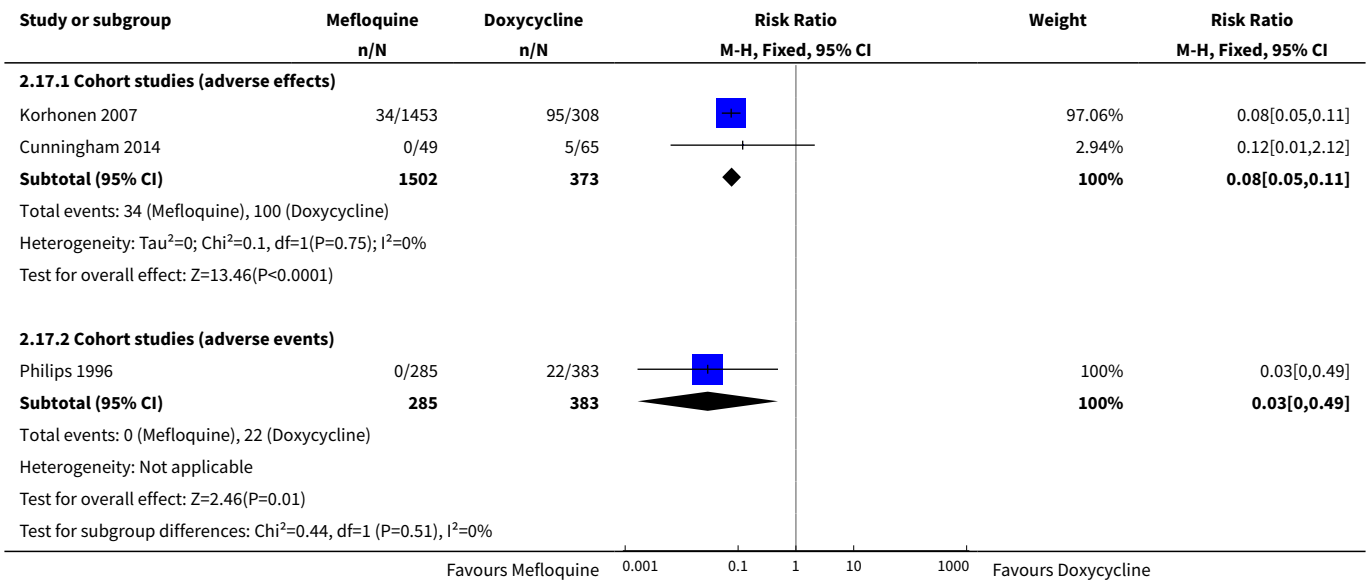
Analysis 2.15. Comparison 2 Mefloquine versus doxycycline, Outcome 15 Abnormal thoughts and perceptions.



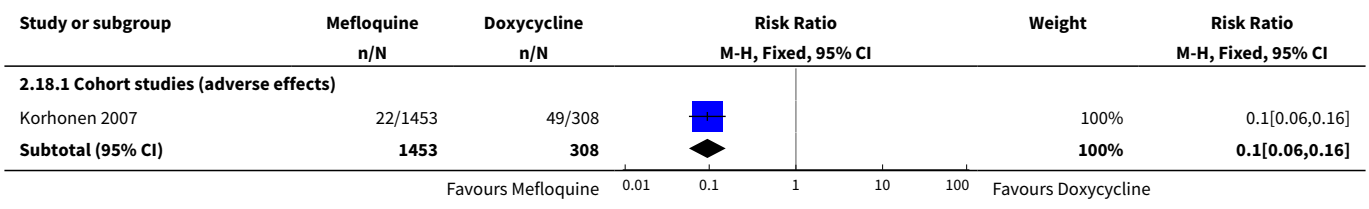
Analysis 2.16. Comparison 2 Mefloquine versus doxycycline, Outcome 16 Pruritis (all studies).

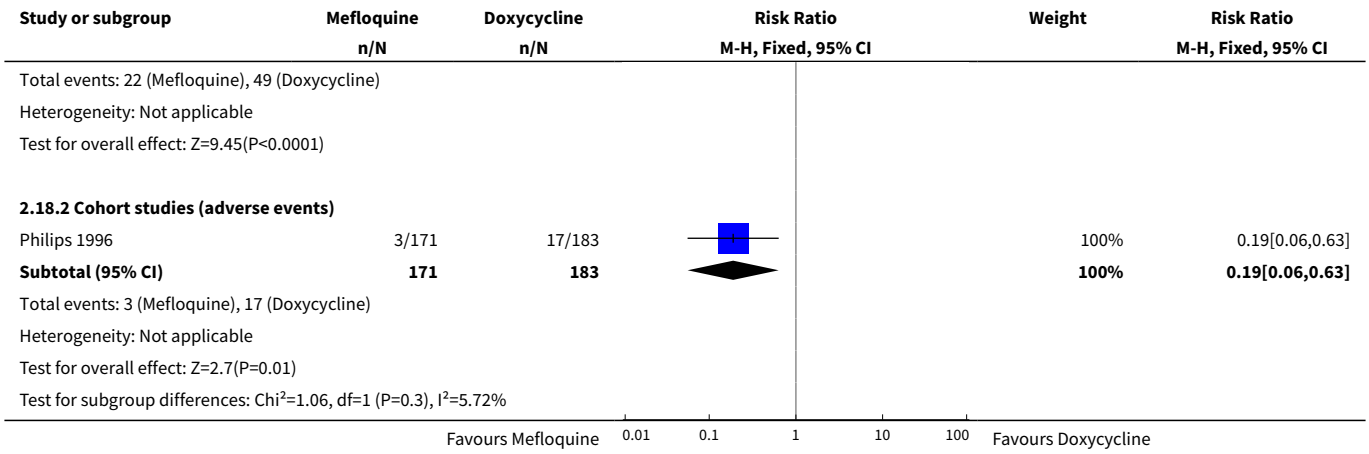


Analysis 2.17. Comparison 2 Mefloquine versus doxycycline, Outcome 17 Photosensitivity (all studies).

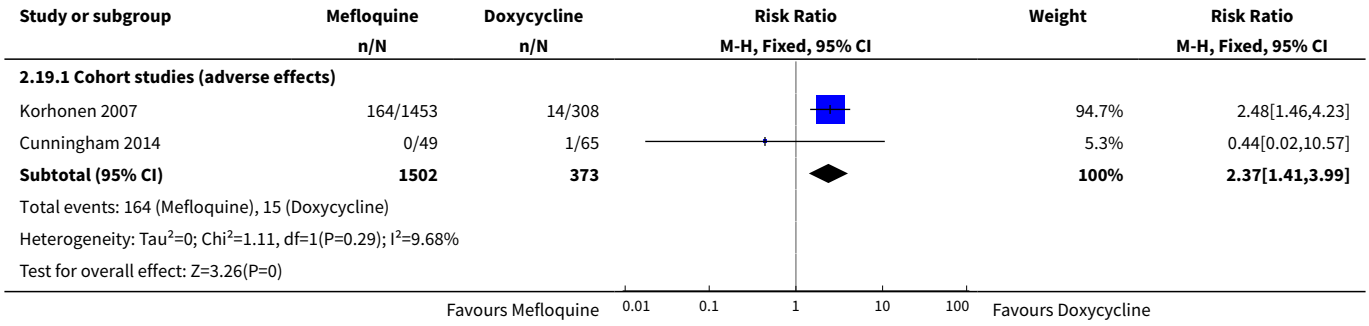


Analysis 2.18. Comparison 2 Mefloquine versus doxycycline, Outcome 18 Yeast infection (all studies).

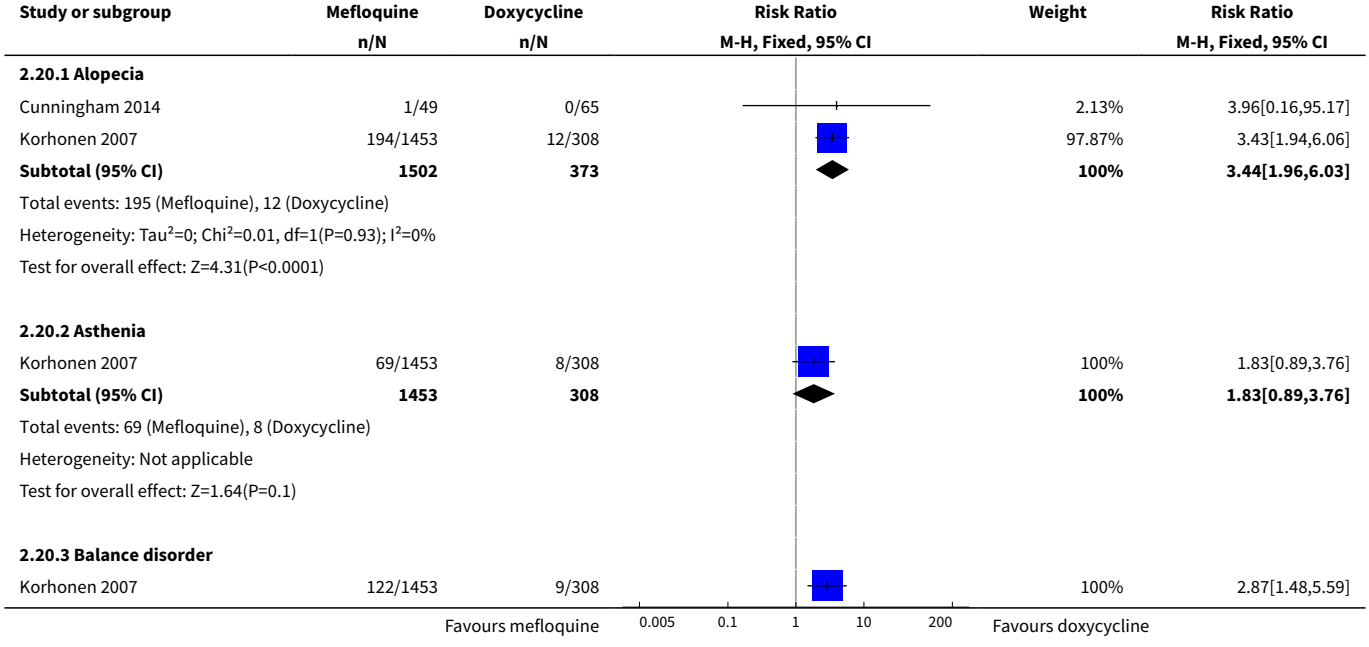


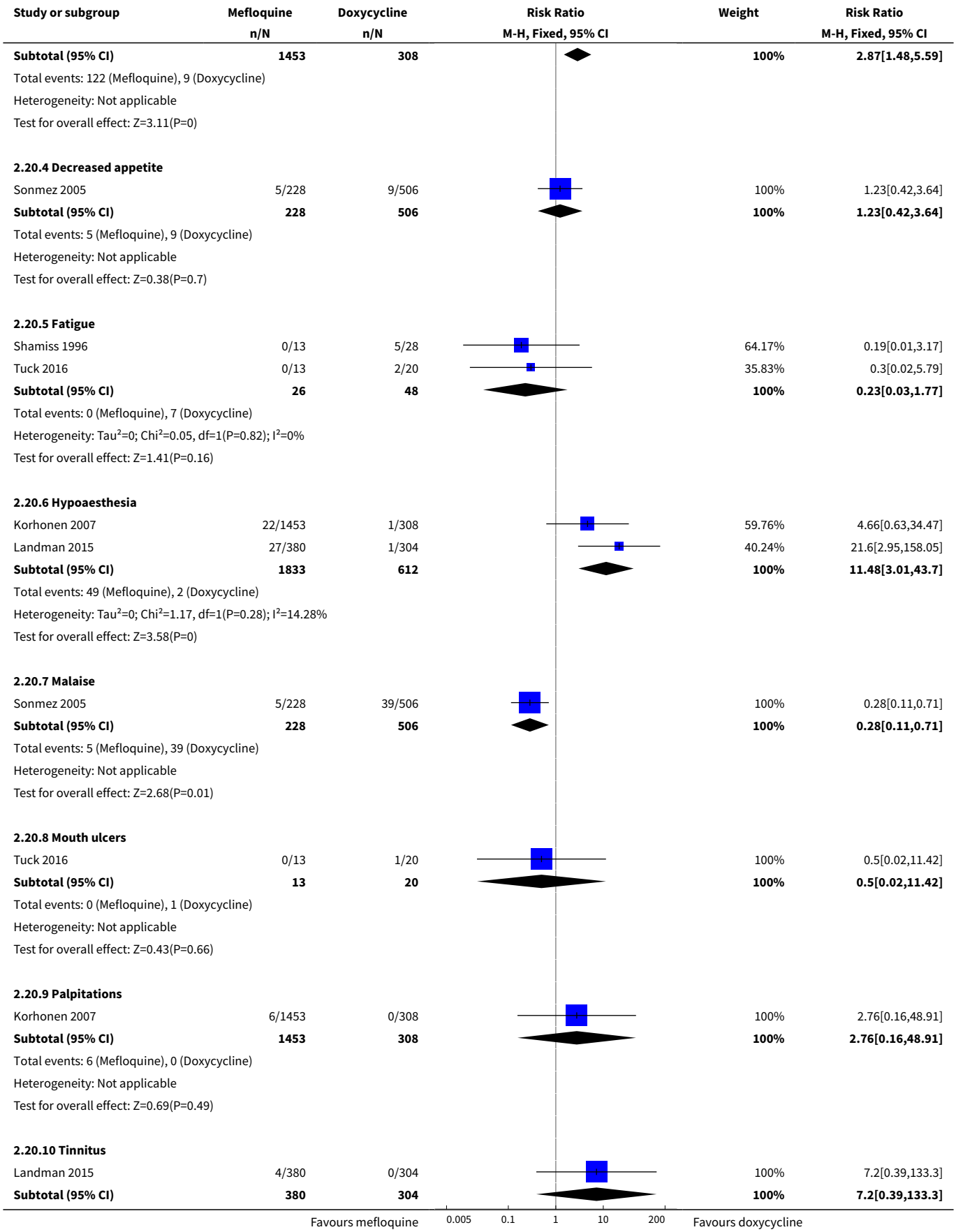


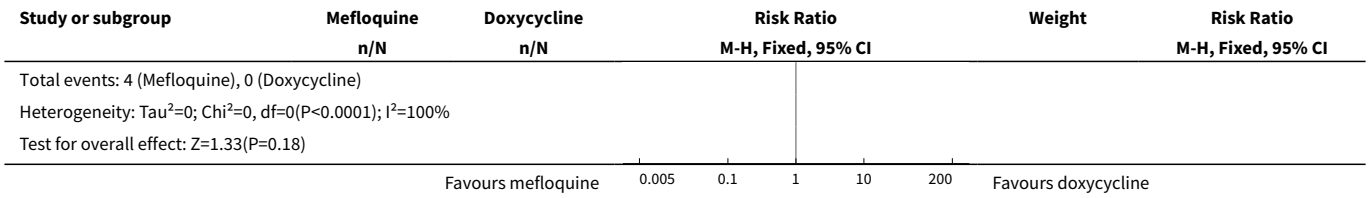
Analysis 2.19. Comparison 2 Mefloquine versus doxycycline, Outcome 19 Visual impairment (all studies).



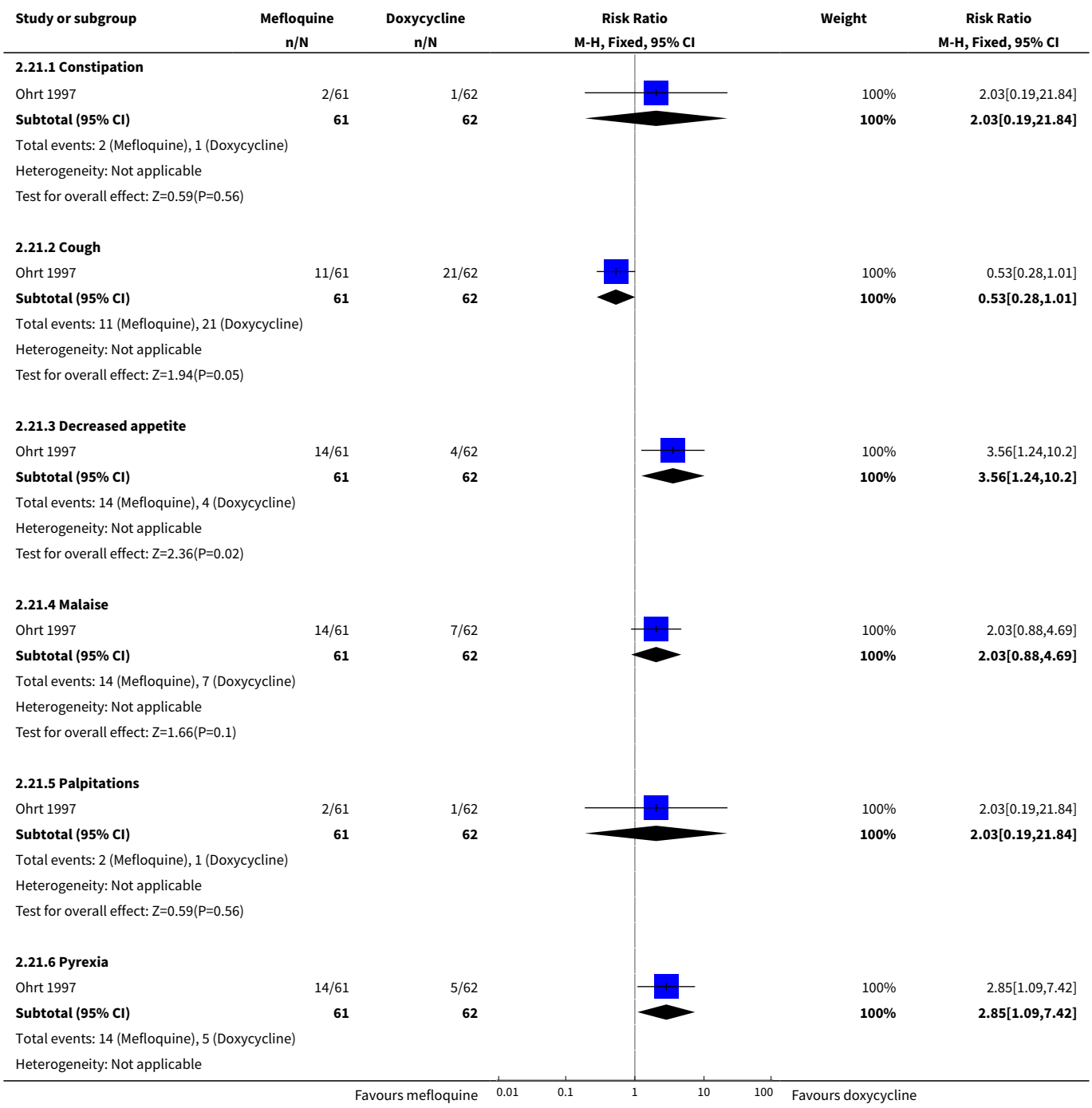
Analysis 2.20. Comparison 2 Mefloquine versus doxycycline, Outcome 20 Other adverse effects (cohort studies).

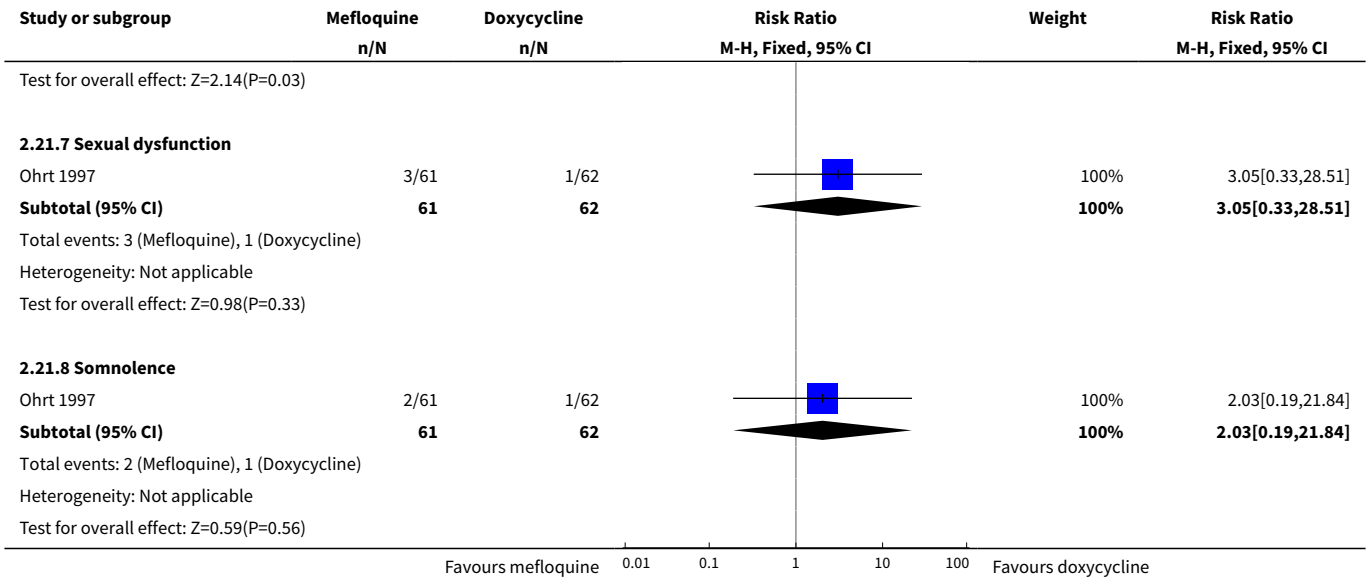




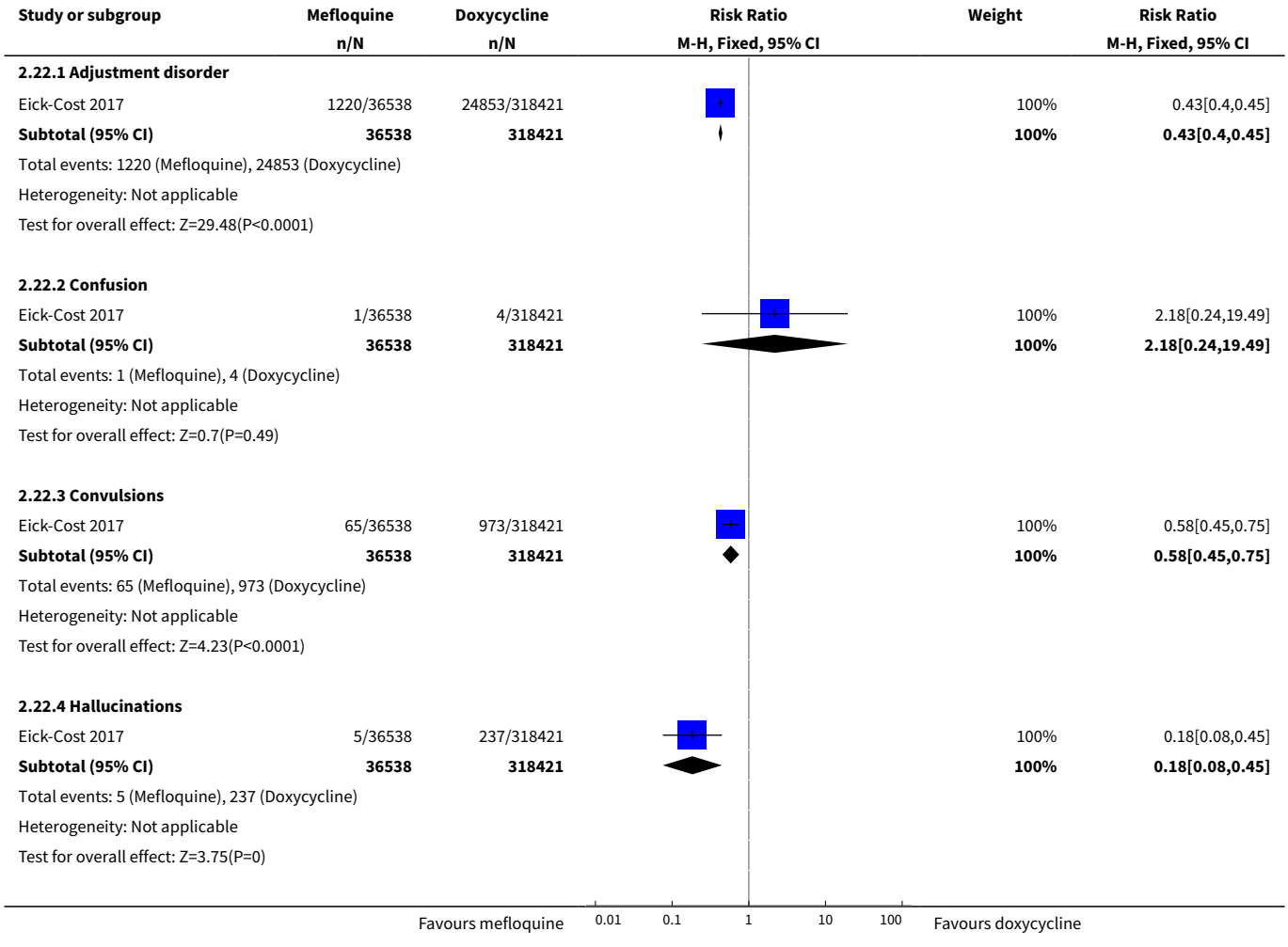


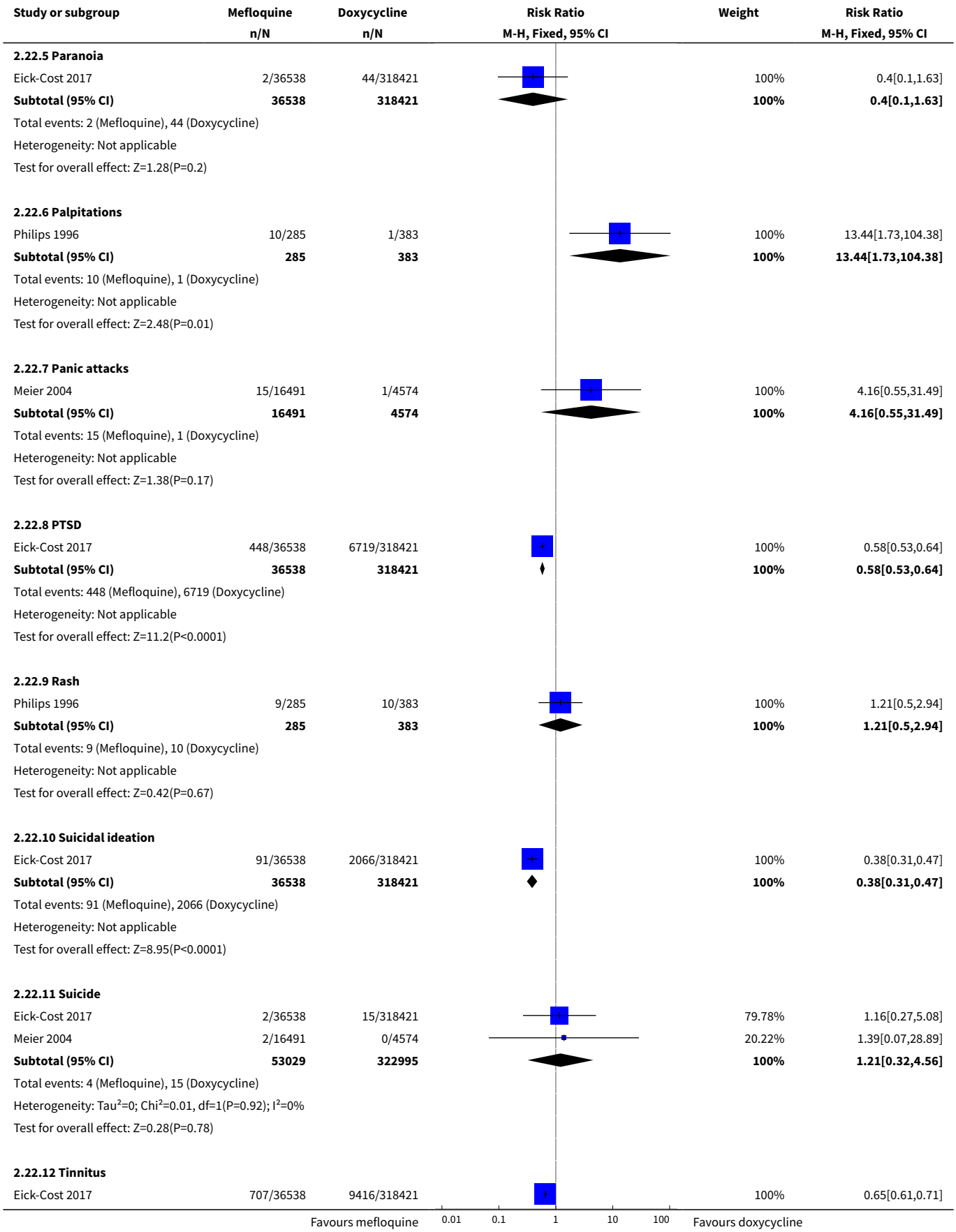
Analysis 2.21. Comparison 2 Mefloquine versus doxycycline, Outcome 21 Other adverse events (RCTs).

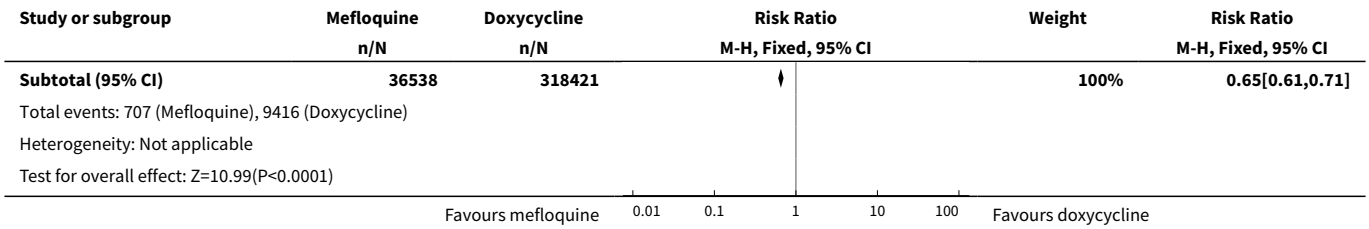




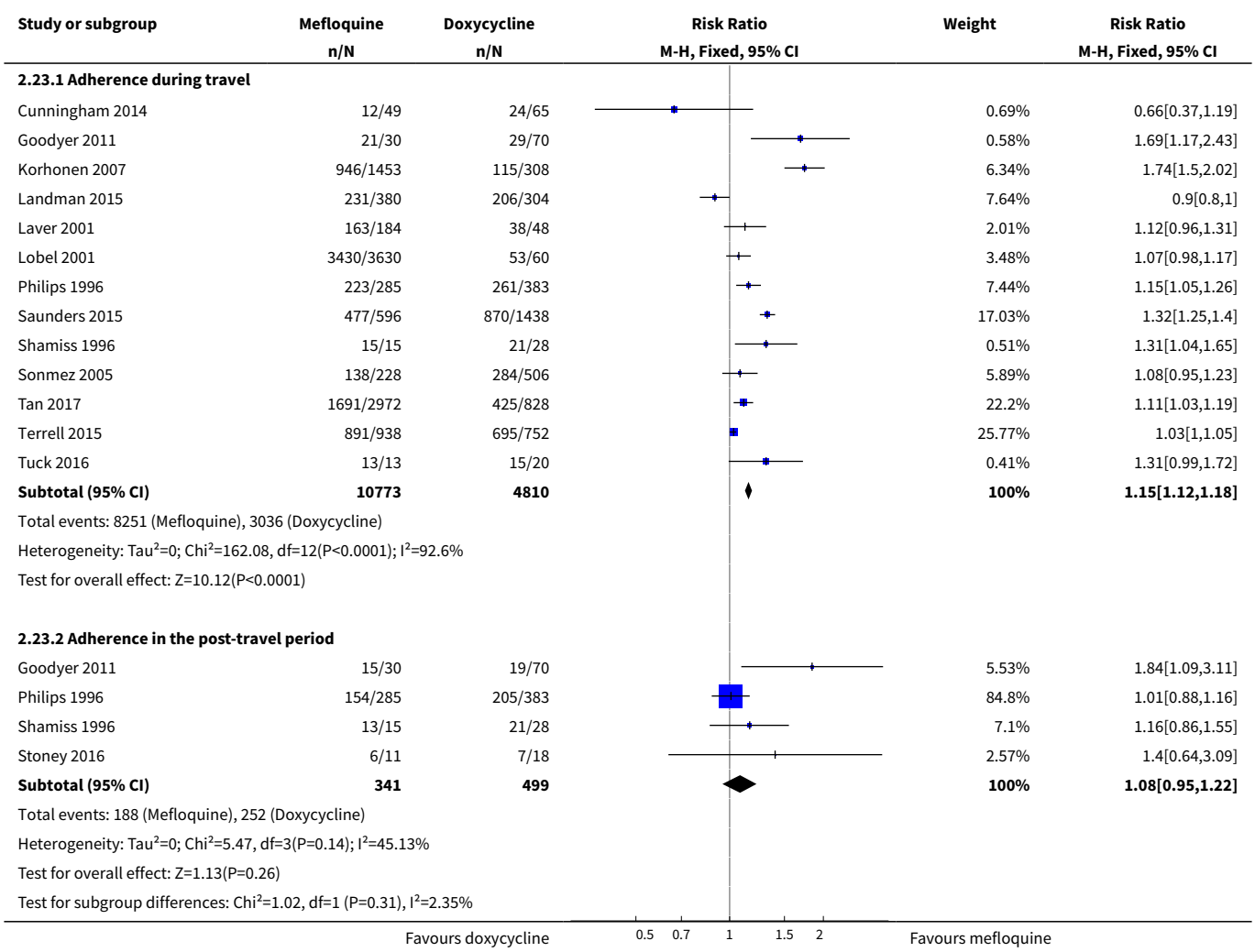
Analysis 2.22. Comparison 2 Mefloquine versus doxycycline, Outcome 22 Other adverse events (cohort studies).







Analysis 2.23. Comparison 2 Mefloquine versus doxycycline, Outcome 23 Adherence (cohort studies).



Comparison 3. Mefloquine versus atovaquone-proguanil

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical cases of malaria (RCTs)	2	1293	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Serious adverse events or effects (all studies)	3	3591	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.08, 23.22]
2.1 Cohort studies	3	3591	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.08, 23.22]
3 Discontinuations due to adverse effects (all studies)	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 RCTs	3	1438	Risk Ratio (M-H, Random, 95% CI)	2.86 [1.53, 5.31]
3.2 Cohort studies	9	7785	Risk Ratio (M-H, Random, 95% CI)	2.73 [1.83, 4.08]
4 Nausea (all studies)	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 RCTs (adverse effects)	1	976	Risk Ratio (M-H, Fixed, 95% CI)	2.72 [1.52, 4.86]
4.2 Cohort studies (adverse effects)	7	3509	Risk Ratio (M-H, Fixed, 95% CI)	2.50 [1.54, 4.06]
5 Vomiting (all studies)	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 RCTs (adverse effects)	1	976	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.49, 3.50]
5.2 Cohort studies (adverse effects)	3	2180	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.08, 4.09]
6 Abdominal pain (all studies)	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 RCTs (adverse effects)	1	976	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.52, 1.56]
6.2 Cohort studies (adverse effects)	7	3509	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.38, 1.07]
7 Diarrhoea (all studies)	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 RCTs (adverse effects)	1	976	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.60, 1.47]
7.2 Cohort studies (adverse effects)	7	3509	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.53, 1.35]
8 Mouth ulcers (all studies)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 RCTs (adverse effects)	1	976	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.70, 3.00]
8.2 Cohort studies (adverse effects)	2	783	Risk Ratio (M-H, Fixed, 95% CI)	0.12 [0.04, 0.37]
9 Headache (all studies)	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 RCTs (adverse effects)	1	976	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [0.99, 2.99]
9.2 Cohort studies (adverse effects)	8	4163	Risk Ratio (M-H, Fixed, 95% CI)	3.42 [1.71, 6.82]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 Dizziness (all studies)	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 RCTs (adverse effects)	1	976	Risk Ratio (M-H, Fixed, 95% CI)	3.99 [2.08, 7.64]
10.2 Cohort studies (adverse effects)	8	3986	Risk Ratio (M-H, Fixed, 95% CI)	3.83 [2.23, 6.58]
10.3 Retrospective health-care record analysis (adverse events)	1	49419	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [1.04, 1.46]
11 Abnormal dreams (all studies)	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 RCTs (adverse effects)	1	976	Risk Ratio (M-H, Random, 95% CI)	2.04 [1.37, 3.04]
11.2 Cohort studies (adverse effects)	7	3848	Risk Ratio (M-H, Random, 95% CI)	6.81 [1.65, 28.15]
12 Insomnia (all studies)	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 RCTs (adverse effects)	1	976	Risk Ratio (M-H, Fixed, 95% CI)	4.42 [2.56, 7.64]
12.2 Cohort studies (adverse effects)	8	3986	Risk Ratio (M-H, Fixed, 95% CI)	7.29 [4.37, 12.16]
12.3 Retrospective health-care record analysis (adverse events)	1	49419	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [1.06, 1.44]
13 Anxiety (all studies)	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 RCTs (adverse effects)	1	976	Risk Ratio (M-H, Fixed, 95% CI)	6.12 [1.82, 20.66]
13.2 Cohort studies (adverse effects)	4	2664	Risk Ratio (M-H, Fixed, 95% CI)	10.10 [3.48, 29.32]
13.3 Retrospective health-care record analysis (adverse events)	1	49419	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [1.28, 1.85]
14 Depressed mood (all studies)	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 RCTs (adverse effects)	1	976	Risk Ratio (M-H, Fixed, 95% CI)	5.78 [1.71, 19.61]
14.2 Cohort studies (adverse effects)	6	3624	Risk Ratio (M-H, Fixed, 95% CI)	8.02 [3.56, 18.07]
14.3 Retrospective health-care record analysis (adverse events)	1	49419	Risk Ratio (M-H, Fixed, 95% CI)	1.93 [1.56, 2.38]
15 Abnormal thoughts and perceptions (all studies)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1 Cohort studies (adverse effects)	3	2433	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.30, 7.42]
15.2 Retrospective health-care record analysis (adverse events)	1	49419	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.69, 12.97]
16 Pruritis (all studies)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 RCTs (adverse effects)	1	976	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.60, 2.70]
16.2 Cohort studies (adverse effects)	3	1824	Risk Ratio (M-H, Fixed, 95% CI)	2.07 [0.40, 10.68]
17 Visual impairment (all studies)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 RCTs (adverse effects)	1	976	Risk Ratio (M-H, Fixed, 95% CI)	2.04 [0.88, 4.73]
17.2 Cohort studies (adverse effects)	2	1956	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.29, 4.72]
18 Other adverse effects (cohort studies)	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 Allergic reaction	1	316	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.04, 14.48]
18.2 Alopecia	1	1469	Risk Ratio (M-H, Fixed, 95% CI)	4.55 [0.30, 70.01]
18.3 Asthenia	2	1956	Risk Ratio (M-H, Fixed, 95% CI)	1.84 [0.26, 13.12]
18.4 Balance disorder	1	1469	Risk Ratio (M-H, Fixed, 95% CI)	2.86 [0.19, 44.19]
18.5 Cough	1	652	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.08, 2.92]
18.6 Disturbance in attention	3	1363	Risk Ratio (M-H, Fixed, 95% CI)	4.45 [1.84, 10.77]
18.7 Dyspepsia	2	362	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.17, 1.46]
18.8 Fatigue	2	618	Risk Ratio (M-H, Fixed, 95% CI)	4.62 [0.47, 45.56]
18.9 Hypoaesthesia	2	1946	Risk Ratio (M-H, Fixed, 95% CI)	4.45 [0.93, 21.26]
18.10 Loss of appetite	1	652	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.33, 1.43]
18.11 Muscle pain	1	652	Risk Ratio (M-H, Fixed, 95% CI)	7.57 [0.45, 127.80]
18.12 Palpitations	3	2180	Risk Ratio (M-H, Fixed, 95% CI)	3.34 [0.73, 15.26]
18.13 Photosensitization	2	718	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.10, 4.92]
18.14 Pyrexia	1	652	Risk Ratio (M-H, Fixed, 95% CI)	4.28 [0.24, 75.57]
18.15 Rash	2	711	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.15, 6.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.16 Restlessness	1	487	Risk Ratio (M-H, Fixed, 95% CI)	5.24 [0.32, 84.52]
18.17 Slight illness	1	487	Risk Ratio (M-H, Fixed, 95% CI)	5.83 [0.36, 93.84]
18.18 Somnolence	1	487	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [0.21, 11.40]
18.19 Tinnitus	1	477	Risk Ratio (M-H, Fixed, 95% CI)	2.31 [0.13, 42.64]
18.20 Circulatory disorders	1	224	Risk Ratio (M-H, Fixed, 95% CI)	6.38 [0.36, 114.01]
19 Other adverse events (cohort studies)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 Adjustment disorder	1	49419	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [1.54, 2.02]
19.2 Confusion	1	49419	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.04, 25.96]
19.3 Convulsions	1	49419	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.79, 2.30]
19.4 Hallucinations	1	49419	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.08, 0.79]
19.5 Paranoia	1	49419	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [0.08, 36.72]
19.6 PTSD	1	49419	Risk Ratio (M-H, Fixed, 95% CI)	2.51 [1.93, 3.26]
19.7 Suicidal ideation	1	49419	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [1.03, 2.77]
19.8 Suicide	1	49419	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.06, 7.78]
19.9 Tinnitus	1	49419	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [1.21, 1.68]
20 Adherence (RCTs)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
20.1 van Riemsdijk 2002	1	119	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.88, 1.02]
20.2 Overbosch 2001; during travel	1	966	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.95, 1.01]
20.3 Overbosch 2001; post-travel	1	966	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.74, 0.85]
21 Adherence (cohort studies)	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
21.1 During travel	6	5577	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.86, 1.34]
21.2 Post-travel	2	422	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.64, 1.23]

Analysis 3.1. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 1 Clinical cases of malaria (RCTs).

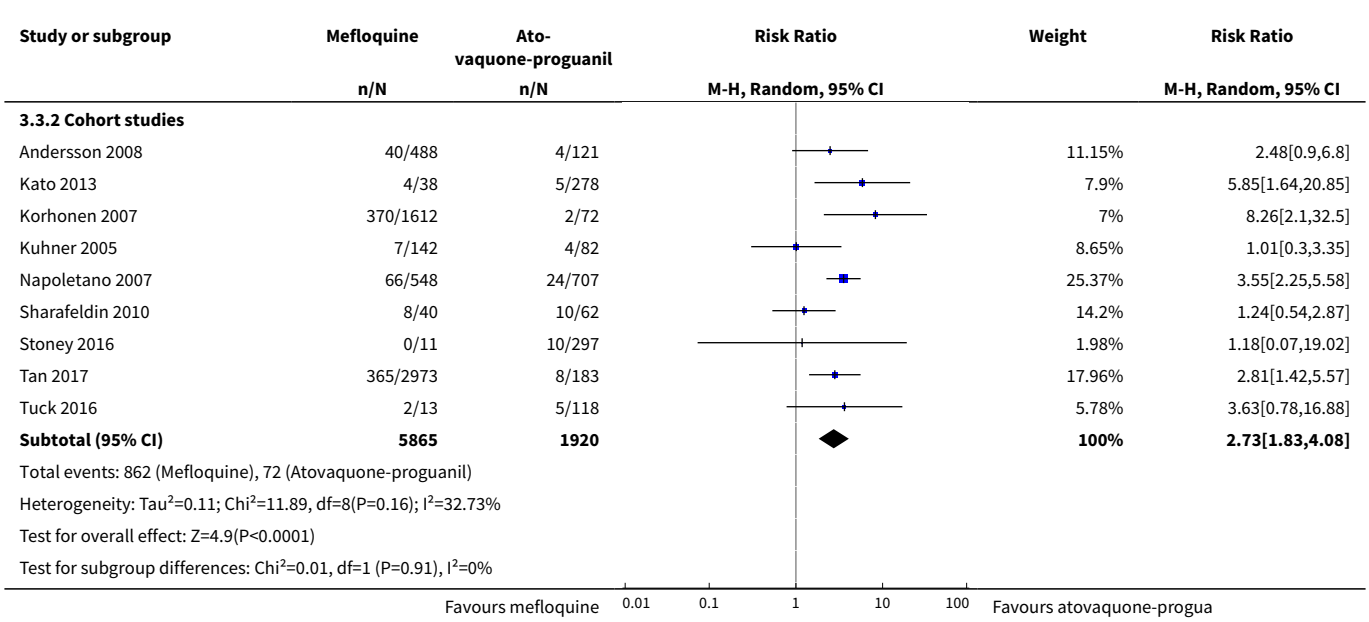
Study or subgroup	Mefloquine n/N	Ato-vaquone-proguanil n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Overbosch 2001	0/483	0/493			Not estimable
Schlagenhauf 2003	0/153	0/164			Not estimable
Total (95% CI)	**636**	**657**			**Not estimable**
Total events: 0 (Mefloquine), 0 (Atovaquone-proguanil)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Analysis 3.2. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 2 Serious adverse events or effects (all studies).

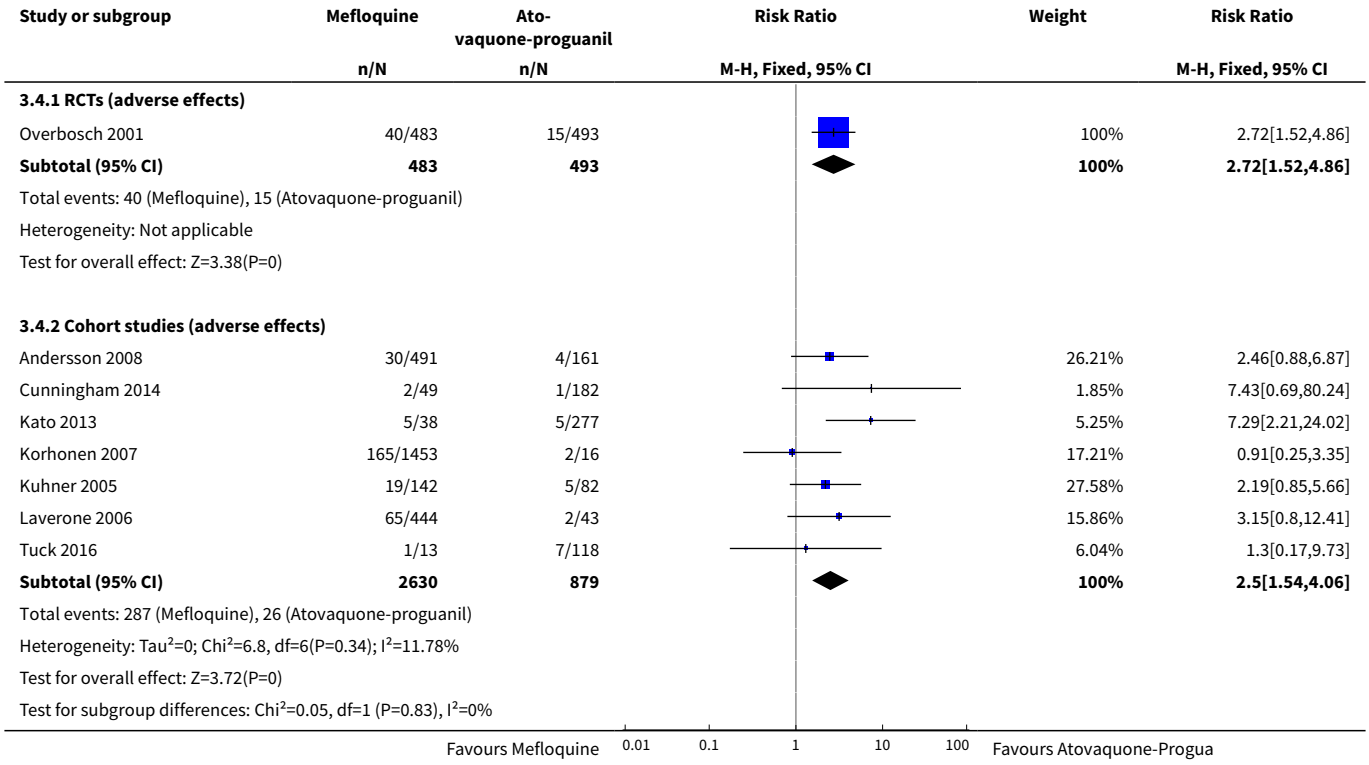
Study or subgroup	Mefloquine n/N	Ato-vaquone-proguanil n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 Cohort studies					
Andersson 2008	0/491	0/161			Not estimable
Korhonen 2007	15/1612	0/72		100%	1.4[0.08,23.22]
Napoletano 2007	0/548	0/707			Not estimable
Subtotal (95% CI)	**2651**	**940**		**100%**	**1.4[0.08,23.22]**
Total events: 15 (Mefloquine), 0 (Atovaquone-proguanil)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.24(P=0.81)					
Total (95% CI)	**2651**	**940**		**100%**	**1.4[0.08,23.22]**
Total events: 15 (Mefloquine), 0 (Atovaquone-proguanil)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.24(P=0.81)					

Analysis 3.3. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 3 Discontinuations due to adverse effects (all studies).

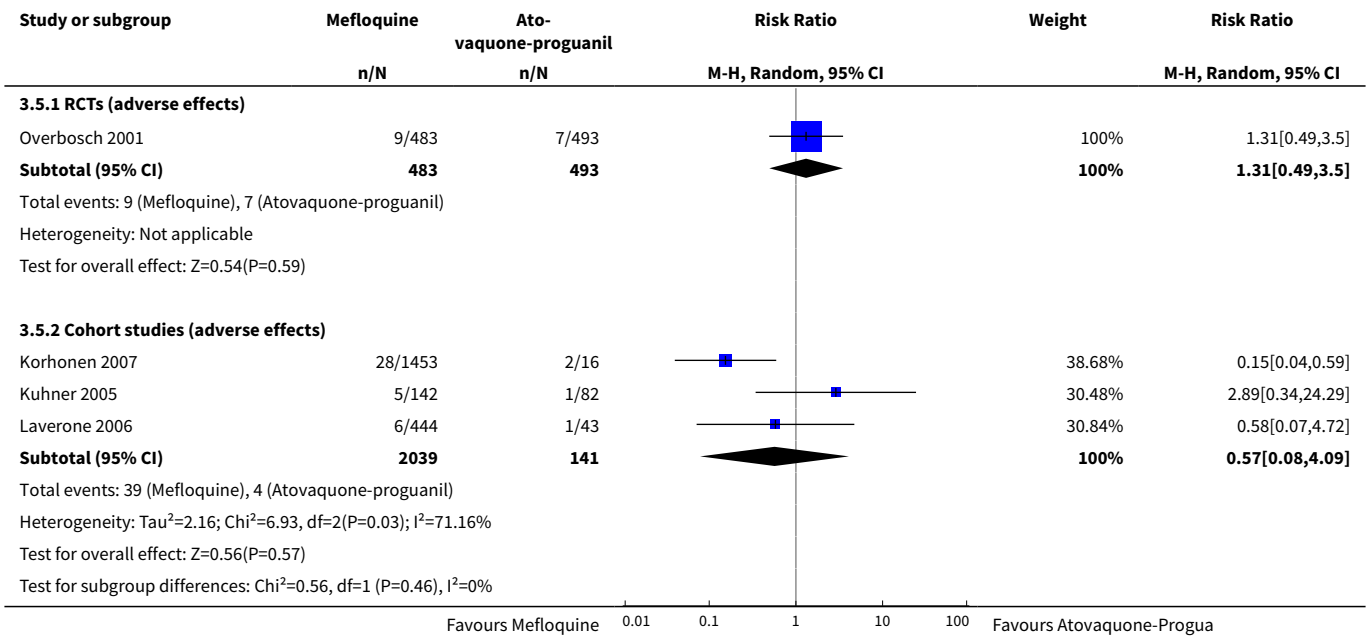
Study or subgroup	Mefloquine n/N	Ato-vaquone-proguanil n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.3.1 RCTs					
Overbosch 2001	24/483	6/493		49.18%	4.08[1.68,9.9]
Schlagenhauf 2003	6/156	3/166		20.6%	2.13[0.54,8.36]
van Riemsdijk 2002	9/75	4/65		30.22%	1.95[0.63,6.04]
Subtotal (95% CI)	**714**	**724**		**100%**	**2.86[1.53,5.31]**
Total events: 39 (Mefloquine), 13 (Atovaquone-proguanil)					
Heterogeneity: $Tau^2=0$; $Chi^2=1.25$, df=2(P=0.53); $I^2=0\%$					
Test for overall effect: Z=3.31(P=0)					



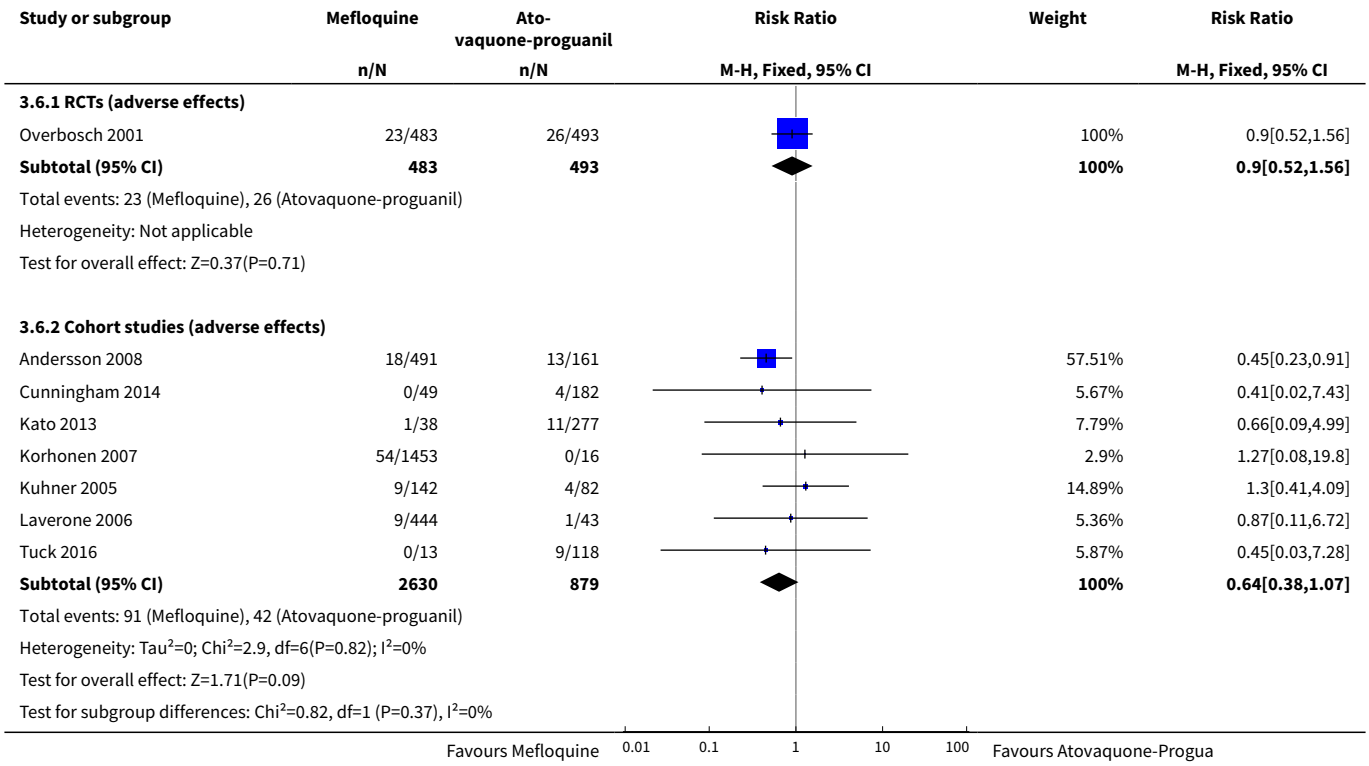
Analysis 3.4. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 4 Nausea (all studies).



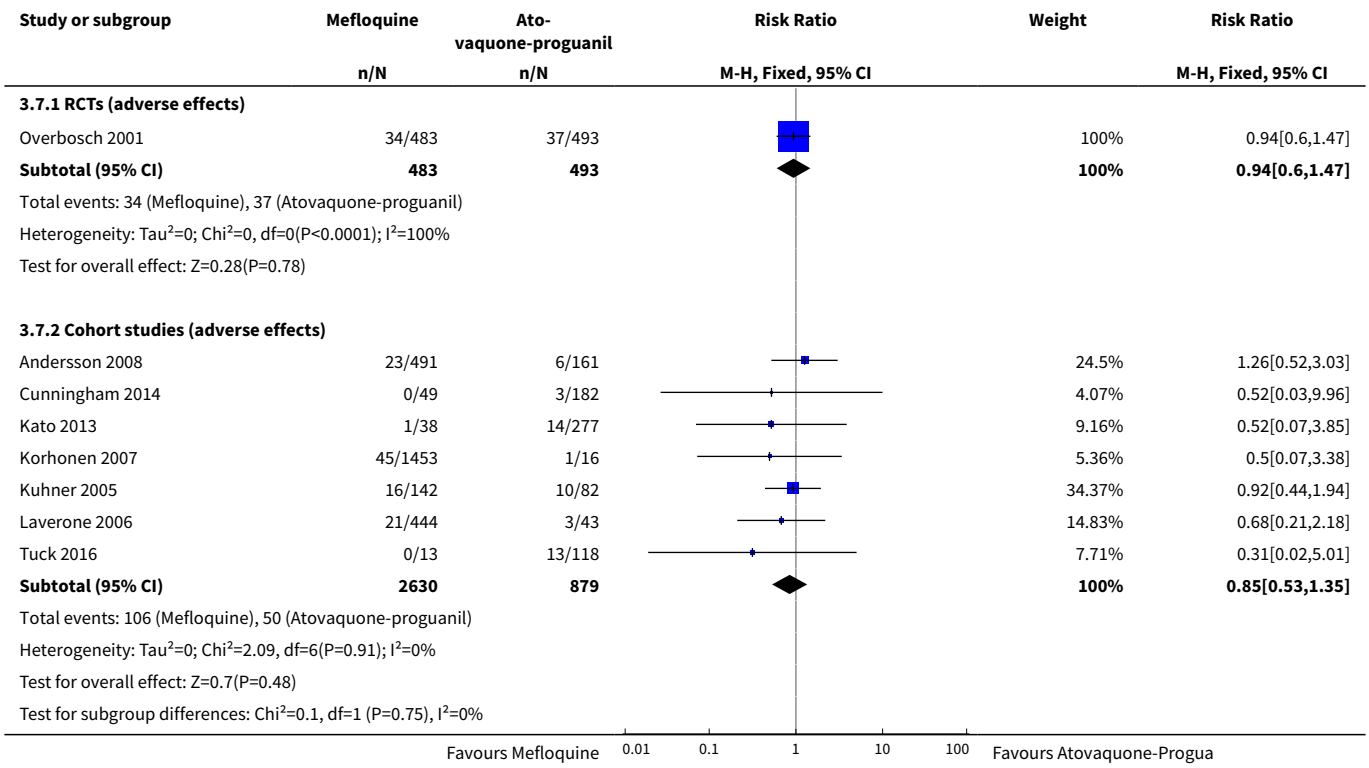
Analysis 3.5. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 5 Vomiting (all studies).



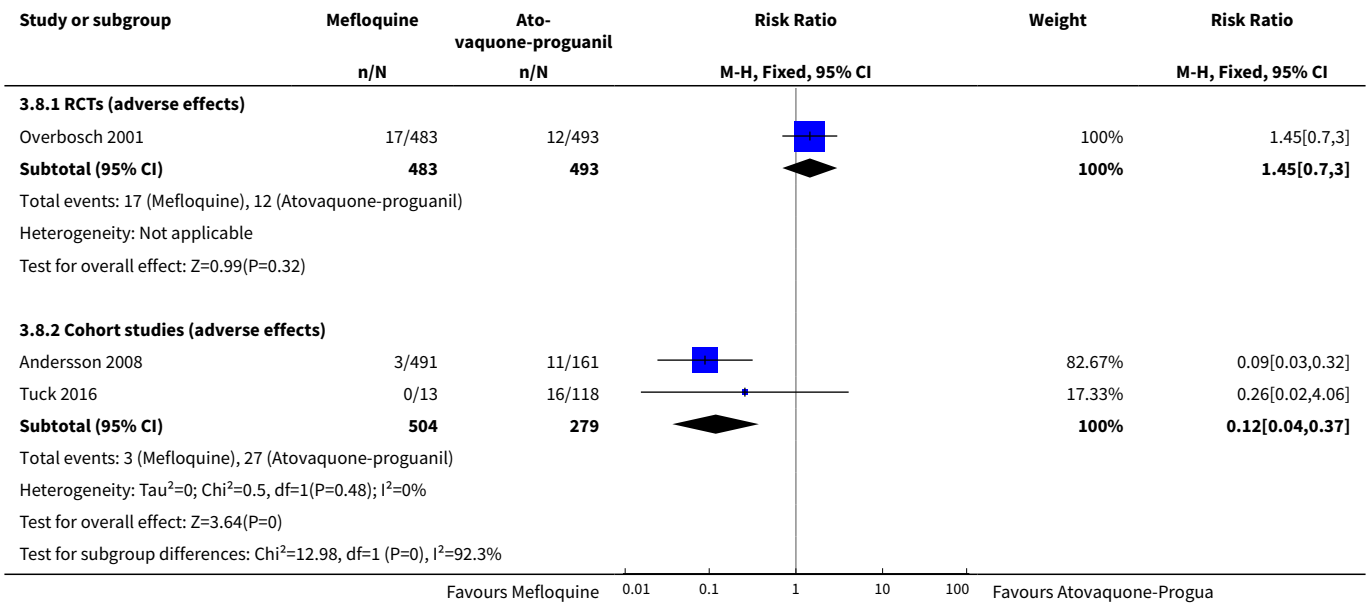
Analysis 3.6. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 6 Abdominal pain (all studies).



Analysis 3.7. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 7 Diarrhoea (all studies).

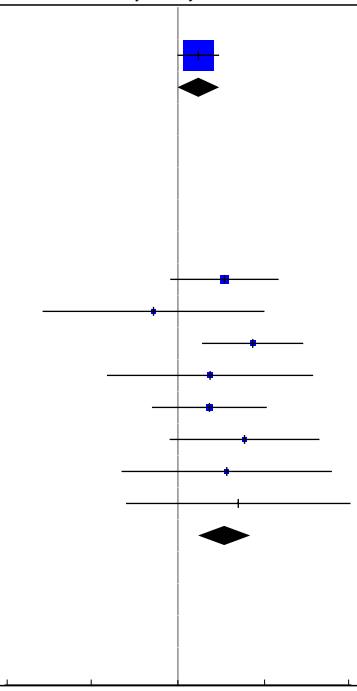


Analysis 3.8. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 8 Mouth ulcers (all studies).



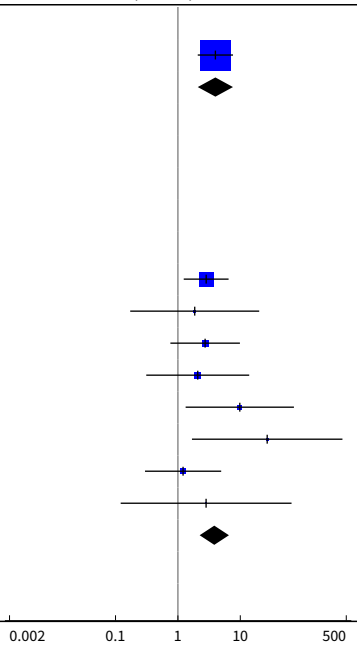
Analysis 3.9. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 9 Headache (all studies).

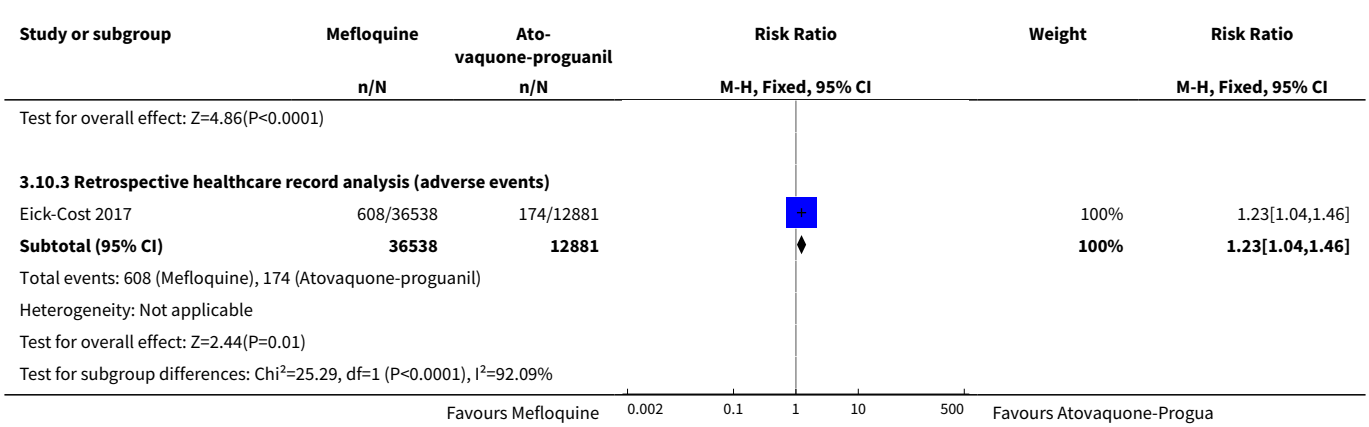
Study or subgroup	Mefloquine n/N	Ato-vaquone-proguanil n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.9.1 RCTs (adverse effects)					
Overbosch 2001	32/483	19/493		100%	1.72[0.99,2.99]
Subtotal (95% CI)	**483**	**493**		**100%**	**1.72[0.99,2.99]**
Total events: 32 (Mefloquine), 19 (Atovaquone-proguanil)					
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%					
Test for overall effect: Z=1.92(P=0.06)					
3.9.2 Cohort studies (adverse effects)					
Andersson 2008	21/491	2/161		25.74%	3.44[0.82,14.52]
Cunningham 2014	0/49	3/182		12.84%	0.52[0.03,9.96]
Kato 2013	4/38	4/277		8.25%	7.29[1.9,27.94]
Korhonen 2007	100/1453	0/16		8.45%	2.35[0.15,36.3]
Kuhner 2005	8/142	2/82		21.67%	2.31[0.5,10.62]
Landman 2015	23/380	1/97		13.62%	5.87[0.8,42.94]
Laverone 2006	18/444	0/43		7.78%	3.66[0.22,59.68]
Stoney 2016	0/11	2/297		1.65%	4.97[0.25,97.88]
Subtotal (95% CI)	**3008**	**1155**		**100%**	**3.42[1.71,6.82]**
Total events: 174 (Mefloquine), 14 (Atovaquone-proguanil)					
Heterogeneity: Tau²=0; Chi²=3.45, df=7(P=0.84); I²=0%					
Test for overall effect: Z=3.49(P=0)					
Test for subgroup differences: Chi²=2.32, df=1 (P=0.13), I²=56.9%					



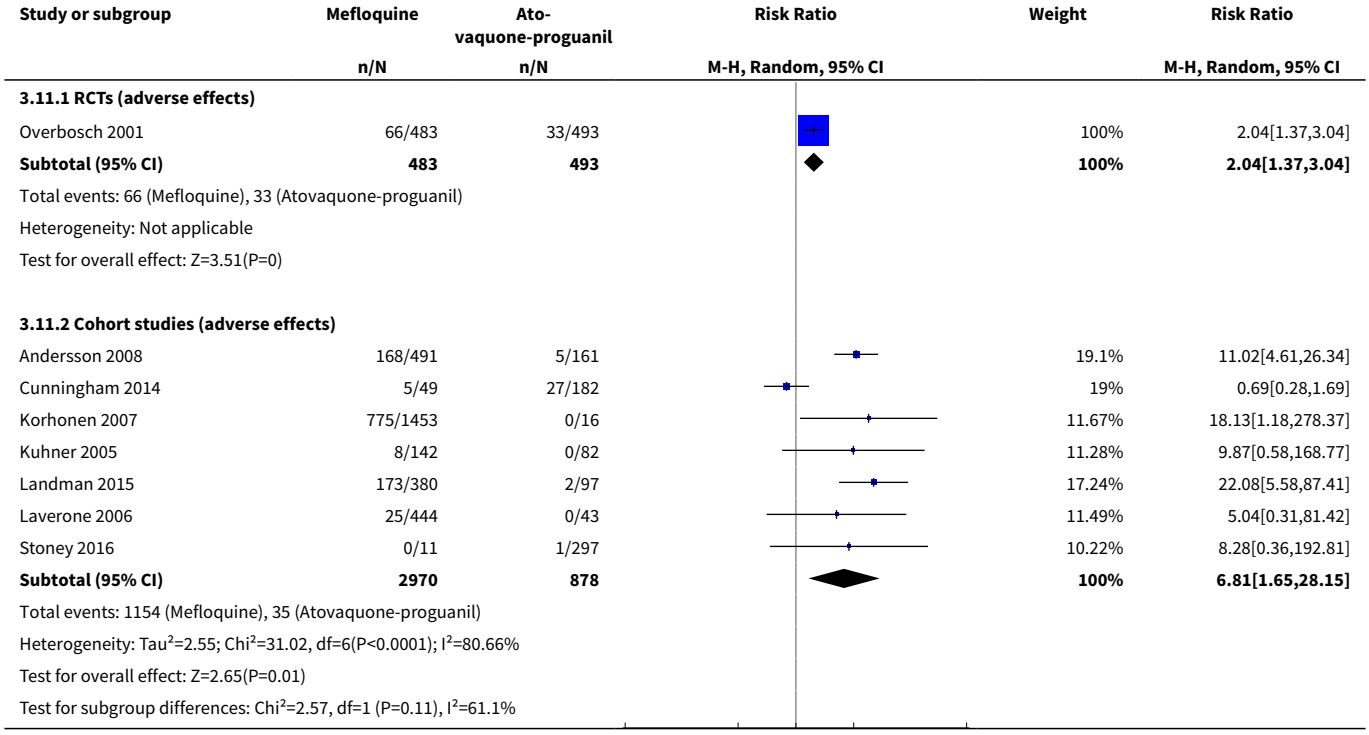
Analysis 3.10. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 10 Dizziness (all studies).

Study or subgroup	Mefloquine n/N	Ato-vaquone-proguanil n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.10.1 RCTs (adverse effects)					
Overbosch 2001	43/483	11/493		100%	3.99[2.08,7.64]
Subtotal (95% CI)	**483**	**493**		**100%**	**3.99[2.08,7.64]**
Total events: 43 (Mefloquine), 11 (Atovaquone-proguanil)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.17(P<0.0001)					
3.10.2 Cohort studies (adverse effects)					
Andersson 2008	52/491	6/161		45.6%	2.84[1.24,6.49]
Cunningham 2014	1/49	2/182		4.28%	1.86[0.17,20.06]
Kato 2013	3/38	8/277		9.74%	2.73[0.76,9.86]
Korhonen 2007	189/1453	1/16		9.98%	2.08[0.31,13.95]
Kuhner 2005	17/142	1/82		6.4%	9.82[1.33,72.42]
Landman 2015	52/380	0/97		4.01%	27.01[1.68,433.65]
Laverone 2006	25/444	2/43		18.4%	1.21[0.3,4.94]
Tuck 2016	0/13	1/118		1.59%	2.83[0.12,66.27]
Subtotal (95% CI)	**3010**	**976**		**100%**	**3.83[2.23,6.58]**
Total events: 339 (Mefloquine), 21 (Atovaquone-proguanil)					
Heterogeneity: Tau²=0; Chi²=6.88, df=7(P=0.44); I²=0%					

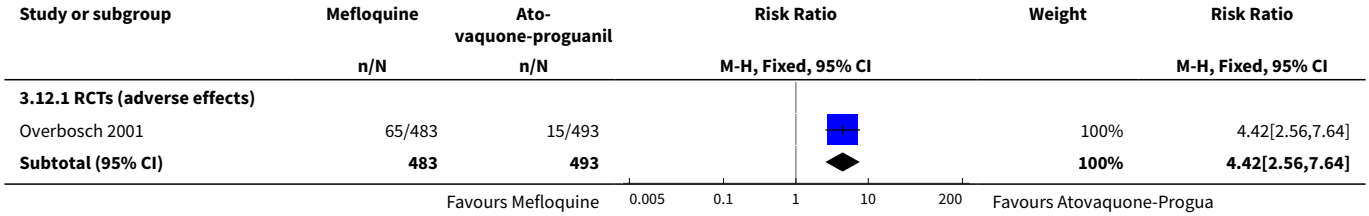


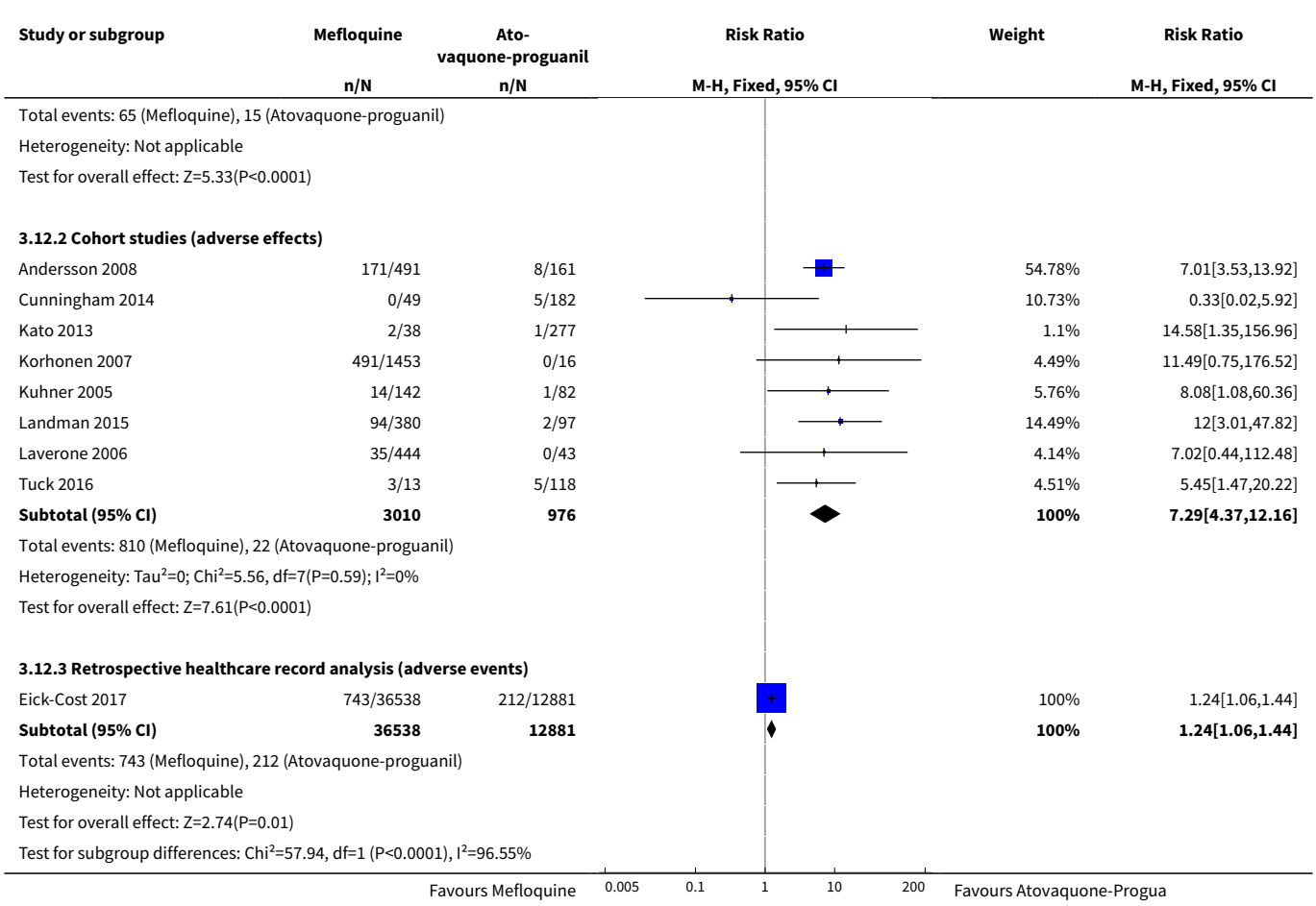


Analysis 3.11. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 11 Abnormal dreams (all studies).

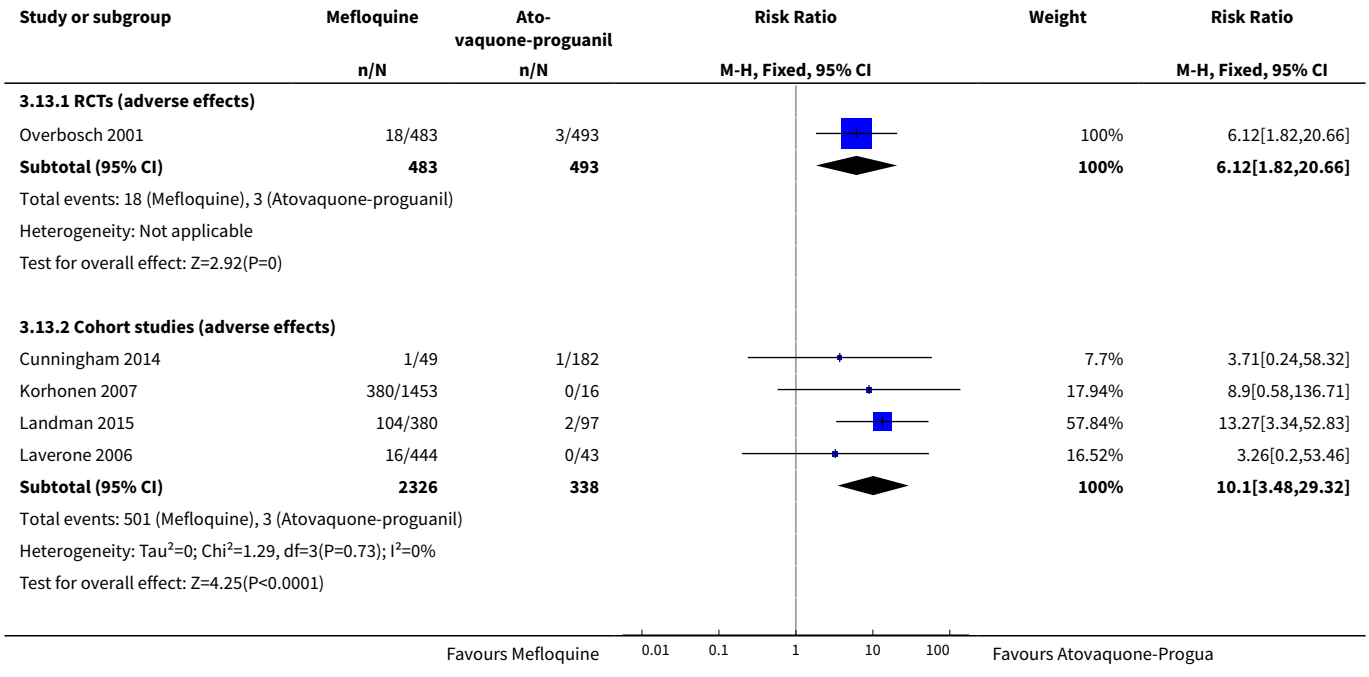


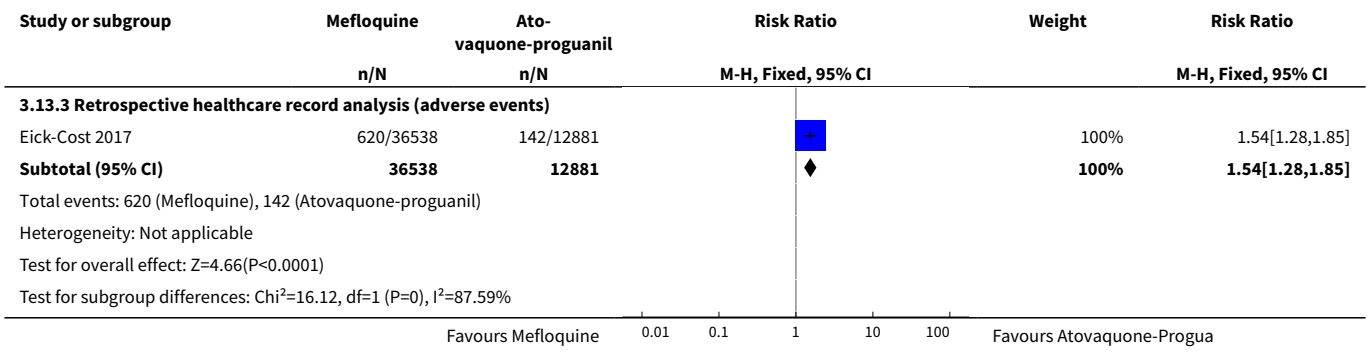
Analysis 3.12. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 12 Insomnia (all studies).



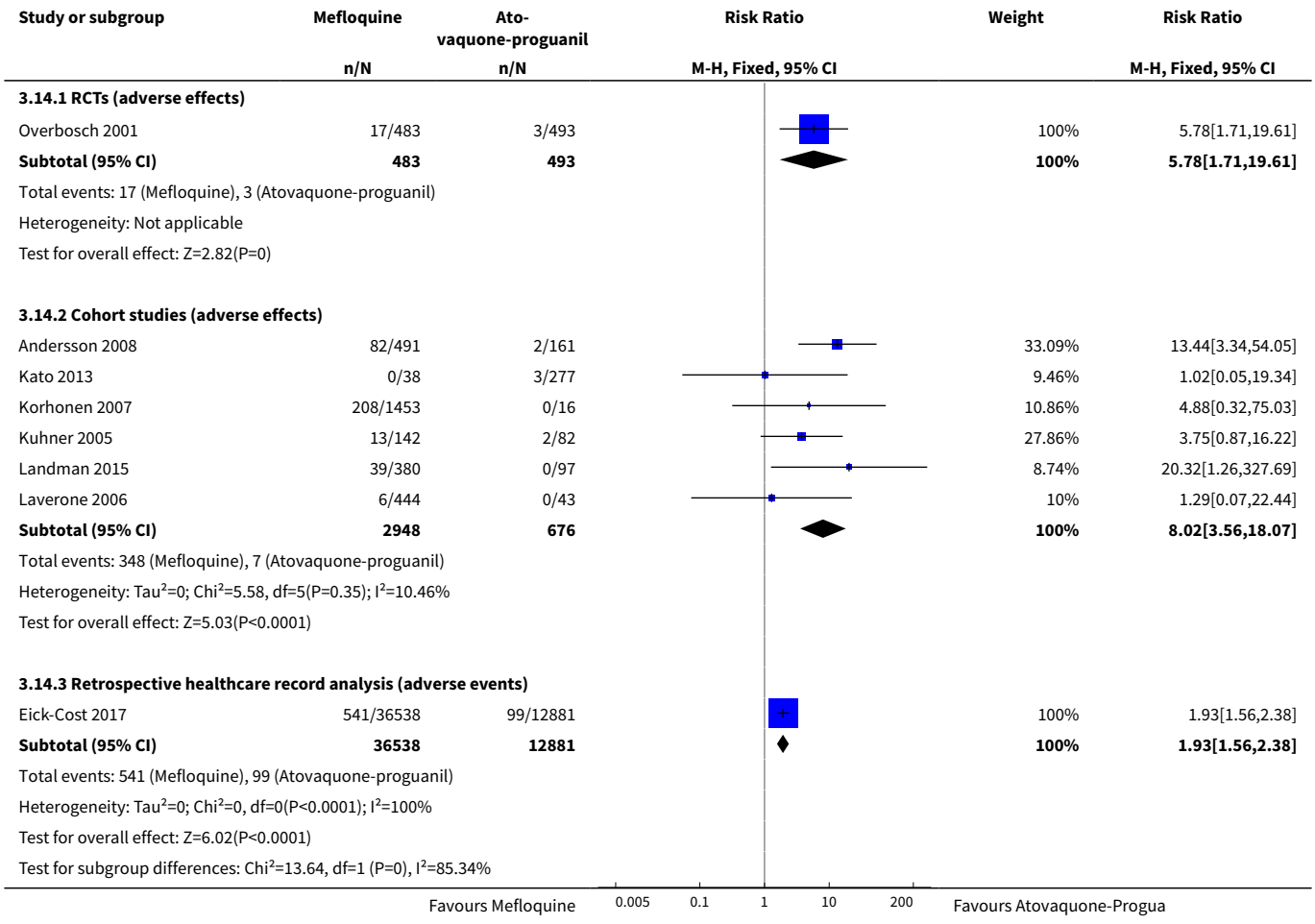


Analysis 3.13. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 13 Anxiety (all studies).

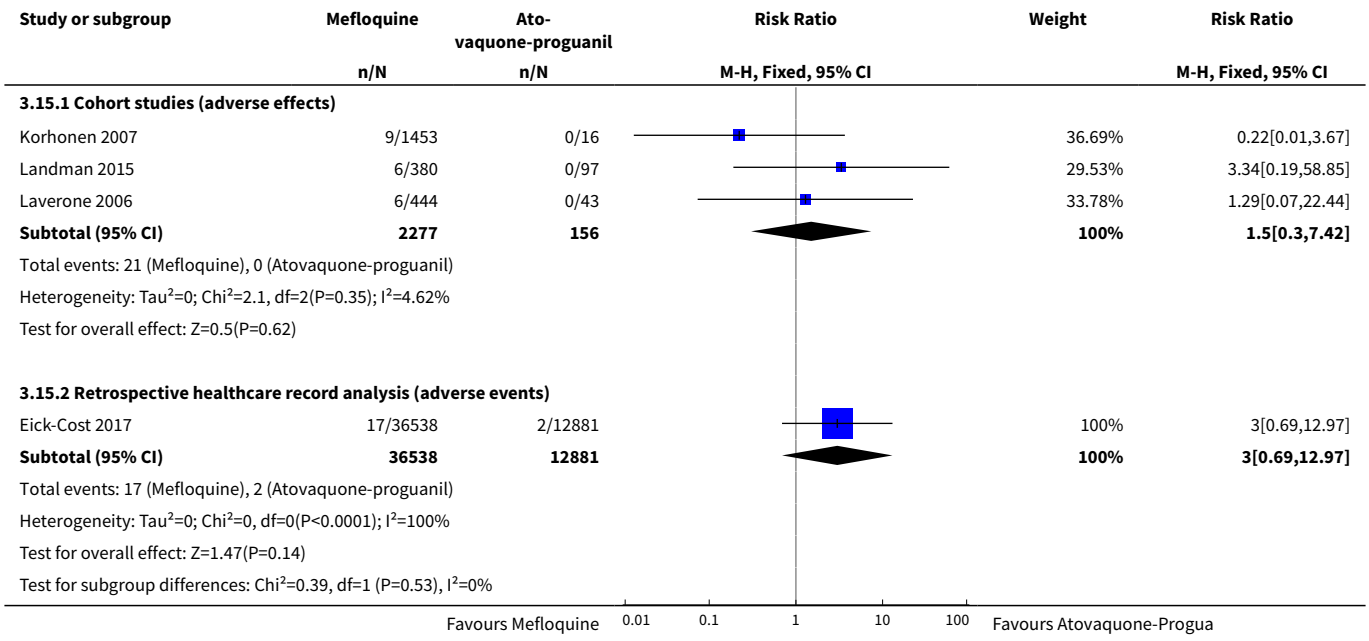




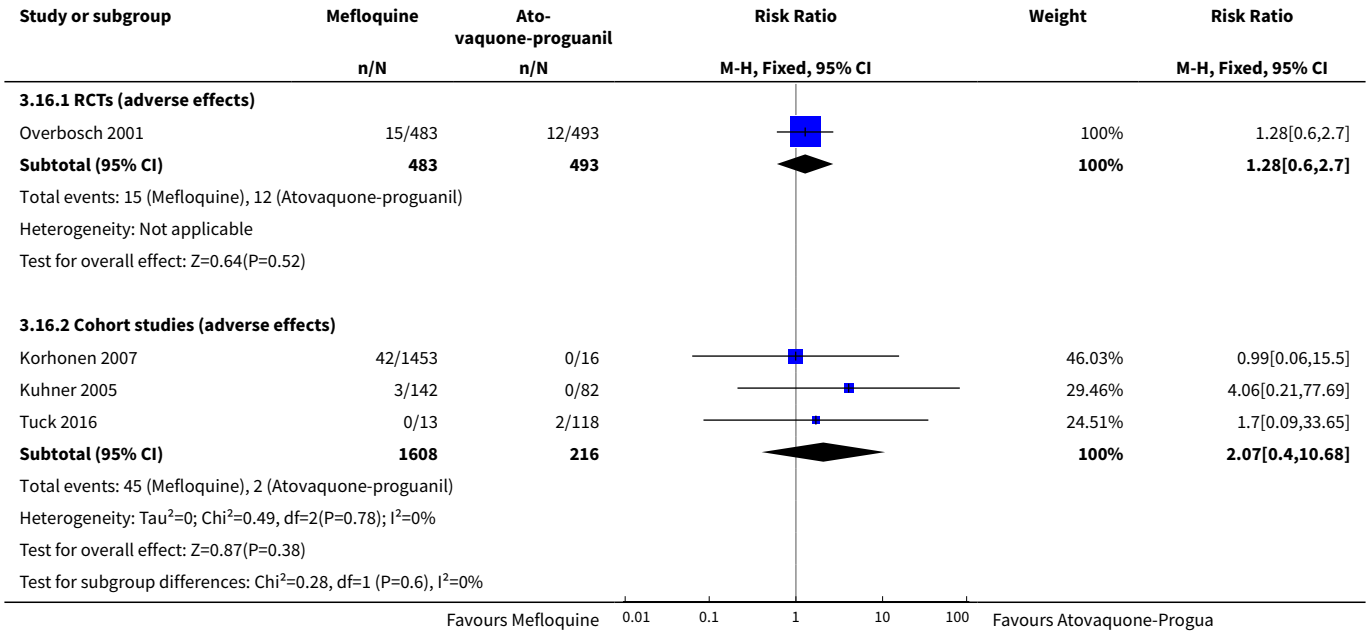
Analysis 3.14. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 14 Depressed mood (all studies).



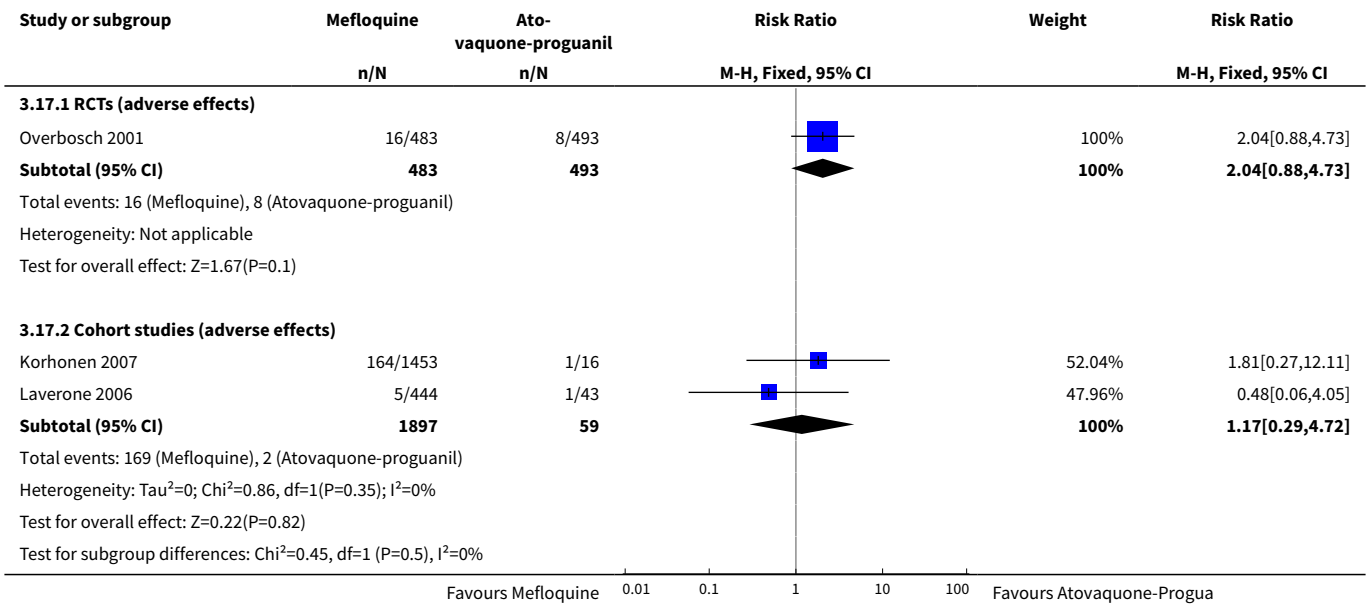
Analysis 3.15. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 15 Abnormal thoughts and perceptions (all studies).



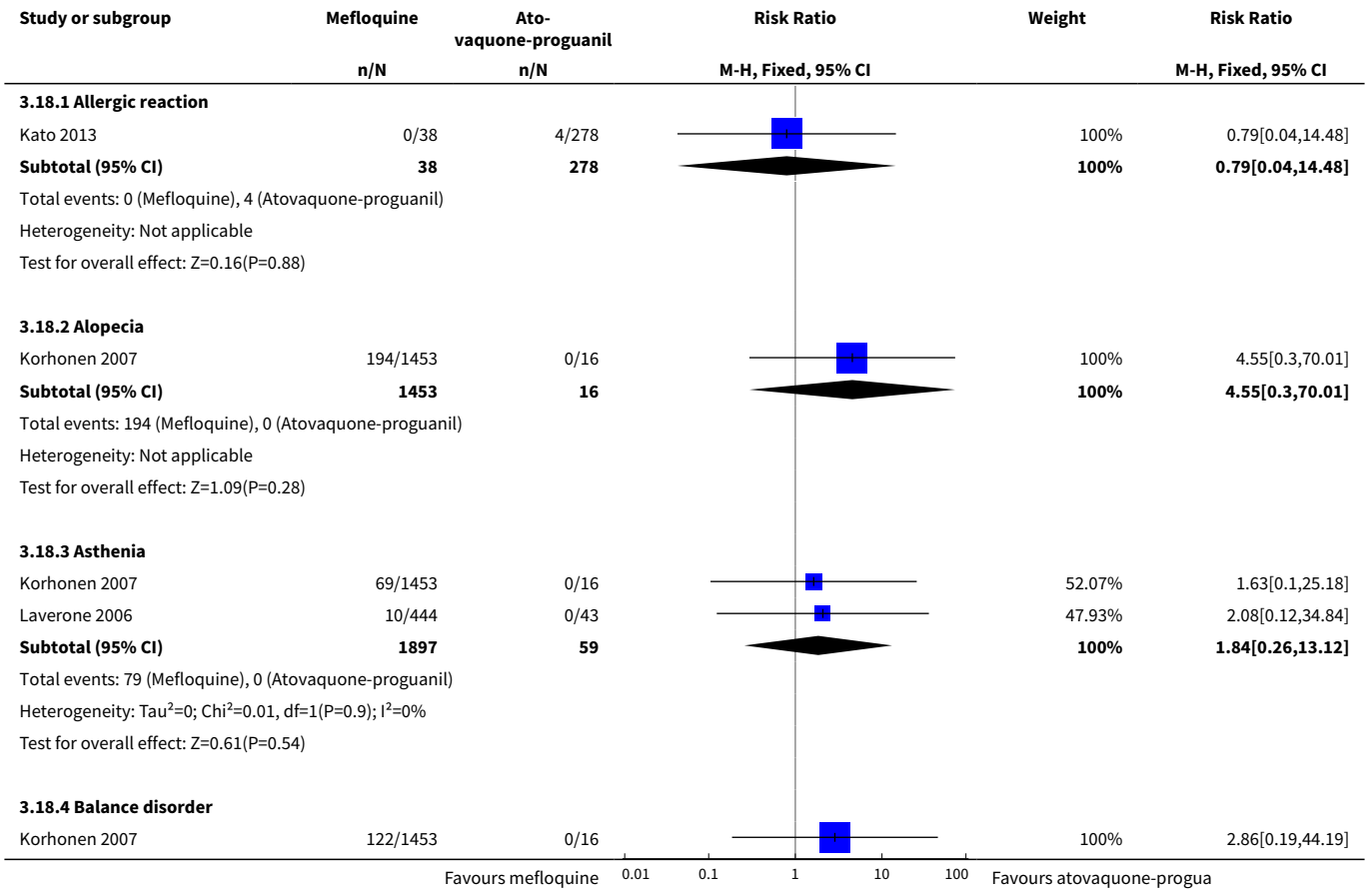
Analysis 3.16. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 16 Pruritis (all studies).

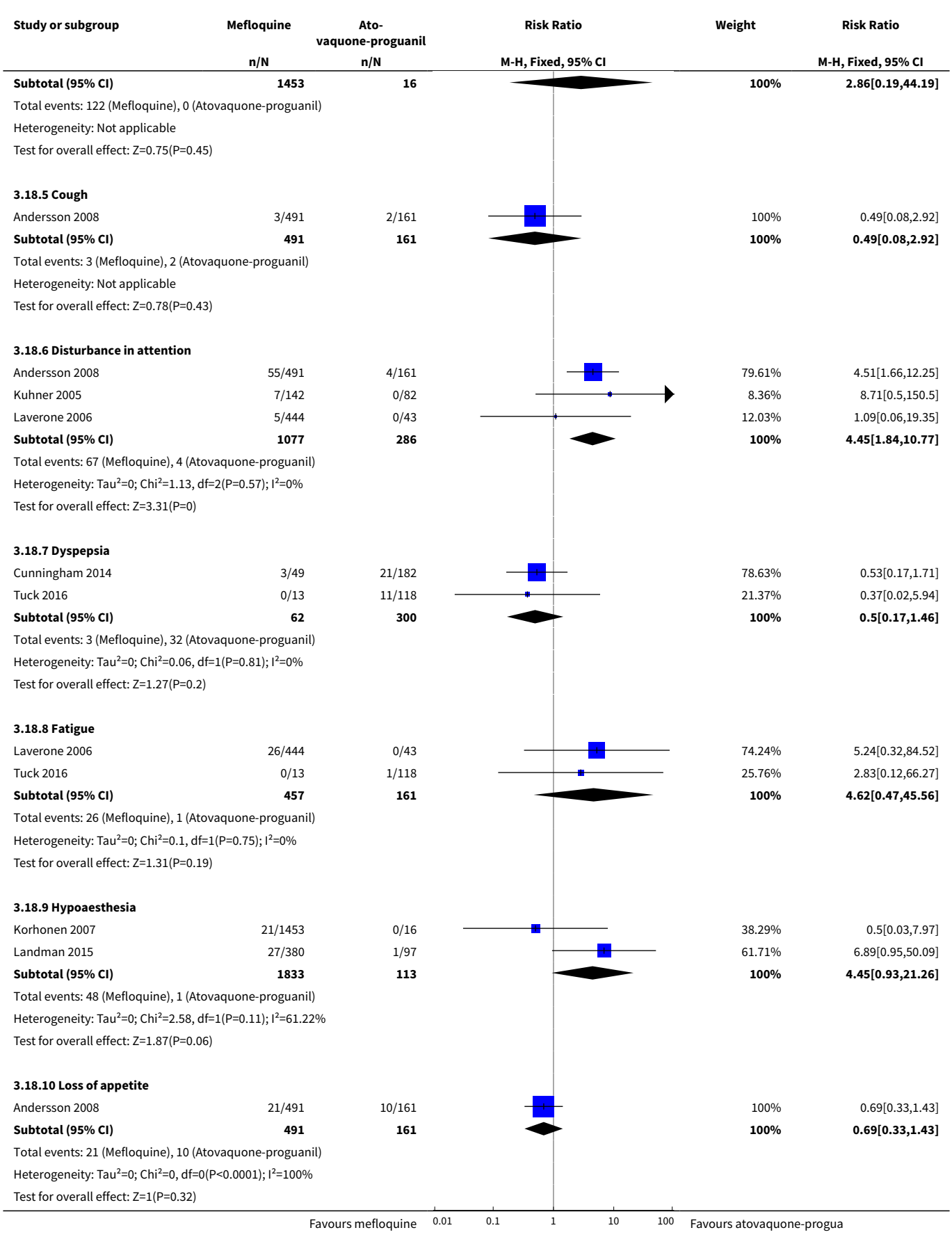


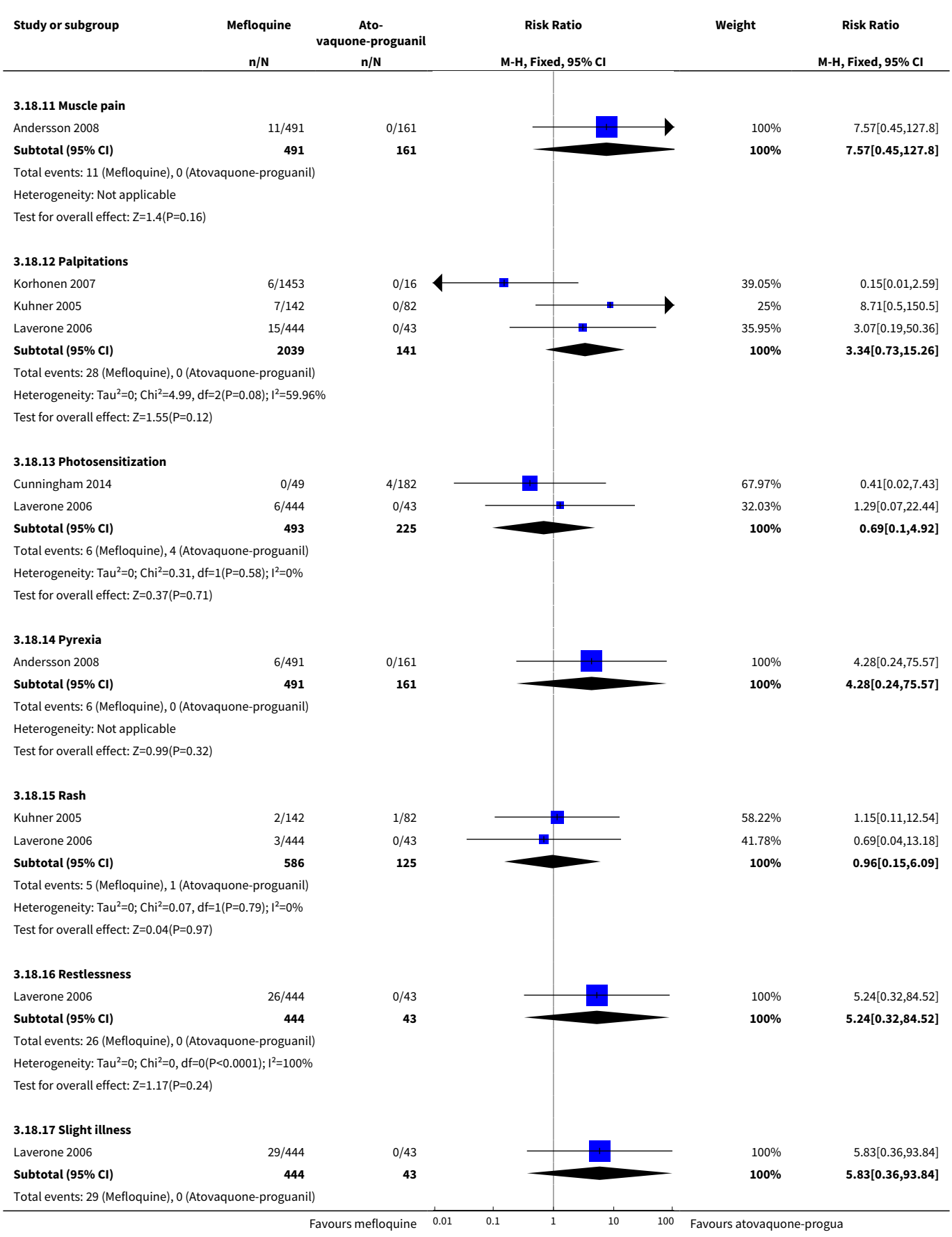
Analysis 3.17. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 17 Visual impairment (all studies).

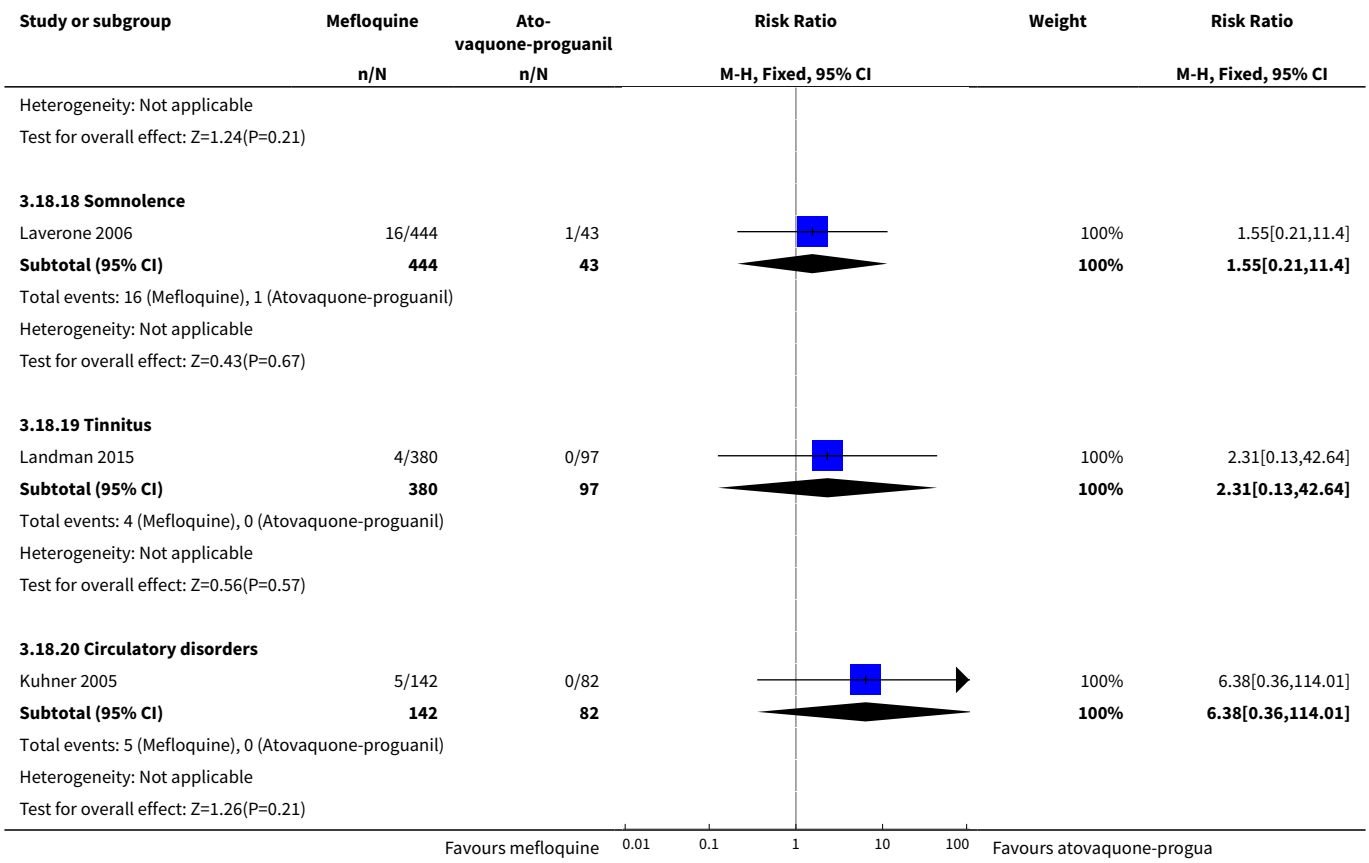


Analysis 3.18. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 18 Other adverse effects (cohort studies).

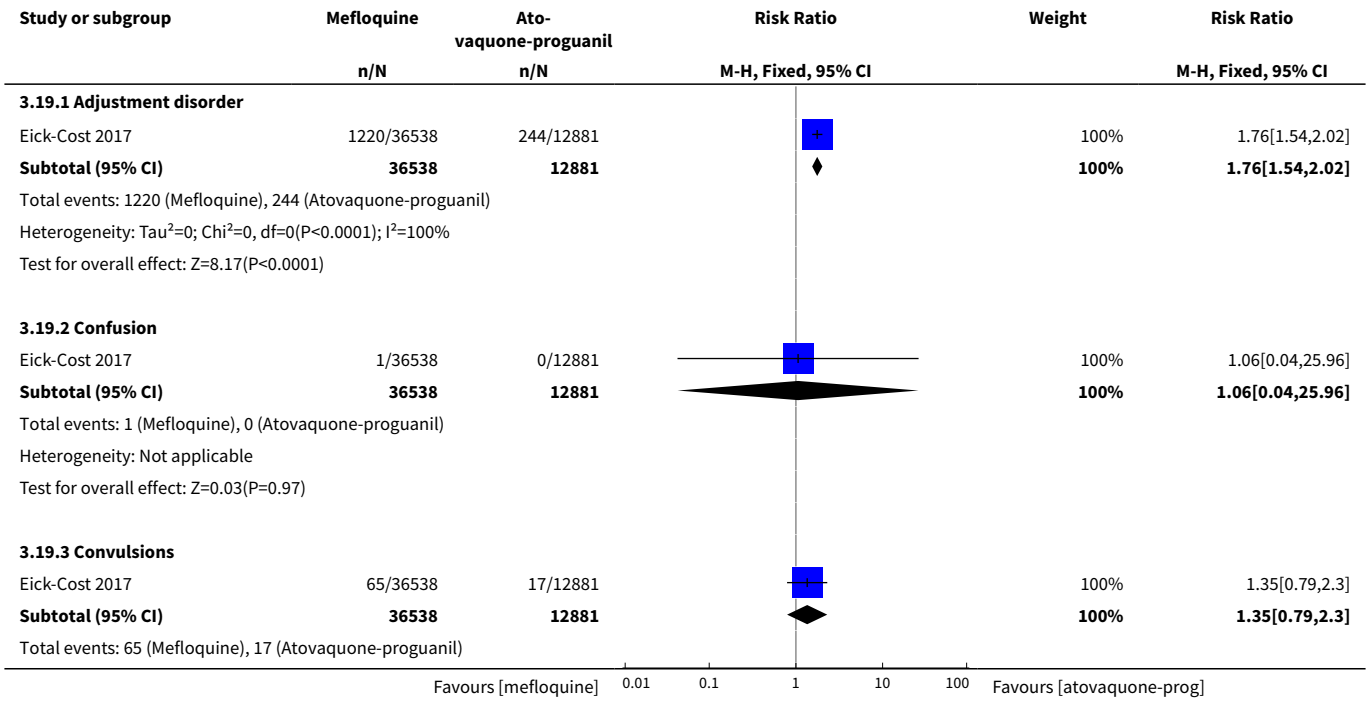


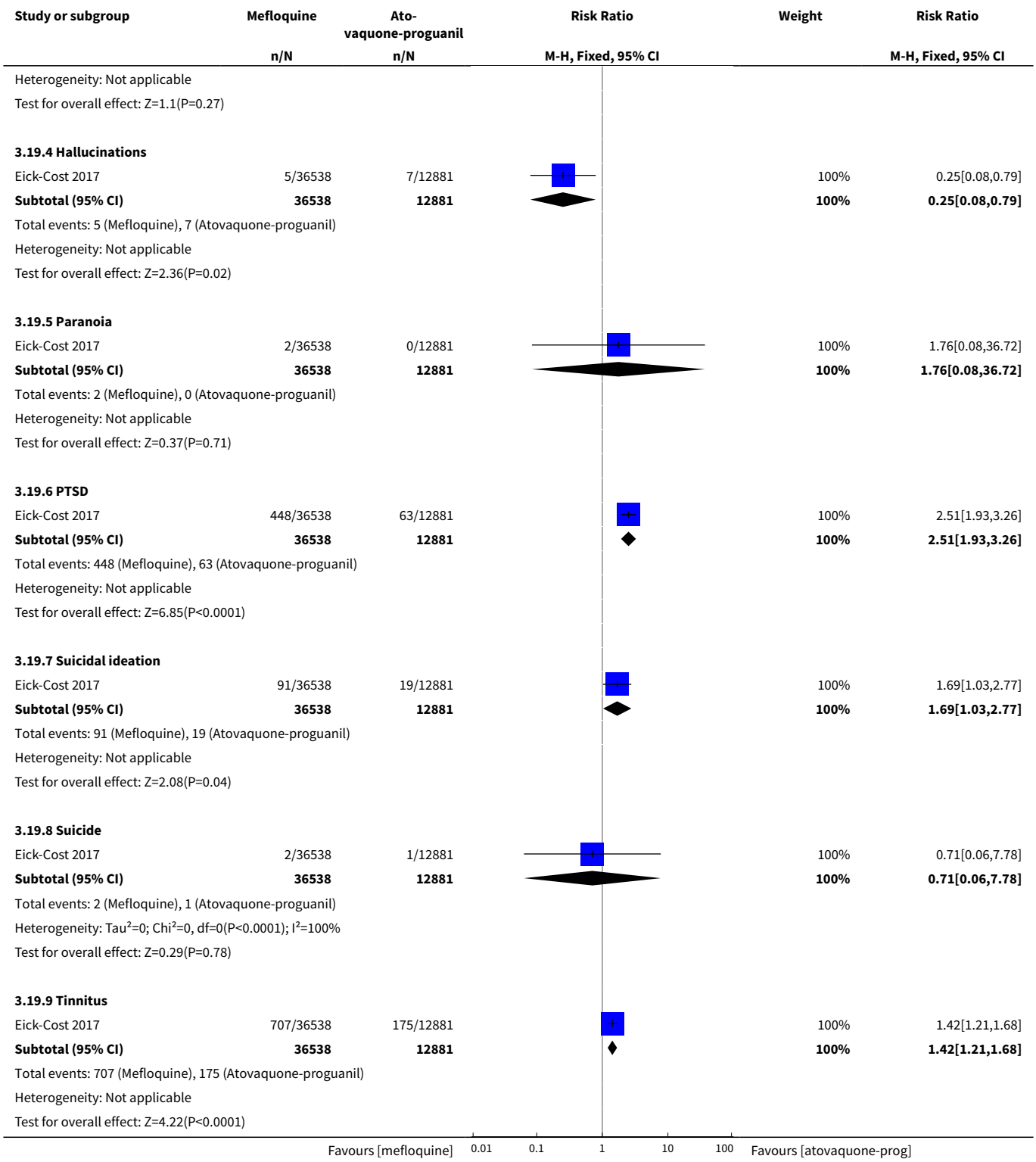




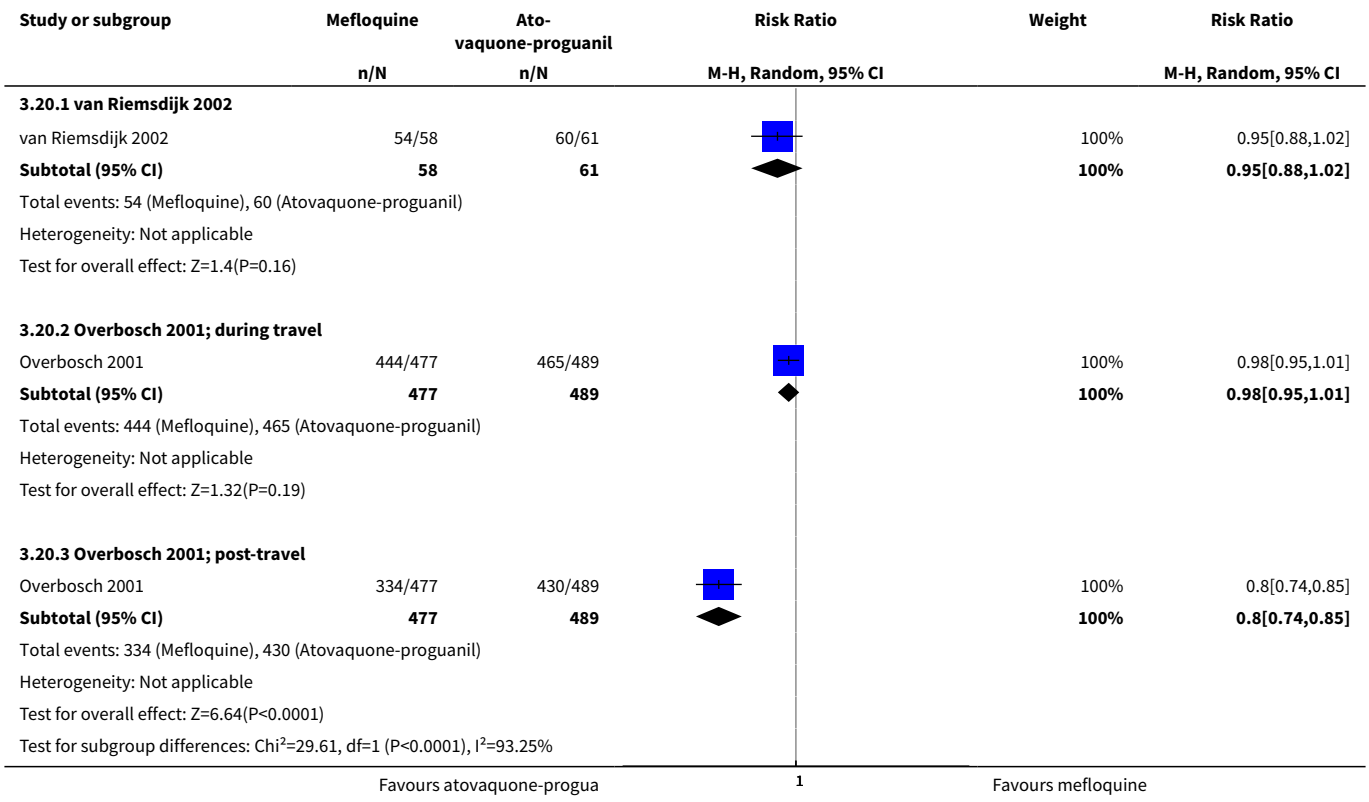


Analysis 3.19. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 19 Other adverse events (cohort studies).

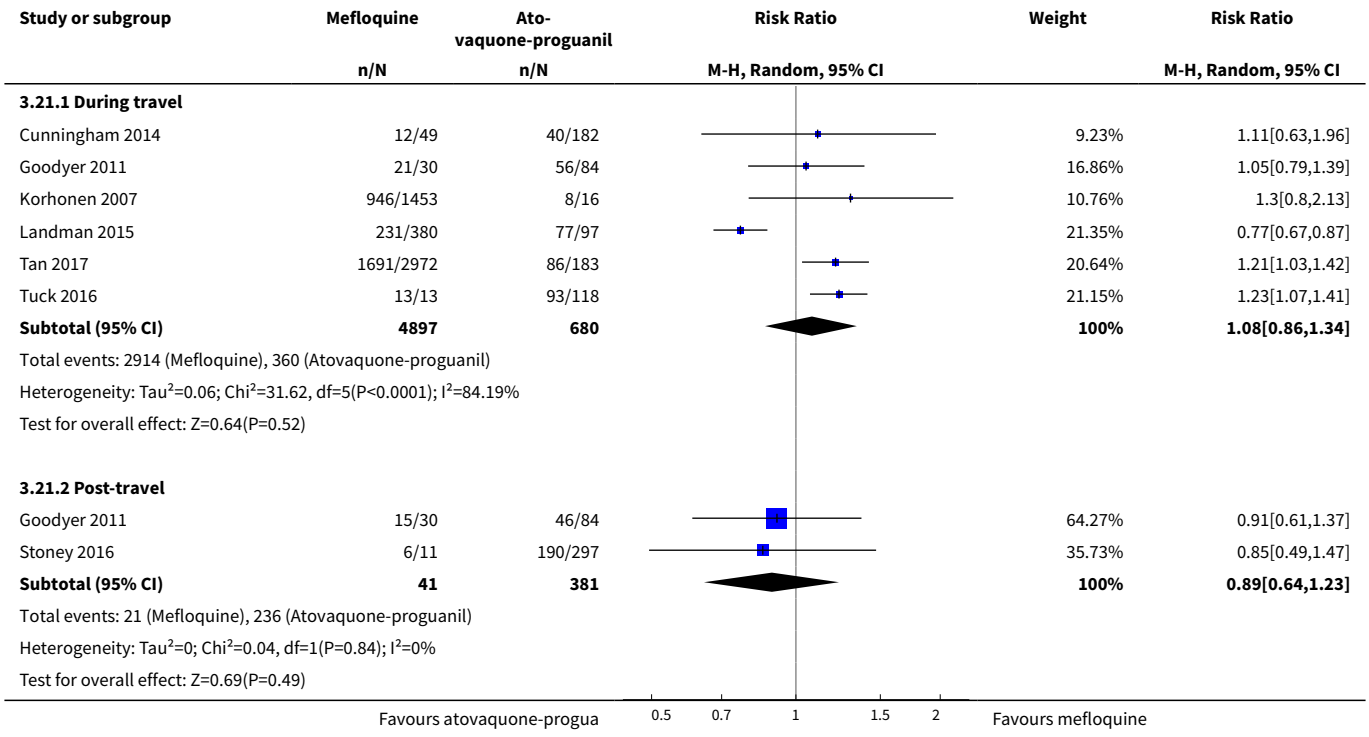


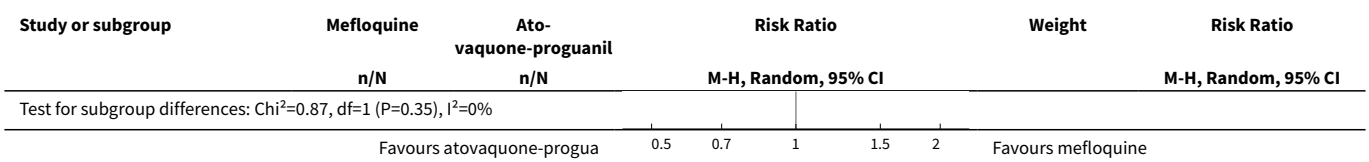


Analysis 3.20. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 20 Adherence (RCTs).



Analysis 3.21. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 21 Adherence (cohort studies).





Comparison 4. Mefloquine versus chloroquine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical cases of malaria (RCTs)	4	877	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.28, 0.52]
2 Serious adverse events or effects (all studies)	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 RCTs	4	1000	Risk Ratio (M-H, Fixed, 95% CI)	2.77 [0.32, 23.85]
2.2 Cohort studies	6	79257	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.62, 2.07]
3 Discontinuations due to adverse effects (all studies)	11		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 RCTs	3	815	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [0.61, 4.18]
3.2 Cohort studies in short-term travellers	6	55397	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.78, 1.26]
3.3 Cohort studies in longer term occupational travellers	2	6085	Risk Ratio (M-H, Fixed, 95% CI)	2.97 [2.41, 3.66]
4 Nausea (all studies)	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Cohort studies (adverse effects)	6	58984	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.89, 1.68]
4.2 RCTs (adverse events)	1	359	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.57, 1.79]
5 Vomiting (all studies)	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Cohort studies (adverse effects)	5	5577	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.78, 1.40]
5.2 RCTs (adverse events)	1	359	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.36, 3.49]
6 Abdominal pain (all studies)	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Cohort studies (adverse effects)	4	5440	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.80, 1.22]
6.2 RCTs (adverse events)	2	569	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.37, 1.36]
7 Diarrhoea (all studies)	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Cohort studies (adverse effects)	5	5577	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.74, 0.95]
7.2 RCTs (adverse events)	3	772	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.46, 1.50]
8 Headache (all studies)	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Cohort studies (adverse effects)	6	56998	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.53, 1.34]
8.2 RCTs (adverse events)	3	772	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.61, 1.31]
9 Dizziness (all studies)	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Cohort studies (adverse effects)	5	58847	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [1.34, 1.70]
9.2 RCTs (adverse events)	2	569	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.35, 1.46]
10 Abnormal dreams (all studies)	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Cohort studies (adverse effects)	4	2845	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [1.10, 1.33]
10.2 RCTs (adverse events)	1	359	Risk Ratio (M-H, Fixed, 95% CI)	2.70 [1.05, 6.95]
11 Insomnia (all studies)	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Cohort studies (adverse effects)	5	56952	Risk Ratio (M-H, Random, 95% CI)	1.81 [0.73, 4.51]
11.2 RCTs (adverse events)	1	359	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.76, 1.84]
12 Anxiety (all studies)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Cohort studies (adverse effects)	3	3408	Risk Ratio (M-H, Fixed, 95% CI)	6.30 [4.37, 9.09]
13 Depressed mood (all studies)	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 Cohort studies (adverse effects)	5	58855	Risk Ratio (M-H, Random, 95% CI)	3.14 [1.15, 8.57]
14 Abnormal thoughts and perceptions	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 Cohort studies (adverse effects)	4	4831	Risk Ratio (M-H, Fixed, 95% CI)	5.49 [2.65, 11.35]
15 Pruritis (all studies)	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
15.1 Cohort studies (adverse effects)	2	55544	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.92, 1.40]

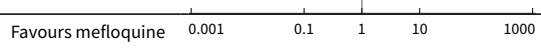
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.2 RCTs (adverse events)	2	413	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.03, 2.93]
16 Visual impairment (all studies)	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
16.1 Cohort studies (adverse effects)	5	58847	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.50, 2.44]
16.2 RCTs (adverse events)	1	210	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.63]
17 Vertigo (all studies)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 Cohort studies (adverse effects)	1	746	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.05, 23.43]
18 Cohort studies in travellers; prespecified adverse effects	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
18.1 Vertigo	1	746	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.05, 23.43]
18.2 Nausea	5	56847	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.94, 2.13]
18.3 Vomiting	4	3440	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.55, 1.42]
18.4 Abdominal pain	3	3303	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.74, 1.30]
18.5 Diarrhoea	4	3440	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.57, 2.64]
18.6 Headache	5	54861	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.48, 2.65]
18.7 Dizziness	4	56710	Risk Ratio (M-H, Random, 95% CI)	1.52 [1.10, 2.10]
18.8 Abnormal dreams	3	708	Risk Ratio (M-H, Random, 95% CI)	4.21 [0.57, 31.33]
18.9 Insomnia	4	54815	Risk Ratio (M-H, Random, 95% CI)	1.56 [0.40, 6.10]
18.10 Anxiety	2	1271	Risk Ratio (M-H, Random, 95% CI)	3.94 [0.53, 29.48]
18.11 Depressed mood	4	56710	Risk Ratio (M-H, Random, 95% CI)	2.49 [0.75, 8.31]
18.12 Abnormal thoughts or perceptions	3	2694	Risk Ratio (M-H, Random, 95% CI)	4.42 [1.58, 12.40]
18.13 Pruritis	1	53407	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.94, 1.48]
18.14 Visual impairment	4	56710	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.55, 0.79]
19 Other adverse effects (cohort studies)	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 Altered spatial perception	1	2032	Risk Ratio (M-H, Fixed, 95% CI)	3.16 [1.55, 6.45]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.2 Alopecia	1	2137	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [1.27, 2.25]
19.3 Asthenia	3	3408	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.97, 2.40]
19.4 Balance disorder	1	2137	Risk Ratio (M-H, Fixed, 95% CI)	3.59 [2.15, 6.00]
19.5 Confusion	1	525	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [0.11, 36.31]
19.6 Decreased appetite	1	2032	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.87, 1.57]
19.7 Fatigue	1	525	Risk Ratio (M-H, Fixed, 95% CI)	2.37 [0.57, 9.80]
19.8 Hypoaesthesia	1	2137	Risk Ratio (M-H, Fixed, 95% CI)	20.26 [1.23, 333.93]
19.9 Irritability	1	746	Risk Ratio (M-H, Fixed, 95% CI)	4.75 [0.28, 80.59]
19.10 Mouth ulcers	2	55439	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [1.01, 1.87]
19.11 Paraesthesia	2	2778	Risk Ratio (M-H, Fixed, 95% CI)	2.22 [1.27, 3.89]
19.12 Palpitations	3	3408	Risk Ratio (M-H, Fixed, 95% CI)	4.71 [0.91, 24.26]
19.13 Photosensitization	2	2662	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.52, 1.53]
19.14 Restlessness	1	525	Risk Ratio (M-H, Fixed, 95% CI)	4.74 [0.65, 34.46]
19.15 Slight illness	1	525	Risk Ratio (M-H, Fixed, 95% CI)	2.65 [0.64, 10.87]
19.16 Somnolence	1	525	Risk Ratio (M-H, Fixed, 95% CI)	6.08 [0.37, 100.36]
19.17 Yeast infection	1	2137	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.53, 2.49]
20 Other adverse events (RCTs)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20.1 Abdominal distension	1	359	Risk Ratio (M-H, Fixed, 95% CI)	3.13 [0.64, 15.27]
20.2 Anger	1	359	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.07, 1.55]
20.3 Disturbance in attention	1	359	Risk Ratio (M-H, Fixed, 95% CI)	3.16 [0.61, 16.47]
20.4 Irritability	1	359	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.45, 2.64]
20.5 Loss of appetite	1	359	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.35, 3.25]
20.6 Malaise	1	203	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.85]
20.7 Mood altered	1	359	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.29, 4.34]
21 Pregnancy related outcomes (RCTs)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
21.1 Spontaneous abortions	1	2334	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.36, 1.79]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21.2 Still births	1	2334	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.67, 1.52]
21.3 Congenital malformations	1	2334	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
22 Adherence (cohort studies)	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
22.1 Short-term travellers	3	852	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.90, 1.13]
22.2 Short-term travellers: after return	1	46	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.54, 1.87]
22.3 Longer-term occupational travellers	2	5777	Risk Ratio (M-H, Random, 95% CI)	2.02 [1.80, 2.26]

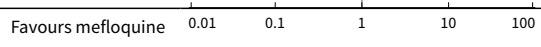
Analysis 4.1. Comparison 4 Mefloquine versus chloroquine, Outcome 1 Clinical cases of malaria (RCTs).

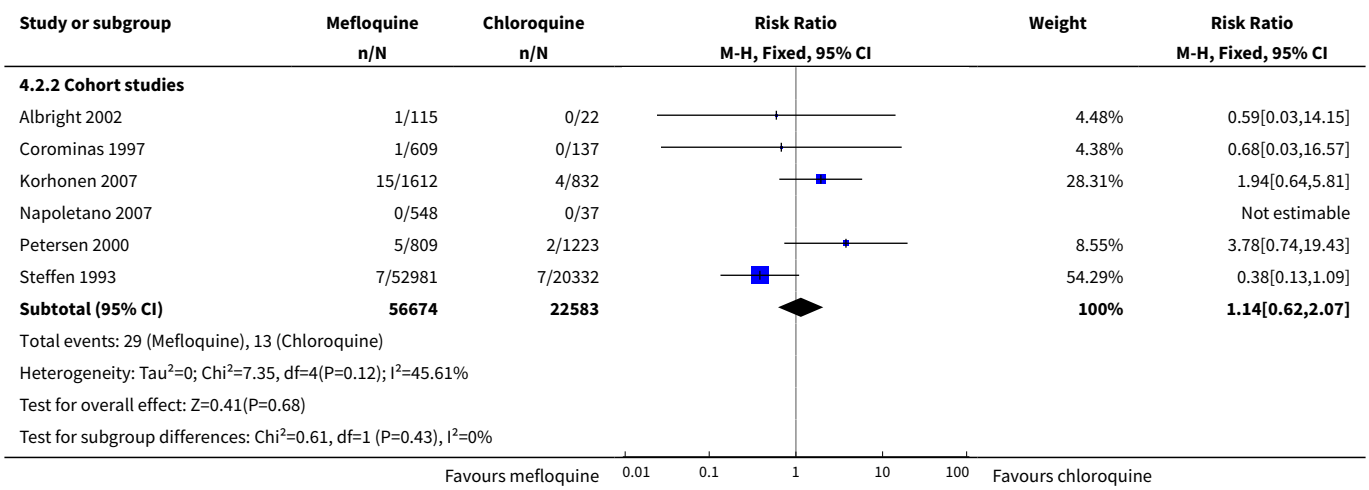
Study or subgroup	Mefloquine n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Boudreau 1991	38/145	53/77		93.16%	0.38[0.28,0.52]
Bunnag 1992	2/123	5/119		6.84%	0.39[0.08,1.96]
Salako 1992	0/107	0/103			Not estimable
Sossouhounto 1995	0/103	0/100			Not estimable
Total (95% CI)	**478**	**399**		**100%**	**0.38[0.28,0.52]**
Total events: 40 (Mefloquine), 58 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.98); I^2=0%					
Test for overall effect: Z=6.08(P<0.0001)					



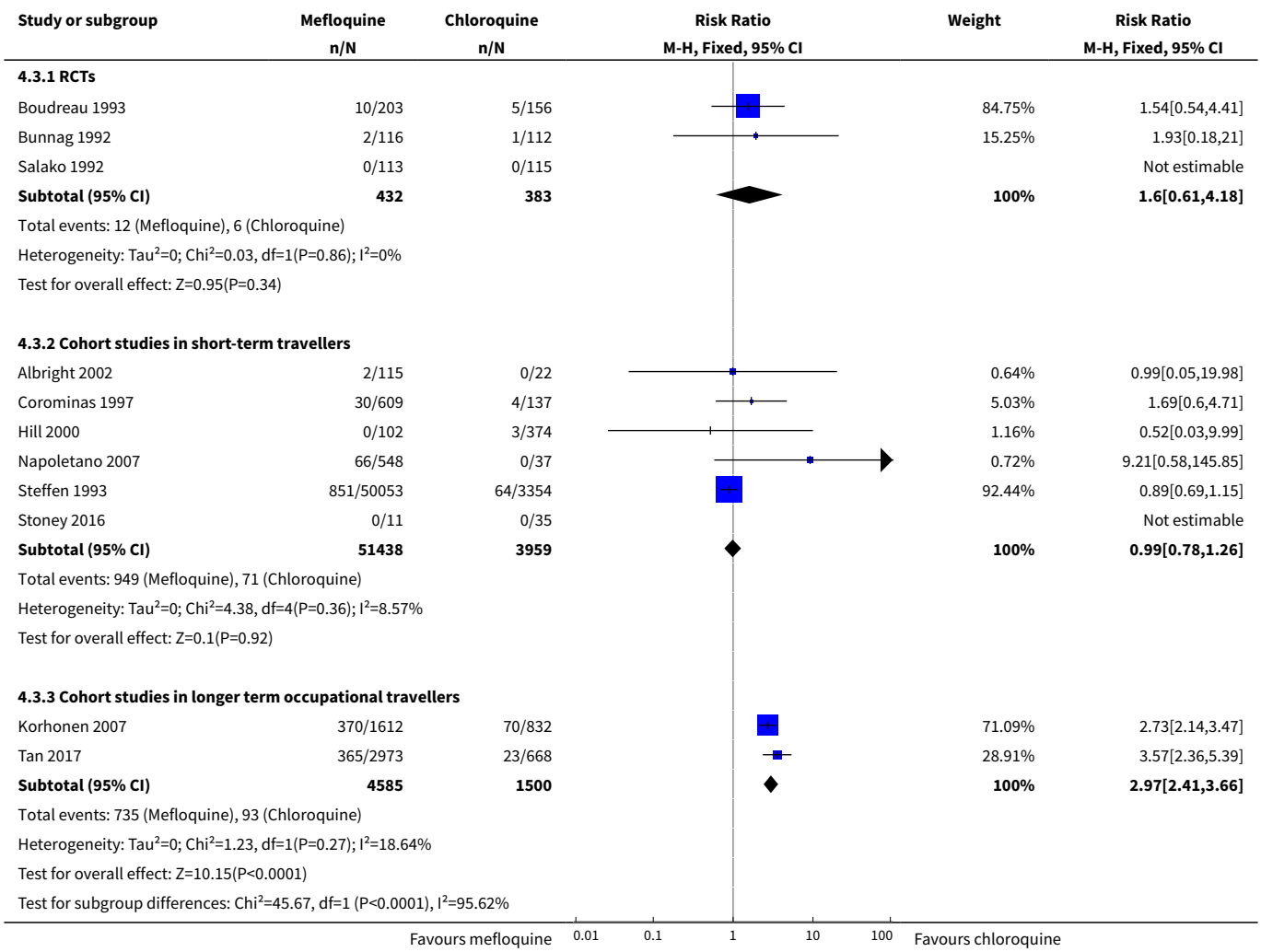
Analysis 4.2. Comparison 4 Mefloquine versus chloroquine, Outcome 2 Serious adverse events or effects (all studies).

Study or subgroup	Mefloquine n/N	Chloroquine n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.2.1 RCTs					
Boudreau 1993	1/46	0/78		35.88%	5.04[0.21,121.28]
Boudreau 1993	1/157	0/78		64.12%	1.5[0.06,36.4]
Bunnag 1992	0/116	0/112			Not estimable
Salako 1992	0/107	0/103			Not estimable
Sossouhounto 1995	0/103	0/100			Not estimable
Subtotal (95% CI)	**529**	**471**		**100%**	**2.77[0.32,23.85]**
Total events: 2 (Mefloquine), 0 (Chloroquine)					
Heterogeneity: Tau^2=0; Chi^2=0.28, df=1(P=0.6); I^2=0%					
Test for overall effect: Z=0.93(P=0.35)					





Analysis 4.3. Comparison 4 Mefloquine versus chloroquine, Outcome 3 Discontinuations due to adverse effects (all studies).



Analysis 4.4. Comparison 4 Mefloquine versus chloroquine, Outcome 4 Nausea (all studies).

Study or subgroup	Mefloquine n/N	Chloroquine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.4.1 Cohort studies (adverse effects)					
Albright 2002	1/115	2/22		1.7%	0.1[0.01,1.01]
Corominas 1997	15/609	0/137		1.21%	7.01[0.42,116.5]
Korhonen 2007	165/1453	89/684		28.56%	0.87[0.69,1.11]
Laverone 2006	65/444	3/81		6.32%	3.95[1.27,12.27]
Petersen 2000	130/809	126/1223		29.06%	1.56[1.24,1.96]
Steffen 1993	6157/50053	362/3354		33.15%	1.14[1.03,1.26]
Subtotal (95% CI)	**53483**	**5501**		**100%**	**1.23[0.89,1.68]**
Total events: 6533 (Mefloquine), 582 (Chloroquine)					
Heterogeneity: Tau^2=0.08; Chi^2=22.34, df=5(P=0); I^2=77.62%					
Test for overall effect: Z=1.27(P=0.2)					
4.4.2 RCTs (adverse events)					
Boudreau 1993	22/157	10/78		67.77%	1.09[0.54,2.19]
Boudreau 1993	5/46	10/78		32.23%	0.85[0.31,2.33]
Subtotal (95% CI)	**203**	**156**		**100%**	**1.01[0.57,1.79]**
Total events: 27 (Mefloquine), 20 (Chloroquine)					
Heterogeneity: Tau^2=0; Chi^2=0.16, df=1(P=0.68); I^2=0%					
Test for overall effect: Z=0.02(P=0.98)					

Analysis 4.5. Comparison 4 Mefloquine versus chloroquine, Outcome 5 Vomiting (all studies).

Study or subgroup	Mefloquine n/N	Chloroquine n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.5.1 Cohort studies (adverse effects)					
Albright 2002	3/115	2/22		4%	0.29[0.05,1.62]
Corominas 1997	8/609	0/137		0.97%	3.85[0.22,66.23]
Korhonen 2007	28/1453	6/684		9.71%	2.2[0.91,5.28]
Laverone 2006	6/444	0/81		1%	2.4[0.14,42.11]
Petersen 2000	53/809	89/1223		84.32%	0.9[0.65,1.25]
Subtotal (95% CI)	**3430**	**2147**		**100%**	**1.05[0.78,1.4]**
Total events: 98 (Mefloquine), 97 (Chloroquine)					
Heterogeneity: Tau^2=0; Chi^2=6.82, df=4(P=0.15); I^2=41.36%					
Test for overall effect: Z=0.29(P=0.77)					
4.5.2 RCTs (adverse events)					
Boudreau 1993	9/157	3/78		68.25%	1.49[0.42,5.35]
Boudreau 1993	0/46	2/78		31.75%	0.34[0.02,6.85]
Subtotal (95% CI)	**203**	**156**		**100%**	**1.12[0.36,3.49]**
Total events: 9 (Mefloquine), 5 (Chloroquine)					
Heterogeneity: Tau^2=0; Chi^2=0.8, df=1(P=0.37); I^2=0%					
Test for overall effect: Z=0.2(P=0.84)					

Analysis 4.6. Comparison 4 Mefloquine versus chloroquine, Outcome 6 Abdominal pain (all studies).

Study or subgroup	Mefloquine n/N	Chloroquine n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.6.1 Cohort studies (adverse effects)					
Corominas 1997	30/609	4/137		3.91%	1.69[0.6,4.71]
Korhonen 2007	54/1453	25/684		20.34%	1.02[0.64,1.62]
Laverone 2006	9/444	0/81		0.51%	3.5[0.21,59.57]
Petersen 2000	97/809	158/1223		75.25%	0.93[0.73,1.18]
Subtotal (95% CI)	**3315**	**2125**		**100%**	**0.99[0.8,1.22]**
Total events: 190 (Mefloquine), 187 (Chloroquine)					
Heterogeneity: Tau^2=0; Chi^2=2.09, df=3(P=0.55); I^2=0%					
Test for overall effect: Z=0.11(P=0.91)					
4.6.2 RCTs (adverse events)					
Boudreau 1993	5/46	8/78		32.14%	1.06[0.37,3.05]
Boudreau 1993	8/157	9/78		65.11%	0.44[0.18,1.1]
Salako 1992	1/107	0/103		2.76%	2.89[0.12,70.11]
Subtotal (95% CI)	**310**	**259**		**100%**	**0.71[0.37,1.36]**
Total events: 14 (Mefloquine), 17 (Chloroquine)					
Heterogeneity: Tau^2=0; Chi^2=2.33, df=2(P=0.31); I^2=14.31%					
Test for overall effect: Z=1.04(P=0.3)					

Analysis 4.7. Comparison 4 Mefloquine versus chloroquine, Outcome 7 Diarrhoea (all studies).

Study or subgroup	Mefloquine n/N	Chloroquine n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.7.1 Cohort studies (adverse effects)					
Albright 2002	3/115	0/22		0.2%	1.39[0.07,25.97]
Corominas 1997	21/609	1/137		0.4%	4.72[0.64,34.82]
Korhonen 2007	45/1453	24/684		7.95%	0.88[0.54,1.44]
Laverone 2006	21/444	2/81		0.82%	1.92[0.46,8.01]
Petersen 2000	249/809	467/1223		90.62%	0.81[0.71,0.91]
Subtotal (95% CI)	**3430**	**2147**		**100%**	**0.84[0.74,0.95]**
Total events: 339 (Mefloquine), 494 (Chloroquine)					
Heterogeneity: Tau^2=0; Chi^2=4.69, df=4(P=0.32); I^2=14.68%					
Test for overall effect: Z=2.85(P=0)					
4.7.2 RCTs (adverse events)					
Boudreau 1993	11/157	10/78		63.46%	0.55[0.24,1.23]
Boudreau 1993	5/46	9/78		31.71%	0.94[0.34,2.64]
Salako 1992	1/107	0/103		2.42%	2.89[0.12,70.11]
Sossouhounto 1995	2/103	0/100		2.41%	4.86[0.24,99.9]
Subtotal (95% CI)	**413**	**359**		**100%**	**0.83[0.46,1.5]**
Total events: 19 (Mefloquine), 19 (Chloroquine)					
Heterogeneity: Tau^2=0; Chi^2=2.98, df=3(P=0.4); I^2=0%					
Test for overall effect: Z=0.61(P=0.54)					

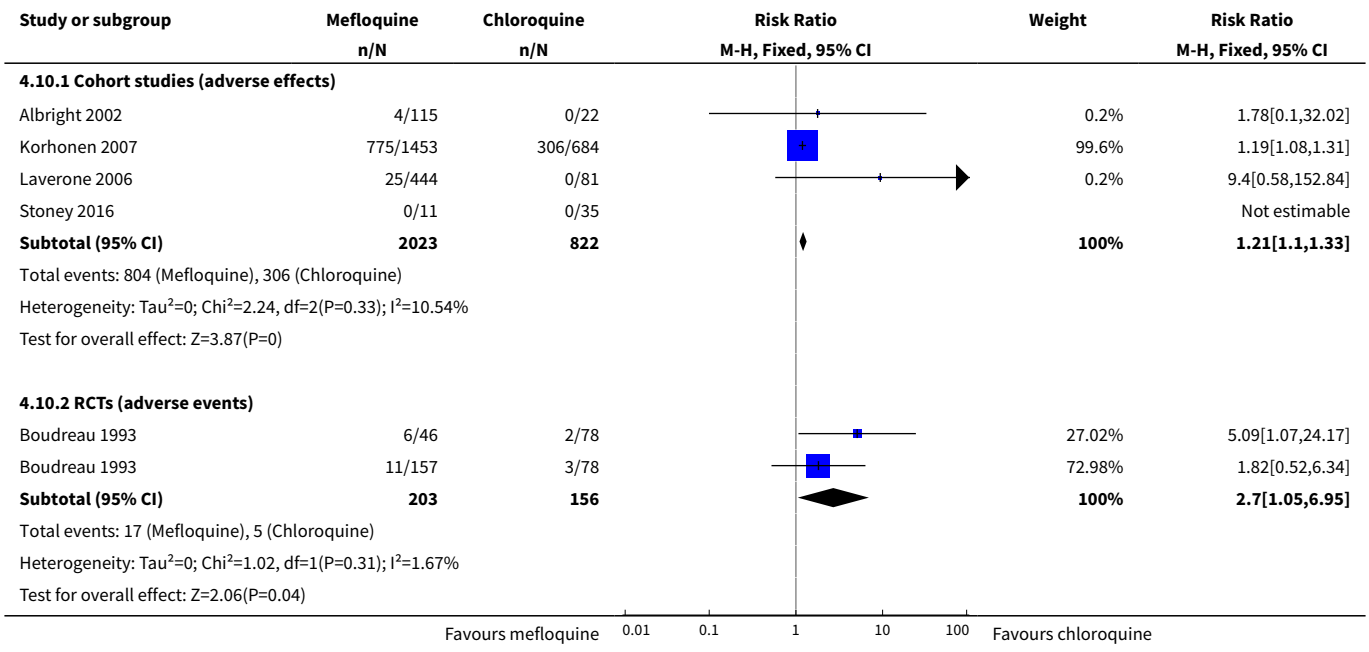
Analysis 4.8. Comparison 4 Mefloquine versus chloroquine, Outcome 8 Headache (all studies).

Study or subgroup	Mefloquine n/N	Chloroquine n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.8.1 Cohort studies (adverse effects)					
Albright 2002	3/115	2/22		6.2%	0.29[0.05,1.62]
Corominas 1997	17/609	1/137		4.77%	3.82[0.51,28.49]
Korhonen 2007	100/1453	78/684		39.58%	0.6[0.46,0.8]
Laverone 2006	18/444	1/81		4.8%	3.28[0.44,24.26]
Steffen 1993	3103/50053	215/3354		44.65%	0.97[0.85,1.11]
Stoney 2016	0/11	0/35			Not estimable
Subtotal (95% CI)	**52685**	**4313**		**100%**	**0.84[0.53,1.34]**
Total events: 3241 (Mefloquine), 297 (Chloroquine)					
Heterogeneity: Tau^2=0.12; Chi^2=14.15, df=4(P=0.01); I^2=71.73%					
Test for overall effect: Z=0.72(P=0.47)					
4.8.2 RCTs (adverse events)					
Boudreau 1993	35/157	20/78		63.8%	0.87[0.54,1.4]
Boudreau 1993	11/46	19/78		34.77%	0.98[0.51,1.87]
Salako 1992	0/107	1/103		1.43%	0.32[0.01,7.79]
Sossouhounto 1995	0/103	0/100			Not estimable
Subtotal (95% CI)	**413**	**359**		**100%**	**0.89[0.61,1.31]**
Total events: 46 (Mefloquine), 40 (Chloroquine)					
Heterogeneity: Tau^2=0; Chi^2=0.49, df=2(P=0.78); I^2=0%					
Test for overall effect: Z=0.58(P=0.57)					

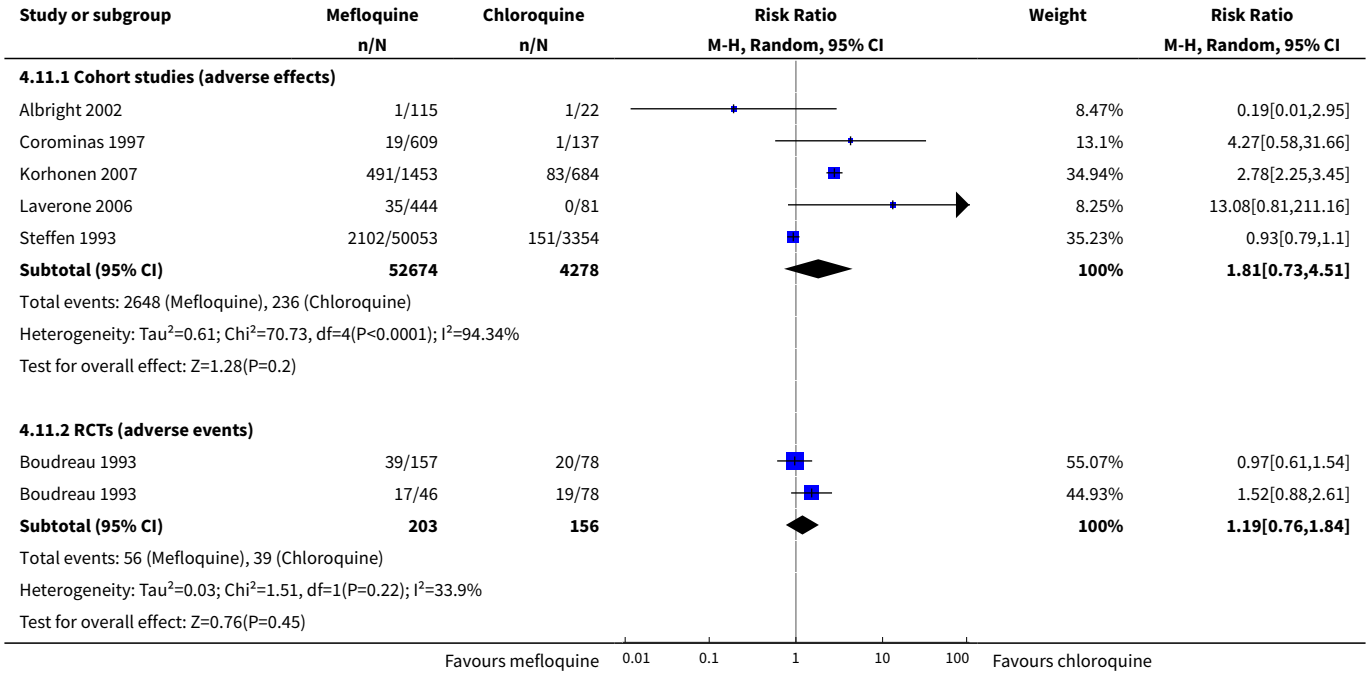
Analysis 4.9. Comparison 4 Mefloquine versus chloroquine, Outcome 9 Dizziness (all studies).

Study or subgroup	Mefloquine n/N	Chloroquine n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.9.1 Cohort studies (adverse effects)					
Corominas 1997	33/609	9/137		3.07%	0.82[0.4,1.68]
Korhonen 2007	189/1453	55/684		15.62%	1.62[1.22,2.15]
Laverone 2006	25/444	1/81		0.35%	4.56[0.63,33.19]
Petersen 2000	88/809	68/1223		11.3%	1.96[1.44,2.65]
Steffen 1993	3804/50053	178/3354		69.66%	1.43[1.24,1.66]
Subtotal (95% CI)	**53368**	**5479**		**100%**	**1.51[1.34,1.7]**
Total events: 4139 (Mefloquine), 311 (Chloroquine)					
Heterogeneity: Tau^2=0; Chi^2=7.47, df=4(P=0.11); I^2=46.45%					
Test for overall effect: Z=6.88(P<0.0001)					
4.9.2 RCTs (adverse events)					
Boudreau 1993	9/157	7/78		58.18%	0.64[0.25,1.65]
Boudreau 1993	4/46	7/78		32.31%	0.97[0.3,3.13]
Salako 1992	0/107	1/103		9.51%	0.32[0.01,7.79]
Subtotal (95% CI)	**310**	**259**		**100%**	**0.72[0.35,1.46]**
Total events: 13 (Mefloquine), 15 (Chloroquine)					
Heterogeneity: Tau^2=0; Chi^2=0.55, df=2(P=0.76); I^2=0%					
Test for overall effect: Z=0.92(P=0.36)					

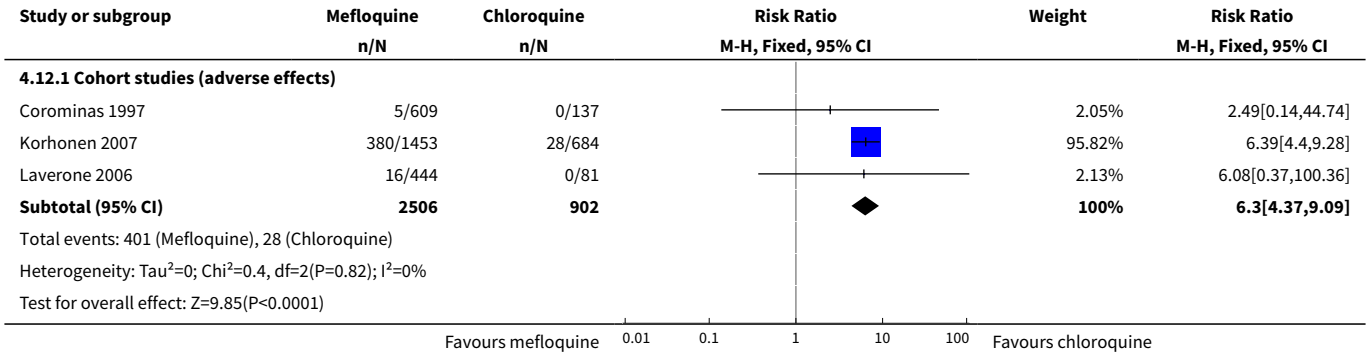
Analysis 4.10. Comparison 4 Mefloquine versus chloroquine, Outcome 10 Abnormal dreams (all studies).



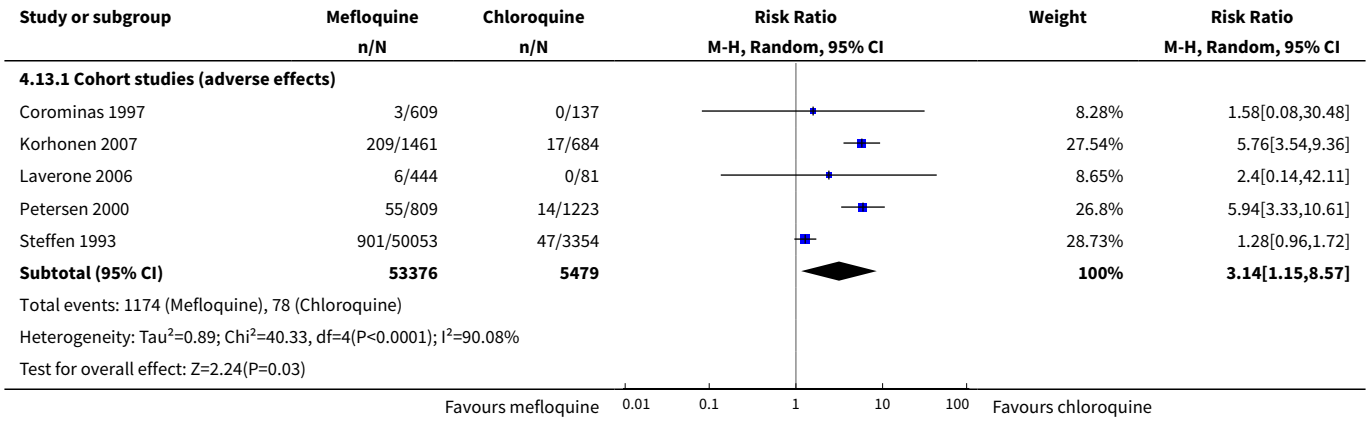
Analysis 4.11. Comparison 4 Mefloquine versus chloroquine, Outcome 11 Insomnia (all studies).



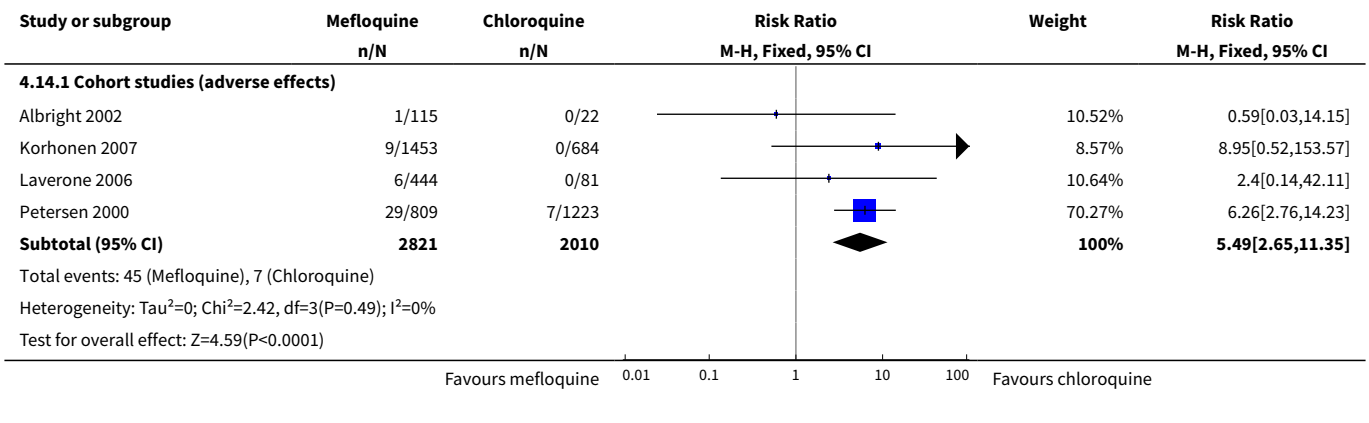
Analysis 4.12. Comparison 4 Mefloquine versus chloroquine, Outcome 12 Anxiety (all studies).



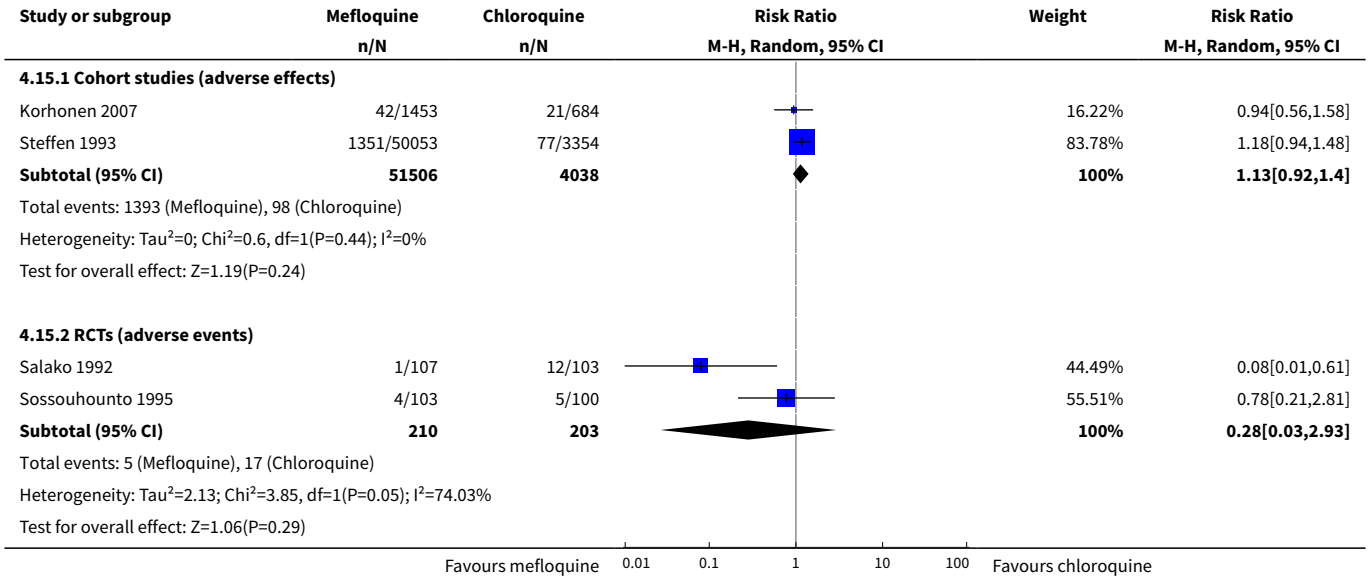
Analysis 4.13. Comparison 4 Mefloquine versus chloroquine, Outcome 13 Depressed mood (all studies).



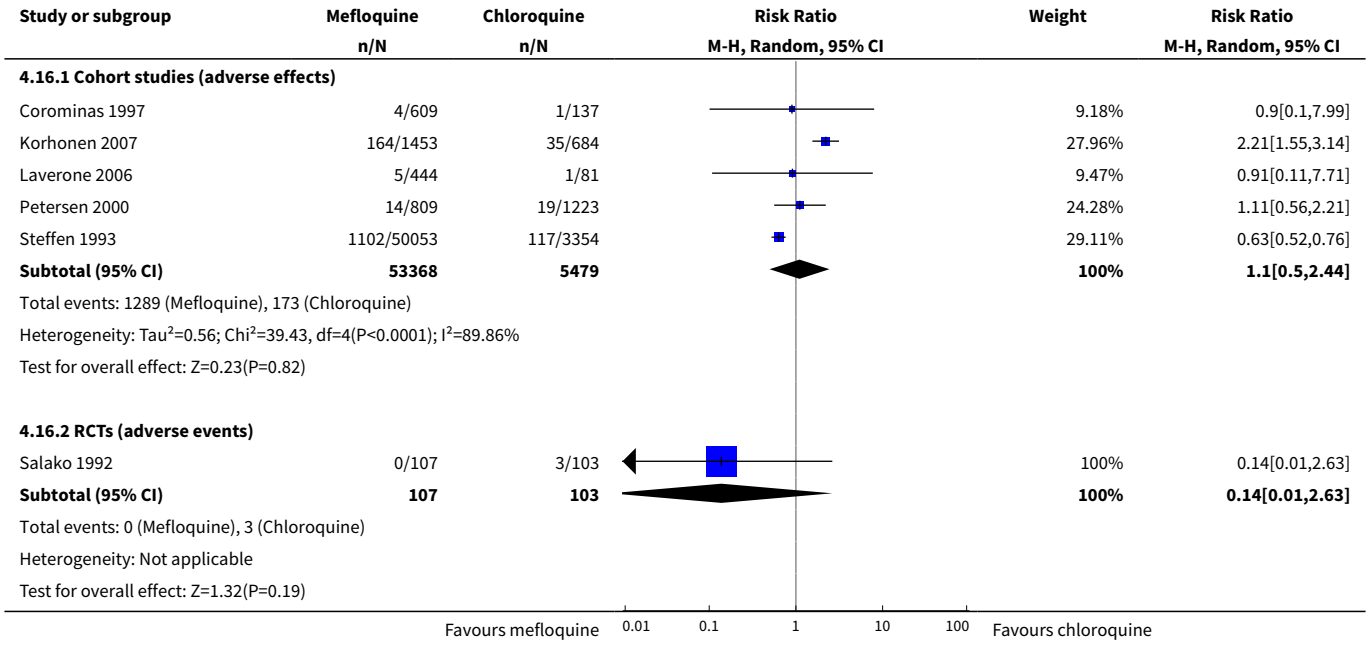
Analysis 4.14. Comparison 4 Mefloquine versus chloroquine, Outcome 14 Abnormal thoughts and perceptions.



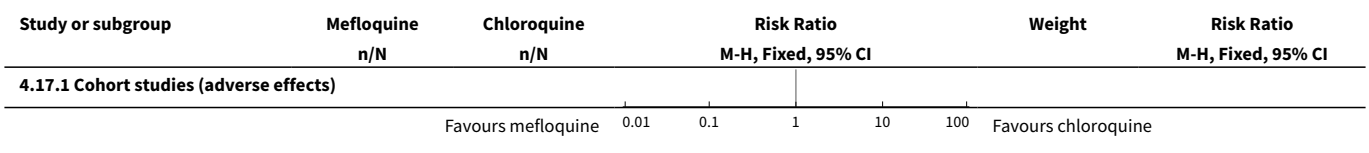
Analysis 4.15. Comparison 4 Mefloquine versus chloroquine, Outcome 15 Pruritis (all studies).

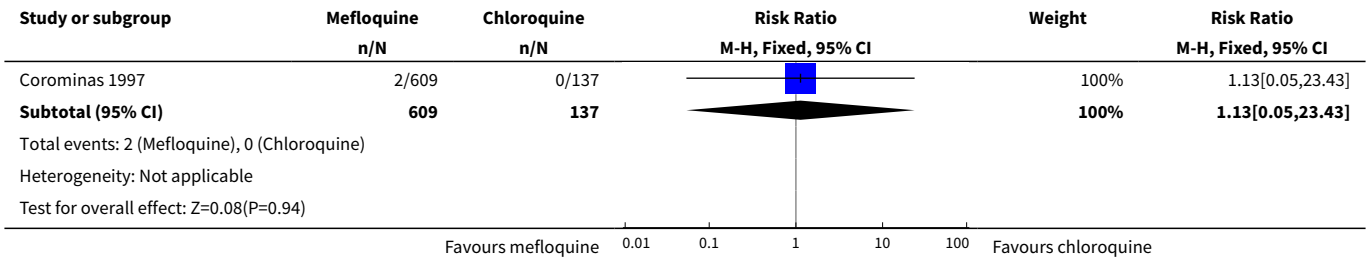


Analysis 4.16. Comparison 4 Mefloquine versus chloroquine, Outcome 16 Visual impairment (all studies).

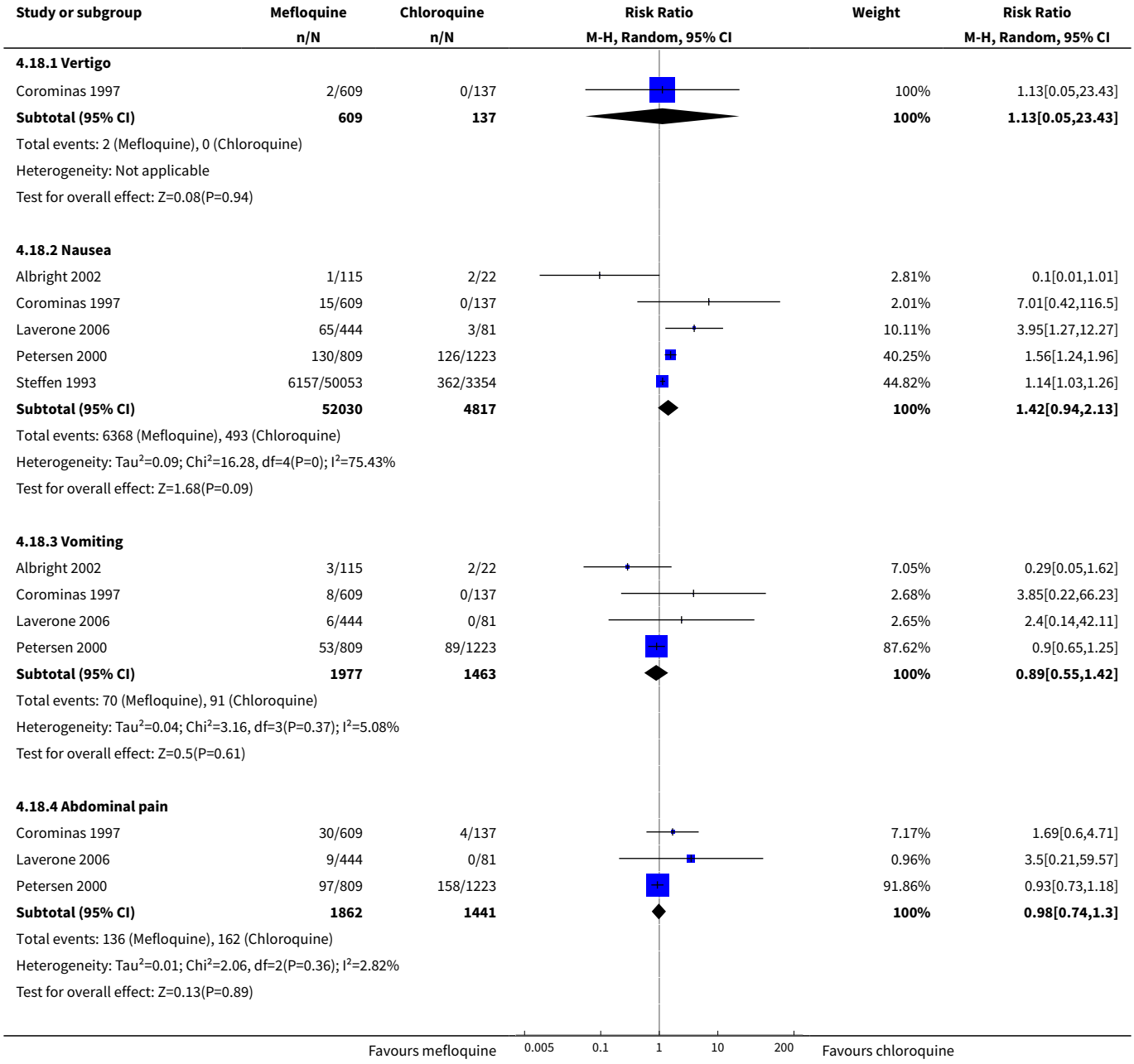


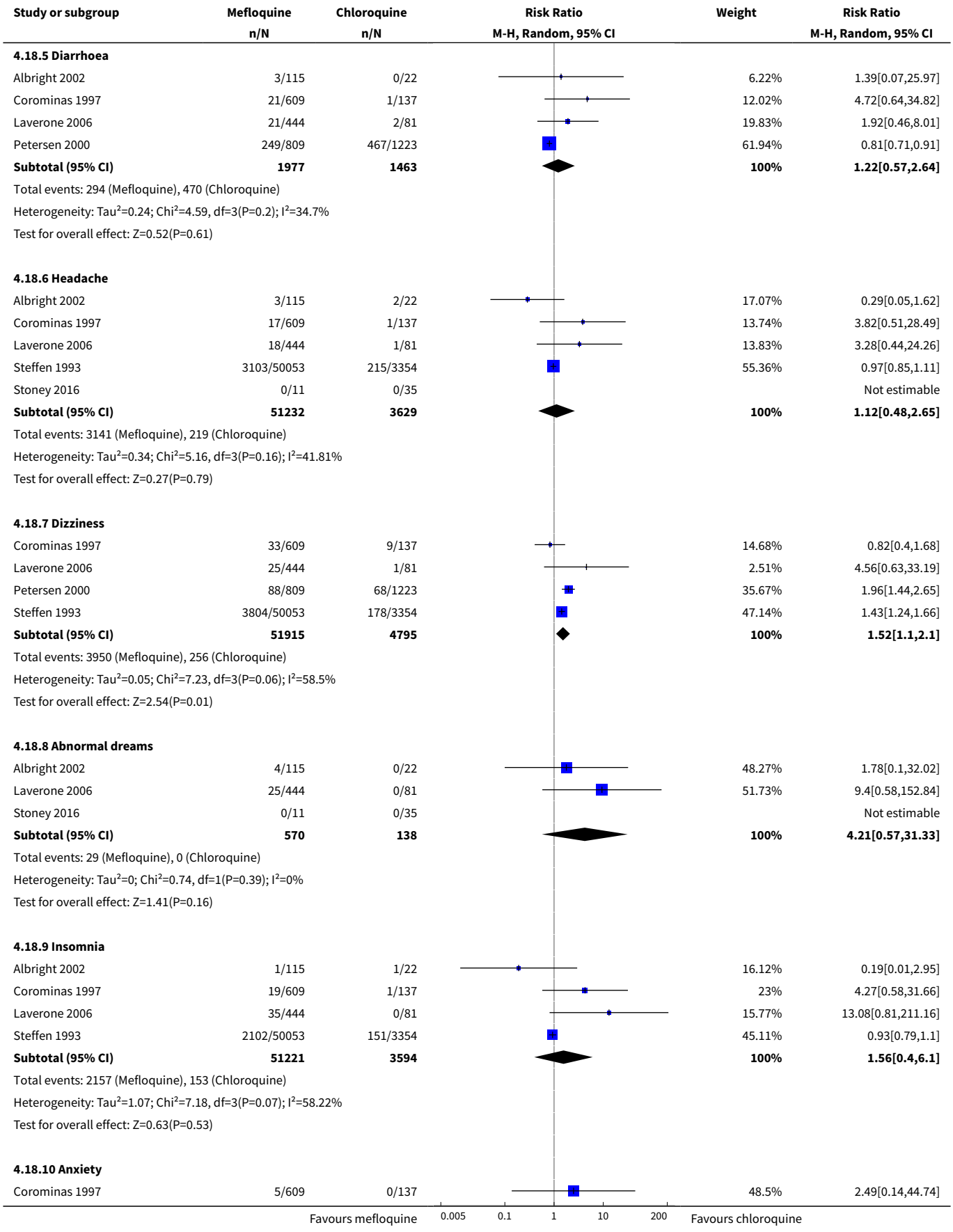
Analysis 4.17. Comparison 4 Mefloquine versus chloroquine, Outcome 17 Vertigo (all studies).

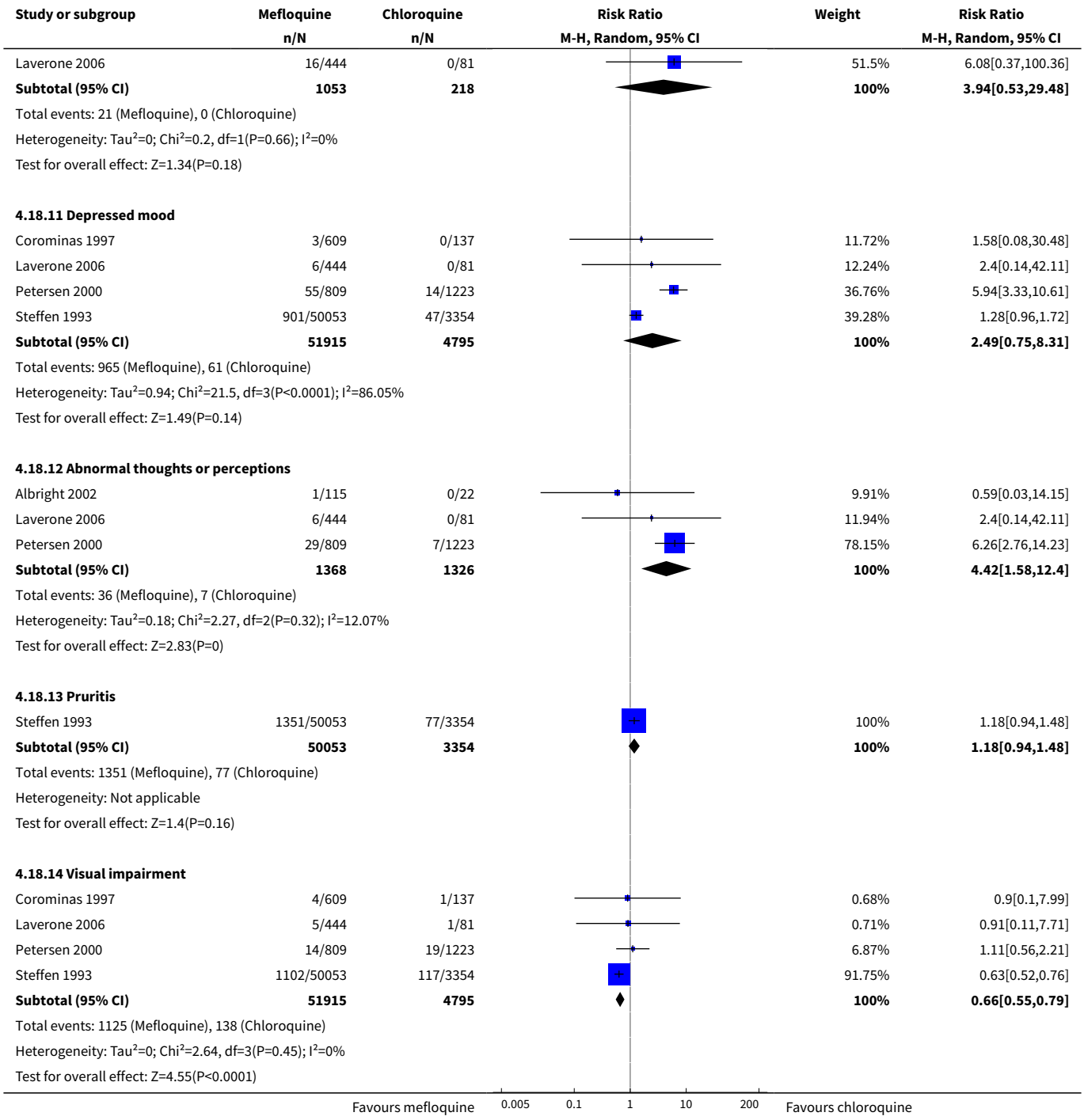




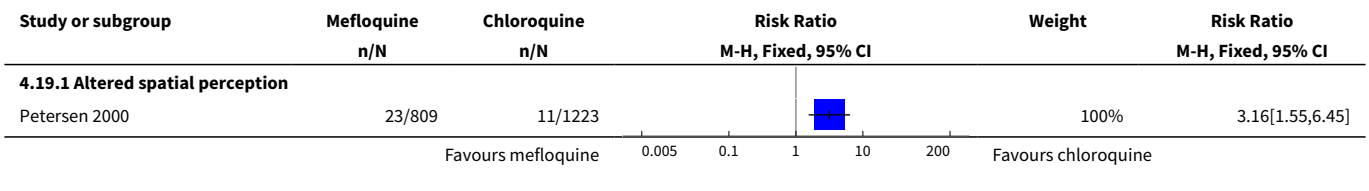
Analysis 4.18. Comparison 4 Mefloquine versus chloroquine, Outcome 18 Cohort studies in travellers; prespecified adverse effects.

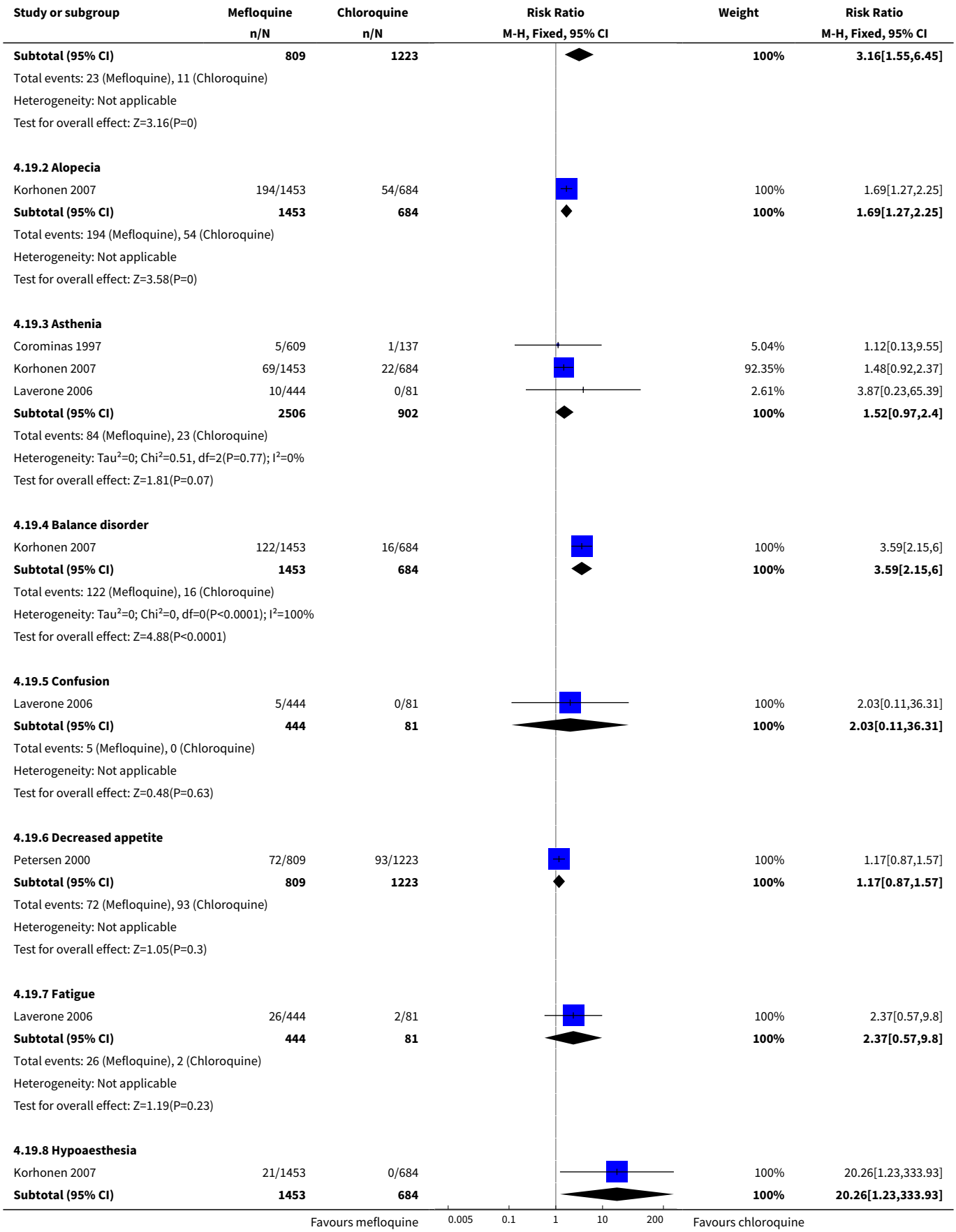


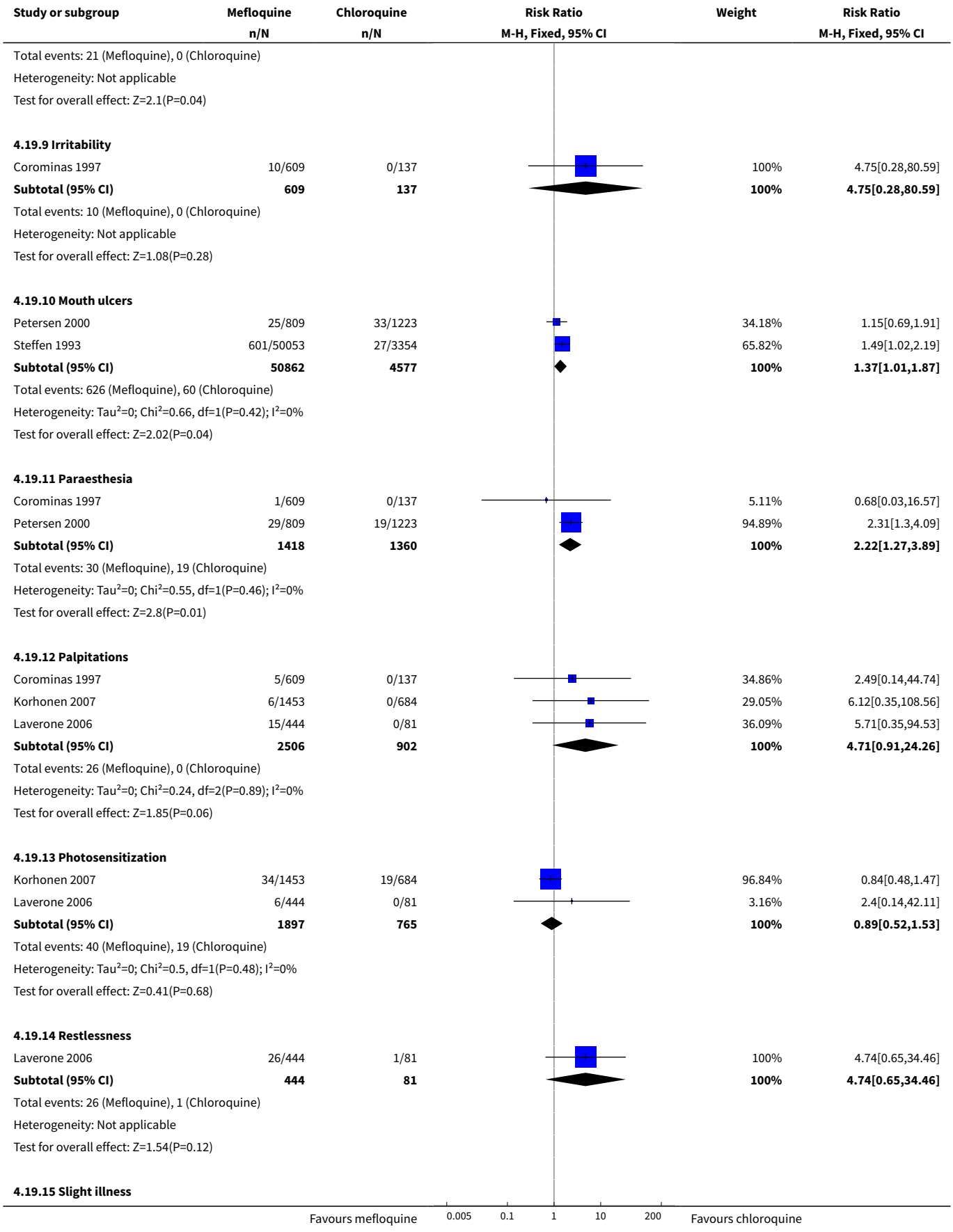


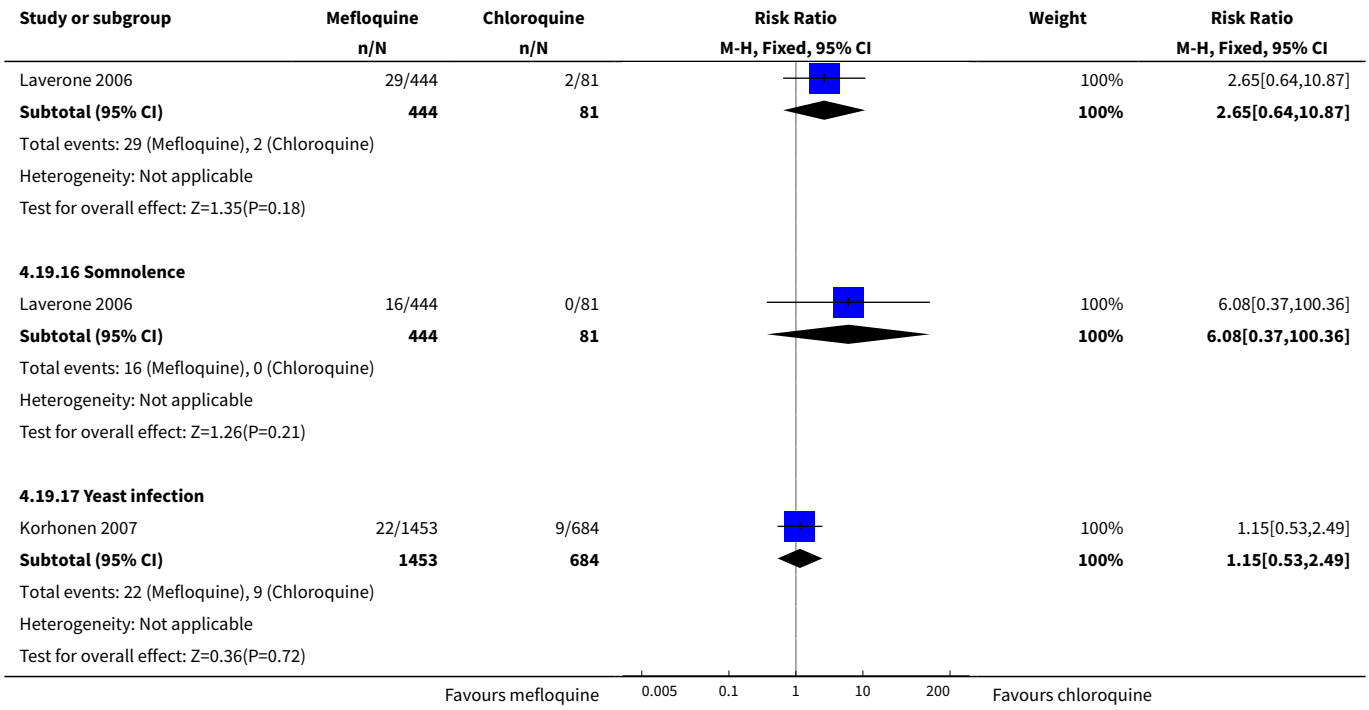


Analysis 4.19. Comparison 4 Mefloquine versus chloroquine, Outcome 19 Other adverse effects (cohort studies).

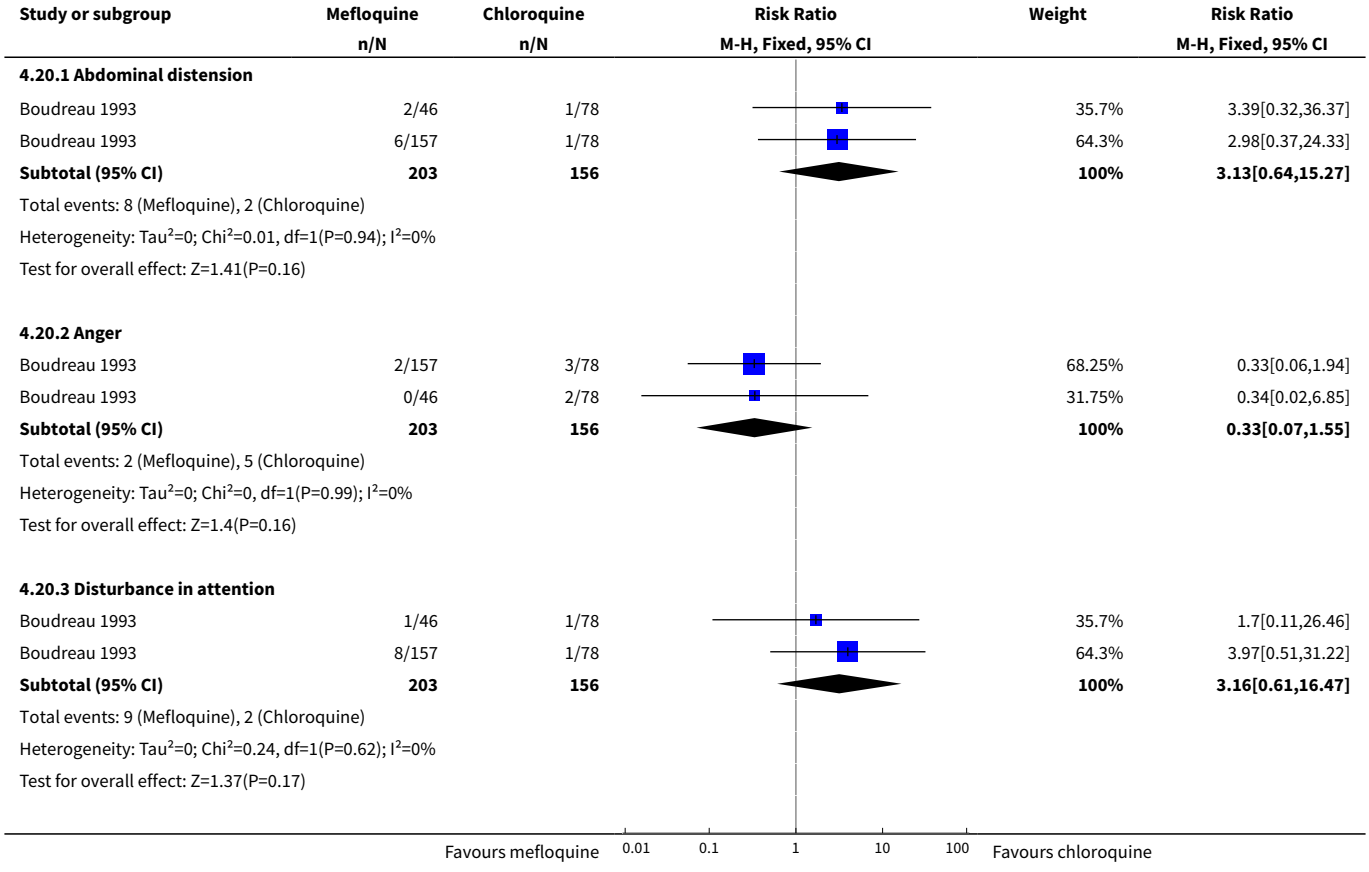


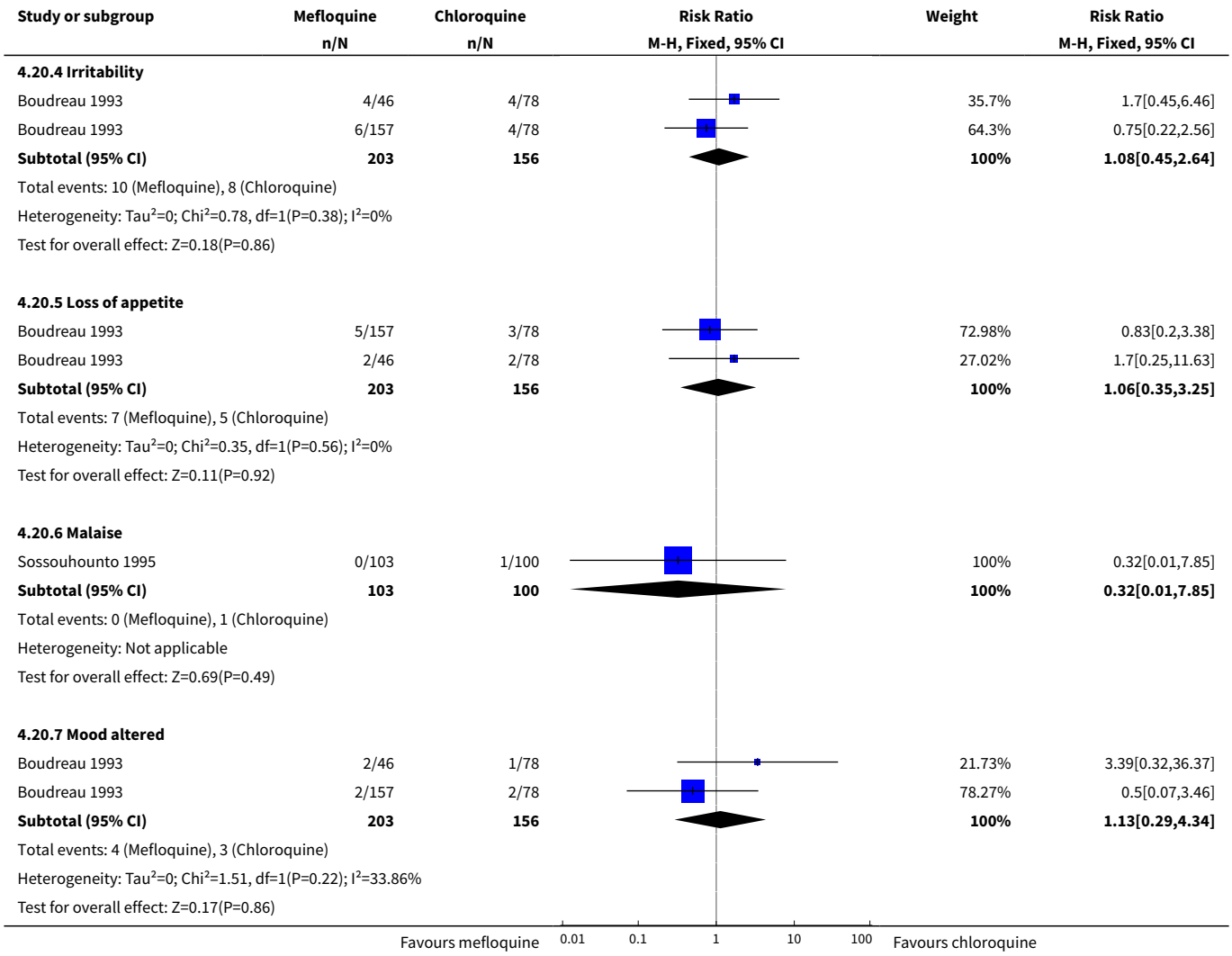




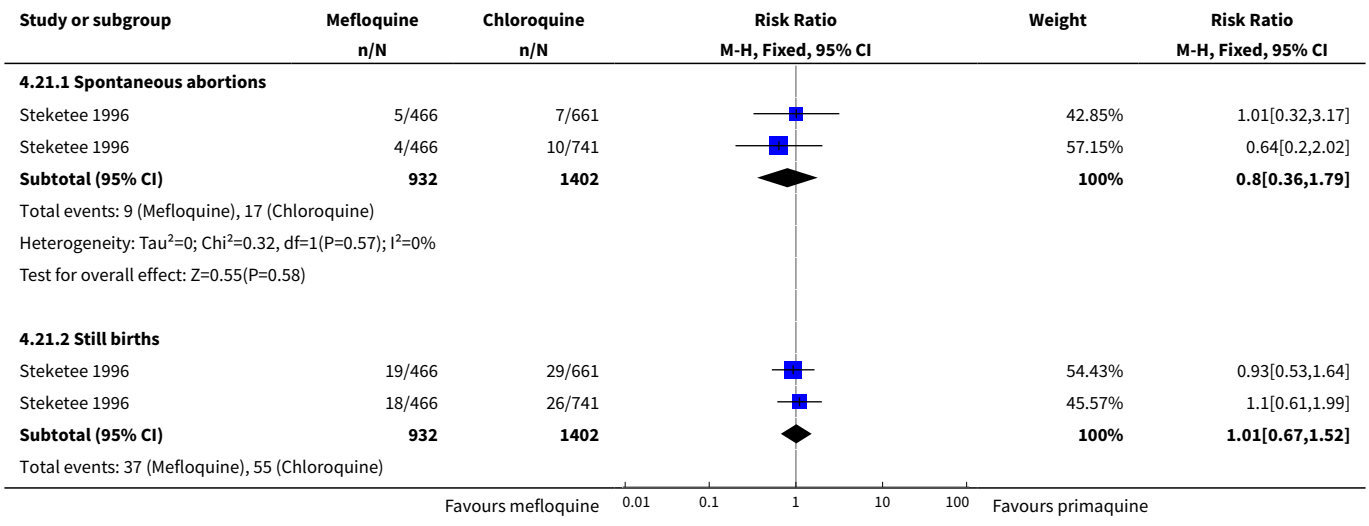


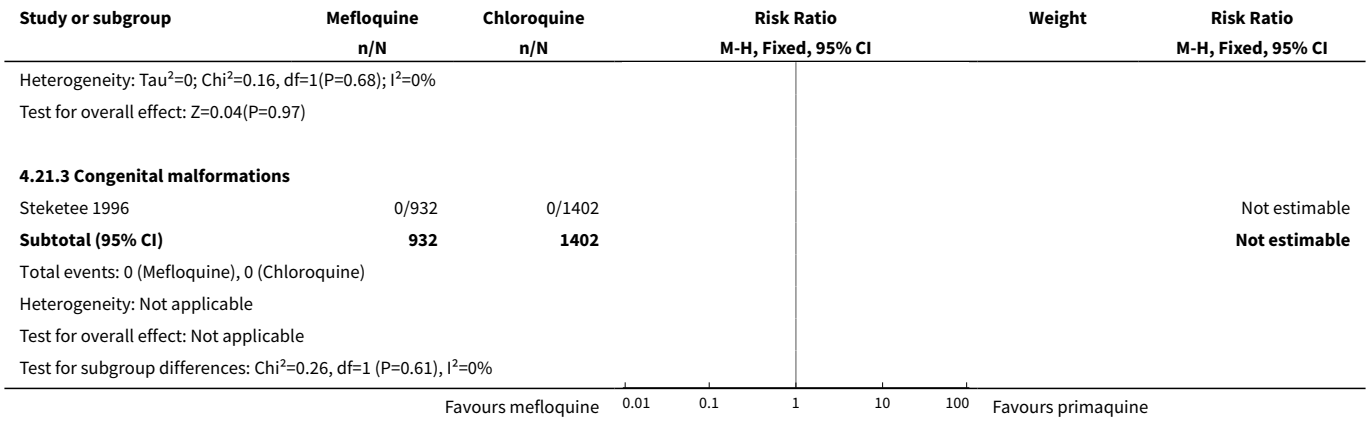
Analysis 4.20. Comparison 4 Mefloquine versus chloroquine, Outcome 20 Other adverse events (RCTs).



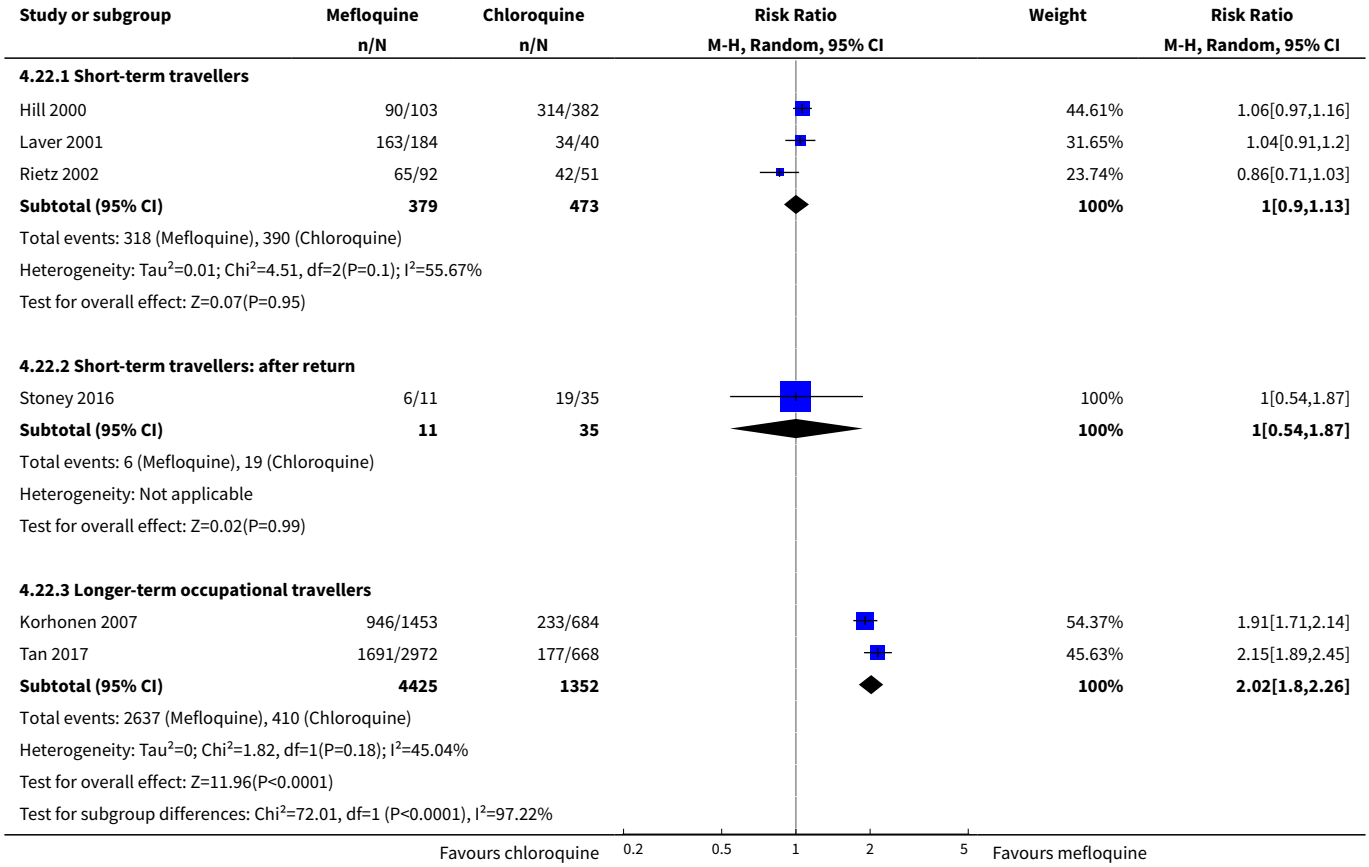


Analysis 4.21. Comparison 4 Mefloquine versus chloroquine, Outcome 21 Pregnancy related outcomes (RCTs).





Analysis 4.22. Comparison 4 Mefloquine versus chloroquine, Outcome 22 Adherence (cohort studies).



Comparison 5. Mefloquine versus currently used regimens; by study design

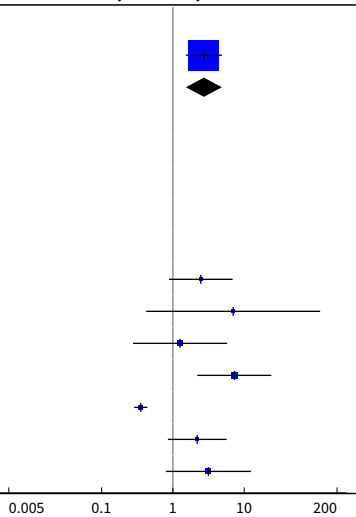
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Nausea; effects	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

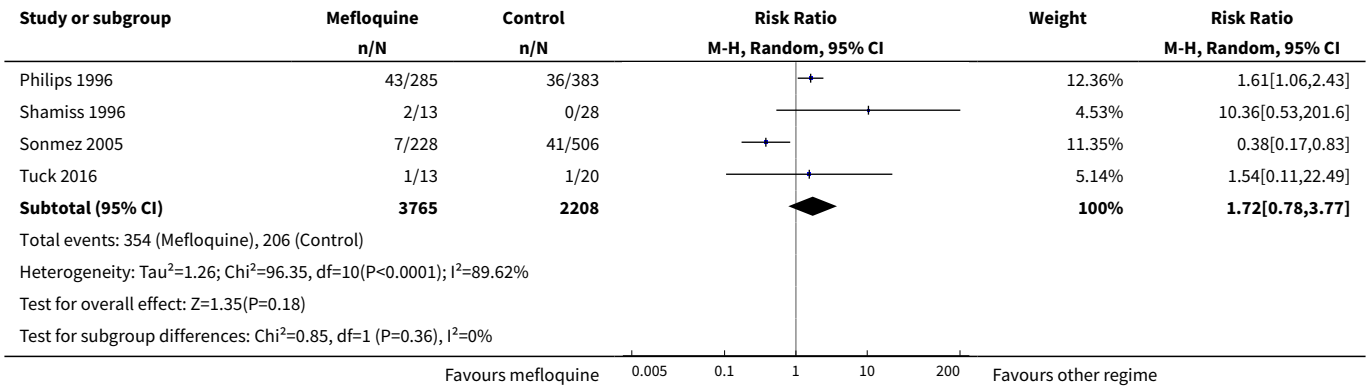
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 RCTs	1	976	Risk Ratio (M-H, Random, 95% CI)	2.72 [1.52, 4.86]
1.2 Cohort studies	11	5973	Risk Ratio (M-H, Random, 95% CI)	1.72 [0.78, 3.77]
2 Abdominal pain; effects	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 RCTs	1	976	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.52, 1.56]
2.2 Cohort studies	9	4494	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.27, 0.87]
3 Diarrhoea; effects	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 RCTs	1	976	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.60, 1.47]
3.2 Cohort studies	10	7648	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.28, 1.34]
4 Headache; effects	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 RCTs	1	976	Risk Ratio (M-H, Random, 95% CI)	1.72 [0.99, 2.99]
4.2 Cohort studies	9	5592	Risk Ratio (M-H, Random, 95% CI)	2.19 [1.22, 3.93]
5 Dizziness; effects	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 RCTs	1	976	Risk Ratio (M-H, Random, 95% CI)	3.99 [2.08, 7.64]
5.2 Cohort studies	9	4606	Risk Ratio (M-H, Random, 95% CI)	3.17 [1.58, 6.35]
6 Abnormal dreams; effects	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 RCTs	1	976	Risk Ratio (M-H, Random, 95% CI)	2.04 [1.37, 3.04]
6.2 Cohort studies	7	4543	Risk Ratio (M-H, Random, 95% CI)	7.30 [2.51, 21.18]
7 Insomnia; effects	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 RCTs	1	976	Risk Ratio (M-H, Random, 95% CI)	4.42 [2.56, 7.64]
7.2 Cohort studies	9	5299	Risk Ratio (M-H, Random, 95% CI)	5.70 [2.83, 11.47]
8 Anxiety; effects	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 RCTs	1	976	Risk Ratio (M-H, Random, 95% CI)	6.12 [1.82, 20.66]
8.2 Cohort studies	4	3390	Risk Ratio (M-H, Random, 95% CI)	15.26 [8.66, 26.89]
9 Depressed mood; effects	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 RCTs	1	976	Risk Ratio (M-H, Random, 95% CI)	5.78 [1.71, 19.61]
9.2 Cohort studies	6	4236	Risk Ratio (M-H, Random, 95% CI)	7.82 [3.79, 16.12]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 Abnormal thoughts or perceptions; effects	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Cohort studies	3	3045	Risk Ratio (M-H, Random, 95% CI)	4.20 [0.81, 21.87]
11 Pruritis; effects	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 RCTs	1	976	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.60, 2.70]
11.2 Cohort studies	3	2034	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.16, 4.76]
12 Visual impairment; effects	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 RCTs	1	976	Risk Ratio (M-H, Random, 95% CI)	2.04 [0.88, 4.73]
12.2 Cohort studies	3	2560	Risk Ratio (M-H, Random, 95% CI)	2.06 [1.05, 4.02]
13 Adherence; during travel	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 RCTs	1	119	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.88, 1.02]
13.2 Cohort studies	11	12131	Risk Ratio (M-H, Random, 95% CI)	1.16 [1.03, 1.30]
14 Adherence; after return	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 Cohort studies	4	1221	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.92, 1.17]

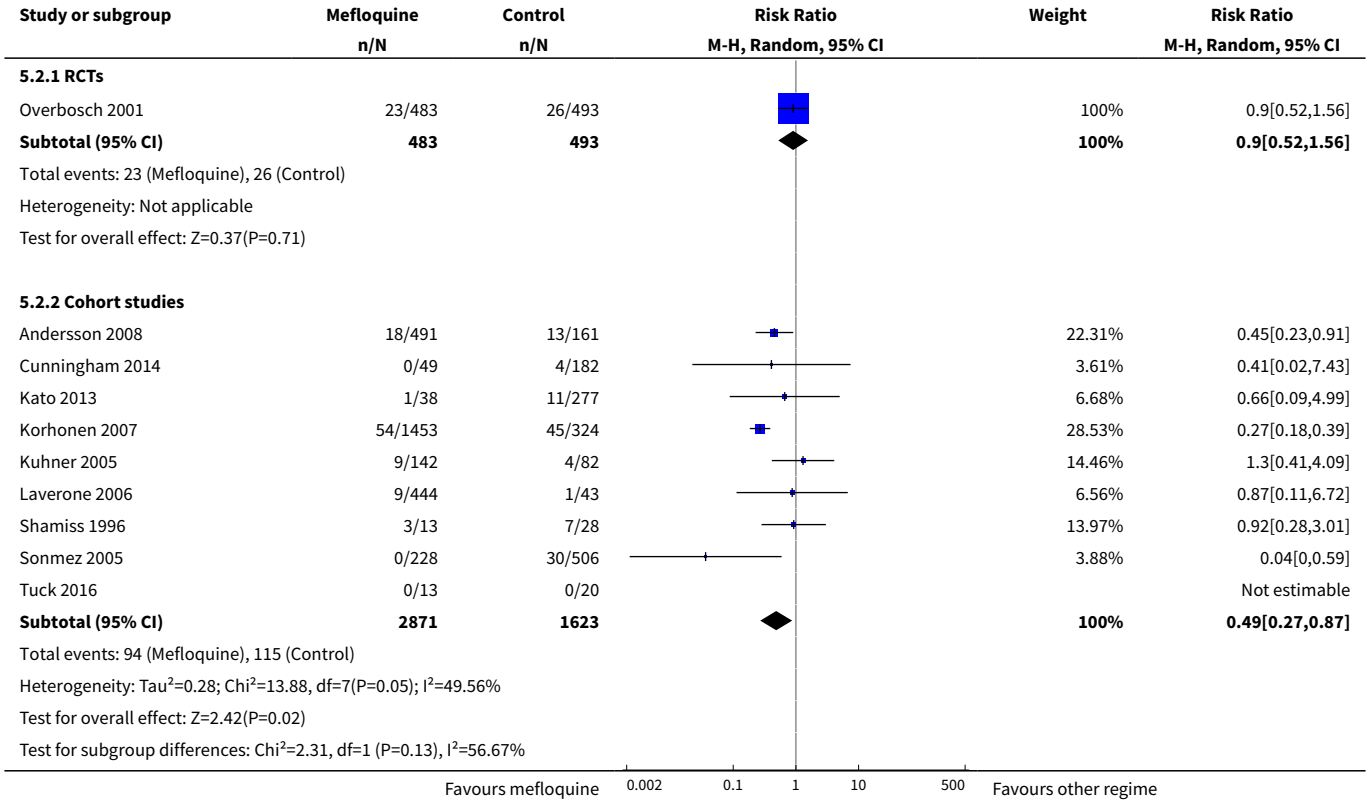
Analysis 5.1. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 1 Nausea; effects.

Study or subgroup	Mefloquine n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.1.1 RCTs					
Overbosch 2001	40/483	15/493		100%	2.72[1.52,4.86]
Subtotal (95% CI)	**483**	**493**		**100%**	**2.72[1.52,4.86]**
Total events: 40 (Mefloquine), 15 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.38(P=0)					
5.1.2 Cohort studies					
Andersson 2008	30/491	4/161		10.5%	2.46[0.88,6.87]
Corominas 1997	15/609	0/137		4.86%	7.01[0.42,116.5]
Cunningham 2014	2/49	8/247		8.66%	1.26[0.28,5.76]
Kato 2013	5/38	5/277		9.89%	7.29[2.21,24.02]
Korhonen 2007	165/1453	104/324		12.68%	0.35[0.29,0.44]
Kuhner 2005	19/142	5/82		10.8%	2.19[0.85,5.66]
Laverone 2006	65/444	2/43		9.21%	3.15[0.8,12.41]

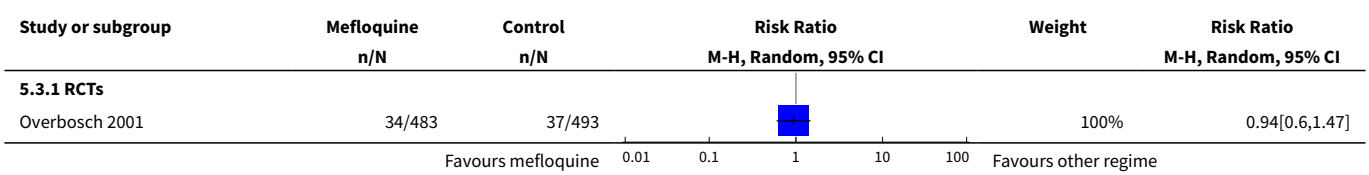


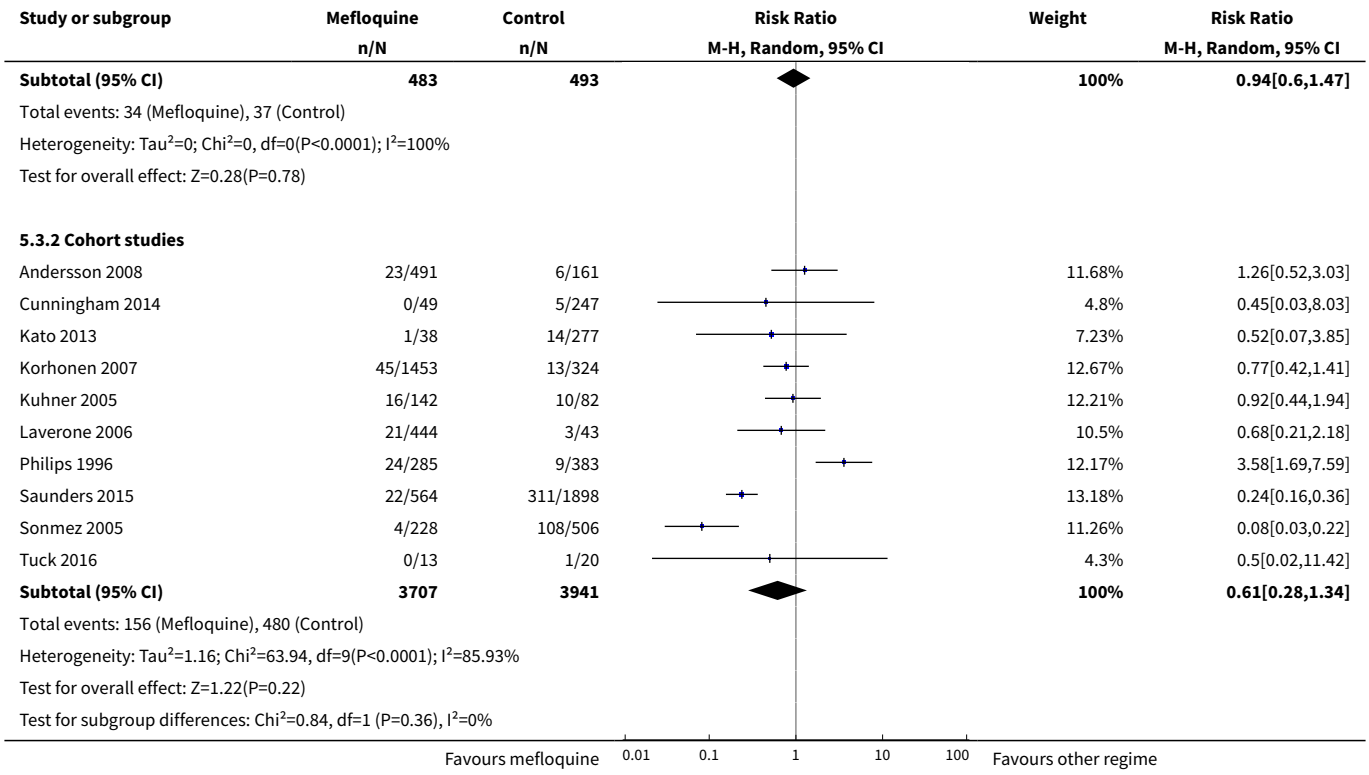


Analysis 5.2. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 2 Abdominal pain; effects.

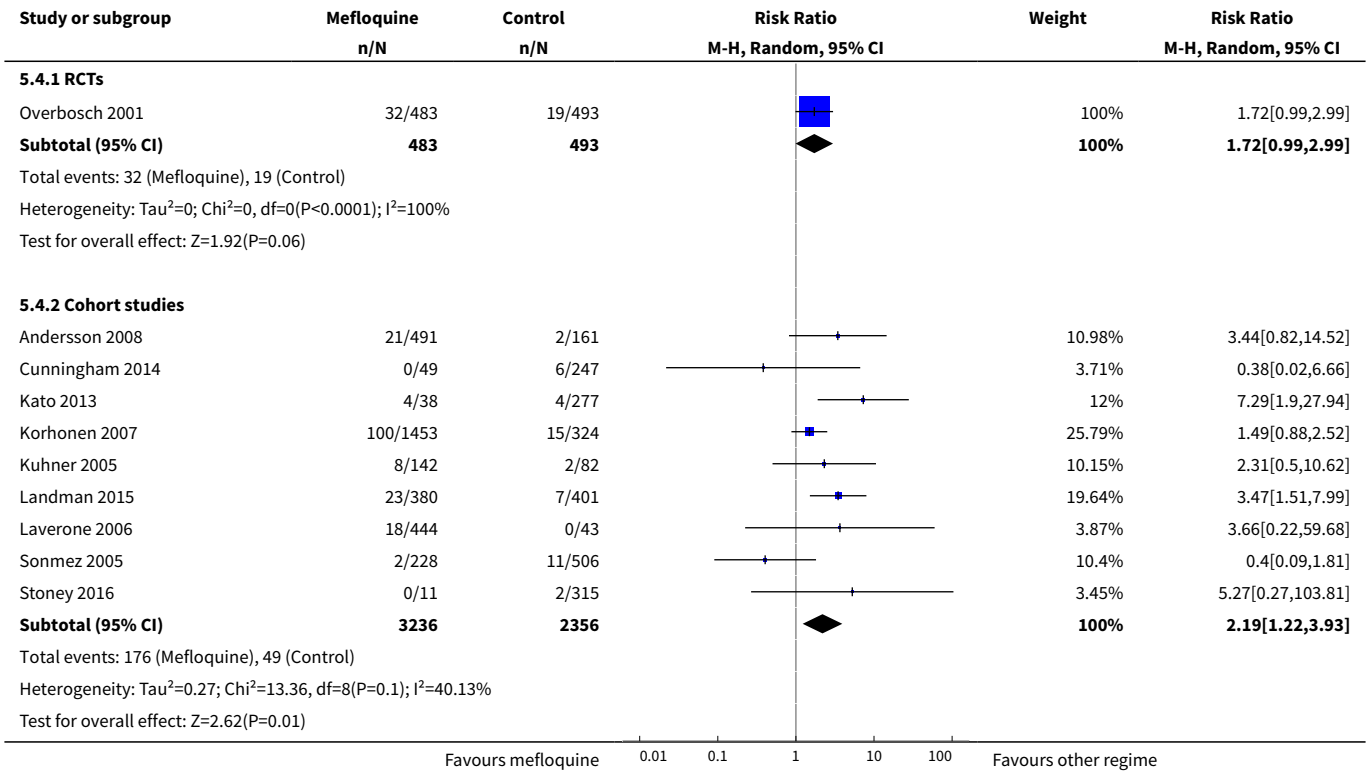


Analysis 5.3. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 3 Diarrhoea; effects.





Analysis 5.4. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 4 Headache; effects.

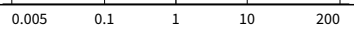


Study or subgroup	Mefloquine n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for subgroup differences: Chi²=0.34, df=1 (P=0.56), I²=0%					

Favours mefloquine — Favours other regime

Analysis 5.5. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 5 Dizziness; effects.

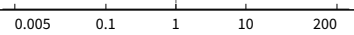
Study or subgroup	Mefloquine n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.5.1 RCTs					
Overbosch 2001	43/483	11/493		100%	3.99[2.08,7.64]
Subtotal (95% CI)	**483**	**493**		**100%**	**3.99[2.08,7.64]**
Total events: 43 (Mefloquine), 11 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.17(P<0.0001)					
5.5.2 Cohort studies					
Andersson 2008	52/491	6/161		17.28%	2.84[1.24,6.49]
Cunningham 2014	1/49	2/247		6.2%	2.52[0.23,27.25]
Kato 2013	3/38	8/277		12.84%	2.73[0.76,9.86]
Korhonen 2007	189/1453	23/324		21.14%	1.83[1.21,2.78]
Kuhner 2005	17/142	1/82		7.9%	9.82[1.33,72.42]
Landman 2015	52/380	3/401		14%	18.29[5.76,58.07]
Laverone 2006	25/444	2/43		11.8%	1.21[0.3,4.94]
Shamiss 1996	2/13	0/28		4.41%	10.36[0.53,201.6]
Tuck 2016	0/13	2/20		4.43%	0.3[0.02,5.79]
Subtotal (95% CI)	**3023**	**1583**		**100%**	**3.17[1.58,6.35]**
Total events: 341 (Mefloquine), 47 (Control)					
Heterogeneity: Tau²=0.55; Chi²=20.61, df=8(P=0.01); I²=61.19%					
Test for overall effect: Z=3.26(P=0)					
Test for subgroup differences: Chi²=0.22, df=1 (P=0.64), I²=0%					



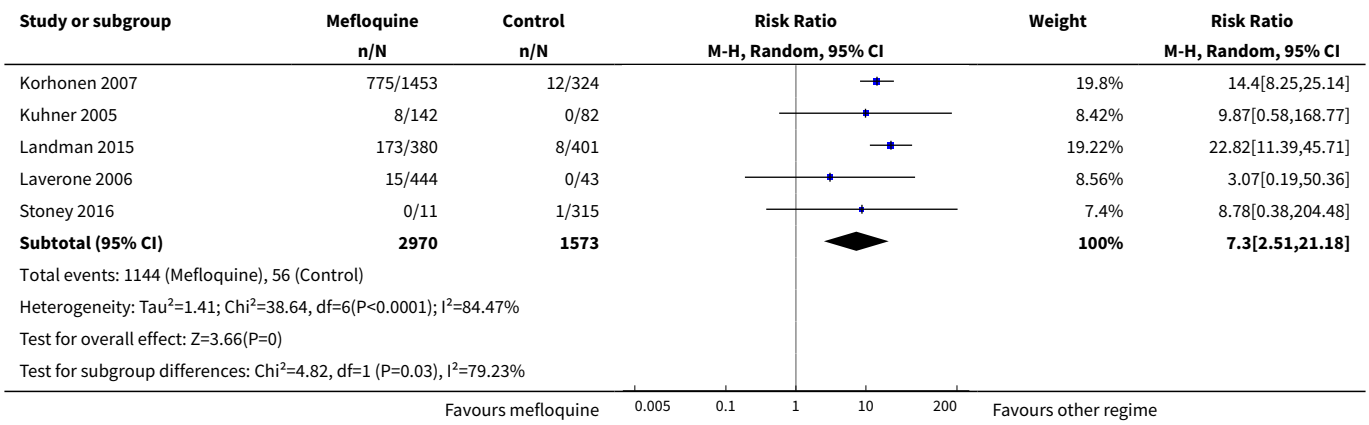
Favours mefloquine — Favours other regime

Analysis 5.6. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 6 Abnormal dreams; effects.

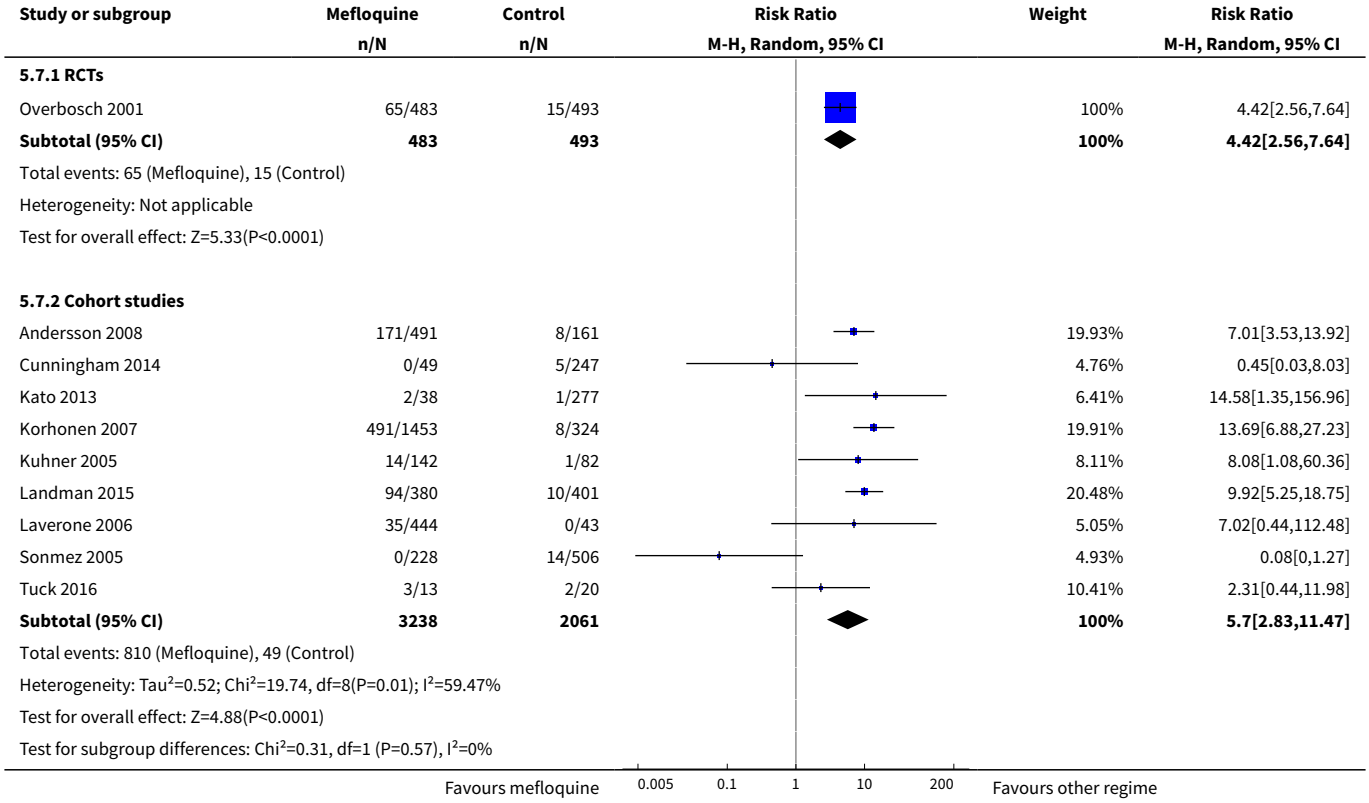
Study or subgroup	Mefloquine n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.6.1 RCTs					
Overbosch 2001	66/483	33/493		100%	2.04[1.37,3.04]
Subtotal (95% CI)	**483**	**493**		**100%**	**2.04[1.37,3.04]**
Total events: 66 (Mefloquine), 33 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.51(P=0)					
5.6.2 Cohort studies					
Andersson 2008	168/491	5/161		18.36%	11.02[4.61,26.34]
Cunningham 2014	5/49	30/247		18.23%	0.84[0.34,2.06]



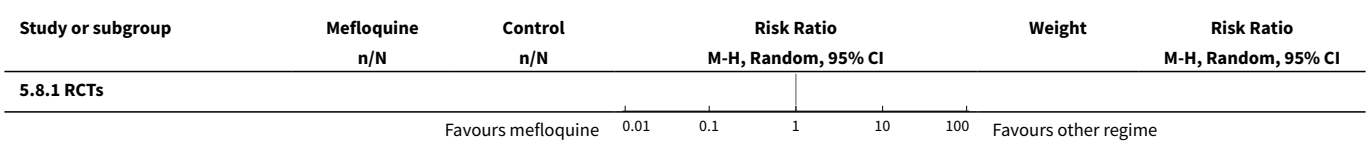
Favours mefloquine — Favours other regime

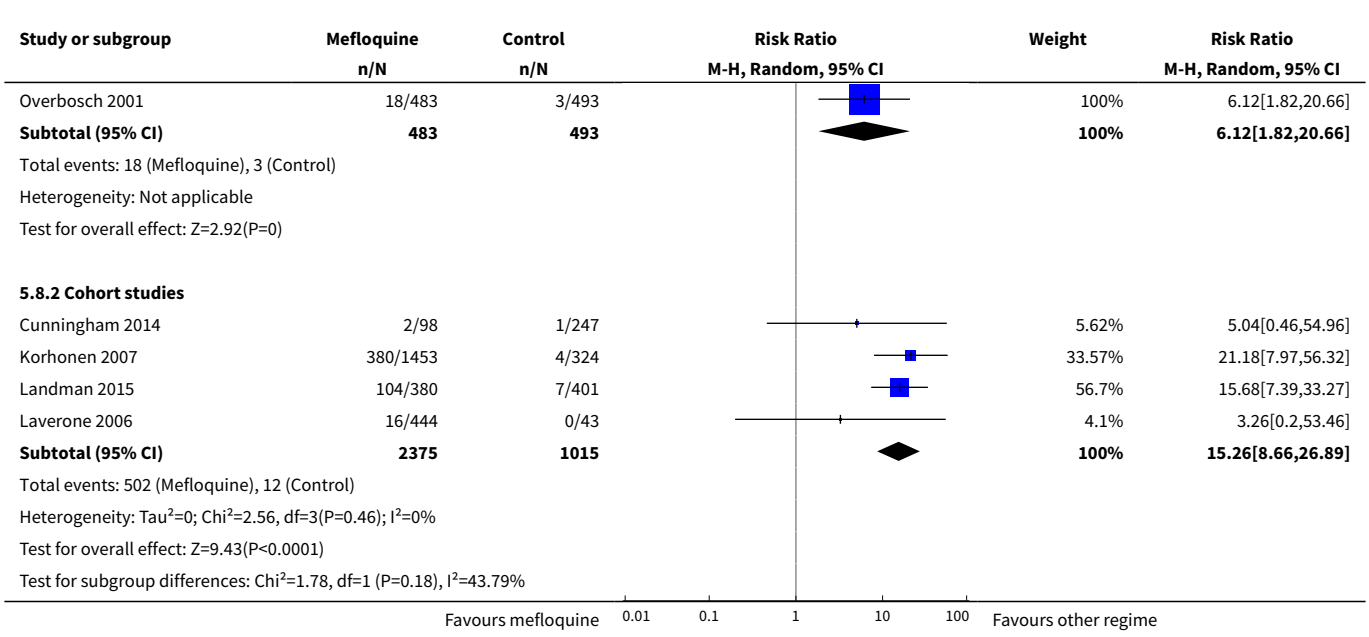


Analysis 5.7. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 7 Insomnia; effects.

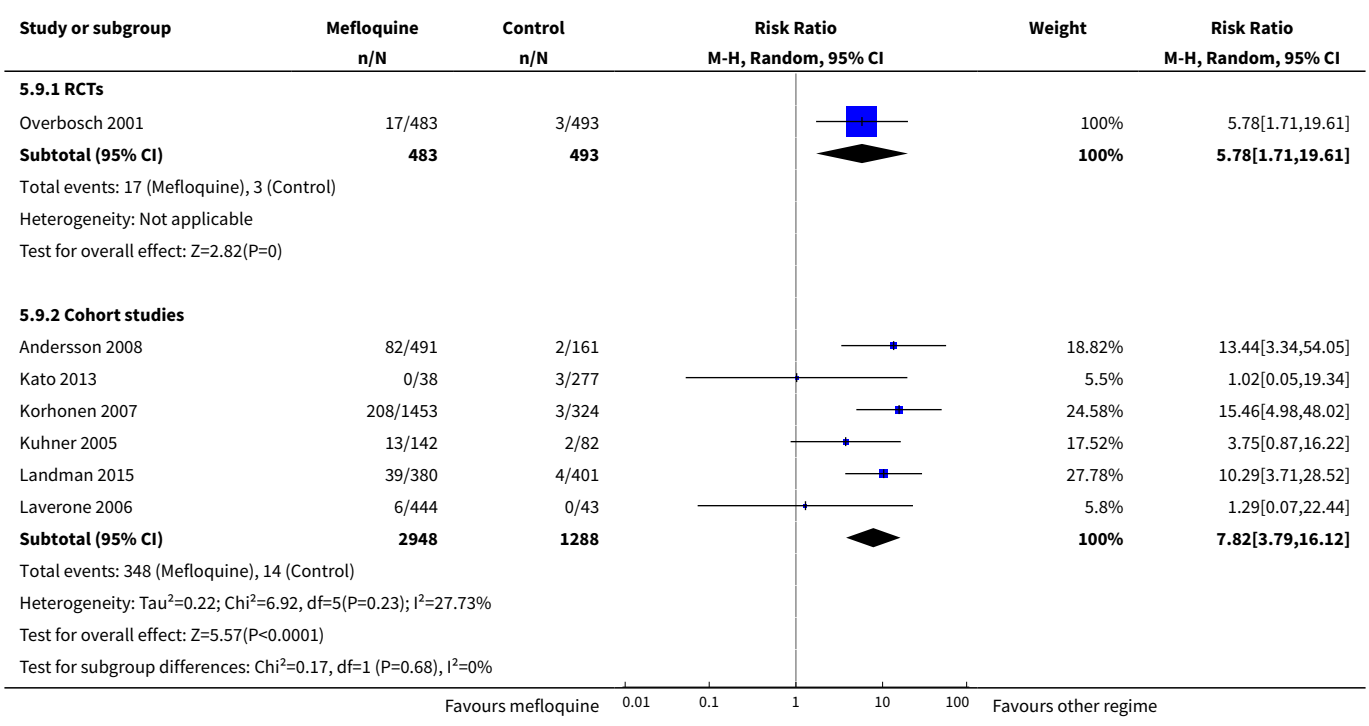


Analysis 5.8. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 8 Anxiety; effects.

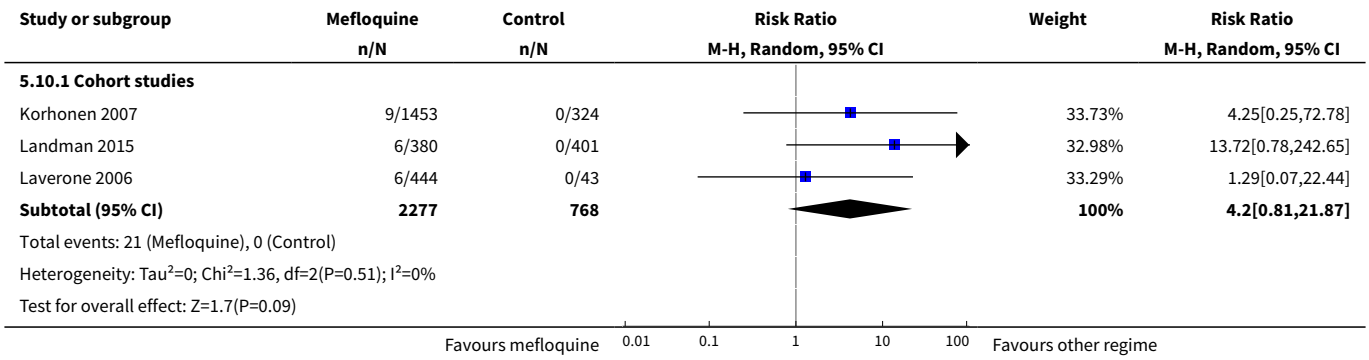




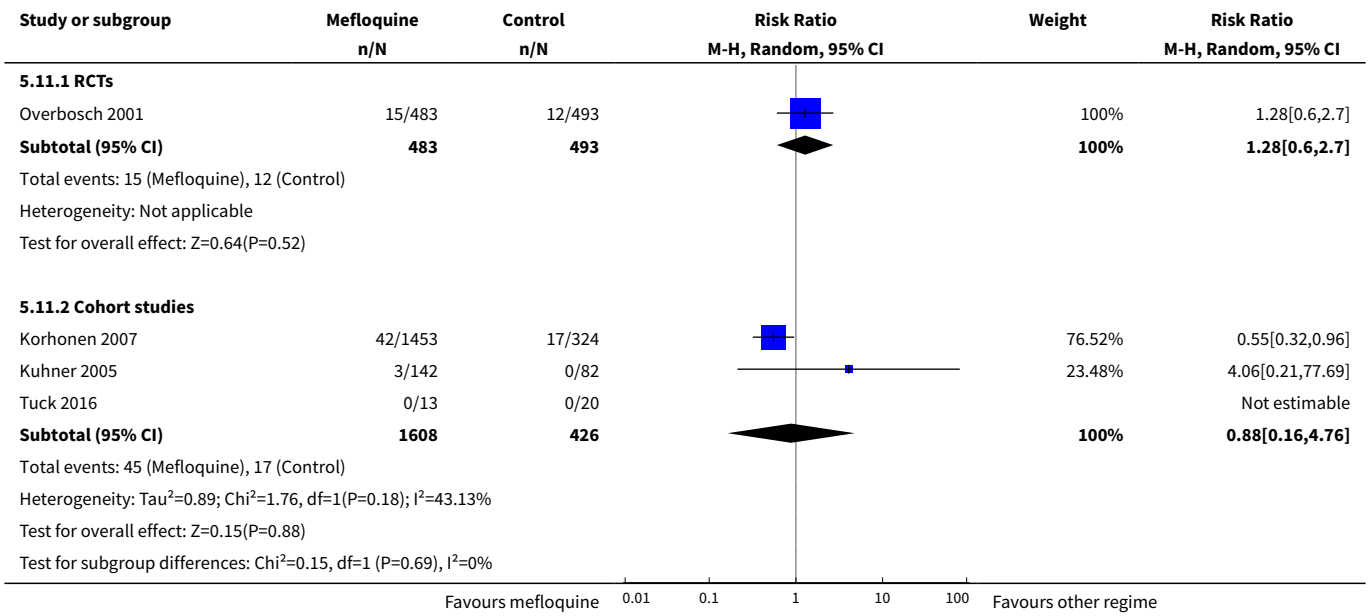
Analysis 5.9. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 9 Depressed mood; effects.



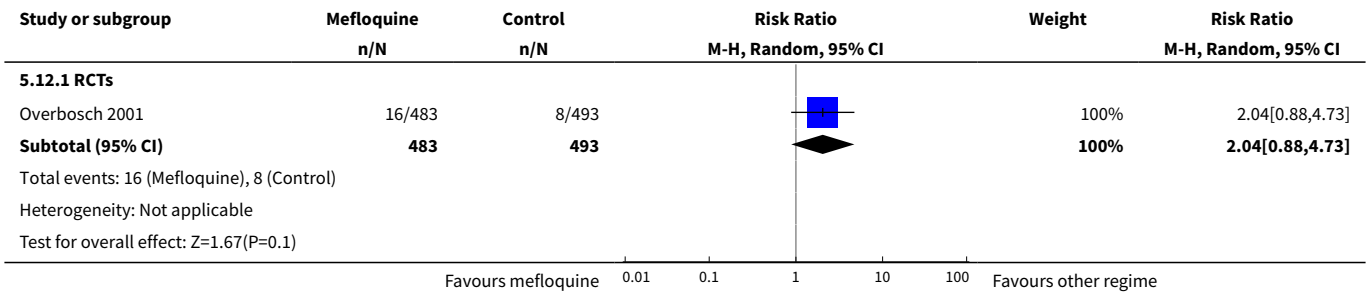
Analysis 5.10. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 10 Abnormal thoughts or perceptions; effects.

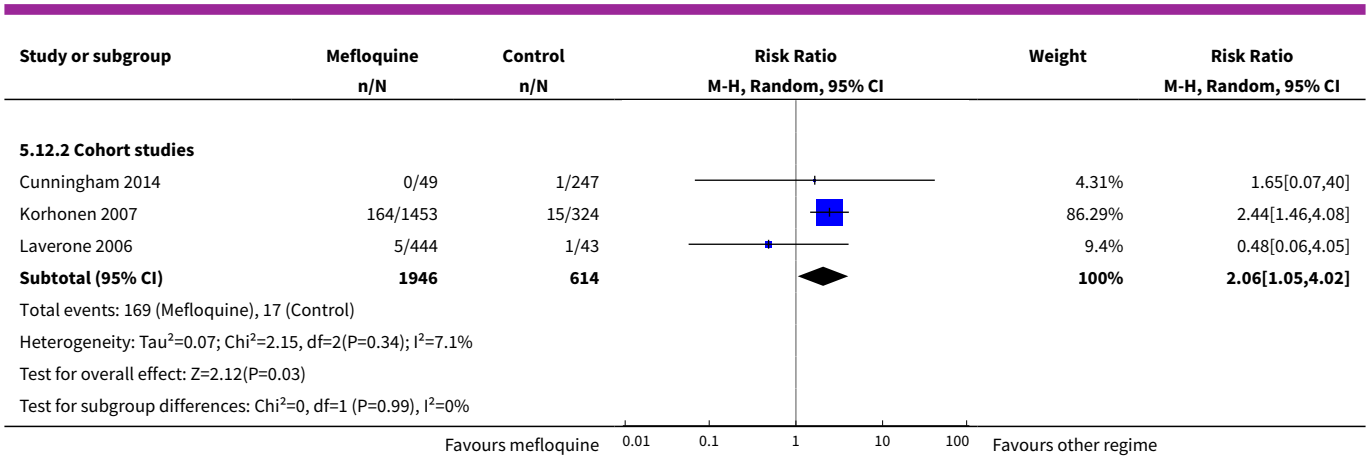


Analysis 5.11. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 11 Pruritis; effects.

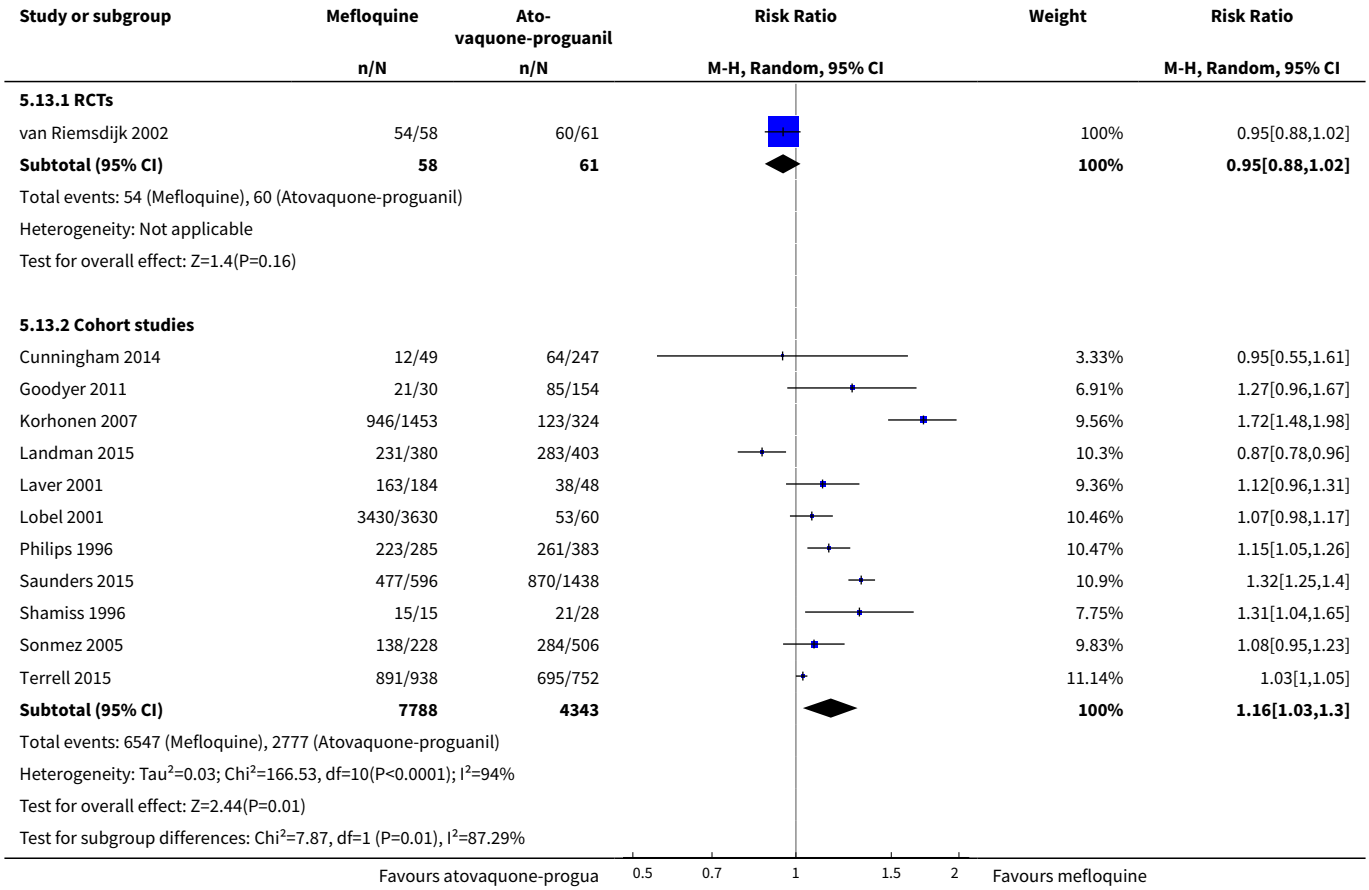


Analysis 5.12. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 12 Visual impairment; effects.

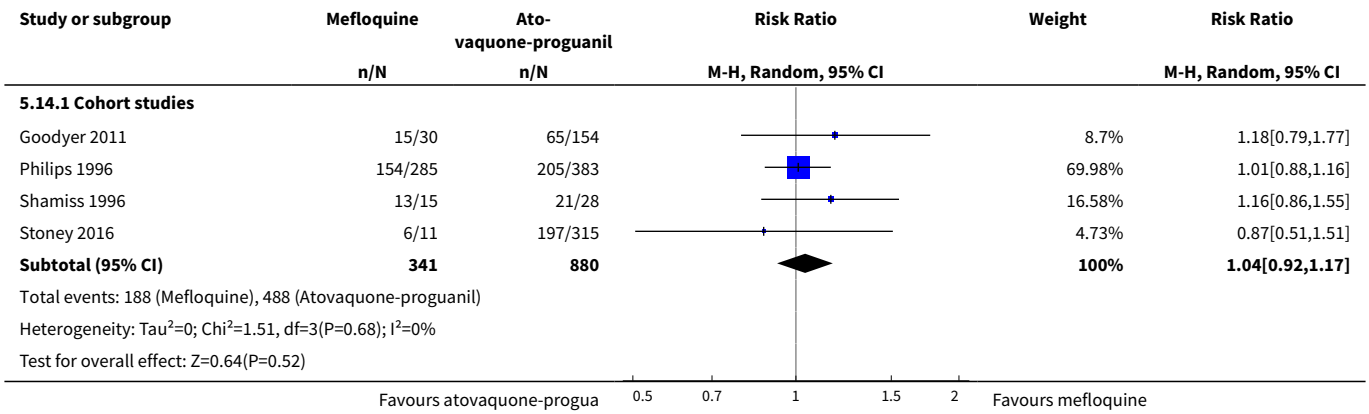




Analysis 5.13. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 13 Adherence; during travel.



Analysis 5.14. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 14 Adherence; after return.



ADDITIONAL TABLES

Table 1. Risk of bias assessment methods for cohort studies

Bias	Authors' judgement	Support for judgement
Confounding	Low risk Moderate risk Serious risk Critical risk No information	We used the following criteria: Low risk: identified confounders were measured and were balanced across groups (age, sex, destination and duration of travel) Moderate risk: identified confounders were measured and not balanced across groups, or several confounders had not been measured or not reported across groups Serious risk: a critical confounder has been measured and is not balanced across groups
Selection of participants into the study	Low risk Moderate risk Serious risk Critical risk No information	We assessed whether selection into the study was unrelated to intervention or unrelated to outcome, and whether start of intervention and start of follow up coincided for most subjects. Non-responder bias at the point of selection was considered here for cohort studies. We used the following cut offs for non-response rate: low risk < 10%, moderate risk 10% to 20%, serious risk > 20%.
Measurement of interventions	Low risk Moderate risk Serious risk Critical risk No information	We used the following criteria: Low risk: the prescription was provided by a travel clinic which also performed the study, and discontinuations were recorded and reported, or all participants were issued with their medication e.g. soldiers or participants were asked to self-report which medication they took whilst they were taking it. Moderate risk: the prescription was provided by a travel clinic which also performed the study but no information regarding switches and discontinuations was available or patients are asked to self-report which prophylaxis they took shortly after they finished taking it.

Table 1. Risk of bias assessment methods for cohort studies *(Continued)*

		Serious risk: Participants were asked to self-report which prophylaxis they took a long time after they finished taking it.
Departures from intended interventions	Low risk Moderate risk Serious risk Critical risk No information	We assessed whether switches between interventions of interest were available. We assessed whether discontinuations and switches between prophylactic regimens had been recorded and reported.
Missing data	Low risk Moderate risk Serious risk Critical risk No information	We assessed whether outcome data was reasonably complete for most participants. We recorded missing data for included participants e.g. loss to follow up rates and treatment withdrawals.
Measurement of outcomes	Low risk Moderate risk Serious risk Critical risk No information	We assessed whether the outcome measure was objective or subjective. We assessed whether participants or study personnel were blinded to the intervention received. We assessed whether the methods of outcome assessment were comparable across intervention groups.
Selection of the reported result	Low risk Moderate risk Serious risk Critical risk No information	We used the following criteria: Low risk: If the questionnaire was provided in full, or it was clear what was asked within it. Moderate risk: If it is unclear which questions are asked, or information was provided on aggregate. Serious risk: If data captured within the questionnaire was clearly missing.
Other	Low risk Moderate risk Serious risk Critical risk No information	We reported the study sponsor. We classified the analysis of studies sponsored by pharmaceutical companies as independent of the sponsor when it was clearly stated that the sponsor had no input to the trial analysis.

Adapted from Higgins 2011 and ACROBAT-NSRI tool

Table 2. Adverse events and adverse effects risk of bias assessment methods

Criterion	Assessment	Explanation
On conduct		

Table 2. Adverse events and adverse effects risk of bias assessment methods *(Continued)*

Were harms pre-defined using standardised or precise definitions?	Adequate Inadequate Unclear	We classified as 'adequate' if the study reported explicit definitions for adverse events and effects that allow for reproducible ascertainment e.g. what adverse events were being investigated and what constituted an "event", what was defined as a serious or severe adverse event.
Was ascertainment technique adequately described?	Adequate Inadequate Unclear	We classified as 'adequate' if the study reported methods used to ascertain complications, including who ascertained, timing, and methods used.
Was monitoring active or passive?	Active Passive Unclear	We classified monitoring as 'active' when authors reviewed participants at set time points during treatment and enquired about symptoms.
Was data collection prospective or retrospective?	Prospective Retrospective Unclear	We classified as 'prospective' if data collection occurred during treatment, or 'retrospective' if data collection occurred following treatment.
For laboratory investigations or other tests		
Was the number and timing of tests adequate?	Adequate Inadequate Unclear	We classified the number and timing of tests as 'adequate', when tests were taken at baseline and at least one time point during prophylaxis.

Adapted from Bukiwra 2014

Table 3. Characteristics of included studies for efficacy

Study ID	Participants (immune status)	Number of randomised participants	Mefloquine dose	Drug comparisons of interest	Duration of exposure to malaria	Country of malaria exposure	Local drug resistance
Bunnag 1992	Thai male adults (presumed semi-immune)	605	250 mg weekly for first 4 weeks, then 125 mg weekly	Placebo	24 weeks (trial duration)	Thailand	Chloroquine, sulphadoxine-pyrimethamine and quinine resistance
Nosten 1994	Pregnant women from the Thai-Burma border (presumed semi-immune)	339	250 mg weekly for first 4 weeks, then 125 mg weekly until delivery	Placebo	Various in endemic area (monitored until delivery)	Thai-Burma border	Not mentioned
Pearlman 1980	Thai residents aged 10 to 60 years (semi-immune)	990	180 mg tablet weekly, 360 mg tablet weekly, 360 mg every 2 weeks with appropriate adjustments for children	Placebo	26 weeks	Thailand	Chloroquine resistant *Plasmodium falciparum*
Santos 1993	Brazilian civilians and soldiers aged 12 to 55 years (semi-immune)	128	500 mg every 4 weeks, 250mg every 2 weeks	Placebo	17 weeks	Brazil	*P falciparum* resistant to chloroquine and “high prevalence of multiresistant *Plasmodium falciparum* transmission”
Sossouhounto 1995	Ivory Coast adult males (semi-immune)	500	250 mg weekly for first 4 weeks, then 125 mg weekly	Placebo	20 weeks	Ivory C oast	Not mentioned
Ohrt 1997	Indonesian soldiers ('largely' non-immune)	204	250 mg weekly	Placebo, doxycycline	'approximately 13 weeks'	Indonesia	Sulfadoxine-pyrimethamine and chloroquine resistance
Weiss 1995	Kenyan children (semi-immune)	169	125 mg weekly	Placebo (multivitamin), doxycycline, primaquine	11 weeks	Kenya	Not mentioned
Salako 1992	Nigerian adult males (semi-immune)	567	250 mg weekly for first 4 weeks, then 125 mg weekly	Placebo, chloroquine	24 weeks (trial duration)	Nigeria	"...at the time of the trial, chloroquine resistance was not a problem"
Hale 2003	Ghanain adults (semi-immune)	530	250 mg weekly	Placebo	12 weeks	Ghana	Not mentioned

Table 3. Characteristics of included studies for efficacy *(Continued)*

Arthur 1990	USA soldiers (non-immune)	270	250 mg weekly	Doxycycline	8 weeks	Thailand	Local chloroquine resistance
Boudreau 1991	Thai adult males (semi-immune)	501	500 mg fortnightly	Chloroquine	14 weeks (trial duration)	Cambodia	Local chloroquine resistance
Steketee 1996	Pregnant Malawian residents (semi-immune)	4220	250 mg weekly	Chloroquine	Various in endemic area (monitored until delivery)	Malawi	*P falciparum* resistant to chloroquine, documented sensitivity of *P falciparum* to mefloquine

Table 4. Mefloquine versus placebo/no treatment; characteristics of included studies for safety

Study ID	Participants	Number enrolled	Method of adverse event monitoring	Exclusions for psychiatric adverse effects	Trial duration	Source of funding
RCTs						
Bunnag 1992	Thai male adults	605	Interview with study personnel	None	24 weeks	Roche
Davis 1996	Australian adults who did not travel	106	Daily self-reported diary	Past history of psychiatric conditions	7 weeks	Roche
Hale 2003	Ghanain adults	530	Interview with study personnel	History of neuropsychiatric illness	12 weeks	USA Army
Nosten 1994	Pregnant women, Thai-Burma border	339	**Phase 1**: weekly symptom questionnaire. Babies were assessed at birth and at 3, 6, 12, and 24 months. **Phase 2**: weekly symptom questionnaire. Babies were assessed at birth and at 2 and 9 months	None	Various	Government funding
Ohrt 1997	Indonesian soldiers	204	Two symptom questionnaires. Daily interview with study personnel	History of underlying illness	13 weeks	Roche, Pfizer, USA Army
Pearlman 1980	Thai residents aged 10 to 60 years	990	Weekly sick call by study personnel	None	26 weeks	Not mentioned
Potasman 2002	Israeli adults who did not travel	90	Self-reporting diary	History of depression	48 hours	Mepha Ltd
Salako 1992	Nigerian adult males	567	Interview with study personnel	None	24 weeks	Not mentioned
Santos 1993	Brazilian civilians and soldiers aged 12 to 55	128	Interview w ith study personnel	None	17 weeks	Roche
Schlagenhauf 1997	Swissair trainee pilots who did not travel	23	Interview with study personnel	Psychosis or severe depression	4 weeks	Roche
Sossouhounto 1995	Ivory C oast adult males	500	Access to the village health centre	None	20 weeks	Not mentioned
Vuurman 1996	Dutch adult who did not travel	42	Interview with study personnel	H istory of any serious psychiatric disorder; evidence	30 days	Roche

Table 4. Mefloquine versus placebo/no treatment; characteristics of included studies for safety *(Continued)*

				of drug or alcohol abuse		
Weiss 1995	Kenyan children	169	Interview with study personnel	None	4 months	USA Army

Cohort studies

	Participants	Number enrolled	Method of adverse event monitoring	Factors influencing drug allocation	Duration of travel	Source of funding
Hoebe 1997	Danish travellers	300	Telephone interview	Allocation based on guidelines and patient preference	Mean 3 weeks, range 1 to 9 weeks	Not mentioned
Petersen 2000	Danish travellers	4154	Participant self-reported questionnaire	Allocation based on guidelines and patient preference	Various, not specified	Not mentioned
Rietz 2002	Swedish travellers	491	Participant self-reported questionnaire	Allocation based on guidelines and patient preference	" Most", range 2 to 4 weeks	Not mentioned
van Riemsdijk 1997	Danish travellers	1501	Participant self-reported questionnaire	Allocation based on guidelines and patient preference	Mean = 23 days	Not mentioned
Wells 2006	USA soldiers	397,442	Restrospective analysis of hospital records	No information available	Minimum 1 month	Government funding

Table 5. Mefloquine versus placebo/no treatment; quality of adverse events reporting

Study ID	Description of how adverse outcomes were defined and recorded[1]	Description of ascertainment technique[2]	Active or passive monitoring?	Prospective or retrospective data collection?
Bunnag 1992	Inadequate Comment: No definition of adverse events or effects was provided, it is unclear whether or how causality was assessed	Adequate	Active	Prospective
Davis 1996	Adequate	Adequate	Active	Prospective
Hale 2003	Inadequate Comment: 'serious' adverse events were not defined, and methods for determining causality not described	Adequate	Active	Prospective
Nosten 1994	Inadequate	Adequate	Active	Prospective

Table 5. Mefloquine versus placebo/no treatment; quality of adverse events reporting *(Continued)*

	Comment: It is unclear what questions were included within the questionnaire and whether and how causality was assessed. 'Serious' adverse effects not defined			
Ohrt 1997	Inadequate Comment: No definition of adverse events or effects provided, it was unclear whether or how causality was assessed	Adequate	Active	Prospective
Pearlman 1980	Inadequate Comment: No definition of adverse events or effects was provided, it was unclear whether or how causality was assessed	Inadequate Comment: Weekly sick call for all villagers	Passive	Prospective
Potasman 2002	Inadequate Comment: No definition of adverse events or effects was provided, it was unclear whether or how causality was assessed	Adequate	Active	Prospective
Salako 1992	Inadequate Comment: No definition of adverse events or effects was provided, it was unclear whether or how causality was assessed	Adequate	Active	Prospective
Santos 1993	Inadequate Comment: No information given in the methods section on definition of adverse outcomes	Inadequate Comment: No description of ascertainment method	Active	Prospective
Schlagenhauf 1997	Inadequate Comment: No definition of adverse events or effects was provided, it was unclear whether or how causality was assessed	Adequate	Active	Prospective
Sossouhounto 1995	Inadequate Comment: No definitions of adverse events or effects were provided, it was unclear whether or how causality was assessed	Unclear	Passive	Prospective
Vuurman 1996	Adequate	Unclear	Active	Prospective
Weiss 1995	Inadequate Comment: No definitions of adverse events or effects were provided, it was unclear whether or how causality was assessed.	Adequate	Active	Prospective
Cohort studies				
Hoebe 1997	Adequate	Adequate	Active	Retrospective

Table 5. Mefloquine versus placebo/no treatment; quality of adverse events reporting *(Continued)*

Petersen 2000	Adequate	Adequate	Active	Retrospective
Rietz 2002	Adequate	Adequate	Active	Unclear 'Filled in after their return'
Steffen 1993	Adequate	Adequate	Passive	Unclear Comment: information was collected during the flight home, when travellers should still have been taking their prophylactic regimen
van Riemsdijk 1997	Adequate	Adequate	Active	Prospective
Wells 2006	Adequate	Adequate	Passive	Retrospective

1. Were harms pre-defined using standardised or precise definitions?
2. Was ascertainment technique adequately described?

Table 6. Serious adverse events; mefloquine versus comparators

Study ID	Study design	Mefloquine users		Drug comparators		
		Events/ participants	Description	Drug	Events/ participants	Description
Events (not attributed by study authors or participants to the drug regimen)						
Bunnag 1992	RCT	0/116	-	Placebo	1/121	None provided
Nosten 1994	RCT	1/159 (women)	One death • Septic shock after an emergency caesarean section Four congenital malformations: • Limb dysplasia (1 case), ventricular septal defect (2 cases), amniotic bands (1 case)	Placebo	0/152 (women)	One congenital malformation: • anencephaly
Sossouhounto 1995	RCT	0/103	-	Placebo	1/96	One death (not described)
Ohrt 1997	RCT	0/61	-	Placebo	0/65	-

Table 6. Serious adverse events; mefloquine versus comparators *(Continued)*

				Doxycycline	1/62	Acute hysteria[1]
Lobel 2001	Cohort study	8/3703	8 hospitalisations • for "fainting, gastrointestinal symptoms, rashes, headaches, ophthalmologic symptoms, and fever"	Doxycycline	0/69	-
				Chloroquine	0/119	-
Overbosch 2001	RCT	10/483	"...infectious illnesses in 7 subjects and breast cancer, anaphylaxis, or fractured femur in 1 subject each"	Atovaquone-proguanil	4/493	"...infectious illnesses in 3 subjects and cerebral ischemia in 1 subject"
Studies reporting no serious events or effects						
Salako 1992	RCT	0/107	"Adverse events were all mild and there were no deaths"	Placebo	0/101	-
				Chloroquine	0/103	-
Arthur 1990	RCT	0/134	"No serious side effects occurred with either drug regimen"	Doxycycline	0/119	-
Schlagenhauf 2003	RCT	0/153	"Although a large number of adverse events were reported, none were serious"	Doxycycline	0/153	-
				Atovaquone-proguanil	0/164	-
Sonmez 2005	Cohort study	0/228	"No drug induced side effects necessitating emergency care were observed"	Doxycycline	0/506	-
Andersson 2008	Cohort study	0/491	"No serious adverse events were recorded"	Atovaquone-proguanil	0/161	-
Napoletano 2007	Cohort study	0/548	Records hospitalisations, and reports that none occurred in either group of participants	Atovaquone-proguanil	0/707	-
				Chloroquine	0/37	-
Sossouhounto 1995	RCT	0/103	"All side effects were transient (and)... mild"	Chloroquine	0/100	-

[1] This trial described a potentially serious adverse event, but did not provide enough detail to meet our definition.

Table 7. Serious adverse effects; mefloquine versus comparators

Study ID	Study design	Mefloquine users		Drug comparators		
		Events/participants	Description	Drug	Events/participants	Description

Table 7. Serious adverse effects; mefloquine versus comparators *(Continued)*

Effects (attributed by study authors or participants to the drug regimen)

Hoebe 1997	Cohort study	2/104	Two "serious acute adverse reactions"[1] • Depressed mood • Dizziness	No treatment	0/93	-
Petersen 2000	Cohort study	5/809	5 hospitalisations: • Depressed mood • Depressed mood • Depressed mood, "strange thoughts" • Depressed mood, "strange thoughts", itching, vertigo • Vertigo, fever, mouth ulcers, diarrhoea	Chloroquine	6/1223	2 hospitalisations: • Blurred vision, nausea, headache, general skin itching, paraesthesia • Depressed mood
				No treatment	0/161	-
Korhonen 2007	Cohort study	15/1612	15 hospitalisations: • Dizziness (3) • Heart palpitations (2) • Limb numbness (1) • Abdominal pain (1) • Yeast infection (1) • Anxiety and depression (1) • Visual disturbance, photosensitivity (1) • Passing out, extreme fatigue (1) • "Went crazy", anxiety, nausea, vomiting (1) • "Psychotic reaction", anxiety, abnormal dreams (1) • Anxiety, abnormal dreams, insomnia, unsteadiness (1) • Nausea, dizziness, blackout (1)	Doxycycline	9/708	9 hospitalisations: • Gastrointestinal disturbance (6) • Photosensitivity (1), • Coughing (1) • Anaemia (1)
				Atovaquone-proguanil	0/72	-
				Chloroquine	4/832	4 hospitalisations: • Nausea, dizziness, visual disturbance, insomnia, abnormal dreams, unsteadiness, weakness • Abnormal dreams • Seizures • Abdominal pain, diarrhoea
Philips 1996	Cohort-study	4/285	3 hospitalisations with "either gastrointestinal or neurologic symptoms" and one seizure	Doxycycline	1/383	Severe oesophagitis

Table 7. Serious adverse effects; mefloquine versus comparators *(Continued)*

Steketee 1996	RCT	1/?	One "neuropsychiatric side effect" • Disorientation to time and place[1]	Chloroquine	0/?	-
Albright 2002	Cohort study	1/115	One "serious side effect"[1] • Hallucinations	Chloroquine	0/22	-
Corominas 1997	Cohort study	1/609	One hospitalisation: • Heart palpitations, convulsions, paraesthesia and vertigo	Chloroquine	0/137	-
Steffen 1993	Cohort study	7/52981	7 hospitalisations, including: • Seizures (2) • Psychosis (2) • Vertigo (1) • 2 not characterised	Chloroquine	7/20332	7 hospitalisations. 'Includes': • Seizures (2) • Psychosis (1) • 4 not characterised
Studies reporting no serious events or effects						
Hale 2003	RCT	0/46	Nine serious adverse events in the trial (trial arm not specified) "none of which were considered by study physicians to be related to the study drug"	Placebo	0/94	-
Salako 1992	RCT	0/107	"Adverse events were all mild and there were no deaths"	Placebo Chloroquine	0/101 0/103	- -
Arthur 1990	RCT	0/134	"No serious side effects occurred with either drug regimen"	Doxycycline	0/119	-
Schlagenhauf 2003	RCT	0/153	"Although a large number of adverse events were reported, none were serious"	Doxycycline Atovaquone-proguanil	0/153 0/164	- -
Sonmez 2005	Cohort study	0/228	"No drug induced side effects necessitating emergency care were observed"	Doxycycline	0/506	-
Andersson 2008	Cohort study	0/491	"No serious adverse events were recorded"	Atovaquone-proguanil	0/161	-
Napoletano 2007	Cohort study	0/548	Records hospitalisations, and reports that none occurred in either group of participants	Atovaquone-proguanil Chloroquine	0/707 0/37	- -
Sossouhounto 1995	RCT	0/103	"All side effects were transient (and)... mild"	Chloroquine	0/100	-

[1] This trial described a potentially serious adverse effect, but did not provide enough detail to meet our strict definition.

Table 8. Mefloquine versus doxycycline; characteristics of included studies for safety

Study ID	Participants	Number enrolled	Method of adverse event monitoring	Significant exclusions for psychiatric adverse effects	Duration of travel	Source of funding
Randomized controlled trials						
Arthur 1990	USA soldiers	270	Blood tests, stool samples. Interview with study personnel	None	5 weeks	Not mentioned
Ohrt 1997	Indonesian soldiers	204	Interview with study personnel. Exit questionnaire	" History of underlying illness"	13 weeks	Pfizer and Roche
Schlagenhauf 2003	Non-immune adult short-term travellers	674	Participant self-reported questionnaire	History of seizures or psychiatric disorders	4 to 6 weeks	GlaxoSmithKline and Roche
Weiss 1995	Kenyan children	169	Interview with study personnel	None	4 months	Government funding
Non-randomized studies						
	Participants	**Number enrolled**	**Method of adverse event monitoring**	**Factors influencing drug allocation**	**Duration of travel**	**Source of funding**
Cunningham 2014	UK Foreign and Commonwealth Office staff	327	Participant self-reported questionnaire	Allocation based on guidelines and participant preference	0 to 36 months	Not mentioned
Eick-Cost 2017	USA s oldiers	367,840	Data from the Defense Medical Surveillance System, the Pharmacy Data Transaction Service and the Theater Medical Data Store	No information available	Various, not specified	Not mentioned
Goodyer 2011	UK adult short-term travellers	185	Participant self-reported questionnaire	Allocation based on guidelines and participant preference	< 28 days	GlaxoSmithKline
Korhonen 2007	Peace Corps volunteers	2701	Participant self-reported questionnaire	Allocation based on guidelines and participan t preference	≥ 6 months	Two staff employed by Peace Corps
Landman 2015	Peace Corps volunteers	1184	Participant self-reported questionnaire	Allocation based on guidelines and participant preference	Various, not specified	Not mentioned
Laver 2001	Adult short-term travellers	660	Participant self-reported questionnaire	No information available	93% < 4 weeks	" No financial interests to disclose"

Table 8. Mefloquine versus doxycycline; characteristics of included studies for safety *(Continued)*

Lobel 2001	Adult short-term travellers	5626	Participant self-reported questionnaire	No information available	< 5 weeks	" No financial interests to disclose"
Meier 2004	UK adults enrolled in UK g eneral p ractice research database	35,370	Incident cases of depression, psychoses and panic attacks within the UK general practice research database	No information available	Various, not specified	Roche
Napoletano 2007	Italian short-term travellers	1906	Telephone interview	Allocation based on guidelines and participant preference	Mean 2 weeks, range 0 to > 35 days	Not mentioned
Philips 1996	Australian short-term travellers	741	Participant self-reported questionnaire	Allocation based on guidelines and participant preference	Various, mean 3 weeks, maximum 3 months	Roche and Pfizer
Saunders 2015	USA soldiers	2351	Participant self-reported questionnaire	Primarily doxycycline, soldiers with contra-indications received mefloquine	> 90% for 10 months or more	Not mentioned
Schwartz 1999	Israeli short-term travellers	158	Participant self-reported questionnaire	"... daily doxycycline or daily primaquine... was recommended"	14 to 20 days	Not mentioned
Shamiss 1996	Israeli soldiers	45	Participant self-reported questionnaire	Allocation based on guidelines and participant preference	"... an average of 4 hours stay in the field over a period of 2 months"	Not mentioned
Sharafeldin 2010	Dutch medical students	180	Participant self-reported questionnaire	Allocation based on guidelines and participant preference	Mean 74 days (range 10 to 224 days)	No dedicated funding
Sonmez 2005	Turkish soldiers	1400	Participant self-reported questionnaire	Prior to March 2002: doxycyline After July 2002: mefloquine	A pprox. 6 months	Not mentioned
Stoney 2016	USA short-term travellers	370	Participant self-reported questionnaire	Allocation based on guidelines and participant preference	Median duration 13 days	Government funding
Tan 2017	Peace Corps volunteers	8931	Participant self-reported questionnaire	No information available	Various, not specified	No dedicated funding

Table 8. Mefloquine versus doxycycline; characteristics of included studies for safety *(Continued)*

Terrell 2015	UK soldiers	2032	Participant self-reported questionnaire	Allocation based on guidelines and participant preference	Median duration 13 days	"... not funded by an external body"
Tuck 2016	UK soldiers	151	Participant self-reported questionnaire	Allocation based on guidelines and participant preference	Various, not specified	No dedicated funding
Waner 1999	Adult short-term travellers	3051	Participant self-reported questionnaire	No information available	A pprox. 6 weeks	Not mentioned

Table 9. Mefloquine versus doxycycline; quality of adverse event reporting

Study ID	Harms predefined[1]	Description of ascertainment technique[2]	Active or passive monitoring?[3]	Prospective or retrospective data collection?
RCTs				
Arthur 1990	Inadequate: No definitions provided for serious side effects	Unclear: it is not reported who conducted the interviews	Active	Prospective
Ohrt 1997	Inadequate Comment: No definitions of adverse events or effects were provided, it wa s unclear whether or how causality was assessed	Adequate	Active	Prospective
Schlagenhauf 2003	Adequate	Adequate	Active	Prospective
Weiss 1995	Inadequate " Each subject was visited daily at home by an assigned field worker, who asked about symptoms of malaria or drug side effects"	Adequate	Active	Prospective
Cohort studies				
Cunningham 2014	Inadequate Comment: questionnaire included a targeted list of side effects, including " other psychological problems" . What was included within this was not defined	Adequate	Passive	Unclear Comment: questionnaire was performed while participants were still taking chemoprophylaxis medication, although 75% were non-compliant
Eick-Cost 2017	Adequate	Adequate	Passive	Prospective
Goodyer 2011	Inadequate	Adequate	Active	Retrospective

Table 9. Mefloquine versus doxycycline; quality of adverse event reporting *(Continued)*

	" Also included on the questionnaire was a single free-text question asking travellers to describe any side effects of antimalarial medication"			
Korhonen 2007	Adequate	Adequate	Passive	Unclear Comment: n o information wa s provided regarding the timing of the questionnaire during treatment
Landman 2015	Adequate	Adequate	Passive	Unclear Comment: all participants were emailed the questionnaire at one time point, which occurred at varying points during the prophylactic regimen
Lobel 2001	Inadequate "Travellers… were given a questionnaire that asked for... adverse health events attributed to those drugs"	Adequate	Passive	Unclear Comment: information was collected at the airport, when travellers should still have been taking the prophylactic regimen
Meier 2004	Adequate	Adequate	Passive	Retrospective
Napoletano 2007	Unclear Comment: adverse events were categorised on a scale of one to four, but it is unclear whether and how causality was assessed	Adequate	Active	Retrospective
Philips 1996	Inadequate Comment: it wa s unclear what constituted a serious or severe event and insufficient information on the questions that travellers were asked	Inadequate "... a mailed questionnaire approximately 2 weeks after their anticipated return home date' 'if a reply had not been received within 4 weeks an abbreviated questionnaire was sent out." Comment: no details provided regarding abbreviated questionnaire	Active	Retrospective
Saunders 2015	Inadequate	Adequate	Passive	Retrospective

Table 9. Mefloquine versus doxycycline; quality of adverse event reporting *(Continued)*

	Comment: insufficient information of the questions that travellers were asked			
Schwartz 1999	Inadequate "... we directly contacted all travelers for complete follow-up and assessment of compliance. Fifty travelers taking primaquine completed a questionnaire regarding side effects"	Inadequate Comment: see quote. Different methods of follow up for different forms of prophylaxis	Unclear	Unclear
Shamiss 1996	Inadequate Comment: insufficient information provided on the questions that travellers were asked	Inadequate " Questionnaires were distributed and collected by the flight surgeon to 45 aircrew…questionnaires were immediately evaluated and further data collection was done by telephone, if necessary"	Passive	Unclear Comment: it wa s unclear at which time point data collection occurred
Sharafeldin 2010	Inadequate Comment: n o information wa s provided on how information on adverse effects was sought	Inadequate Comment: n o mention of how adverse events were recorded in the questionnaire	Passive	Retrospective
Sonmez 2005	Inadequate Comment: insufficient information provided on the questions that travellers were asked	Adequate	Active	Prospective
Stoney 2016	Inadequate Comment: insufficient information provided on the questions that travellers were asked	Inadequate Comment: n o information is reported on how adverse events were ascertained	Active	Prospective
Tan 2017	Adequate	Adequate	Active	Retrospective
Terrell 2015	Inadequate " The questionnaire approved by the MODREC included the 19 commonest adverse effects described in the manufacturers' product documentation" Comment: Adverse events listed in the questionnaire are not reported	Adequate	Passive	Unclear Comment: information obtained during transit through Nairobi back to the UK. It wa s unclear whether participants were still taking prophylaxis at this time point

Table 9. Mefloquine versus doxycycline; quality of adverse event reporting *(Continued)*

Tuck 2016	Inadequate Comment: insufficient information provided on the questions that travellers were asked	Adequate	Active	Unclear Comment: i t wa s not specified at which point during treatment the questionnaire was administered
Waner 1999	Inadequate Comment: insufficient information provided on the questions that travellers were asked	Adequate	Passive	Unclear Comment: information was collected during the flight home, when travellers should still have been taking their prophylactic regimen

1. Were harms pre-defined using standardised or precise definitions?
2. Was ascertainment technique adequately described?
3. Monitoring classed as 'active' if it occurred at set time points during treatment.
For full description of analysis methods, see Table 2.

Table 10. Mefloquine versus atovaquone-proguanil; characteristics of included studies for safety

Study ID	Participants	Number enrolled	Method of adverse event monitoring	Significant exclusions for psychiatric adverse effects	Duration of travel	Source of funding
Randomized controlled trials						
Overbosch 2001	Travellers from Canada, Germany, Netherlands, South Africa, UK	1013	Interview with study personnel	"... history of alcoholism, seizures or psychiatric or severe neurological disorders"	Mean 2.5 weeks	GlaxoSmithKline
Schlagenhauf 2003	Non-immune adult short-term travellers	674	Participant self-reported questionnaire	" History of seizures or psychiatric disorders"	4 to 6 weeks	GlaxoSmithKline and Roche
van Riemsdijk 2002	Dutch short-term travellers	140	Interview and testing with study personnel	"H istory of alcoholism, seizures, psychiatric disorders, severe neurological disorders"	Mean 19 days	Government funding
Non-randomis ed studies						
	Participants	**Number enrolled**	**Method of adverse event monitoring**	**Factors influencing drug allocation**	**Duration of travel**	**Source of funding**
Andersson 2008	Swedish soldiers	609	Participant self-reported questionnaire	Mainly mefloquine, soldiers with contra-indications received atovaquone-proguanil	6 months	Not mentioned

Table 10. Mefloquine versus atovaquone-proguanil; characteristics of included studies for safety *(Continued)*

Belderok 2013	Dutch short-term travellers	945	Participant self-reported questionnaire (measured adherence)	Allocation based on guidelines and participant preference	84% < 29 days	Government funding
Cunningham 2014	UK Foreign and Commonwealth Office staff	327	Participant self-reported questionnaire	Allocation based on guidelines and p articipant preference	0-36 months	Not mentioned
Eick-Cost 2017	USA s oldiers	367,840	Data from the Defense Medical Surveillance System, the Pharmacy Data Transaction Service and the Theater Medical Data Store	No information available	Various, not specified	Not mentioned
Goodyer 2011	UK adult short-term travellers	185	Participant self-reported questionnaire	Allocation based on guidelines and p articipant preference	< 28 days	GlaxoSmithKline
Kato 2013	Japanese short-term travellers	316	Participant self-reported questionnaire	Allocation based on guidelines and participant preference	Mean 20.0 ± 9.6 days in the atovaquone-proguanil group and 59.0 ± 15.9 days in the mefloquine group	Not mentioned
Korhonen 2007	Peace Corps volunteers	2701	Participant self-reported questionnaire	Allocation based on guidelines and participant preference	≥ 6 months	Two staff employed by Peace Corps
Kuhner 2005	German short-term travellers	495	Participant self-reported questionnaire	Allocation based on guidelines and participant preference	A atovaquone-proguanil mean 2.6 weeks, mefloquine mean 7 weeks	Not mentioned
Landman 2015	Peace Corps volunteers	1184	Participant self-reported questionnaire	Allocation based on guidelines and participant preference	Various, not specified	Not mentioned
Laverone 2006	Italian short-term travellers	1176	Participant self-reported questionnaire	Allocation based on guidelines and participant preference	> 90% 0 to 30 days	Not mentioned
Napoletano 2007	Italian short-term travellers	1906	Telephone interview	Allocation based on guidelines and participant preference	Mean 2 weeks, range 0 to > 35 days	Not mentioned
Schneider 2013	UK adults enrolled in UK g eneral p rac-	Not available	Incident cases of a neuropsychiatric dis-	No information available	Various, not specified	Roche

Table 10. Mefloquine versus atovaquone-proguanil; characteristics of included studies for safety *(Continued)*

	tice research database		orders during or after antimalarial drug use			
Sharafeldin 2010	Dutch medical students	180	Participant self-reported questionnaire	Allocation based on guidelines and participant preference	Mean duration of stay 74 days (range 10 to 224 days)	" N o dedicated funding for this project"
Stoney 2016	USA short-term travellers	370	Participant self-reported questionnaire	Allocation based on guidelines and participant preference	Median duration 13 days	Government funding
Tan 2017	Peace Corps volunteers	8931	Participant self-reported questionnaire	No information available	Various, not specified	No dedicated funding
Tuck 2016	UK soldiers	151	Participant self-reported questionnaire	Allocation based on guidelines and participant preference	Various, not specified	No dedicated funding

Table 11. Mefloquine versus atovaquone-proguanil; quality of adverse event reporting

Study ID	Harms predefined[1]	Description of ascertainment technique[2]	Active or passive monitoring?[3]	Prospective or retrospective data collection?
RCTs				
Overbosch 2001	Adequate	Adequate	Active	Prospective
Schlagenhauf 2003	Adequate	Adequate	Active	Prospective
van Riemsdijk 2002	Adequate	Adequate	Active	Prospective
Cohort studies				
Andersson 2008	Inadequate Comment: insufficient information provided on the questions which soldiers were asked	Inadequate Comment: different ascertainment technique used for one of the three groups, which is inadequately described	Active	Unclear Comment: d ata collection was prospective for 448/609 participants (LA04 and LA05), but retrospective for 161 participants (LA02)
Cunningham 2014	Inadequate Comment: questionnaire included a targeted list of side effects, including " other psychological problems" . What was included within this was not defined	Adequate	Passive	Unclear Comment: questionnaire was performed while participants were still taking chemoprophylaxis medication, although 75% were non-compliant

Table 11. Mefloquine versus atovaquone-proguanil; quality of adverse event reporting *(Continued)*

Eick-Cost 2017	Adequate	Adequate	Passive	Prospective
Goodyer 2011	Inadequate " Also included on the questionnaire was a single free-text question asking travelers to describe any side effects of antimalarial medication"	Adequate	Active	Retrospective
Kato 2013	Adequate	Adequate	Passive	Unclear Comment: the timing of this questionnaire has not been made clear
Korhonen 2007	Adequate	Adequate	Passive	Unclear Comment: n o information wa s provided regarding the timing of the questionnaire during treatment
Kuhner 2005	Inadequate Comment: insufficient information provided on the questions that participants were asked	Adequate	Active	Retrospective
Landman 2015	Adequate	Adequate	Passive	Unclear Comment: all participants were emailed the questionnaire at one time point, which occurred at varying points during the prophylactic regimen
Laverone 2006	Adequate	Adequate	Passive	Retrospective
Napoletano 2007	Unclear Comment: adverse events were categorised on a scale of one to four, but it is unclear whether and how causality was assessed	Adequate	Active	Retrospective
Schneider 2013	Adequate	Adequate	Passive	Retrospective
Sharafeldin 2010	Inadequate Comment: n o information is provided on how information on adverse effects was sought	Inadequate Comment: n o mention of how adverse events were recorded in the questionnaire.	Passive	Retrospective
Stoney 2016	Inadequate Comment: insufficient information provided on the questions that travellers were asked	Inadequate Comment: n o information is reported on how	Active	Prospective

Table 11. Mefloquine versus atovaquone-proguanil; quality of adverse event reporting *(Continued)*

		adverse events were ascertained		
Tan 2017	Adequate	Adequate	Active	Retrospective
Tuck 2016	Inadequate Comment: insufficient information provided on the questions that travellers were asked	Adequate	Active	Unclear Comment: i t wa s not specified at which point during treatment the questionnaire was administered

1. Were harms pre-defined using standardised or precise definitions?
2. Was ascertainment technique adequately described?
3. Monitoring classed as 'active' if it occurred at set time points during treatment.
For full description of analysis methods, see Table 2.

Table 12. Mefloquine versus chloroquine; characteristics of included studies for safety

Study ID	Participants	Number enrolled	Method of adverse event monitoring	Significant exclusions for psychiatric side effects	Trial duration	Source of funding
RCT s						
Boudreau 1991	Thai gem miners	501	Interview with study personnel	None	14 weeks	USA Army
Boudreau 1993	USA soldiers	359	Interview with study personnel and computerised questionnaire	"M edical history of psychiatric or neurological problems within the last 5 years"	13 weeks	Not mentioned
Bunnag 1992	Thai adult mal es	605	Interview with study personnel	None	24 weeks	Roche
Salako 1992	Nigerian adult males	567	Interview with study personnel	None	24 weeks	Not mentioned
Sossouhounto 1995	Ivory C oast adult males	500	" Access to the village health centre. Clinical examination with study personnel"	None	20 weeks	Not mentioned
Steketee 1996	Pregnant Malawian women	4220	Interview with study personnel	None	Monitored from enrolment to delivery	Government funding
Non-randomised studies						
	Participants	**Number enrolled**	**Method of adverse event monitoring**	**Factors influencing drug allocation**	**Duration of travel**	**Source of funding**
Albright 2002	USA travelling children aged < 13 years	177	Interview with study personnel	Allocation based on guidelines and participant preference	Various, not specified	Not mentioned

Table 12. Mefloquine versus chloroquine; characteristics of included studies for safety *(Continued)*

Corominas 1997	Spanish short-term adult travellers	1054	Participant self-reported questionnaire	Allocation based on guidelines and participant preference	Maximum 6 weeks	Not mentioned
Cunningham 2014	UK Foreign and Commonwealth Office staff	327	Participant self-reported questionnaire	Allocation based on guidelines and participant preference	0 to 36 months	Not mentioned
Hill 2000	USA short-term travellers	822	Interview with study personnel	Allocation based on guidelines and participant preference	Median 19 days, up to 90 days	Not mentioned
Korhonen 2007	Peace Corps volunteers	2701	Participant self-reported questionnaire	Allocation based on guidelines and participant preference	≥ 6 months	Two staff employed by Peace Corps
Laver 2001	Adult short-term travellers	660	Participant self-reported questionnaire	No information available	93% < 4 weeks	" No financial interests to disclose"
Laverone 2006	Italian short-term travellers	1176	Participant self-reported questionnaire	Allocation based on guidelines and participant preference	> 90% 0 to 30 days	Not mentioned
Lobel 2001	Adult short-term travellers	5626	Participant self-reported questionnaire	No information available	M ost < 5 weeks	" No financial interests to disclose"
Napoletano 2007	Italian short-term travellers	1906	Telephone interview	Allocation based on guidelines and participant preference	Mean 2 weeks, range 0 to > 35 days	Not mentioned
Petersen 2000	Danish travellers	4154	Participant self-reported questionnaire	Allocation based on guidelines and participant preference	Various, 65% < 3 weeks	Not mentioned
Rietz 2002	Swedish short-term travellers	491	Participant self-reported questionnaire	Allocation based on guidelines and participant preference	" Most" 2 to 4 weeks	Not mentioned
Steffen 1993	Adult short-term travellers	145,003	Participant self-reported questionnaire	No information available	98% stayed between 1 and 4 weeks	Roche
Stoney 2016	USA short-term travellers	370	Participant self-reported questionnaire	Allocation based on guidelines and participant preference	Median duration 13 days	Government funding
Tan 2017	Peace Corps volunteers	8931	Participant self-reported questionnaire	No information available	Various, not specified	No dedicated funding

Table 12. Mefloquine versus chloroquine; characteristics of included studies for safety *(Continued)*

Waner 1999	Adult short-term travellers	3051	Participant self-reported questionnaire	No information available	A pprox. 6 weeks	" not funded by an external body"

Table 13. Mefloquine versus chloroquine; quality of adverse events reporting

Study ID	Harms predefined[1]	Description of ascertainment technique[2]	Active or passive monitoring?[3]	Prospective or retrospective data collection?
RCTs				
Boudreau 1991	Adequate	Adequate	Active	Prospective
Boudreau 1993	Adequate	Adequate	Active	Prospective
Bunnag 1992	Inadequate " Adverse events were defined clinically, and starting week 14, volunteers reporting adverse events were interviewed by members of the hospital team"	Adequate	Active	Prospective
Salako 1992	Inadequate " Particular attention was paid to complaints such as fever, chills, malaise, nausea and vomiting, rashes and other symptoms and signs that could be regarded as adverse events." Comment: no clear definition of adverse events wa s provided	Adequate	Active	Prospective
Sossouhounto 1995	Inadequate " Participants had access to a village health center, where they could notify personnel of any malaise or side effects"	Unclear " Clinical examinations and parasitologic tests were performed every 4 weeks"	Passive	Prospective
Steketee 1996	Adequate	Adequate	Active	Prospective
Cohort studies				
Albright 2002	Adequate	Adequate	Passive	Retrospective
Corominas 1997	Inadequate Comment: insufficient information wa s provided about the questions that travellers were asked	Adequate	Active	Retrospective
Cunningham 2014	Inadequate	Adequate	Passive	Unclear

Table 13. Mefloquine versus chloroquine; quality of adverse events reporting *(Continued)*

	Comment: questionnaire included a targeted list of side effects, including " other psychological problems" . What was included within this was not defined			Comment: questionnaire was performed while participants were still taking chemoprophylaxis medication, although 75% were non-compliant
Hill 2000	Inadequate Comment: insufficient information wa s provided about the questions that travellers were asked	Adequate	Active	Retrospective
Korhonen 2007	Adequate	Adequate	Passive	Unclear Comment: No information wa s provided regarding the timing of the questionnaire during treatment
Laverone 2006	Adequate	Adequate	Passive	Retrospective
Lobel 2001	Inadequate "Travellers… were given a questionnaire that asked for... adverse health events attributed to those drugs"	Adequate	Passive	Unclear Comment: information was collected at the airport, when travellers should still have been taking the prophylactic regimen
Napoletano 2007	Unclear Comment: adverse events were categorised on a scale of one to four, but it is unclear whether and how causality was assessed	Adequate	Active	Retrospective
Petersen 2000	Inadequate Comment: i t wa s unclear whether the questionnaire implied causality to the drug regimen	Adequate	Active	Retrospective
Rietz 2002	Adequate	Adequate	Active	Retrospective
Steffen 1993	Adequate	Adequate	Passive	Unclear Comment: information was collected during the flight home, when travellers should still have been taking the prophylactic regimen
Stoney 2016	Inadequate Comment: insufficient information provided on the questions that travellers were asked	Inadequate Comment: n o information wa s reported on how	Active	Prospective

Table 13. Mefloquine versus chloroquine; quality of adverse events reporting *(Continued)*

		adverse events were ascertained		
Tan 2017	Adequate	Adequate	Active	Retrospective
Waner 1999	Inadequate Comment: insufficient information provided on the questions that travellers were asked	Adequate	Passive	Unclear Comment: information was collected during the flight home, when travellers should still have been taking the prophylactic regimen

1. Were harms pre-defined using standardised or precise definitions?
2. Was ascertainment technique adequately described?
3. Monitoring classed as 'active' if it occurred at set time points during treatment.
For full description of analysis methods, see Table 2.

Table 14. Mefloquine versus currently used regimens; by duration of travel

	Mefloquine versus atovaquone-proguanil and doxycycline		
Outcome	**Short- term travellers[1]**	**Longer- term travellers[2]**	**Test for subgroup differences**
	Relative effect (RR) (95% CI) Studies (participants)	**Relative effect (RR) (95% CI) Studies (participants)**	
Serious adverse effects	**RR 5.38** (0.60 to 47.84) 3 cohort studies (2657)	**RR 0.93** (0.43 to 2.01) 3 cohort studies (3147)	P = 0.14
Discontinuations due to adverse effects (RCTs)	**RR 2.64** (1.51 to 4.62) 5 RCTs (2048)	-	-
Discontinuations due to adverse effects (cohort studies)	**RR 1.81** (0.86 to 3.80) 7 cohort studies (2907)	**RR 1.19** (0.45 to 3.17) 4 cohort studies (5711)	P = 0.50
Nausea	**RR 2.02** (0.87 to 4.68) 6 cohort studies (2469)	**RR 0.96** (0.22 to 4.18) 3 cohort studies (2725)	P = 0.39
Abdominal pain	**RR 0.66** (0.22 to 1.98) 5 cohort studies (1801)	**RR 0.30** (0.22 to 0.42) 3 cohort studies (2725)	P = 0.18
Diarrhoea	**RR 0.64**	**RR 0.57**	P = 0.89

Table 14. Mefloquine versus currently used regimens; by duration of travel *(Continued)*

	(0.15 to 2.71)	(0.22 to 1.49)	
	5 cohort studies (2428)	4 cohort studies (5187)	
Headache	**RR 2.39**	**RR 2.09**	P = 0.85
	(0.69 to 8.22)	(1.10 to 3.95)	
	5 cohort studies (2086)	4 cohort studies (3506)	
Dizziness	**RR 3.05**	**RR 3.84**	P = 0.76
	(1.15 to 8.12)	(1.34 to 11.00)	
	4 cohort studies (1067)	4 cohort studies (3506)	
Abnormal dreams	**RR 6.25**	**RR 7.62**	P = 0.86
	(1.16 to 33.67)	(2.06 to 28.18)	
	3 cohort studies (1037)	4 cohort studies (3506)	
Insomnia	**RR 3.09**	**RR 8.67**	P = 0.40
	(0.30 to 32.21)	(4.73 to 15.89)	
	4 cohort studies (1760)	4 cohort studies (3506)	
Anxiety	**RR 3.26**	**RR 18.05**	P = 0.24
	(0.20 to 53.46)	(9.75 to 33.42)	
	1 cohort study (487)	3 cohort studies (2854)	
Depressed mood	**RR 2.52**	**RR 12.59**	P = 0.02
	(0.76 to 8.29)	(6.47 to 24.49)	
	3 cohort studies (1026)	3 cohort studies (3210)	
Abnormal thoughts and behaviours	**RR 1.29**	**RR 7.78**	P = 0.31
	(0.07 to 22.44)	(1.12 to 54.06)	
	1 cohort study (487)	2 cohort studies (2558)	
Adherence: during travel	**RR 1.10**	**RR 1.20**	P = 0.61
	(1.03 to 1.18)	(0.88 to 1.62)	
	7 cohort studies (7241)	4 cohort studies (4890)	
Adherence: after return	**RR 1.04**	-	-
	(0.92 to 1.17)		
	4 cohort studies (1221)		

[1] Short- term travellers: Approximately 3 weeks (range 1 day to 3 months). References: Goodyer 2011; Kato 2013; Kuhner 2005; Napoletano 2007; Laver 2001; Laverone 2006; Lobel 2001; Philips 1996; Schwartz 1999; Shamiss 1996; Sonmez 2005; Stoney 2016; Terrell 2015

[2] Longer- term travellers: Approximately 6 months (range 0 to 36 months in Cunningham 2014 . Otherwise 3 months or longer). References Andersson 2008; Cunningham 2014; Korhonen 2007; Landman 2015; Saunders 2015; Sharafeldin 2010

Table 15. Mefloquine versus currently used regimens; by military or non-military participants

	Mefloquine versus atovaquone-proguanil and doxycycline		
Outcome	**Military[1]**	**Non-military[2]**	**Test for subgroup differences**
	Relative effect (RR) (95% CI) Studies (participants)	**Relative effect (RR) (95% CI) Studies (participants)**	
Serious adverse effects	0 events in 1386 participants	**RR 1.21** (0.60 to 2.44) 4 cohort studies (4418)	-
Discontinuations due to adverse effects (RCTs)	**RR 2.08** (0.13 to 32.73) 2 RCTs (441)	**RR 2.22** (1.17 to 4.21) 4 RCTs (1669)	P = 0.96
Discontinuations due to adverse effects (cohorts)	**RR 1.24** (0.32 to 4.88) 4 cohort studies (3408)	**RR 1.89** (1.35 to 2.64) 8 cohort studies (8938)	P = 0.56
Nausea	**RR 1.39** (0.36 to 5.36) 4 cohort studies (1578)	**RR 1.70** (0.60 to 4.81) 6 cohort studies (3767)	P = 0.26
Abdominal pain	**RR 0.43** (0.14 to 1.29) 4 cohort studies (1578)	**RR 0.56** (0.23 to 1.35) 5 cohort studies (3099)	P = 0.72
Diarrhoea	**RR 0.30** (0.09 to 0.96) 4 cohort studies (3999)	**RR 1.05** (0.54 to 2.06) 6 cohort studies (3767)	P = 0.07
Headache	**RR 1.19** (0.14 to 9.79) 2 cohort studies (1386)	**RR 2.48** (1.40 to 4.40) 7 cohort studies (4206)	P = 0.51
Dizziness	**RR 2.95** (1.37 to 6.36) 3 cohort studies (844)	**RR 3.58** (1.39 to 9.25) 6 cohort studies (3880)	P = 0.76
Abnormal dreams	**RR 11.02** (4.61 to 26.34)	**RR 6.59** (1.74 to 25.00)	P = 0.53

Table 15. Mefloquine versus currently used regimens; by military or non-military participants *(Continued)*

	1 cohort study (652)	6 cohort studies (3891)	
Insomnia	**RR 2.34** (0.41 to 13.35) 3 cohort studies (1537)	**RR 10.24** (6.26 to 16.76) 6 cohort studies (3880)	P = 0.11
Anxiety	-	**RR 16.94** (9.36 to 30.64) 4 cohort studies (3390)	-
Depressed mood	**RR 13.44** (3.34 to 54.05) 1 cohort study (652)	**RR 6.49** (2.66 to 15.85) 5 cohort studies (3584)	P = 0.39
Abnormal thoughts and behaviours	-	**RR 5.11** (1.11 to 23.53) 3 cohort studies (3045)	-
Adherence: during travel	**RR 1.18** (1.00 to 1.40) 5 cohort studies (4652)	**RR 1.16** (0.99 to 1.35) 8 cohort studies (10785)	P = 0.85
Adherence: after return	**RR 1.16** (0.86 to 1.55) 1 cohort study (43)	**RR 1.02** (0.89 to 1.16) 3 cohort studies (1178)	P = 0.44

[1] Military participants: References: RCTs: Arthur 1990; Ohrt 1997. Cohort studies: Andersson 2008, Saunders 2015; Shamiss 1996; Sonmez 2005; Terrell 2015; Tuck 2016
[2] Non-military participants: References: RCTs: Overbosch 2001; Schlagenhauf 2003; van Riemsdijk 2002; Weiss 1995. Cohort studies: Cunningham 2014; Goodyer 2011; Kato 2013; Kuhner 2005; Korhonen 2007; Landman 2015; Laver 2001; Laverone 2006; Lobel 2001; Napoletano 2007; Philips 1996; Schwartz 1999; Sharafeldin 2010; Stoney 2016

APPENDICES

Appendix 1. List of study design features

Feature	RCT	Q-RCT	N-RCT	PCS	RCS
Was there a comparison:					
Between two or more groups receiving the intervention?	Y	Y	Y	Y	Y

(Continued)

Within the same group of participants over time?	P	P	N	N	N
Were participants allocated to groups by:					
Concealed randomization?	Y	N	N	N	N
Quasi-randomization?	N	Y	N	N	N
By other action of researchers?	N	N	Y	N	N
Time differences?	N	N	N	N	N
Location differences?	N	N	P	P	P
Treatment decisions?	N	N	N	P	P
Participants' preferences?	N	N	N	P	P
On the basis of outcome?	N	N	N	N	N
Which parts of the study were prospective:					
Identification of participants?	Y	Y	Y	Y	N
Assessment of baseline and allocation to intervention?	Y	Y	Y	Y	N
Assessment of outcomes?	Y	Y	Y	Y	P
Generation of hypotheses?	Y	Y	Y	Y	Y
On what variables was comparability between groups assessed:					
Potential confounders?	P	P	P	P	P
Baseline assessment of outcome variables?	P	P	P	P	P

Footnotes

Y = Yes, N = No, P = Possibly

Abbreviations: RCT = randomized controlled trial; Q-RCT = quasi-randomized controlled trial; NRCT = non-randomized controlled trial; PCS = prospective cohort study; RCS = retrospective cohort study

Adapted from Reeves 2011.

Appendix 2. Search strategies - malaria chemoprophylaxis

Search set	CIDG Specialized Register	CENTRAL	MEDLINE	Embase	LILACS
1	malaria	Malaria ti, ab, MeSH	Malaria ti, ab, MeSH	Malaria ti, ab, Emtree	malaria

(Continued)

2	Mefloquine OR Lariam	Antimalaria* ti, ab	Antimalaria* ti, ab	Antimalaria* ti, ab	Mefloquine OR Lariam
3	Prevent* OR prophyla* OR chemoprevent* OR chemopro-phyla*	1 or 2	1 or 2	1 or 2	Prevent* OR prophyla* OR chemo-prevent* OR chemopro-phyla*
4	1 and 2 and 3	Mefloquine ti, ab, MeSH	Mefloquine ti, ab, MeSH	Mefloquine ti, ab, Emtree	1 and 2 and 3
5	—	Lariam ti, ab	Lariam ti, ab	Lariam ti, ab	—
6	—	4 or 5	4 or 5	4 or 5	—
7	—	Prevent* OR prophyla* OR chemoprevent* OR chemoprophyla* ti, ab	Prevent* OR prophyla* OR chemoprevent* OR chemoprophyla* ti, ab	Prevent* OR prophyla* OR chemoprevent* OR chemoprophyla* ti, ab	—
8	—	6 and 7	6 and 7	6 and 7	—

Footnotes

Date of search: 22 June 2017.

Search terms for MEDLINE, Embase, and LILACS were used in combination with the search strategy for retrieving trials developed by the Cochrane Collaboration (Lefebvre 2011).

Appendix 3. Decision aid for inclusion of meta-analyses in 'Summary of findings' tables

Outcome reported	Study design	Population studied	Preference
Adverse effects	RCTs	Short term international travellers	1
		Other populations	2
	Cohort studies	Short term international travellers	3
		Other populations	4
Adverse events	RCTs	Short term international travellers	5
		Other populations	6
	Cohort studies	Short term international travellers	7
		Other populations	8

Appendix 4. Mefloquine versus placebo: other outcomes and groups of symptoms

Groups of symptoms

RCTs

Potasman 2002 (an RCT) compared 'neuropsychiatric' outcomes between study arms, and did not show a difference (RR 2.28, 95%CI 0.70 to 7.41, 90 participants). The authors did not define what they included within 'neuropsychiatric' although they do note that it 'included sleep disturbances, strange dreams, and inability to concentrate'. Within the RCTs there was no difference in the number of participants experiencing 'any adverse event' (RR 1.04, 95% CI 0.85 to 1.27, 7 trials, 1040 participants).

Other outcomes

RCTs

Three RCTs reported other outcomes which could be used as proxy measures of psychological or neurological adverse effects. These are described in the table below.

Study ID	Mefloquine participants	Drug comparator(s) (N)	Outcome(s) measured	Results reported
Davis 1996	46	Placebo (49)	1. Symbol digit modalities test[1] 2. Digit span backwards and forwards[2] 3. ECG 4. Hearing loss at 6k	Symbol digit modalities test and digit span backwards and forwards: no significant differences between groups ECG: "there was a statistically significant prolongation in the electrocardiographic QTc interval between the first and second assessments in the subjects who received mefloquine (P 0.007); a less pronounced and later trend was in the placebo group (P 0.03)." Hearing loss at 6k: reports no statistically significant differences between groups
Schlagenhauf 1997	23 (cross-over)	Placebo (23, cross-over)	1. POMS[3], 2. ESQ[4], 3. NES[5], 4. Sleep assessment 5. ICA[6] 6. Body sway	POMS: Reports no statistically significant differences between groups. ESQ: Reports no statistically significant differences between groups. NES: Reports no statistically significant differences between groups. Sleep assessment: "the means of participants taking the mefloquine loading dose (456 mm) and weekly dose (450 mm) were less than the corresponding means for those taking the placebo loading (491 mm) and weekly doses (484 mm) by 35 and 34 mm, respectively" ICA: Reports no statistically significant differences between groups. Body sway: "mefloquine users ha[d] a higher mean sway than placebo users but no differences were significant"
Vuurman 1996	22	Placebo (20)	1. Critical flicker/ fusion frequency[7]	Critical flicker/fusion frequency: Reports no statistically significant differences between groups. Critical instability tracking tests: Reports no statistically significant differences between groups.

(Continued)

	2. Critical instability tracking tests[8] 3. Body sway 4. Tests of driving performance	Body sway: Reports no statistically significant differences between groups. Tests of driving performance: "[mefloquine] significantly improved road tracking performance on Day 4"

[1]Symbol digit modalities test: a test of information processing speed.
[2]Digit span backwards and forwards: Participants are presented a series of numbers (for example, 2, 7, 4 at a rate of one digit per second), and asked to repeat them in the same (digit span forwards) or reverse (digit span backwards) sequence. These are usually viewed as simple short-term memory tasks.
[3]Profile of Mood States (POMS): a validated questionnaire designed to measure feelings in five domains: tension, depression, anger, fatigue, and vigor. Answers are graded ranging from 'not at all (0)' to 'extremely (4)'. The total mood disturbance (TMD) is a composite overall score which is calculated by adding the scores across the four categories of tension, anger, fatigue and depression and subtracting the score for vigour. The total ranges from 20 to 108. An increased TMD score indicates a deterioration of mood.
[4]Environmental Symptoms Questionnaire (ESQ): a standardized form containing 68 questions relating to all body systems. Responses consist of six graded answers ranging from 'not at all' to 'extreme'.
[5]Neurobehavioral evaluation system (NES): a series of computerized tests designed to provide quantitative neurobehavioral outcomes which measures performance, such as sustained attention (response latency), coding speed, and visuomotor accuracy.
[6]Instrument co-ordination analyser (ICA): This is a tool used in the selection of trainee pilots, and measures multiple task abilities. It It simulates simplified cockpit tasks with controls for
the altitude, direction, and speed. It is used to test for coordination, psychomotor function, spatial discrimination, fine coordination, and stress resistance.
[7]Critical flicker/fusion frequency: this tests measures the frequency at which a flickering light is perceived as a steady light source. Changes are thought to be indicative of alterations in central nervous system activation, or fatigue.
[8]Critical instability tracking tests: this test is used to measure the ability of the participant to control a displayed error signal using a joystick. It is a first-order, compensatory tracking task.

Additional outcomes

Santos 1993 (RCT) reported only on adverse effects, which the study authors attributed to the drug regime used. They report 1 case of "nervosismo" (anxiety) and discomfort in a participant who took 500 mg of mefloquine every 4 weeks (31 participants in this study arm).

Additionally, Weiss 1995 reported on mean number of symptoms reported per participant. This includes all spontaneously reported symptoms, and included diarrhoea, stomach pains, nausea, fever and headache. No significant differences were found between the multivitamin (placebo) group and the mefloquine groups. Pearlman 1980 reported that "there was no clinical evidence of drug toxicity in the 990 study participants, nor were there significant changes in the measured biochemical parameters". However, they did not actively seek out adverse events, and did not describe how causality was assessed (Table 5). Davis 1996 reports on events occurring in the first week of the study (when both groups had received 1 placebo tablet) and the relative risk of those symptoms worsening over time, for symptoms including headache, lethargy, abdominal pain, diarrhoea, cough and nausea. Diarrhoea increased transiently with mefloquine compared to placebo, there was no difference in the other symptoms. Schlagenhauf 1997 was a cross-over randomized controlled trial including 23 participants. They report one withdrawal due to dizziness, diarrhoea, and flu-like symptoms and three volunteers spontaneously reported minor sleep-related adverse events, including insomnia, unpleasant dreams, superficial sleep, and early awakening. These events all occurred in the mefloquine loading dose phase.

Petersen 2000 had important differences in the numbers of exposed/non-exposed participants and was at high risk of bias. Sensitivity analysis removing this trial did not alter the overall results.

Appendix 5. Mefloquine versus doxycycline: other outcomes and groups of symptoms

Groups of symptoms

RCTs

Ohrt 1997 reported the overall number of adverse events, and Schlagenhauf 2003 reported the overall number of mild, moderate and severe events, and no differences were found between groups (2 RCTs, 429 participants). Both trials also grouped symptoms together by body system, Schlagenhauf 2003 found that mefloquine users were more likely to experience both moderate (RR 1.56, 95% CI 1.09 to 2.22; 306 participants) and severe (RR 8.00, 95% CI 1.01 to 63.19; 306 participants) 'neuropsychological' adverse effects. However, there

was no difference between groups in the number of neuropsychological adverse events overall (RR 1.26, 95% CI 0.91 to 1.75; 2 trials; 429 participants).

Cohort studies

In cohort studies reporting grouped adverse effects, there was no difference between groups for the overall number of adverse effects (RR 0.93, 95% CI 0.74 to 1.17; 12 cohort studies, 13,576 participants). There was also no difference between groups in the only cohort study that reported adverse events (RR 1.39, 95% CI 1.17 to 1.65; 668 participants).

Mefloquine users were more likely to experience 'constitutional' adverse effects (RR 3.53, 95% CI 1.92 to 6.49; 1 study; 684 participants) and 'neuropsychologic' adverse effects (RR 5.48, 95% CI 2.49 to 12.05; 3 studies; 4568 participants). They were less likely to experience gastrointestinal (RR 0.33, 95% CI 0.19 to 0.58; 3 studies; 5190 participants), genitourinary (RR 0.05, 95% CI 0.01 to 0.19; 1 study; 684 participants) or skin and subcutaneous (RR 0.08, 95% CI 0.02 to 0.32; 2 studies; 1915 participants) effects.

Other outcomes

RCTs

Schlagenhauf 2003 reported the Profile of Moods States (POMS) and a quality of life questionnaire, and found no significant differences between groups. Weiss 1995 reported on the mean number of symptoms reported per participant, which included diarrhoea, stomach pains, nausea, fever and headache, but we were unable to reliably include these data.

Cohort studies

Jute 2007, Rack 2005 and Rieckmann 1993 were additional cohort studies including users of both mefloquine and atovaquone-proguanil but did not present their data in a way that could be included in meta-analyses.

Jute 2007 was a cross-sectional cohort study which included 17 users of mefloquine and 16 users of doxycycline and reported that "no significant adverse effects were reported by any users of chemoprophylaxis". Rack 2005 included 167 mefloquine users and 16 users of doxycycline and reported that "side effects were reported by 80 (28.9%) of 276 travelers with malaria prophylaxis, which affected the journey in 27 (9.8%) cases. In users of mefloquine, the most common side effects were central nervous system problems, such as headache, dizziness, sleep disorders,and emotional lability (53 of 167 [31.7%]).These kinds of side effects occurred significantly more often with mefloquine than with other antimalarial drugs (31.7% vs 8.6%, p < .01). Of those patients on atovaquone/proguanil and doxycycline, gastrointestinal side effects were most frequent (15.1% and 25%, respectively). Dermatologic problems occurred significantly more often with doxycycline than with any other antimalarial drug (12.5% vs 1.5%, p < .01)." Rieckmann 1993 included 40 mefloquine users and 115 doxycycline users and reported that "mefloquine was well tolerated and no dizziness or neurotoxicity was observed, the incidence of gastrointestinal disturbance was 24.5%".

Mavrogordato 2012 included a categorical measure of adherence to the drug regime which we could not combine for meta-analysis. The study included 12 mefloquine users and six doxycycline users.

Appendix 6. Mefloquine versus atovaquone-proguanil: other outcomes and groups of symptoms

Groups of symptoms

RCTs

Of the RCTs, Overbosch 2001 reported an increase in any adverse effect (RR 1.40, 95% CI 1.18 to 1.66; 976 participants), and 'any moderate or severe adverse effect' with mefloquine (RR 1.84, 95% CI 1.34 to 2.53; 976 participants). Schlagenhauf 2003 reported the overall number of mild, moderate and severe events, and no differences were found between groups. Schlagenhauf 2003 also grouped symptoms together by body system: 'gastrointestinal', 'neuropsychological', 'skin and subcutaneous' and 'skin and vaginal'. The only statistically significant finding was an increase in moderate 'neuropsychological' symptoms with mefloquine (RR 1.88, 95% CI 1.29 to 2.73; 317 participants).

Cohort studies

Of the cohort studies, mefloquine users were more likely to experience 'cardiovascular' adverse effects (RR 7.32, 95% CI 1.06 to 50.42; 1 cohort study, 316 participants), 'constitutional' adverse effects (RR 13.53, 95% CI 1.89 to 96.60; 1 cohort study, 477 participants), 'gastrointestinal' adverse effects (RR 1.99, 95% CI 1.09 to 3.60; 2 cohort studies, 793 participants) and 'neuropsychologic' adverse effects (RR 8.48, 95% CI 3.18 to 22.62; 3 cohort studies, 1021 participants). Overall participants who took mefloquine were more likely to experience any adverse effect (RR 2.40, 95% CI 1.84 to 3.13; 10 cohort studies; 5404 participants). Although there was moderate statistical heterogeneity among trials (I^2 statistic = 65%), the direction of the effect was consistent.

Other outcomes

RCTs

Two RCTs reported other outcomes which could be used as proxy measures of psychological adverse effects. These are described in the table below.

Study ID	Mefloquine participants	Drug comparator(s) (n)	Outcome(s) measured	Results reported
Schlagenhauf 2003	153	Atovaquone-proguanil (164), doxycycline (153)	1. POMS[1] 2. Quality of life questionnaire[2]	POMS: Reports no statistically significant differences between groups. Quality of life questionnaire: Reports no statistically significant differences between groups
van Riemsdijk 2002	58	Atovaquone-proguanil (61)	1. POMS[1] 2. NES[3]	POMS: "Significant deterioration on the domains of depression, anger, fatigue, and vigor. The TMD increased by 7.52 points (95% confidence interval, 3.32 to 11.71 points)" NES: Both groups showed improvement between the first and second measurement. No differences were observed between groups

[1]Profile of Mood States (POMS): a validated questionnaire designed to measure feelings in five domains: tension, depression, anger, fatigue, and vigor. Answers are graded ranging from 'not at all (0)' to 'extremely (4)'. The total mood disturbance (TMD) is a composite overall score which is calculated by adding the scores across the four categories of tension, anger, fatigue and depression and subtracting the score for vigour. The total ranges from 20 to 108. An increased TMD score indicates a deterioration of mood.

[2]Quality of life questionnaire: participants were asked to grade 13 positive statements (for example, 'I can enjoy my everyday life') on scale of 1 ('not at all true') to 6 ("true")

[3]Neurobehavioral evaluation system (NES): a series of computerized tests designed to provide quantitative neurobehavioral outcomes which measures performance, such as sustained attention (response latency), coding speed, and visuomotor accuracy.

Cohort studies

Schneider 2013 analysed a large UK General Practice research database for incident cases of 'neuropsychiatric' disorders including anxiety, stress-related disorders or psychosis, depression, epilepsy or peripheral neuropathies during or after antimalarial drug use. There was no difference between mefloquine or atovaquone-proguanil for incident cases of depression, epilepsy, neuropathy or 'anxiety or stress-related disorders or psychosis' in 'current' or 'past' users. The authors did not present their data in a way which we could include within meta-analysis.

Napoletano 2007 reports the number of 'neuropsychiatric' and 'gastrointestinal' adverse effects reported in each group. 'Neuropsychiatric' symptoms accounted for 44% of symptoms reported by mefloquine users, and 12% of symptoms reported by users of atovaquone-proguanil. They report a higher incidence of both 'neuropsychiatric' and 'gastrointestinal' symptoms in mefloquine users (data not provided).

Jute 2007 and Rack 2005 were additional cohort studies including users of both mefloquine and atovaquone-proguanil but did not present their data in a way which could be included within meta-analysis.

Jute 2007 was a cross-sectional cohort study which included 17 users of mefloquine and one user of atovaquone-proguanil and reported that "no significant adverse effects were reported by any users of chemoprophylaxis". Rack 2005 included 167 mefloquine users and 86 users of atovaquone-proguanil and reported that "side effects were reported by 80 (28.9%) of 276 travelers with malaria prophylaxis, which affected the journey in 27 (9.8%) cases. In users of mefloquine, the most common side effects were central nervous system problems, such as headache, dizziness, sleep disorders,and emotional lability (53 of 167 [31.7%]).These kinds of side effects occurred significantly more often with mefloquine than with other antimalarial drugs (31.7% vs 8.6%, $p < .01$). Of those patients on atovaquone/proguanil and doxycycline, gastrointestinal side effects were most frequent (15.1% and 25%, respectively). Dermatologic problems occurred significantly more often with doxycycline than with any other antimalarial drug (12.5% vs 1.5%, $p < .01$)".

Mavrogordato 2012 included a categorical measure of adherence to the drug regime which we could not combine within meta-analysis. The study included 12 mefloquine users and 11 users of atovaquone-proguanil.

Appendix 7. Mefloquine versus chloroquine: other outcomes and groups of symptoms

Groups of symptoms

Four RCTs and 12 cohort studies compared participants reporting any adverse symptom. The results are mixed with mefloquine users less likely to report any adverse event in the few small RCTs (RR 0.59, 95% CI 0.42 to 0.83; three RCTs trials; 641 participants), and more likely to report any adverse effect in the cohort studies (RR 1.43, 95% CI 1.19) to 1.73; 11 cohort studies, 63,286 participants).

Within cohort studies, mefloquine users were more likely to report 'gastrointestinal' symptoms (RR 2.88, 95% CI 1.09 to 7.57; 1 cohort study, 3822 participants), 'neuropsychologic' symptoms (RR 2.12, 95% CI 1.24 to 3.60; 2 cohort studies, 3965 participants), and 'skin and subcutaneous' symptoms (RR 1.27, 95% CI 1.08 to 1.50; 2 cohort studies, 53,550 participants).

Other outcomes

Boudreau 1993 also reported outcomes which could be used as proxy markers of psychological or neurological adverse effects, including the POMS (a validated questionnaire designed to measure feelings in five domains: tension, depression, anger, fatigue, and vigor), environmental symptoms questionnaire (ESQ) (a standardized form containing 68 questions relating to all body systems. Responses consist of six graded answers ranging from 'not at all' to 'extreme') and a sleep assessment. They reported as follows:

POMS: "On day 4, depression was significantly greater in the loading dose mefloquine group. At week 6, depression, tension and anger were significantly greater in the mefloquine group. No differences were found between groups for vigour, fatigue or confusion."

ESQ: "On day 4, significant differences were found for depression, dizziness, co-ordination off for both mefloquine groups... eye irritability was more common in the chloroquine group... During week 6: depression, nausea, hands shaking higher in mefloquine weekly group and irritability higher in both [mefloquine] groups."

Sleep assessment: no group differences (in total sleep time) were statistically significant, however, both mefloquine groups slept less (about 20 minutes less per night).

WHAT'S NEW

Date	Event	Description
20 October 2017	New search has been performed	New author team appointed. Protocol rewritten. Criteria for included studies, methods, and outcomes revised. Protocol checked and agreed by two editors. Modifications included: • Scope of protocol changed to cover only efficacy and safety of mefloquine. • Updated search. • Types of studies changed to include non-randomized controlled trials/cohort studies for analysis of safety. • Control changed to include placebo or no intervention. • Types of participants changed to include all adults and children, including pregnant women (now includes immune and partially-immune participants). • Adverse outcomes altered, added adverse events and adverse effects monitoring, measures of adherence and adverse pregnancy outcomes. • 'Risk of bias' assessment modified to include methods of assessment for non-randomized trials and risk of bias in conduct and reporting of adverse events and adverse effects. • We did not include any analysis of deaths, suicides, or parasuicides attributable to mefloquine prophylaxis; these are addressed in a separate review (Tickell-Painter 2017). • Review title modified to reflect the change in the protocol to evaluate mefloquine against alternatives

Date	Event	Description
20 October 2017	New citation required and conclusions have changed	The previous version of this review, 'Drugs for preventing malaria in travellers', was withdrawn. The reason for this was the editorial team detected several errors in a subsidiary analysis of case reports described in the discussion and in appendix 9 of the withdrawn review. This new edition covers only mefloquine and comparisons with alternative drugs. The case reports analysis has been removed entirely. A separate team, including the lead author of this review, carried out a new review of case reports of death and parasuicide associated with mefloquine, published in the journal, 'Travel Medicine and Infectious Disease'.

HISTORY

Protocol first published: Issue 2, 2007
Review first published: Issue 4, 2009

Date	Event	Description
29 September 2015	Amended	This review has been withdrawn. Please see Published notes section for explanation.
16 June 2010	Amended	In-text links to appendices corrected.
9 November 2009	Amended	Tables moved to appendices in order to enhance readability.

CONTRIBUTIONS OF AUTHORS

Maya Tickell-Painter (MTP) and David Sinclair (DS) performed title and abstract and full text screening of the search results. MTP and Nicola Mayaan assessed the methodological quality of trials and extracted and analysed data. MTP completed the first draft of the review. DS, Cheryl Pace and Rachel Saunders provided advice on content and methodology. All authors approved the final version for publication.

DECLARATIONS OF INTEREST

NM was contracted by the Cochrane Infectious Diseases Group (CIDG) as a freelance consultant to work on this review and previously worked for Enhanced Reviews Ltd, a company that conducts systematic reviews mostly for the public sector. NM is currently employed by Cochrane Response, an evidence services unit operated by Cochrane.

CP has been involved in aspects of clinical trial management for trials of antimalarials (other than mefloquine) where the study drug has been supplied free of charge by the manufacturer.

David Sinclair was employed at Liverpool School of Tropical Medicine as an author and editor with the CIDG, funded through a grant from the UK Department for International Development.

RS was employed at Liverpool School of Tropical Medicine as an author with the CIDG, funded through a grant from the UK Department for International Development.

MTP was employed at Liverpool School of Tropical Medicine as an author with the CIDG, funded through a grant from the UK Department for International Development.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.

External sources

- Department for International Development, UK.

  Grant: 5242

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol we planned to use a modified version of the ACROBAT-NRSI tool (now referred to as ROBINS-I) (ACROBAT-NSRI tool). In the full review we used the original version.

In the protocol we stated that we would include "clinical cases of malaria, diagnosed by PCR or microscopy". In the full review we included trials in which the methods of detection for malaria were unclear, or different (one RCT which tested for antibodies to a circumsporozoite protein four weeks after travel). This change occurred due to difficulties in establishing diagnoses of malaria in short-term travellers. No cases of malaria occurred in any study arm in any of these additionally included studies.

In the full review we did not include comparisons with regimens that are currently not routinely used or single-arm cohort studies. These are planned to be analysed in separate systematic reviews (Rodrigo 2016; Tickell-Painter 2017).

Differences between 2015 review and this review update

We amended the review title from 'Drugs for preventing malaria in travellers' to 'Mefloquine for preventing malaria during travel to endemic areas.

We rewrote the protocol. Criteria for included studies, methods, and outcomes were revised. The was externally peer refereed by two editors.

The scope of the review changed to cover only efficacy and safety of mefloquine. The search was updated. The types of studies were changed to include non-RCTs/cohort studies for analysis of safety. The control arm was changed to include placebo or no intervention, as well as the commonly used alternatives of atovaquone-proguanil, doxycycline, and chloroquine. Types of participants were changed to include all adults and children, including pregnant women (now includes immune and partially- immune participants). We altered the inclusion of adverse outcomes; we included measures of adherence to the drug regime and adverse pregnancy outcomes. We modified the 'Risk of bias' assessment to include methods of assessment for non-randomized trials and risk of bias in conduct and reporting of adverse events and adverse effects.

We did not include any analysis of deaths, suicides, or parasuicides attributable to mefloquine prophylaxis; these are addressed in a separate review (Tickell-Painter 2017).

The author team changed from Jacquerioz FA and Croft AM to Tickell-Painter M, Mayaan N, Saunders R, Pace C, and Sinclair D.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Adult; Child; Humans