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

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Tickell-Painter M, Maayan N, Saunders R, Pace C, Sinclair D. Mefloquine for preventing malaria during travel to endemic areas. Cochrane Database of Systematic Reviews 2017, Issue 10. Art. No.: CD006491. DOI: 10.1002/14651858.CD006491.pub4.

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# Table of Contents

- **Header** ........................................... 1
- **Abstract** ....................................... 1
- **Plain Language Summary** ......................... 3
- **Summary of Findings for the Main Comparison** ...... 4
- **Background** .................................... 7
- **Objectives** .................................... 8
- **Methods** ....................................... 8
- **Results** ........................................ 11
  - Figure 1. ........................................ 13
  - Figure 2. ........................................ 14
  - Figure 3. ........................................ 17
  - Figure 4. ........................................ 21
  - Figure 5. ........................................ 25
  - Figure 6. ........................................ 29
- **Additional Summary of Findings** ..................... 32
- **Discussion** ..................................... 36
- **Authors’ Conclusions** ............................ 38
- **Acknowledgements** ................................ 39
- **References** ..................................... 39
- **Characteristics of Studies** ......................... 51
- **Data and Analyses** ................................ 156
  - Analysis 1.1. Comparison 1 Mefloquine versus placebo/non users, Outcome 1 Clinical cases of malaria. ........ 167
  - Analysis 1.2. Comparison 1 Mefloquine versus placebo/non users, Outcome 2 Malaria; episodes of parasitaemia in semi-immune populations. .................. 168
  - Analysis 1.3. Comparison 1 Mefloquine versus placebo/non users, Outcome 3 Serious adverse events or effects (all studies). .................. 169
  - Analysis 1.4. Comparison 1 Mefloquine versus placebo/non users, Outcome 4 Discontinuations due to adverse effects (all studies). .................. 170
  - Analysis 1.5. Comparison 1 Mefloquine versus placebo/non users, Outcome 5 Nausea (all studies). .................. 171
  - Analysis 1.6. Comparison 1 Mefloquine versus placebo/non users, Outcome 6 Vomiting (all studies). .................. 172
  - Analysis 1.7. Comparison 1 Mefloquine versus placebo/non users, Outcome 7 Abdominal pain (all studies). ........ 173
  - Analysis 1.8. Comparison 1 Mefloquine versus placebo/non users, Outcome 8 Diarrhoea (all studies). .................. 174
  - Analysis 1.9. Comparison 1 Mefloquine versus placebo/non users, Outcome 9 Headache (all studies). .................. 175
  - Analysis 1.10. Comparison 1 Mefloquine versus placebo/non users, Outcome 10 Dizziness (all studies). ........ 176
  - Analysis 1.11. Comparison 1 Mefloquine versus placebo/non users, Outcome 11 Abnormal dreams (all studies). .... 177
  - Analysis 1.12. Comparison 1 Mefloquine versus placebo/non users, Outcome 12 Insomnia (all studies). ........ 178
  - Analysis 1.13. Comparison 1 Mefloquine versus placebo/non users, Outcome 13 Anxiety (all studies). ........ 179
  - Analysis 1.14. Comparison 1 Mefloquine versus placebo/non users, Outcome 14 Depressed mood (all studies). .... 180
  - Analysis 1.15. Comparison 1 Mefloquine versus placebo/non users, Outcome 15 Abnormal thoughts and perceptions. .... 181
  - Analysis 1.16. Comparison 1 Mefloquine versus placebo/non users, Outcome 16 Pruritis (all studies). ........ 182
  - Analysis 1.17. Comparison 1 Mefloquine versus placebo/non users, Outcome 17 Visual impairment (all studies). .... 183
  - Analysis 1.18. Comparison 1 Mefloquine versus placebo/non users, Outcome 18 Vertigo (all studies). ........ 184
  - Analysis 1.19. Comparison 1 Mefloquine versus placebo/non users, Outcome 19 Other adverse events (RCTs). .... 185
  - Analysis 1.20. Comparison 1 Mefloquine versus placebo/non users, Outcome 20 Other adverse effects (cohort studies). .... 188
  - Analysis 2.1. Comparison 2 Mefloquine versus doxycycline, Outcome 1 Clinical cases of malaria (RCTs). .... 189
  - Analysis 2.2. Comparison 2 Mefloquine versus doxycycline, Outcome 2 Serious adverse events or effects (all studies). .... 190
  - Analysis 2.3. Comparison 2 Mefloquine versus doxycycline, Outcome 3 Discontinuations due to adverse effects (all studies). .... 191
  - Analysis 2.4. Comparison 2 Mefloquine versus doxycycline, Outcome 4 Nausea (all studies). .... 192
  - Analysis 2.5. Comparison 2 Mefloquine versus doxycycline, Outcome 5 Vomiting (all studies). .... 193
  - Analysis 2.6. Comparison 2 Mefloquine versus doxycycline, Outcome 6 Abdominal pain (all studies). .... 194
Analysis 2.7. Comparison 2 Mefloquine versus doxycycline, Outcome 7 Diarrhoea (all studies) .................................................. 195
Analysis 2.8. Comparison 2 Mefloquine versus doxycycline, Outcome 8 Dyspepsia (all studies) .............................................. 196
Analysis 2.9. Comparison 2 Mefloquine versus doxycycline, Outcome 9 Headache (all studies) .................................................. 197
Analysis 2.10. Comparison 2 Mefloquine versus doxycycline, Outcome 10 Dizziness (all studies) .............................................. 198
Analysis 2.11. Comparison 2 Mefloquine versus doxycycline, Outcome 11 Abnormal dreams (all studies) ............................. 199
Analysis 2.12. Comparison 2 Mefloquine versus doxycycline, Outcome 12 Insomnia (all studies) ............................................. 200
Analysis 2.13. Comparison 2 Mefloquine versus doxycycline, Outcome 13 Anxiety (all studies) ................................................. 201
Analysis 2.14. Comparison 2 Mefloquine versus doxycycline, Outcome 14 Depressed mood (all studies) .............................. 202
Analysis 2.15. Comparison 2 Mefloquine versus doxycycline, Outcome 15 Abnormal thoughts and perceptions ...................... 204
Analysis 2.16. Comparison 2 Mefloquine versus doxycycline, Outcome 16 Pruritis (all studies) .................................................. 205
Analysis 2.17. Comparison 2 Mefloquine versus doxycycline, Outcome 17 Photosensitivity (all studies) ............................... 206
Analysis 2.18. Comparison 2 Mefloquine versus doxycycline, Outcome 18 Yeast infection (all studies) ................................. 207
Analysis 2.19. Comparison 2 Mefloquine versus doxycycline, Outcome 19 Visual impairment (all studies) ............................ 208
Analysis 2.20. Comparison 2 Mefloquine versus doxycycline, Outcome 20 Other adverse effects (cohort studies) ................. 209
Analysis 2.21. Comparison 2 Mefloquine versus doxycycline, Outcome 21 Other adverse events (RCTs) ............................... 210
Analysis 2.22. Comparison 2 Mefloquine versus doxycycline, Outcome 22 Other adverse events (cohort studies) ................. 211
Analysis 2.23. Comparison 2 Mefloquine versus doxycycline, Outcome 23 Adherence (cohort studies) ................................. 212
Analysis 3.1. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 1 Clinical cases of malaria (RCTs) ............... 217
Analysis 3.2. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 2 Serious adverse events or effects (all studies) .................................................................................................................. 218
Analysis 3.3. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 3 Discontinuations due to adverse effects (all studies) .............................................................................................................. 219
Analysis 3.4. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 4 Nausea (all studies) ................................. 220
Analysis 3.5. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 5 Vomiting (all studies) ............................... 221
Analysis 3.6. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 6 Abdominal pain (all studies) .................. 222
Analysis 3.7. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 7 Diarrhoea (all studies) ............................. 223
Analysis 3.8. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 8 Mouth ulcers (all studies) ....................... 224
Analysis 3.9. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 9 Headache (all studies) ............................ 225
Analysis 3.10. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 10 Dizziness (all studies) .......................... 226
Analysis 3.11. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 11 Abnormal dreams (all studies) .......... 227
Analysis 3.12. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 12 Insomnia (all studies) ......................... 228
Analysis 3.13. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 13 Anxiety (all studies) ............................ 229
Analysis 3.14. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 14 Depressed mood (all studies) ............... 230
Analysis 3.15. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 15 Abnormal thoughts and perceptions (all studies) ........................................................................................................ 231
Analysis 3.16. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 16 Pruritis (all studies) ............................. 232
Analysis 3.17. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 17 Visual impairment (all studies) .......... 233
Analysis 3.18. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 18 Other adverse effects (cohort studies) ... 234
Analysis 3.19. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 19 Other adverse events (cohort studies) .... 235
Analysis 3.20. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 20 Adherence (RCTs) .............................. 241
Analysis 3.21. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 21 Adherence (cohort studies) ................. 242
Analysis 4.1. Comparison 4 Mefloquine versus chloroquine, Outcome 1 Clinical cases of malaria (RCTs) ............................ 243
Analysis 4.2. Comparison 4 Mefloquine versus chloroquine, Outcome 2 Serious adverse events or effects (all studies) ......... 244
Analysis 4.3. Comparison 4 Mefloquine versus chloroquine, Outcome 3 Discontinuations due to adverse effects (all studies) ................................................................................................................ 245
Analysis 4.4. Comparison 4 Mefloquine versus chloroquine, Outcome 4 Nausea (all studies) ............................................... 246
Analysis 4.5. Comparison 4 Mefloquine versus chloroquine, Outcome 5 Vomiting (all studies) .......................................... 247
Analysis 4.6. Comparison 4 Mefloquine versus chloroquine, Outcome 6 Abdominal pain (all studies) ............................. 248
Analysis 4.7. Comparison 4 Mefloquine versus chloroquine, Outcome 7 Diarrhoea (all studies) ........................................... 249
Analysis 4.8. Comparison 4 Mefloquine versus chloroquine, Outcome 8 Headache (all studies) ........................................... 250
Analysis 4.9. Comparison 4 Mefloquine versus chloroquine, Outcome 9 Dizziness (all studies) ............................................. 251
Analysis 4.10. Comparison 4 Mefloquine versus chloroquine, Outcome 10 Abnormal dreams (all studies). 252
Analysis 4.11. Comparison 4 Mefloquine versus chloroquine, Outcome 11 Insomnia (all studies). 253
Analysis 4.12. Comparison 4 Mefloquine versus chloroquine, Outcome 12 Anxiety (all studies). 254
Analysis 4.13. Comparison 4 Mefloquine versus chloroquine, Outcome 13 Depressed mood (all studies). 255
Analysis 4.14. Comparison 4 Mefloquine versus chloroquine, Outcome 14 Abnormal thoughts and perceptions. 256
Analysis 4.15. Comparison 4 Mefloquine versus chloroquine, Outcome 15 Pruritis (all studies). 257
Analysis 4.16. Comparison 4 Mefloquine versus chloroquine, Outcome 16 Visual impairment (all studies). 258
Analysis 4.17. Comparison 4 Mefloquine versus chloroquine, Outcome 17 Vertigo (all studies). 259
Analysis 4.18. Comparison 4 Mefloquine versus chloroquine, Outcome 18 Cohort studies in travellers; prespecified adverse effects. 260
Analysis 4.19. Comparison 4 Mefloquine versus chloroquine, Outcome 19 Other adverse effects (cohort studies). 264
Analysis 4.20. Comparison 4 Mefloquine versus chloroquine, Outcome 20 Other adverse events (RCTs). 267
Analysis 4.21. Comparison 4 Mefloquine versus chloroquine, Outcome 21 Pregnancy related outcomes (RCTs). 269
Analysis 4.22. Comparison 4 Mefloquine versus chloroquine, Outcome 22 Adherence (cohort studies). 270
Analysis 5.1. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 1 Nausea; effects. 271
Analysis 5.2. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 2 Abdominal pain; effects. 272
Analysis 5.3. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 3 Diarrhoea; effects. 274
Analysis 5.4. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 4 Headache; effects. 275
Analysis 5.5. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 5 Dizziness; effects. 277
Analysis 5.6. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 6 Abnormal dreams; effects. 278
Analysis 5.7. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 7 Insomnia; effects. 280
Analysis 5.8. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 8 Anxiety; effects. 281
Analysis 5.9. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 9 Depressed mood; effects. 282
Analysis 5.10. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 10 Abnormal thoughts or perceptions; effects. 284
Analysis 5.11. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 11 Pruritis; effects. 285
Analysis 5.12. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 12 Visual impairment; effects. 286
Analysis 5.13. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 13 Adherence; during travel. 287
Analysis 5.14. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 14 Adherence; after return. 288
ADDITIONAL TABLES 289
APPENDICES 323
WHAT’S NEW 331
HISTORY 332
CONTRIBUTIONS OF AUTHORS 333
DECLARATIONS OF INTEREST 333
SOURCES OF SUPPORT 333
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 334
INDEX TERMS 334
Mefloquine for preventing malaria during travel to endemic areas

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Editorial group: Cochrane Infectious Diseases Group.

Publication status and date: Unchanged, published in Issue 10, 2017.

Citation: Tickell-Painter M, Maayan N, Saunders R, Pace C, Sinclair D. Mefloquine for preventing malaria during travel to endemic areas. Cochrane Database of Systematic Reviews 2017, Issue 10. Art. No.: CD006491. DOI: 10.1002/14651858.CD006491.pub4.

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 doxycycline 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.

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 doxycycline (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 doxycycline (very low-certainty evidence). Doxycycline users are more likely to have dyspepsia, photosensitivity, vomiting, and vaginal thrush (very low-certainty evidence).
### Summary of Findings for the Main Comparison

#### 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)                                          | -                                                              | ⊕⊕⊕⊕ low¹,²,³                   |
| Serious adverse effects               | 0 per 100                             | 1 in 100 (0 to 12)      | RR 1.40 (0.08 to 23.22)                                | 4 cohort studies (3693)                                        | ⊕⊕⊕⊕ low¹,²,⁴,⁵                 |
| 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)                                                  | ⊕⊕⊕⊕ high¹,²,⁴,⁶                |
| Abnormal dreams                       | 7 per 100                             | 14 per 100 (10 to 21)   | RR 2.04 (1.37 to 3.04)                                 | 1 RCT (976)                                                    | ⊕⊕⊕⊕ high¹,²,⁴,⁶                |
| Insomnia                              | 3 per 100                             | 13 per 100 (8 to 23)    | RR 4.42 (2.58 to 7.64)                                 | 1 RCT (976)                                                    | ⊕⊕⊕⊕ high¹,²,⁴,⁶                |
| Anxiety                               | 1 per 100                             | 6 per 100 (2 to 21)     | RR 6.12 (1.82 to 20.66)                                | 1 RCT (976)                                                    | ⊕⊕⊕⊕ moderate¹,²,⁴,⁷               |
| Depressed mood                        | 1 per 100                             | 6 per 100 (2 to 20)     | RR 5.78 (1.71 to 19.61)                                | 1 RCT (976)                                                    | ⊕⊕⊕⊕ moderate¹,²,⁴,⁷               |
| 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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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.

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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.
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 repro-
duction 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', 'Larion', 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 experiencing the event and the number analysed in each group.

We also extract medians and ranges where necessary, we attempted to contact the trial authors for further information. However, 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, doxycycline 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 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'.
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 pre-defined 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 Chi² test with a 10% level of statistical significance, and using the I² 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.

R E S U L T S

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.
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.

| Study                                      | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|--------------------------------------------|---------------------------------------------|------------------------------------------|-----------------------------------------------------------|-------------------------------------------------|---------------------------------------|-------------------------------------|------------|
| Arthur 1986                                | ?                                           | ?                                       | ?                                                         | ?                                               | ?                                     | ?                                   | ?          |
| Boudreau 1991                              | ?                                           | ?                                       | ?                                                         | ?                                               | ?                                     | ?                                   | ?          |
| Boudreau 1993                              | ?                                           | ?                                       | ?                                                         | ?                                               | ?                                     | ?                                   | ?          |
| Burnag 1982                                | ?                                           | ?                                       | ?                                                         | ?                                               | ?                                     | ?                                   | ?          |
| Davis 1986                                 | ?                                           | ?                                       | ?                                                         | ?                                               | ?                                     | ?                                   | ?          |
| Hale 2003                                  | ?                                           | ?                                       | ?                                                         | ?                                               | ?                                     | ?                                   | ?          |
| Nestor 1994                                | ?                                           | ?                                       | ?                                                         | ?                                               | ?                                     | ?                                   | ?          |
| Cott 1987                                  | ?                                           | ?                                       | ?                                                         | ?                                               | ?                                     | ?                                   | ?          |
| Overbosch 2001                             | ?                                           | ?                                       | ?                                                         | ?                                               | ?                                     | ?                                   | ?          |
| Pearlman 1960                              | ?                                           | ?                                       | ?                                                         | ?                                               | ?                                     | ?                                   | ?          |
| Pollockman 2002                            | ?                                           | ?                                       | ?                                                         | ?                                               | ?                                     | ?                                   | ?          |
| Saliako 1992                               | ?                                           | ?                                       | ?                                                         | ?                                               | ?                                     | ?                                   | ?          |
| Santeš 1993                                | ?                                           | ?                                       | ?                                                         | ?                                               | ?                                     | ?                                   | ?          |
| Schlagenhaur 1987                          | ?                                           | ?                                       | ?                                                         | ?                                               | ?                                     | ?                                   | ?          |
| Schlagenhaur 2003                          | ?                                           | ?                                       | ?                                                         | ?                                               | ?                                     | ?                                   | ?          |
| Sosseuhounto 1996                          | ?                                           | ?                                       | ?                                                         | ?                                               | ?                                     | ?                                   | ?          |
| Steketee 1988                              | ?                                           | ?                                       | ?                                                         | ?                                               | ?                                     | ?                                   | ?          |
| von Riemadijlik 2002                       | ?                                           | ?                                       | ?                                                         | ?                                               | ?                                     | ?                                   | ?          |
| Vuurman 1996                               | ?                                           | ?                                       | ?                                                         | ?                                               | ?                                     | ?                                   | ?          |
| Weiss 1985                                 | ?                                           | ?                                       | ?                                                         | ?                                               | ?                                     | ?                                   | ?          |
Alloocation
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 Assesses the risk of bias due to influence by a corporate study sponsor.

| Study                  | Confounding | Selection of participants | Measurement of interventions | Departures from intended interventions | Measurement of outcomes | Selection of the reported result | Other |
|------------------------|-------------|---------------------------|-------------------------------|----------------------------------------|-------------------------|----------------------------------|-------|
| Hoebe 1997             | -           | +                         | +                             | -                                      | -                       | -                                | +     |
| Petersen 2000          | -           | -                         | +                             | -                                      | -                       | -                                | ?     |
| Rietz 2002             | -           | -                         | +                             | -                                      | +                       | -                                | +     |
| van Riemsdijk 1997     | +           | -                         | -                             | -                                      | -                       | -                                | ?     |
| Wells 2006             | -           | -                         | -                             | -                                      | +                       | +                                | +     |

+ low, - moderate, = serious, ? no information
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; I² statistic = 48%; Analysis 1.13), depressed mood (RR 2.43, 95% CI 0.65 to 9.07; 3 cohort studies, 1901 participants, I² 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), stillbirths (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; Schlagenhauf 2003). Three studies conducted daily interviews with participants to monitor for adverse events (Arthur 1990; Schlagenhauf 2003). Three studies conducted daily interviews with participants to monitor for adverse events (Arthur 1990; Schlagenhauf 2003). Three studies conducted daily interviews with participants to monitor for adverse events (Arthur 1990; Schlagenhauf 2003). Three studies conducted daily interviews with participants to monitor for adverse events (Arthur 1990; Schlagenhauf 2003). Three studies conducted daily interviews with participants to monitor for adverse events (Arthur 1990; Schlagenhauf 2003). Three studies conducted daily interviews with participants to monitor for adverse events (Arthur 1990; Schlagenhauf 2003).
**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.

| Study          | Confounding | Selection of participants | Measurement of interventions | Measurement of outcome | Missing data | Randomisation of interventions* | Randomisation of outcome* | Other* |
|----------------|-------------|---------------------------|------------------------------|------------------------|--------------|---------------------------------|--------------------------|--------|
| Cunningham 2014| ![Icon]      | ![Icon]                   | ![Icon]                      | ![Icon]                | ![Icon]      | ![Icon]                          | ![Icon]                 | ![Icon] |
| Eck-Cost 2017  | ![Icon]      | ![Icon]                   | ![Icon]                      | ![Icon]                | ![Icon]      | ![Icon]                          | ![Icon]                 | ![Icon] |
| Goodyer 2011   | ![Icon]      | ![Icon]                   | ![Icon]                      | ![Icon]                | ![Icon]      | ![Icon]                          | ![Icon]                 | ![Icon] |
| Kuthanai 2007  | ![Icon]      | ![Icon]                   | ![Icon]                      | ![Icon]                | ![Icon]      | ![Icon]                          | ![Icon]                 | ![Icon] |
| Landman 2015   | ![Icon]      | ![Icon]                   | ![Icon]                      | ![Icon]                | ![Icon]      | ![Icon]                          | ![Icon]                 | ![Icon] |
| Lever 2001     | ![Icon]      | ![Icon]                   | ![Icon]                      | ![Icon]                | ![Icon]      | ![Icon]                          | ![Icon]                 | ![Icon] |
| Lobel 2001     | ![Icon]      | ![Icon]                   | ![Icon]                      | ![Icon]                | ![Icon]      | ![Icon]                          | ![Icon]                 | ![Icon] |
| Motar 2004     | ![Icon]      | ![Icon]                   | ![Icon]                      | ![Icon]                | ![Icon]      | ![Icon]                          | ![Icon]                 | ![Icon] |
| Napolitano 2007| ![Icon]      | ![Icon]                   | ![Icon]                      | ![Icon]                | ![Icon]      | ![Icon]                          | ![Icon]                 | ![Icon] |
| Phillips 1996  | ![Icon]      | ![Icon]                   | ![Icon]                      | ![Icon]                | ![Icon]      | ![Icon]                          | ![Icon]                 | ![Icon] |
| Saunders 2015  | ![Icon]      | ![Icon]                   | ![Icon]                      | ![Icon]                | ![Icon]      | ![Icon]                          | ![Icon]                 | ![Icon] |
| Schwartz 1999  | ![Icon]      | ![Icon]                   | ![Icon]                      | ![Icon]                | ![Icon]      | ![Icon]                          | ![Icon]                 | ![Icon] |
| Shamiis 1996   | ![Icon]      | ![Icon]                   | ![Icon]                      | ![Icon]                | ![Icon]      | ![Icon]                          | ![Icon]                 | ![Icon] |
| Sharaeldin 2010| ![Icon]      | ![Icon]                   | ![Icon]                      | ![Icon]                | ![Icon]      | ![Icon]                          | ![Icon]                 | ![Icon] |
| Sibney 2016    | ![Icon]      | ![Icon]                   | ![Icon]                      | ![Icon]                | ![Icon]      | ![Icon]                          | ![Icon]                 | ![Icon] |
| Tan 2017       | ![Icon]      | ![Icon]                   | ![Icon]                      | ![Icon]                | ![Icon]      | ![Icon]                          | ![Icon]                 | ![Icon] |
| Tunnel 2015    | ![Icon]      | ![Icon]                   | ![Icon]                      | ![Icon]                | ![Icon]      | ![Icon]                          | ![Icon]                 | ![Icon] |
| Tuck 2016      | ![Icon]      | ![Icon]                   | ![Icon]                      | ![Icon]                | ![Icon]      | ![Icon]                          | ![Icon]                 | ![Icon] |
| Water 1999     | ![Icon]      | ![Icon]                   | ![Icon]                      | ![Icon]                | ![Icon]      | ![Icon]                          | ![Icon]                 | ![Icon] |

* Indicates that the risk of bias may not have been assessed in this area.
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 (I² 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, I² 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, 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 doxycycline 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 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.
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, 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 20.60) 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; Wanner 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.
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 events (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; I² 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; I² 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; P 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).
## Additional Summary of Findings [Explanation]

**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) |
|-----------------------------------------------|----------------------------------------|--------------------------|--------------------------------------------------------|-----------------------------------------------------------------|----------------------------------|
| Clinical malaria                              | 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 (1 to 61)                   | RR 1.53 (0.23 to 10.24)  | 3 cohort studies (3722)                                | 3 RCTs, 1 cohort study (682; 3772)                              | ⊕⊕⊕ very low 1,3,6,7             |
| Discontinuations due to adverse effects        | 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 (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 (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 (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 (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 (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           |

33

Mefloquine for preventing malaria during travel to endemic areas (Review)  
Copyright © 2017 The Authors. Cochrane Database of Systematic Reviews published by John Wiley & Sons, Ltd. on behalf of The Cochrane Collaboration.
| Condition               | Incidence | Incidence placebo | RR (95% CI) | Study details | Risk of bias |
|-------------------------|-----------|-------------------|-------------|--------------|--------------|
| Nausea                  | 8 per 100 | 3 per 100          | RR 0.37 (0.30 to 0.45) | 5 cohort studies (2683) | 1 RCT, 1 cohort study (123; 668) | ⊕⊕⊕⊕ very low<sup>3,6,10,11</sup> |
| Vomiting                | 5 per 100 | 1 per 100          | RR 0.18 (0.12 to 0.27) | 4 cohort studies (5071) | 1 RCT (123) | ⊕⊕⊕⊕ very low<sup>3,6,10,11</sup> |
| Abdominal pain          | 15 per 100| 5 per 100          | RR 0.30 (0.09 to 1.07) | 3 cohort studies (2536) | 1 RCT, 1 cohort study (123; 668) | ⊕⊕⊕⊕ very low<sup>6,7,9,11</sup> |
| Diarrhoea               | 5 per 100 | 1 per 100          | RR 0.28 (0.11 to 0.73) | 5 cohort studies (5104) | 2 RCTs; 1 cohort study (376; 668) | ⊕⊕⊕⊕ very low<sup>3,6,10,11</sup> |
| Dyspepsia               | 14 per 100| 4 per 100          | RR 0.26 (0.09 to 0.74) | 5 cohort studies (5104) | - | ⊕⊕⊕⊕ low<sup>2,3,6,10</sup> |
| Headache                | 2 per 100 | 2 per 100          | RR 1.21 (0.50 to 2.92) | 5 cohort studies (3320) | 1 RCT, 1 cohort study (123; 668) | ⊕⊕⊕⊕ very low<sup>3,6,7,11</sup> |
| Dizziness               | 1 per 100 | 3 per 100          | RR 3.49 (0.88 to 13.75) | 5 cohort studies (2633) | 1 RCT, 2 cohort studies (123; 355,627) | ⊕⊕⊕⊕ very low<sup>3,6,7,11</sup> |
| Visual impairment       | 3 per 100 | 7 per 100          | RR 2.37 (1.41 to 3.99) | 2 cohort studies (1875) | - | ⊕⊕⊕⊕ very low<sup>2,6,7,9</sup> |
| Pruritis                | 3 per 100 | 2 per 100          | RR 0.52 (0.30 to 0.91) | 2 cohort studies (1794) | 1 cohort study (688) | ⊕⊕⊕⊕ very low<sup>6,9,10,11</sup> |
| Photosensitivity        | 19 per 100| 2 per 100          | RR 0.08 (0.05 to 0.11) | 2 cohort studies (1875) | 1 cohort study (688) | ⊕⊕⊕⊕ very low<sup>2,6,9,10</sup> |
| Vaginal thrush          | 16 per 100| 2 per 100          | RR 0.10 (0.06 to 0.16) | 1 cohort study (1761) | 1 cohort study (354) | ⊕⊕⊕⊕ very low<sup>2,6,9,10</sup> |
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 inconsistency 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. Downgraded 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.
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 doxycycline, 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...
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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.

ACKNOWLEDGEMENTS

Dr Maya Tickell-Painter, Dr Rachel Saunders, and Dr David Sinclair received support from the by the Effective Health Care Research Consortium. The Consortium and the editorial base of the Cochrane Infectious Diseases Group are funded by UK aid from the UK Government for the benefit of developing countries (Grant: 5242). The funding body had no role in study design, data collection and analysis, or preparation of the manuscript. The views expressed in this review do not necessarily reflect UK government policy.

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

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* Indicates the major publication for the study
## 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 $\leq 13$ 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
2. Serious adverse effects
3. Discontinuations of study drug due to adverse effects

### 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 |
### Albright 2002 (Continued)

| 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
- **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)
### Andersson 2008  
(Continued)

| 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  
**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 |
|          | 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) | 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) | 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 |
### Arthur 1990

(Continued)

| 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 |

### Belderk 2013

**Methods**

- Design: prospective cohort study
- Study dates: October 2006 to October 2007
- 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  
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 sulfadoxine and 25 mg pyrimethamine) fortnightly and chloroquine (1 x 300 mg tablet) weekly*

*matched placebo for each treatment arm*

### Outcomes

**Included in the review:**
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)          | 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)                    | 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” |
Boudreau 1991  (Continued)

|                           |                          | 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” 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 |
| 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” |
| Allocation concealment (selection bias) | Unclear risk | Comment: method allocation concealment not mentioned |
| Blinding of participants and personnel (performance bias) | 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...” |
**Blinding of outcome assessment (detection bias)**

| Outcome | Risk | Details |
|---------|------|---------|
| 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)**

| Outcome | Risk | Details |
|---------|------|---------|
| Efficacy | Unclear risk | N/A |
| 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)**

| Outcome | Risk | Details |
|---------|------|---------|
| Efficacy | Unclear risk | N/A |
| 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**

| Risk | Details |
|------|---------|
| Unclear risk | Comment: study sponsor not mentioned, but the lead author is attributed to ‘Pharmaceutical Systems Incorporated’ |
Methods

Design: RCT  
Study dates: July 1987 to January 1988  
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 |
|------|--------------------|-----------------------|

Mefloquine for preventing malaria during travel to endemic areas (Review)
Copyright © 2017 The Authors. Cochrane Database of Systematic Reviews published by John Wiley & Sons, Ltd. on behalf of The Cochrane Collaboration.
| Bias Type                                           | Risk Level | Comments                                                                                                                                 |
|----------------------------------------------------|------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Random sequence generation                         | Unclear    | “Eligible volunteers were randomly assigned to treatment groups” Comment: method of random sequence generation not reported                  |
| Allocation concealment                              | Unclear    | “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              | Low        | “A randomised double blind trial…the tablets were identical in appearance; they were packed in numbered blister packs”                   |
| Blinding of outcome assessment                       | Unclear    | Comment: described as double blind but no explanation provided of how this was achieved for researchers and outcome assessors            |
| Incomplete outcome data; efficacy                  | Unclear    | “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; safety                     | Unclear    | “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; efficacy                       | Low        | Comment: Malaria cases were fully reported                                                                                               |
| Selective reporting; safety                         | High       | 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 |
### Bunnag 1992

**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.”

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### 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  
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”)

**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**  
*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

**Notes**  
Funding sources: Not mentioned
Corominas 1997  (Continued)

| 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
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)
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. The data 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 |
### 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” |
### Davis 1996  (Continued)

| Source of Bias                           | Risk of Bias      | Description                                                                 |
|-----------------------------------------|-------------------|-----------------------------------------------------------------------------|
| Blinding of participants and personnel  | Low risk          | “Tablets were prepared in individually numbered but otherwise unlabelled con- |
| (performance bias)                      |                   | tainers... identical placebo tablets...”                                   |
| Adverse effects/events                  |                   |                                                                             |
| Blinding of outcome assessment (detection bias) | Unclear risk     | “Allocation of active or placebo formulation was by a random number code gen- |
| All outcomes                            |                   | erated 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 sub- |
|                                         |                   | jects 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

| Study | 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 |
**Eick-Cost 2017 (Continued)**

| 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*
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.
**Methods**

- **Design:** prospective cohort study
- **Study dates:** December 2004 to April 2006
- **Malaria transmission pattern and local antimalarial drug resistance:** various destinations, not specified
- **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  
  No information was captured regarding switches between interventions of interest |
### 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:**
  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*

---

### Goodyer 2011

(Continued)

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. **Others:** serious
   - Funded by GlaxoSmithKline; the role of the study sponsor was not made clear
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/arthritis, 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         | Unclear risk       | “A ‘double-dummy’ design allowed double-blind administration of tafenoquine and mefloquine active drugs and their corresponding placebos” |
| (performance bias) Adverse effects/events     |                     | “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) | 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.” |
| All outcomes                                  |                     | Comment: no other mention of outcome |
### Hale 2003 (Continued)

| Bias Type                          | Risk Level | Description                                                                                                                                                                                                                     |
|-----------------------------------|------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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" |
| 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%, Caribbean 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 |

| 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 |
| Other bias | Unclear risk |
| | Support for judgement |
| | 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; partici- |
### Hill 2000

(Continued)

|    |    |    |
|----|----|----|
|    |    | pants 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-travel

**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** |
Hoebe 1997  (Continued)

13/454 (2.8%) of travellers successfully contacted refused to participate
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
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                                                       |

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

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### Kato 2013 (Continued)

| 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**  
| | | 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 ap-
### Kato 2013 (Continued)

| | |
|---|---|
| | 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

#### 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"
**Korhonen 2007** (Continued)

### 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”
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

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 |
### 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 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
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

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**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 information 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*
* 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**<br>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**<br>“The nonresponse rate was about 10% (n = 65), with the main reason being the short transit time” |
|                             |                    | 3. **Measurement of interventions: low**<br>Participants were asked to self-report which prophylactic regimen they were taking while they were still taking it |
|                             |                    | 4. **Departures from intended interventions: moderate**<br>No information was provided regarding switches between prophylactic regimens |
|                             |                    | 5. **Missing data: low**<br>Adherence information was not available for 4/595 participants |
|                             |                    | 6. **Measurement of outcomes: serious**<br>The outcome measure was based on participant self-reporting; participants and personnel were not blinded |
|                             |                    | 7. **Selection of the reported results: moderate**<br>There was insufficient information provided to know what questions were asked regarding adherence |
|                             |                    | 8. **Other: low**<br>“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
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
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
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”
| **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:  
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 |
Mavrogordato 2012  
(Continued)

|   |   |   |
|---|---|---|
|   |   | **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  
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)  
*dosage 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”

| 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  
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
### 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

### 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 interven- |
Napleton 2007  (Continued)

|   |   |   |
|---|---|---|
|   |   | tion 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 |
|   |   | 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 recrudescent 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
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
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; Welcome Trust of Great Britain; Pravention 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) | Low risk           | "...double blind...women were randomised to receive either mefloquine…or identical placebo" |
| Blinding of outcome assessment (detection bias) | 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 |
### Nosten 1994 (Continued)

| Issue                                                                 | Bias Level | Details                                                                                                                                 |
|----------------------------------------------------------------------|------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| 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 Diseases; Wellcome Trust of Great Britain; Preven tion Foundation. The Hague (to FLK) |

### Ohrt 1997

| Section       | Details                                                                                                                                 |
|---------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| 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
**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:*
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  
|         | 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)  

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

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### 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” (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) | 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)            | 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"

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
Pearlman 1980  *(Continued)*

| Notes | oxaloacetic transaminase, alkaline phosphatase and blood urea nitrogen |
|-------|---------------------------------------------------------------------|
| 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)           | 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" |
| Adverse effects/events                                              |                    |                       |
| Blinding of outcome assessment (detection bias)                    | Unclear risk       | Comment: described as double blind but not clear how this was achieved |
| All outcomes                                                        |                    |                       |
| 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”  
|                                                                    |                    |                       |
### Pearlman 1980  (Continued)

| Risk Factor | Risk Level | Comment |
|-------------|------------|---------|
| 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*
- 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
   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 |
| 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<br>Identified confounders were measured and reported across groups. Mefloquine users were more likely to be female and had longer duration of treatment<br>2. **Selection of participants into the study:** serious<br>Response rate 668 of 918 (73%)<br>3. **Measurement of interventions:** low<br>The prescription was provided by a travel clinic which also performed the study; discontinuations were recorded and reported<br>4. **Departures from intended interventions:** moderate<br>Discontinuations were recorded. It was unclear whether information regarding switches was recorded<br>5. **Missing data:** low<br>All information was collected at one time point and all participants were included in the analysis |
### Philips 1996

| 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 |
| 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...” |
### Potasman 2002  
*(Continued)*

| Bias Type                                      | Risk Level | Comment/Notes                                                                 |
|------------------------------------------------|------------|-------------------------------------------------------------------------------|
| Allocation concealment (selection bias)       | Unclear    | Statmate and InStat”                                                          |
| Blinding of participants and personnel (performance bias) Adverse effects/events | Unclear    | “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        | “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    | N/A                                                                           |
| Incomplete outcome data (attrition bias); safety | Unclear    | Comment: data were provided for all participants who were not excluded on the basis of abnormal baseline EEG |
| Selective reporting (reporting bias); efficacy | Unclear    | N/A                                                                           |
| Selective reporting (reporting bias); safety | Unclear    | “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       | 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

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| 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 |
| 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. |
### Rack 2005  (Continued)

| 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
- **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 |
# Rieckmann 1993  (Continued)

| 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 | 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

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**Note:**

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### Rietz 2002 (Continued)

| 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  
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 preceding 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 | 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” |
| 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” |

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Salako 1992 (Continued)
### Salako 1992 (Continued)

| Source of Bias                          | Risk of Bias | Comment                                                                 |
|---------------------------------------|--------------|-------------------------------------------------------------------------|
| 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 |

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Copyright © 2017 The Authors. Cochrane Database of Systematic Reviews published by John Wiley & Sons, Ltd. on behalf of The Cochrane Collaboration.
| 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 \( P. falciparum \) 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  
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     | Authors' judgement | Support for judgement |
| 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
  - 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
### 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  
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
### Saunders 2015

(Continued)

| 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 cardiovascular 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” |
Schlagenhauf 1997  (Continued)

| 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  |
| Random sequence generation (selection bias)  |
| Allocation concealment (selection bias)  |
| Blinding of participants and personnel (performance bias)  |
| Adverse effects/events  |
| Blinding of outcome assessment (detection bias)  |
| All outcomes  |
| Incomplete outcome data (attrition bias); efficacy  |
| Incomplete outcome data (attrition bias); safety  |

| Authors’ judgement  |
| Unclear risk  |
| Unclear risk  |
| Unclear risk  |
| Unclear risk  |
| Unclear risk  |

| Support for judgement  |
| Comment: method of randomization not reported  |
| Comment: no details of allocation concealment reported  |
| Comment: described as double blind but no mention of whether placebo was identical to the active formulation  |
| Comment: described as double blind but no description of who was blinded and how  |
| N/A  |
| “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 with- |
Schlagenhauf 1997 (Continued)

| 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  
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 |
| 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. GlaxoSmithKline 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
- **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” |
Schneider 2013  

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

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
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)

**Outcomes assessed not included in the review:**

### 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
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 |
|                 |                     | "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" |
Shamiss 1996  

| 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 |
| 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: |

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Sharafeldin 2010  (Continued)

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
   “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*

### 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**<br>Age of participants was balanced across groups. Destination and duration of travel were set by the study design. Sex and BMI were not reported<br><br>**2. Selection of participants into the study: serious** |
Sonmez 2005

|                | 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)

### Risk of bias

| Bias                                      | Authors’ judgement | Support for judgement                                                                 |
|-------------------------------------------|--------------------|----------------------------------------------------------------------------------------|
| Random sequence generation (selection bias) | Unclear risk       | “Five-hundred male volunteers… were randomised”<br>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)<br>Adverse effects/events | Low risk           | “double blind”. “The medications and placebo were identical in appearance”              |
| Blinding of outcome assessment (detection bias)<br>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”<br>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”<br>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                 |

### Notes

Funding sources: not mentioned
### Sossouhounto 1995  (Continued)

| 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
- **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 | 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**
   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
### 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  
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 |
|------|-------------------|-----------------------|

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Steketee 1996

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| Bias Type                                           | Risk Level | Description                                                                                                                                                                                                                                                                                                                                 |
|----------------------------------------------------|------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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) | High risk  | Comment: no mention of participants being blinded to which prophylactic regimen they were taking                                                                                                                                                                                                                     |
| Blinding of outcome assessment (detection bias)     | 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” |
|                                                    |            | 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...”                                                                                                                                                     |
Steketee 1996  (Continued)

| 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
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 |
|               |                     | 5. Missing data: low
|               |                     | 364/370 (98%) participants were included in the analysis |
|               |                     | 6. Measurement of outcomes: serious
|               |                     | Comment: the outcome measure was subjective, partici-
| **Stoney 2016**  
(Continued) | pants 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:**
  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** |
Continued

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"

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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"

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
"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
Terrell 2015  (Continued)

| Mefloquine: 71 participants, doxycycline: 67 participants | 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
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 transferred.
### 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
- 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 |
|------|---------------------|-----------------------|

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  
(Continued)

| Other bias       | Unclear risk |
|------------------|--------------|
| 1. Confounding:  | low          |
| Identified       |              |
| confounders were |              |
| measured and     |              |
| balanced across  |              |
| groups           |              |
| 2. Selection of | moderate     |
| participants into|              |
| the study:       |              |
| moderate         |              |
| 1501/1791 (86%  |              |
| response rate)   |              |
| 3. Measurement  | moderate     |
| 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    | moderate     |
| from intended   |              |
| interventions:   |              |
| moderate         |              |
| No information   |              |
| was provided on  |              |
| discontinuations |              |
| or switches      |              |
| 5. Missing data:| moderate     |
| serious          |              |
| 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 | serious      |
| outcomes:       |              |
| Comment: the     |              |
| outcome measure  |              |
| was subjective;  |              |
| participants and |              |
| personnel were   |              |
| not blinded      |              |
| 7. Selection of | moderate     |
| 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  |
| 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

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### 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* |

*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) |
| Outcome Assessment | Risk Assessment | Risk Level | Comments |
|--------------------|----------------|------------|----------|
| 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 | “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) |
| Incomplete outcome data (attrition bias); safety | High risk | “Data were collected on concurrent medications, as well as subject’s use of coffee, alcohol and illicit drugs” “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 |
| 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” “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” |
**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**

| 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 |
**Vuurman 1996  (Continued)**

| Bias Type                                      | Risk   | Comment                                                                 |
|-----------------------------------------------|--------|-------------------------------------------------------------------------|
| Blinding of participants and personnel        | Low risk| "They received mefloquine 250 mg or placebo in identically appearing tablets" |
| (performance bias) Adverse effects/events     |        |                                                                         |
| Blinding of outcome assessment (detection     | Unclear risk| Comment: described as double blind but no description of how this was achieved for researchers and outcome assessors |
| bias) All outcomes                            |        |                                                                         |
| Incomplete outcome data (attrition bias);     | Unclear risk| N/A                                                                     |
| efficacy                                      |        |                                                                         |
| Incomplete outcome data (attrition bias);     | 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 |
| safety                                        |        |                                                                         |
| 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'” |
| 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       | “a high risk Malaria area... Chloroquine-resistant |
| antimalarial drug resistance                 | *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                                                    |
| 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**
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. Mefloquine (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  
**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 LHFX. 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 a 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        | Unclear risk       | Comment: no mention of whether participants were blinded                                                                                                                                                  |
| (performance bias)                            |                    |                                                                                                                                                                                                                  |
| Adverse effects/events                        |                    |                                                                                                                                                                                                                  |
| Blinding of outcome assessment (detection     | 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” |
| bias)                                         |                    |                                                                                                                                                                                                                  |
| All outcomes                                  |                    |                                                                                                                                                                                                                  |
| Incomplete outcome data (attrition bias)      | Unclear risk       | N/A                                                                                                                                                                                                                |
| efficacy                                      |                    |                                                                                                                                                                                                                  |
| Incomplete outcome data (attrition bias)      | Unclear risk       | Comment: number included in the safety analysis not reported                                                                                                                                                  |
| safety                                        |                    |                                                                                                                                                                                                                  |
| Selective reporting (reporting bias); efficacy| Unclear risk       | N/A                                                                                                                                                                                                                |
| Safety                                        |                    |                                                                                                                                                                                                                  |
| 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.                                                                                       |
## 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:  
|               | 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 possibility 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 |
| Reference           | Description                                                                 |
|--------------------|------------------------------------------------------------------------------|
| 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 randomized 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. Compared 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. Reported 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 randomized or cohort study e.g. case report or case control study       |
| Brenier-Pinchart 2000 | Not a randomized or cohort study e.g. case report or case control study     |
| Brisson 2012       | No relevant outcomes reported                                                |
| Bruguera 2007      | Not a randomized or cohort study e.g. case report or case control study       |
| Reference | Description |
|-----------|-------------|
| Burke 1993 | Not a research study of malaria prophylaxis e.g. letter to the editor or editorial |
| Caillon 1992 | Not a randomized or cohort study e.g. case report or case control study |
| Carme 1997 | Cohort study. Compared mefloquine with a regimen that is no longer used routinely |
| Castot 1988 | Not a randomized 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 randomized 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. Compared 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 randomized or cohort study e.g. case report or case control study |
| Croft 1997 | RCT. Compared mefloquine with a regimen that is no longer used routinely |
| Del Cacho 2001 | Cohort study. Compared mefloquine with a regimen that is no longer used routinely |
| Dia 2010 | No relevant outcomes reported |
| Durrheim 1999 | Cohort study. Compared mefloquine with a regimen that is no longer used routinely |
| Eamsila 1993 | Cohort study. Compared mefloquine with a regimen that is no longer used routinely |
| El Jaoudi 2010 | Single-arm cohort study |
| Study          | Description                                                                 |
|---------------|-----------------------------------------------------------------------------|
| 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 randomized or cohort study e.g. case report or case control study     |
| Karbwang 1991 | Mefloquine not used at a prophylactic dose (e.g. treatment dose or intermittent preventive treatment of malaria in pregnancy dose) |
| Karbwang 1991a| Mefloquine was used as a combination regimen with sulphadoxine 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                                               |
| Kirchener 2003| No relevant outcomes reported                                               |
| Kirchener 2005| Cohort study. Allocation 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                                                     |
| Lapiere 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. Compared mefloquine with a regimen that is no longer used routinely. Chloroquine users were 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. Reported 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 randomized or cohort study e.g. case report or case control study
Michel 2007  | Cohort study. Reported 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
Molle 2000  | Cohort selected on basis of adverse events
Namikawa 2008  | No relevant outcomes reported
Nasveld 2010  | RCT. Compared 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 intermittent 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
| Reference          | Study Type | Summary                                                                 |
|--------------------|------------|-------------------------------------------------------------------------|
| 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 intermittent 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. Compared mefloquine with a regimen that is no longer used routinely | |
| Rieckmann 1974     | Mefloquine not used at a prophylactic dose (e.g. treatment dose or intermittent 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 randomized or cohort study e.g. case report or case control study | |
| Ringqvist 2015     | Cohort selected on basis of adverse events |                                                                                       |
| Rombo 1993         | RCT. Compared mefloquine with a regimen that is no longer used routinely | |
| Rønn 1998          | Mefloquine not used at a prophylactic dose (e.g. treatment dose or intermittent 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 |                                                                                   |
| Author            | Study Type                                      | Description                                                                                       |
|-------------------|------------------------------------------------|--------------------------------------------------------------------------------------------------|
| Suriyamongkol 1991| Single arm cohort study                        |                                                                                                  |
| Tansley 2010      | Mefloquine not used at a prophylactic dose (e.g. treatment dose or intermittent 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 intermittent 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. Compared 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] |
| 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] |
| Adverse Event | RCTs (all studies) | Cohort studies (all studies) | Cohort studies (adverse events) | Cochrane Collaboration (all studies) | Methodology | Subtotals only |
|---------------|--------------------|-----------------------------|--------------------------------|---------------------------------|------------|---------------|
| 12 Insomnia (all studies) | 2 | Risk Ratio (M-H, Fixed, 95% CI) | 1.46 [1.06, 2.02] | Subtotals only |
| 13 Anxiety (all studies) | 2 | Risk Ratio (M-H, Fixed, 95% CI) | 1.21 [0.67, 2.21] | Subtotals only |
| 14 Depressed mood (all studies) | 3 | Risk Ratio (M-H, Random, 95% CI) | 2.43 [0.65, 9.07] | Subtotals only |
| 15 Abnormal thoughts and perceptions | 1 | Risk Ratio (M-H, Fixed, 95% CI) | 5.77 [0.79, 42.06] | Subtotals only |
| 16 Pruritis (all studies) | 4 | Risk Ratio (M-H, Fixed, 95% CI) | 0.86 [0.60, 1.24] | Subtotals only |
| 17 Visual impairment (all studies) | 2 | Risk Ratio (M-H, Fixed, 95% CI) | 0.98 [0.66, 1.46] | Subtotals only |
| 18 Vertigo (all studies) | 1 | Risk Ratio (M-H, Fixed, 95% CI) | 1.02 [0.78, 1.34] | Subtotals only |
| 19 Other adverse events (RCTs) | 4 | Risk Ratio (M-H, Fixed, 95% CI) | 0.50 [0.23, 1.10] | Subtotals only |
| 19.1 Arthralgia | 1 | Risk Ratio (M-H, Fixed, 95% CI) | 0.29 [0.02, 5.48] | Subtotals only |
| 19.2 Back pain | 1 | Risk Ratio (M-H, Fixed, 95% CI) | 0.10 [0.01, 1.61] | Subtotals only |
| 19.3 Blurred vision | 1 | Risk Ratio (M-H, Fixed, 95% CI) | 0.19 [0.01, 3.89] | Subtotals only |
| 19.4 Cough | 1 | Risk Ratio (M-H, Fixed, 95% CI) | 0.90 [0.71, 1.14] | Subtotals only |
| 19.5 Constipation | 1 | Risk Ratio (M-H, Fixed, 95% CI) | 0.77 [0.53, 1.11] | Subtotals only |
| 19.6 Decreased appetite | 1 | Risk Ratio (M-H, Fixed, 95% CI) | 1.10 [0.95, 1.28] | Subtotals only |
| 19.7 Fatigue | 1 | Risk Ratio (M-H, Fixed, 95% CI) | 1.08 [0.82, 1.43] | Subtotals only |
| 19.8 Gastritis | 1 | Risk Ratio (M-H, Fixed, 95% CI) | 0.91 [0.14, 5.86] | Subtotals only |
| 19.9 Myalgia | 1 | Risk Ratio (M-H, Fixed, 95% CI) | 1.02 [0.10, 10.98] | Subtotals only |
| 19.10 Rash | 1 | Risk Ratio (M-H, Fixed, 95% CI) | 1.53 [0.36, 6.57] | Subtotals only |
| 19.11 Tingling | 1 | Risk Ratio (M-H, Fixed, 95% CI) | 0.29 [0.04, 2.30] | Subtotals only |
| 19.12 Respiratory tract infection | 1 | Risk Ratio (M-H, Fixed, 95% CI) | 2.63 [1.04, 6.61] | Subtotals only |
| 19.13 Sore throat | 1 | Risk Ratio (M-H, Fixed, 95% CI) | 0.82 [0.00, 82.00] | Subtotals only |
| 19.14 Unsteadiness | 1 | Risk Ratio (M-H, Fixed, 95% CI) | 1.06 [0.74, 1.52] | Subtotals only |
| 19.15 Weakness | 1 | Risk Ratio (M-H, Fixed, 95% CI) | 1.06 [0.96, 1.17] | Subtotals only |
| 20 Other adverse effects (cohort studies) | 3 | Risk Ratio (M-H, Fixed, 95% CI) | 1.06 [0.61, 1.82] | Subtotals only |
| 20.1 Agitation | 1 | Risk Ratio (M-H, Fixed, 95% CI) | 0.34 [0.04, 2.75] | Subtotals only |
| 20.2 Altered spatial perception | 1 | Risk Ratio (M-H, Fixed, 95% CI) | 0.94 [0.57, 153.97] | Subtotals only |
| 20.3 Confusion | 1 | Risk Ratio (M-H, Fixed, 95% CI) | 0.67 [0.25, 1.78] | Subtotals only |
| 20.4 Loss of appetite | 1 | Risk Ratio (M-H, Fixed, 95% CI) | 0.90 [0.54, 1.50] | Subtotals only |
| 20.5 Mouth ulcers | 1 | Risk Ratio (M-H, Fixed, 95% CI) | 1.00 [0.39, 2.56] | Subtotals only |
| 20.6 Palpitations | 1 | Risk Ratio (M-H, Fixed, 95% CI) | 8.06 [0.44, 147.68] | Subtotals only |
| 20.7 Tingling | 1 | Risk Ratio (M-H, Fixed, 95% CI) | 1.92 [0.59, 6.24] | Subtotals only |
## 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] |
| 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] |
| 10.3 Cohort studies (adverse events) | 668 | Risk Ratio (M-H, Random, 95% CI) | 2.40 [1.47, 3.90] |
| 10.4 Retrospective healthcare record analysis (adverse events) | 354959 | Risk Ratio (M-H, Random, 95% CI) | 0.68 [0.62, 0.73] |
| 11 Abnormal dreams (all studies) | 2588 | Risk Ratio (M-H, Random, 95% CI) | 4.33 [2.08, 9.00] |
| 11.1 Cohort studies (adverse effects) | 6 | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 11.2 RCTs (adverse events) | 123 | Risk Ratio (M-H, Random, 95% CI) | 1.02 [0.07, 15.89] |
| 11.3 Cohort studies (adverse events) | 1668 | Risk Ratio (M-H, Random, 95% CI) | 10.49 [3.79, 29.10] |
| 12 Insomnia (all studies) | 123 | Risk Ratio (M-H, Random, 95% CI) | 4.54 [2.09, 9.83] |
| 12.1 Cohort studies (adverse effects) | 3212 | Risk Ratio (M-H, Random, 95% CI) | 4.14 [1.19, 14.44] |
| 12.2 RCTs (adverse events) | 1668 | Risk Ratio (M-H, Random, 95% CI) | 0.46 [0.43, 0.49] |
| 12.3 Cohort studies (adverse events) | 354959 | Risk Ratio (M-H, Random, 95% CI) | Subtotals only |
| 12.4 Retrospective healthcare record analysis (adverse events) | 0.46 [0.43, 0.49] |
| 13 Anxiety (all studies) | 2559 | Risk Ratio (M-H, Fixed, 95% CI) | 18.04 [9.32, 34.93] |
| 13.1 Cohort studies (adverse effects) | 6 | Risk Ratio (M-H, Fixed, 95% CI) | 8.74 [1.99, 38.40] |
| 13.2 Cohort studies (adverse effects) | 1668 | Risk Ratio (M-H, Fixed, 95% CI) | 0.51 [0.47, 0.56] |
| 13.3 Retrospective healthcare record analysis (adverse events) | 3212 | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 14 Depressed mood (all studies) | 2445 | Risk Ratio (M-H, Fixed, 95% CI) | 11.43 [5.21, 25.07] |
| 14.1 Cohort studies (adverse effects) | 1668 | Risk Ratio (M-H, Fixed, 95% CI) | 6.27 [1.82, 21.62] |
| 14.2 Cohort studies (adverse events) | 376024 | Risk Ratio (M-H, Fixed, 95% CI) | 0.55 [0.51, 0.60] |
| 15 Abnormal thoughts and perceptions | 2445 | Risk Ratio (M-H, Fixed, 95% CI) | 2.69 [0.93, 7.78] |
| 15.1 Cohort studies (adverse effects) | 376024 | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 15.2 Retrospective healthcare record analyses (adverse events) | 0.41 [0.26, 0.66] |
| 16 Pruritis (all studies) | 1794 | Risk Ratio (M-H, Fixed, 95% CI) | 0.52 [0.30, 0.91] |
| 16.1 Cohort studies (adverse effects) | 1668 | Risk Ratio (M-H, Fixed, 95% CI) | 2.69 [0.93, 7.78] |
| 16.2 Cohort studies (adverse events) | 376024 | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 17 Photosensitivity (all studies) | 1875 | Risk Ratio (M-H, Fixed, 95% CI) | 0.08 [0.05, 0.11] |
| 17.1 Cohort studies (adverse effects) | 1794 | Risk Ratio (M-H, Fixed, 95% CI) | 0.03 [0.00, 0.49] |
| 17.2 Cohort studies (adverse events) | 1668 | Risk Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 18 Yeast infection (all studies) | 1761 | Risk Ratio (M-H, Fixed, 95% CI) | 0.10 [0.06, 0.16] |
| Section                                                                 | N  | Study Details                                                                 | Risk Ratio (M-H, Fixed, 95% CI) |
|------------------------------------------------------------------------|----|-------------------------------------------------------------------------------|---------------------------------|
| 18.2 Cohort studies (adverse events)                                   | 1  | 354                                                                           | 0.19 [0.06, 0.63]               |
| 19 Visual impairment (all studies)                                     | 2  |                                                                               |                                 |
| 19.1 Cohort studies (adverse effects)                                 | 2  | 1875                                                                         | 2.37 [1.41, 3.99]               |
| 20 Other adverse effects (cohort studies)                             | 6  |                                                                               |                                 |
| 20.1 Alopecia                                                          | 2  | 1875                                                                         | 3.44 [1.96, 6.03]               |
| 20.2 Asthenia                                                          | 1  | 1761                                                                         | 1.83 [0.89, 3.76]               |
| 20.3 Balance disorder                                                 | 1  | 1761                                                                         | 2.87 [1.48, 5.59]               |
| 20.4 Decreased appetite                                               | 1  | 734                                                                          | 1.23 [0.42, 3.64]               |
| 20.5 Fatigue                                                          | 2  | 74                                                                           | 0.23 [0.03, 1.77]               |
| 20.6 Hypoaesthesia                                                    | 2  | 2445                                                                         | 11.48 [3.01, 43.70]             |
| 20.7 Malaise                                                          | 1  | 734                                                                          | 0.28 [0.11, 0.71]               |
| 20.8 Mouth ulcers                                                    | 1  | 33                                                                           | 0.5 [0.02, 11.42]               |
| 20.9 Palpitations                                                    | 1  | 1761                                                                         | 2.76 [0.16, 48.91]              |
| 20.10 Tinnitus                                                        | 1  | 684                                                                          | 7.20 [0.39, 133.30]             |
| 21 Other adverse events (RCTs)                                        | 1  |                                                                               |                                 |
| 21.1 Constipation                                                     | 1  | 123                                                                          | 2.03 [0.19, 21.84]              |
| 21.2 Cough                                                            | 1  | 123                                                                          | 0.53 [0.28, 1.01]               |
| 21.3 Decreased appetite                                               | 1  | 123                                                                          | 3.56 [1.24, 10.20]              |
| 21.4 Malaise                                                          | 1  | 123                                                                          | 2.03 [0.88, 4.69]               |
| 21.5 Palpitations                                                    | 1  | 123                                                                          | 2.03 [0.19, 21.84]              |
| 21.6 Pyrexia                                                          | 1  | 123                                                                          | 2.85 [1.09, 7.42]               |
| 21.7 Sexual dysfunction                                               | 1  | 123                                                                          | 3.05 [0.33, 28.51]              |
| 21.8 Somnolence                                                      | 1  | 123                                                                          | 2.03 [0.19, 21.84]              |
| 22 Other adverse events (cohort studies)                             | 3  |                                                                               |                                 |
| 22.1 Adjustment disorder                                              | 1  | 354959                                                                       | 0.43 [0.40, 0.45]               |
| 22.2 Confusion                                                        | 1  | 354959                                                                       | 2.18 [0.24, 19.49]              |
| 22.3 Convulsions                                                      | 1  | 354959                                                                       | 0.58 [0.45, 0.75]               |
| 22.4 Hallucinations                                                   | 1  | 354959                                                                       | 0.18 [0.08, 0.45]               |
| 22.5 Paranoia                                                         | 1  | 354959                                                                       | 0.40 [0.10, 1.63]               |
| 22.6 Palpitations                                                    | 1  | 668                                                                           | 13.44 [1.73, 104.38]            |
| 22.7 Panic attacks                                                    | 1  | 21065                                                                         | 4.16 [0.55, 31.49]              |
| 22.8 PTSD                                                             | 1  | 354959                                                                       | 0.58 [0.53, 0.64]               |
| 22.9 Rash                                                             | 1  | 668                                                                           | 1.21 [0.50, 2.94]               |
| 22.10 Suicidal ideation                                              | 1  | 354959                                                                       | 0.38 [0.31, 0.47]               |
| 22.11 Suicide                                                         | 2  | 376024                                                                       | 1.21 [0.82, 4.56]               |
| 22.12 Tinnitus                                                        | 1  | 354959                                                                       | 0.65 [0.61, 0.71]               |
| 23 Adherence (cohort studies)                                         | 14 |                                                                               |                                 |
| 23.1 Adherence during travel                                          | 13 | 15583                                                                        | 1.15 [1.12, 1.18]               |
| 23.2 Adherence in the post-travel period                              | 4  | 840                                                                           | 1.08 [0.95, 1.22]               |
## 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]            |
| 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 Discontinuations due to adverse effects (all studies) | 12             | 3591                | Risk Ratio (M-H, Fixed, 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)    | Subtotals only            |
| 4 Nausea (all studies)                           | 8              | 976                 | Risk Ratio (M-H, Fixed, 95% CI)     | 0.90 [0.52, 1.56]         |
| 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, Fixed, 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)     | 0.64 [0.38, 1.07]         |
| 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]         |
| 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 healthcare 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 [2.16, 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]        |
| Topic                                                                 | Total   | Risk Ratio (M-H, Fixed, 95% CI) | Reference                                                                 |
|----------------------------------------------------------------------|---------|---------------------------------|---------------------------------------------------------------------------|
| 12.3 Retrospective healthcare record analysis (adverse events)      | 1       | 4,9419 Risk Ratio (M-H, Fixed, 95% CI) 1.24 [1.06, 1.44] | Subtotals only                                                             |
| 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]       | Subtotals only                                                             |
| 13.2 Cohort studies (adverse effects)                               | 4       | 2,664 Risk Ratio (M-H, Fixed, 95% CI) 10.10 [3.48, 29.32] | Subtotals only                                                             |
| 13.3 Retrospective healthcare record analysis (adverse events)      | 1       | 4,9419 Risk Ratio (M-H, Fixed, 95% CI) 1.54 [1.28, 1.85] | Subtotals only                                                             |
| 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]     | Subtotals only                                                             |
| 14.2 Cohort studies (adverse effects)                               | 6       | 3,624 Risk Ratio (M-H, Fixed, 95% CI) 8.02 [3.56, 18.07] | Subtotals only                                                             |
| 14.3 Retrospective healthcare record analysis (adverse events)      | 1       | 4,9419 Risk Ratio (M-H, Fixed, 95% CI) 1.93 [1.56, 2.38] | Subtotals only                                                             |
| 15 Abnormal thoughts and perceptions (all studies)                  | 4       |                                 | Risk Ratio (M-H, Fixed, 95% CI) Subtotals only                             |
| 15.1 Cohort studies (adverse effects)                               | 3       | 2,433 Risk Ratio (M-H, Fixed, 95% CI) 1.50 [0.30, 7.42]   | Subtotals only                                                             |
| 15.2 Retrospective healthcare record analysis (adverse effects)      | 1       | 4,9419 Risk Ratio (M-H, Fixed, 95% CI) 3.00 [0.69, 12.97] | Subtotals only                                                             |
| 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]     | Subtotals only                                                             |
| 16.2 Cohort studies (adverse effects)                               | 3       | 1,824 Risk Ratio (M-H, Fixed, 95% CI) 2.07 [0.40, 10.68]  | Subtotals only                                                             |
| 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]     | Subtotals only                                                             |
| 17.2 Cohort studies (adverse effects)                               | 2       | 1,956 Risk Ratio (M-H, Fixed, 95% CI) 1.17 [0.29, 4.72]   | Subtotals only                                                             |
| 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]     | Subtotals only                                                             |
| 18.2 Alopecia                                                       | 1       | 1,469 Risk Ratio (M-H, Fixed, 95% CI) 4.55 [0.30, 70.01]  | Subtotals only                                                             |
| 18.3 Asthenia                                                       | 2       | 1,956 Risk Ratio (M-H, Fixed, 95% CI) 1.84 [0.26, 13.12]  | Subtotals only                                                             |
| 18.4 Balance disorder                                               | 1       | 1,469 Risk Ratio (M-H, Fixed, 95% CI) 2.86 [0.19, 44.19]  | Subtotals only                                                             |
| 18.5 Cough                                                         | 1       | 652 Risk Ratio (M-H, Fixed, 95% CI) 0.49 [0.08, 2.92]      | Subtotals only                                                             |
| 18.6 Disturbance in attention                                       | 3       | 1,363 Risk Ratio (M-H, Fixed, 95% CI) 4.45 [1.84, 10.77]  | Subtotals only                                                             |
| 18.7 Dyspepsia                                                     | 2       | 362 Risk Ratio (M-H, Fixed, 95% CI) 0.50 [0.17, 1.46]      | Subtotals only                                                             |
| 18.8 Fatigue                                                       | 2       | 618 Risk Ratio (M-H, Fixed, 95% CI) 4.62 [0.47, 45.56]     | Subtotals only                                                             |
| 18.9 Hypoaesthesia                                                  | 2       | 1,946 Risk Ratio (M-H, Fixed, 95% CI) 4.45 [0.93, 21.26]   | Subtotals only                                                             |
| 18.10 Loss of appetite                                              | 1       | 652 Risk Ratio (M-H, Fixed, 95% CI) 0.69 [0.33, 1.43]      | Subtotals only                                                             |
| 18.11 Muscle pain                                                   | 1       | 652 Risk Ratio (M-H, Fixed, 95% CI) 7.57 [0.45, 127.80]    | Subtotals only                                                             |
| 18.12 Palpitations                                                 | 3       | 2,180 Risk Ratio (M-H, Fixed, 95% CI) 3.34 [0.73, 15.26]   | Subtotals only                                                             |
| 18.13 Photosensitization                                            | 2       | 718 Risk Ratio (M-H, Fixed, 95% CI) 0.69 [0.10, 4.92]       | Subtotals only                                                             |
| 18.14 Pyrexia                                                       | 1       | 652 Risk Ratio (M-H, Fixed, 95% CI) 4.28 [0.24, 75.57]     | Subtotals only                                                             |
| 18.15 Rash                                                         | 2       | 711 Risk Ratio (M-H, Fixed, 95% CI) 0.96 [0.15, 6.09]       | Subtotals only                                                             |
| 18.16 Restlessness                                                 | 1       | 487 Risk Ratio (M-H, Fixed, 95% CI) 5.24 [0.32, 84.52]      | Subtotals only                                                             |
| 18.17 Slight illness                                                | 1       | 487 Risk Ratio (M-H, Fixed, 95% CI) 5.83 [0.36, 93.84]      | Subtotals only                                                             |
| 18.18 Somnolence                                                   | 1       | 487 Risk Ratio (M-H, Fixed, 95% CI) 1.55 [0.21, 11.40]      | Subtotals only                                                             |
| 18.19 Tinnitus                                                     | 1       | 477 Risk Ratio (M-H, Fixed, 95% CI) 2.31 [0.13, 42.64]      | Subtotals only                                                             |
| 18.20 Circulatory disorders                                         | 1       | 224 Risk Ratio (M-H, Fixed, 95% CI) 6.38 [0.36, 114.01]     | Subtotals only                                                             |

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

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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 |
| 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** | **56998** | 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** | **58847** | 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** | **2845** | 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** | **56952** | 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** | **3408** | 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** | **58855** | 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 percepts** | **4** | **4831** | 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** | **5544** | Risk Ratio (M-H, Random, 95% CI) | **Subtotals only** |
| 15.1 Cohort studies (adverse effects) | 2 | 5544 | Risk Ratio (M-H, Random, 95% CI) | 1.13 [0.92, 1.40] |
| 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** | **58847** | 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** | **746** | 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; preads adverse effects** | **6** | **708** | 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] |
| 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 [0.67, 2.07] |
| 19.7 Fatigue | 1 | 525 | Risk Ratio (M-H, Fixed, 95% CI) | 2.37 [0.57, 10.80] |
| 19.8 Hypoaesthesia | 1 | 2137 | Risk Ratio (M-H, Fixed, 95% CI) | 20.26 [1.23, 333.93] |
| 19.9 Irritability | 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] |
| 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] |
## 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 |
| 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] |
| 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 1.1. Comparison 1 Mefloquine versus placebo/non users, Outcome 1 Clinical cases of malaria.

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 1 Mefloquine versus placebo/non users

Outcome: 1 Clinical cases of malaria

| Study or subgroup | Mefloquine | Placebo | Risk Ratio | Weight | Risk Ratio |
|------------------|------------|---------|------------|--------|------------|
|                  | n/N        | n/N     |            |        |            |
| Bunnag 1992 (1)  | 2/123      | 6/121   | 10.2 %     | 0.33   | [0.07, 1.59] |
| Hale 2003 (2)    | 0/46       | 4/94    | 5.0 %      | 0.22   | [0.01, 4.08] |
| Nosten 1994 (3)  | 5/159      | 37/152  | 14.5 %     | 0.13   | [0.05, 0.32] |
| Ohrt 1997 (4)    | 0/61       | 53/65   | 5.4 %      | 0.01   | [0.00, 0.16] |
| Pearlman 1980 (5)| 1/160      | 6/12    | 8.0 %      | 0.01   | [0.00, 0.10] |
| Pearlman 1980 (6)| 0/169      | 6/12    | 5.2 %      | 0.01   | [0.00, 0.10] |
| Pearlman 1980 (7)| 2/158      | 7/12    | 11.0 %     | 0.02   | [0.01, 0.09] |
| Salako 1992 (8)  | 0/107      | 7/101   | 5.2 %      | 0.06   | [0.00, 1.09] |
| Santos 1993 (9)  | 1/31       | 3/15    | 7.3 %      | 0.16   | [0.02, 1.42] |
| Santos 1993 (10) | 2/32       | 3/15    | 9.7 %      | 0.31   | [0.06, 1.68] |
| Sossouhounto 1995 (11)| 0/103 | 1/96 | 4.4 % | 0.31 | [0.01, 7.54] |
| Weiss 1995 (12)  | 4/30       | 20/34   | 14.2 %     | 0.23   | [0.09, 0.59] |

Total (95% CI) 1179 729 100.0 % 0.09 [0.04, 0.19]

Total events: 17 (Mefloquine), 153 (Placebo)

Heterogeneity: Tau² = 0.83; Chi² = 23.36, df = 11 (P = 0.02); I² = 53%

Test for overall effect: Z = 6.21 (P < 0.00001)

Test for subgroup differences: Not applicable
Analysis 1.2. Comparison 1 Mefloquine versus placebo/non users, Outcome 2 Malaria; episodes of parasitaemia in semi-immune populations.

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 1 Mefloquine versus placebo/non users

Outcome: 2 Malaria; episodes of parasitaemia in semi-immune populations

| Study or subgroup | Mefloquine | Risk Ratio M-H (Random) 95% CI | Weight | Risk Ratio M-H (Random) 95% CI |
|-------------------|------------|--------------------------------|--------|--------------------------------|
|                   | n/N        | n/N                            |        |                                |
| 1 Trials reporting number of participants with parasitaemia | | | | |
| Hale 2003         | 6/46       | 86/94                          | 38.3 % | 0.14 [0.07, 0.30] |
| Salako 1992       | 1/107      | 19/103                         | 18.9 % | 0.05 [0.01, 0.37] |
| Weiss 1995        | 11/30      | 34/34                          | 42.8 % | 0.38 [0.24, 0.60] |
| **Subtotal (95% CI)** | **183** | **231**                       | **100.0 %** | **0.18 [0.06, 0.55]** |

Total events: 18 (Mefloquine), 139 ()

Heterogeneity: Tau² = 0.71; Chi² = 10.18, df = 2 (P = 0.01); I² =80%

Test for overall effect: Z = 3.01 (P = 0.0026)

2 Trials reporting number of episodes of parasitaemia

| 0.001 | 0.01 | 0.1 | 1 | 10 | 100 | 1000 |
|-------|------|-----|--|----|-----|-----|
| Favours mefloquine | Favours placebo |

(Continued...)

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

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 1 Mefloquine versus placebo/non users

Outcome: 3 Serious adverse events or effects (all studies)

| Study or subgroup | Mefloquine | Placebo | Risk Ratio M-H,Fixed,95% CI | Weight |
|-------------------|------------|---------|---------------------------|--------|
| Nosten 1994       | 22/159     | 89/152  | 54.2 % 0.24 [ 0.16, 0.36 ] |        |
| Sossouhounto 1995 | 0/103      | 68/96   | 45.8 % 0.01 [ 0.00, 0.11 ] |        |
| **Subtotal (95% CI)** | **262** | **248** | **100.0 % 0.05 [ 0.00, 5.25 ]** |        |

Heterogeneity: Tau² = 10.69; Chi² = 11.49, df = 1 (P = 0.00070); I² = 91%
Test for overall effect: Z = 1.27 (P = 0.20)

| Study or subgroup | Mefloquine | Placebo | Risk Ratio M-H,Fixed,95% CI | Weight |
|-------------------|------------|---------|---------------------------|--------|
| Bunnag 1992       | 0/116      | 1/121   | 41.6 % 0.35 [ 0.01, 8.45 ] |        |
| Hale 2003         | 0/46       | 0/94    | Not estimable              |        |
| Nosten 1994       | 1/159      | 0/152   | 14.5 % 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    | 43.9 % 0.31 [ 0.01, 7.54 ] |        |
| **Subtotal (95% CI)** | **592** | **629** | **100.0 % 0.70 [ 0.14, 3.53 ]** |        |

Total events: 1 (Mefloquine), 2 (Placebo)
Heterogeneity: Chi² = 1.18, df = 2 (P = 0.55); I² = 0.0%
Test for overall effect: Z = 0.44 (P = 0.66)

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

**Review:** Mefloquine for preventing malaria during travel to endemic areas  
**Comparison:** 1 Mefloquine versus placebo/non users  
**Outcome:** 4 Discontinuations due to adverse effects (all studies)

| Study or subgroup | Mefloquine | Control | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|---------|------------|--------|------------|
|                   | n/N        | n/N     | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| Bunnag 1992       | 2/116      | 1/119   | 18.6 % 2.05 [0.19, 22.32] |        |             |
| Hale 2003         | 0/46       | 3/94    | 43.7 % 0.29 [0.02, 5.48] |        |             |
| Nosten 1994       | 1/159      | 0/152   | 9.6 % 2.87 [0.12, 69.88] |        |             |
| Ohrt 1997         | 1/61       | 0/65    | 9.1 % 3.19 [0.13, 76.93] |        |             |
| Salako 1992       | 0/113      | 0/101   |             |        | Not estimable |
| Vuurman 1996      | 1/22       | 0/20    | 9.9 % 2.74 [0.12, 63.63] |        |             |
| Weiss 1995        | 1/30       | 0/32    | 9.1 % 3.19 [0.14, 75.49] |        |             |
| **Total (95% CI)** | **547**    | **583** | **100.0 % 1.64 [0.55, 4.88]** |    |            |

Total events: 6 (Mefloquine), 4 (Control)  
Heterogeneity: $\chi^2 = 1.93$, df = 5 ($P = 0.86$); $I^2 = 0.0\%$  
Test for overall effect: $Z = 0.88$ ($P = 0.38$)  
Test for subgroup differences: Not applicable

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(1) Hoebe 1997. Event described by study authors as ‘serious’, but not enough detail provided to meet our definition.
### Analysis 1.5. Comparison 1 Mefloquine versus placebo/non users, Outcome 5 Nausea (all studies).

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 1 Mefloquine versus placebo/non users

**Outcome:** 5 Nausea (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 RCTs (adverse events) | | | | | |
| Nosten 1994 (1) | 65/102 | 48/100 | 1.33 [1.03, 1.71] | 95.9 % | 1.33 [1.03, 1.71] |
| Vuurman 1996 | 4/22 | 2/20 | 1.82 [0.37, 8.88] | 4.1 % | 1.82 [0.37, 8.88] |
| **Subtotal (95% CI)** | **124** | **120** | | **100.0 %** | **1.35 [1.05, 1.73]** |
| **Total events:** | **69 (Mefloquine), 50 (Control)** | | | | |
| Heterogeneity: Chi² = 0.15, df = 1 (P = 0.70); I² =0.0% | | | | | |
| Test for overall effect: Z = 2.33 (P = 0.020) | | | | | |
| 2 Cohort studies (adverse events) | | | | | |
| Hoebe 1997 | 16/104 | 9/93 | 1.59 [0.74, 3.42] | 12.4 % | 1.59 [0.74, 3.42] |
| Petersen 2000 | 130/809 | 14/161 | 1.85 [1.09, 3.12] | 30.4 % | 1.85 [1.09, 3.12] |
| van Piirnsdijk 1997 | 91/394 | 41/340 | 1.92 [1.36, 2.69] | 57.3 % | 1.92 [1.36, 2.69] |
| **Subtotal (95% CI)** | **1307** | **594** | | **100.0 %** | **1.85 [1.42, 2.43]** |
| **Total events:** | **237 (Mefloquine), 64 (Control)** | | | | |
| Heterogeneity: Chi² = 0.19, df = 2 (P = 0.91); I² =0.0% | | | | | |
| Test for overall effect: Z = 4.51 (P < 0.00001) | | | | | |
| Test for subgroup differences: Chi² = 2.90, df = 1 (P = 0.09), I² =66% | | | | | |

(1) Nosten 1994. All non-serious adverse event data only reported from phase 2 of the trial
### Analysis 1.6. Comparison 1 Mefloquine versus placebo/non users, Outcome 6 Vomiting (all studies).

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 1 Mefloquine versus placebo/non users

**Outcome:** 6 Vomiting (all studies)

| Study or subgroup | Mefloquine | Control | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|---------|------------|--------|-----------|
|                   | n/N        | n/N     | M-H,Fixed, 95% CI |        | M-H,Fixed, 95% CI |
| RCTs (adverse events) |            |         |         |        |           |
| Nosten 1994       | 26/102     | 33/100  | 0.77 [0.50, 1.19] | 100.0% |           |
| **Subtotal (95% CI)** | 102        | 100     |           |        | 0.77 [0.50, 1.19] |
| Total events: 26 (Mefloquine), 33 (Control) |
| Heterogeneity: not applicable |
| Test for overall effect: Z = 1.17 (P = 0.24) |
| Cohort studies (adverse events) |            |         |         |        |           |
| Hoebe 1997        | 6/104      | 6/93    | 0.89 [0.30, 2.68] | 20.2%  |           |
| Petersen 2000     | 53/809     | 15/161  | 0.70 [0.41, 1.22] | 79.8%  |           |
| **Subtotal (95% CI)** | 913        | 254     |           |        | 0.74 [0.45, 1.21] |
| Total events: 59 (Mefloquine), 21 (Control) |
| Heterogeneity: Chi² = 0.15, df = 1 (P = 0.70); I² = 0.0% |
| Test for overall effect: Z = 1.19 (P = 0.23) |
| Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.90), I² = 0.0% |
Comparison 1 Mefloquine versus placebo/non users, Outcome 7 Abdominal pain (all studies).

| Study or subgroup | Mefloquine | Control | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|---------|------------|--------|------------|
|                   | n/N        | n/N     | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| RCTs (adverse events) |           |         |             |        |            |
| Hale 2003          | 3/46       | 6/94    | 6.9 % 1.02 [ 0.27, 3.90 ] | 6.9 % 1.02 [ 0.27, 3.90 ] |
| Nosten 1994 (1)    | 57/102     | 52/100  | 92.2 % 1.07 [ 0.83, 1.39 ] | 92.2 % 1.07 [ 0.83, 1.39 ] |
| Salako 1992        | 1/107      | 0/101   | 0.9 % 2.83 [ 0.12, 68.76 ] | 0.9 % 2.83 [ 0.12, 68.76 ] |
| Subtotal (95% CI)  | 255        | 295     | 100.0 % 1.09 [ 0.84, 1.40 ] | 100.0 % 1.09 [ 0.84, 1.40 ] |
| Cohort studies (adverse events) |          |         |            |        |            |
| Hoebe 1997         | 13/104     | 12/93   | 27.5 % 0.97 [ 0.47, 2.02 ] | 27.5 % 0.97 [ 0.47, 2.02 ] |
| Petersen 2000 (2)  | 97/809     | 20/161  | 72.5 % 0.97 [ 0.62, 1.51 ] | 72.5 % 0.97 [ 0.62, 1.51 ] |
| Subtotal (95% CI)  | 913        | 254     | 100.0 % 0.97 [ 0.66, 1.42 ] | 100.0 % 0.97 [ 0.66, 1.42 ] |

Total events: 61 (Mefloquine), 58 (Control)
Heterogeneity: Chi^2 = 0.36, df = 2 (P = 0.83); I^2 =0.0%
Test for overall effect: Z = 0.64 (P = 0.52)

Total events: 110 (Mefloquine), 32 (Control)
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.99); I^2 =0.0%
Test for overall effect: Z = 0.18 (P = 0.86)
Test for subgroup differences: Chi^2 = 0.25, df = 1 (P = 0.62), I^2 =0.0%

(1) Nosten 1994. 'Upper' abdominal pain.
(2) Petersen 2000. Reported in the original paper as 'stomach pain'
### Analysis 1.8. Comparison 1 Mefloquine versus placebo/non users, Outcome 8 Diarrhoea (all studies).

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 1 Mefloquine versus placebo/non users

**Outcome:** 8 Diarrhoea (all studies)

| Study or subgroup | Mefloquine | Placebo/no treatment | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|-------------------|------------|----------------------|-------------------------------|--------|-------------------------------|
| **1 RCTs (adverse events)** |            |                      |                               |        |                               |
| Hale 2003 (1)     | 4/46       | 15/94                | 0.54 [0.19, 1.55]             | 60.3%  |                               |
| Salako 1992       | 1/107      | 0/101                | 2.83 [0.12, 68.76]            | 6.5%   |                               |
| Sossouhounto 1995 | 2/103      | 3/96                 | 0.62 [0.11, 3.64]            | 21.1%  |                               |
| Vuurman 1996      | 2/22       | 1/20                 | 1.82 [0.18, 18.55]           | 12.2%  |                               |
| **Subtotal (95% CI)** | **278**   | **311**              | **0.72 [0.32, 1.62]**        | 100.0% |                               |

Total events: 9 (Mefloquine), 19 (Placebo/no treatment)
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.62$, df = 3 ($P = 0.65$); $I^2 = 0.0$
Test for overall effect: $Z = 0.79$ ($P = 0.43$)

| 2 Cohort studies (adverse events) |            |                      |                               |        |                               |
| Hoebe 1997                  | 29/104     | 29/93                | 0.89 [0.58, 1.38]             | 24.1%  |                               |
| Petersen 2000               | 249/809    | 41/161               | 1.21 [0.91, 1.61]            | 34.0%  |                               |
| van Reemtsaik 1997          | 206/394    | 114/340              | 1.56 [1.31, 1.86]            | 41.9%  |                               |
| **Subtotal (95% CI)**       | **1307**   | **594**              | **1.25 [0.93, 1.68]**        | 100.0% |                               |

Total events: 484 (Mefloquine), 184 (Placebo/no treatment)
Heterogeneity: $\tau^2 = 0.05$; $\chi^2 = 6.58$, df = 2 ($P = 0.04$); $I^2 = 70$
Test for overall effect: $Z = 1.47$ ($P = 0.14$)
Test for subgroup differences: $\chi^2 = 1.55$, df = 1 ($P = 0.21$); $I^2 = 36$

(1) Hale 2003. Reported in the original paper as ‘dysentry/ diarrhoea’
### Analysis 1.9. Comparison 1 Mefloquine versus placebo/non users, Outcome 9 Headache (all studies).

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 1 Mefloquine versus placebo/non users

**Outcome:** 9 Headache (all studies)

| Study or subgroup | Mefloquine | Placebo/ no treatment | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|-----------------------|------------|--------|------------|
|                   | n/N        | n/N                  | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| 1 RCTs (adverse events) | | | | | |
| Hale 2003         | 1/46       | 6/94                  | 4.4 %      | 0.34 [ 0.04, 2.75 ] |
| Nosten 1994       | 70/102     | 83/100                | 93.3 %     | 0.83 [ 0.71, 0.97 ] |
| Salako 1992       | 0/107      | 0/101                 | Not estimable |
| Sossouhounto 1995 | 0/103      | 1/96                  | 1.7 %      | 0.31 [ 0.01, 7.54 ] |
| Vuurman 1996      | 4/22       | 0/20                  | 0.6 %      | 8.22 [ 0.47, 143.66 ] |
| **Subtotal (95% CI)** | **380** | **411**               | **100.0 %** | **0.84 [ 0.71, 0.99 ]** |
| Total events: 75 (Mefloquine), 90 (Placebo/ no treatment) |
| Heterogeneity: $\chi^2 = 3.57, df = 3 (P = 0.31); I^2 = 16\%$ |
| Test for overall effect: $Z = 2.02 (P = 0.043)$ |
| 2 Cohort studies (adverse events) | | | | | |
| Hoebe 1997        | 1/104      | 6/93                  | 1000 %     | 1.64 [ 0.63, 4.26 ] |
| **Subtotal (95% CI)** | **104** | **93**                | **100.0 %** | **1.64 [ 0.63, 4.26 ]** |
| Total events: 11 (Mefloquine), 6 (Placebo/ no treatment) |
| Heterogeneity: not applicable |
| Test for overall effect: $Z = 1.01 (P = 0.31)$ |
| Test for subgroup differences: $\chi^2 = 1.83, df = 1 (P = 0.18), I^2 = 45\%$ |

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

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

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** Mefloquine versus placebo/non users

**Outcome:** Dizziness (all studies)

| Study or subgroup | Mefloquine n/N | Placebo/ no treatment n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|-------------------|----------------|---------------------------|-----------------------------|--------|-----------------------------|
| Nosten 1994       | 84/102         | 81/100                    | 97.5 % 1.02 [ 0.89, 1.16 ]  |        |                             |
| Salako 1992       | 0/107          | 0/101                     | Not estimable               |        |                             |
| Vuurman 1996      | 3/22           | 2/20                      | 2.5 % 1.36 [ 0.25, 7.34 ]   |        |                             |
| **Subtotal (95% CI)** | **231** | **221** | **100.0 %** | **1.03** [ **0.90**, **1.17** ] |        |                             |

Total events: 87 (Mefloquine), 83 (Placebo/no treatment)

Heterogeneity: \( \chi^2 = 0.13, \text{df} = 1 (P = 0.72); I^2 = 0.0\%

Test for overall effect: \( Z = 0.36 (P = 0.72) \)

2 Cohort studies (adverse events)

| Study or subgroup | Mefloquine n/N | Placebo/ no treatment n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|-------------------|----------------|---------------------------|-----------------------------|--------|-----------------------------|
| Hoebe 1997        | 13/104         | 3/93                      | 5.8 % 3.88 [ 1.14, 13.18 ]  |        |                             |
| Petersen 2000     | 88/809         | 7/161                     | 21.4 % 2.50 [ 1.18, 5.30 ]  |        |                             |
| van Reemsdijk 1997| 61/394         | 37/340                    | 72.8 % 1.42 [ 0.97, 2.08 ]  |        |                             |
| **Subtotal (95% CI)** | **1307** | **594** | **100.0 %** | **1.80** [ **1.29**, **2.49** ] |        |                             |

Total events: 162 (Mefloquine), 47 (Placebo/no treatment)

Heterogeneity: \( \chi^2 = 3.70, \text{df} = 2 (P = 0.16); I^2 = 46\%

Test for overall effect: \( Z = 3.49 (P = 0.00048) \)

Test for subgroup differences: \( \chi^2 = 9.54, \text{df} = 1 (P = 0.00), I^2 = 90\% \)
**Analysis 1.11. Comparison 1 Mefloquine versus placebo/non users, Outcome 11 Abnormal dreams (all studies).**

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 1 Mefloquine versus placebo/non users

Outcome: 11 Abnormal dreams (all studies)

| Study or subgroup | Mefloquine  | Placebo/ no treatment | Risk Ratio | Weight | Risk Ratio |
|-------------------|-------------|-----------------------|------------|--------|-----------|
|                   | n/N         | n/N                   | M-H Fixed 95% CI |        | M-H Fixed 95% CI |
| Cohort studies (adverse events) |             |                       |             |        |            |
| Hoebe 1997 (1)    | 9/104       | 2/93                  | 19.7 %      | 4.02   | [ 0.89, 18.15 ] |
| van Riemstijk 1997 (2) | 18/394     | 8/340                 | 80.3 %      | 1.94   | [ 0.86, 4.41 ] |
| **Subtotal (95% CI)** | **498**     | **433**               | **100.0 %** | **2.35** | **[ 1.15, 4.80 ]** |

Total events: 27 (Mefloquine), 10 (Placebo/ no treatment)

Heterogeneity: Chi² = 0.70, df = 1 (P = 0.40); I² =0.0%

Test for overall effect: Z = 2.35 (P = 0.019)

Test for subgroup differences: Not applicable

(1) Hoebe 1997. Reported in the original paper as ‘nightmares’

(2) van Riemstijk 1997. Reported in the original paper as ‘nightmares’
### Analysis 1.12. Comparison 1 Mefloquine versus placebo/non users, Outcome 12 Insomnia (all studies).

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 1 Mefloquine versus placebo/non users

Outcome: 12 Insomnia (all studies)

| Study or subgroup | Mefloquine | Placebo/ no treatment | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|-------------------|------------|-----------------------|-----------------------------|--------|-----------------------------|
| Cohort studies (adverse events) | | | | | |
| Hoebe 1997 | 14/104 | 8/93 | 1.56 [0.69, 3.56] | 15.5% | |
| van Rensburg 1997 | 72/394 | 43/340 | 1.44 [1.02, 2.05] | 84.5% | |
| Subtotal (95% CI) | 498 | 433 | 1.46 [1.06, 2.02] | 100.0% | |

Total events: 86 (Mefloquine), 51 (Placebo/ no treatment)

Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² = 0.0%

Test for overall effect: Z = 2.32 (P = 0.020)

Test for subgroup differences: Not applicable
Analysis 1.13. Comparison 1 Mefloquine versus placebo/non users, Outcome 13 Anxiety (all studies).

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 1 Mefloquine versus placebo/non users

Outcome: 13 Anxiety (all studies)

| Study or subgroup | Placebo/ no treatment Risk Ratio M-H,Fixed,95% CI | Weight M-H,Fixed,95% CI |
|-------------------|--------------------------------------------------|-------------------------|
| Cohort studies (adverse events) | | |
| Hoebe 1997        | 4/104 0/93                                       | 2.8 % 8.06 [0.44, 147.68] |
| van Piensdijk 1997 | 20/394 17/340                                    | 97.2 % 1.02 [0.54, 1.91] |
| **Subtotal (95% CI)** | 498 433                                         | 100.0 % 1.21 [0.67, 2.21] |

Total events: 24 (Mefloquine), 17 (Placebo/ no treatment)

Heterogeneity: Chi² = 1.93, df = 1 (P = 0.16); I² = 48%

Test for overall effect: Z = 0.63 (P = 0.53)

Test for subgroup differences: Not applicable
### Analysis 1.14. Comparison 1 Mefloquine versus placebo/non users, Outcome 14 Depressed mood (all studies).

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 1 Mefloquine versus placebo/non users

**Outcome:** 14 Depressed mood (all studies)

| Study or subgroup | Mefloquine | Placebo/ no treatment | Risk Ratio M-H, Random, 95% CI | Weight |
|-------------------|------------|-----------------------|-------------------------------|--------|
| Hoebe 1997 (1)    | 12/104     | 4/93                  | 2.68 [0.90, 8.03]              | 36.1%  |
| Petersen 2000     | 55/809     | 1/161                 | 10.95 [1.53, 78.52]            | 23.2%  |
| van Riemsdijk 1997 (2) | 12/394     | 11/340               | 0.94 [0.42, 2.11]              | 40.8%  |

**Subtotal (95% CI)**

| Risk Ratio M-H, Random, 95% CI | 1307 | 594 | 100.0% | 2.43 [0.65, 9.07] |

Total events: 79 (Mefloquine), 16 (Placebo/no treatment)

Heterogeneity: $\tau^2 = 0.94$; $\chi^2 = 7.21$, df = 2 ($p = 0.03$); $I^2 = 72$

Test for overall effect: $Z = 1.32$ ($p = 0.19$)

Test for subgroup differences: Not applicable

---

(1) Hoebe 1997. Reported in the original paper as ‘depression’

(2) van Riemsdijk. 1997. Reported in the original paper as ‘depression’
### Analysis 1.15. Comparison 1 Mefloquine versus placebo/non users, Outcome 15 Abnormal thoughts and perceptions.

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 1 Mefloquine versus placebo/non users

**Outcome:** 15 Abnormal thoughts and perceptions

| Study or subgroup | Mefloquine | Placebo/ no treatment | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|-----------------------|------------|--------|------------|
| | n/N | n/N | M-H Fixed 95% CI | | M-H Fixed 95% CI |
| **Cohort studies (adverse events)** | | | | | |
| Petersen 2000 (1) | 29/809 | 1/161 | 5.77 [0.79, 42.06] | 100.0% | |
| **Subtotal (95% CI)** | | | | | |
| | 809 | 161 | 5.77 [0.79, 42.06] | 100.0% | |

Total events: 29 (Mefloquine), 1 (Placebo/ no treatment)

Heterogeneity: not applicable

Test for overall effect: Z = 1.73 (P = 0.084)

Test for subgroup differences: Not applicable

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(1) Petersen 2000. Reported in the original paper as 'strange thoughts'
Analysis 1.16. Comparison 1 Mefloquine versus placebo/non users, Outcome 16 Pruritis (all studies).

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 1 Mefloquine versus placebo/non users

Outcome: 16 Pruritis (all studies)

| Study or subgroup | Mefloquine | Placebo/ no treatment | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|------------------|------------|------------------------|-----------------------------|--------|-----------------------------|
|                  | n/N        | n/N                    |                             |        |                             |
| 1 RCTs (adverse events) |            |                        |                             |        |                             |
| Nosten 1994 (1)  | 34/102     | 34/100                 | 76.9 % 0.98 [0.67, 1.44]    |        |                             |
| Salako 1992 (2)  | 1/107      | 5/101                  | 11.5 % 0.19 [0.02, 1.59]    |        |                             |
| Sossouhounto 1995 | 4/103      | 5/96                   | 11.6 % 0.75 [0.21, 2.70]    |        |                             |
| Subtotal (95% CI) | 312        | 297                    | 100.0 % 0.86 [0.60, 1.24]   |        |                             |
| Total events: 39 (Mefloquine), 44 (Placebo/ no treatment) |
| Heterogeneity: $\chi^2 = 2.43$, df = 2 ($P = 0.30$); $I^2 = 18\%$ |
| Test for overall effect: $Z = 0.80$ ($P = 0.43$) |
| 2 Cohort studies (adverse events) |            |                        |                             |        |                             |
| Hoebe 1997 (3)   | 15/104     | 2/93                   | 100.0 % 6.71 [1.58, 28.55]  |        |                             |
| Subtotal (95% CI) | 104        | 93                     | 100.0 % 6.71 [1.58, 28.55]  |        |                             |
| Total events: 15 (Mefloquine), 2 (Placebo/ no treatment) |
| Heterogeneity: not applicable |
| Test for overall effect: $Z = 2.57$ ($P = 0.010$) |
| Test for subgroup differences: $\chi^2 = 7.25$, df = 1 ($P = 0.01$); $I^2 = 86\%$ |

(1) Nosten 1994. Reported in the original paper as 'itching'.
(2) Salako 1992. Reported in the original paper as 'pruritis/itching'.
(3) Hoebe 1997. Reported in the original paper as 'itching'.
Analysis 1.17. Comparison 1 Mefloquine versus placebo/non users, Outcome 17 Visual impairment (all studies).

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 1 Mefloquine versus placebo/non users

Outcome: 17 Visual impairment (all studies)

| Study or subgroup | Mefloquine n/N | Placebo/ no treatment n/N | Risk Ratio M-H,Fixed 95% CI | Weight | Risk Ratio M-H,Fixed 95% CI |
|------------------|----------------|---------------------------|-----------------------------|--------|-----------------------------|
| Nosten 1994 (1)  | 33/102         | 33/100                    | 1.00 [0.66, 1.46]           | 100.0% | 0.98 [0.66, 1.46]           |
| **Subtotal (95% CI)** | **102**         | **100**                    |                             |        |                             |
| Petersen 2000 (2) | 14/809         | 3/161                     | 0.93 [0.27, 3.19]           | 100.0% | 0.93 [0.27, 3.19]           |
| **Subtotal (95% CI)** | **809**         | **161**                    |                             |        |                             |

Total events: 33 (Mefloquine), 33 (Placebo/no treatment)

Heterogeneity: not applicable

Test for overall effect: Z = 0.10 (P = 0.92)

Test for subgroup differences: Chi² = 0.12, df = 1 (P = 0.91), I² = 0.0%

(1) Nosten 1994. Reported in the original paper as ‘visual abnormalities’.

(2) Petersen 2000. Reported in the original paper as ‘blurred vision’.
### Analysis 1.18. Comparison 1 Mefloquine versus placebo/non users, Outcome 18 Vertigo (all studies).

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 1 Mefloquine versus placebo/non users

**Outcome:** 18 Vertigo (all studies)

| Study or subgroup | Mefloquine | Placebo/ no treatment | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|------------------------|------------|--------|-----------|
|                   | n/N        | n/N                    | M-H, Fixed, 95% CI |        | M-H, Fixed, 95% CI |
| 1 RCTs (adverse events) | | | | | |
| Nosten 1994       | 52/102     | 50/100                 | 1.02 [0.78, 1.34] | 100.0 % | 1.02 [0.78, 1.34] |

**Subtotal (95% CI)**

Total events: 52 (Mefloquine), 50 (Placebo/ no treatment)

Heterogeneity: not applicable

Test for overall effect: Z = 0.14 (P = 0.89)

Test for subgroup differences: Not applicable
### Analysis 1.19. Comparison 1 Mefloquine versus placebo/non users, Outcome 19 Other adverse events (RCTs).

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 1 Mefloquine versus placebo/non users

Outcome: 19 Other adverse events (RCTs)

| Study or subgroup | Mefloquine n/N | Control n/N | Risk Ratio M-H,Fixed 95% CI | Weight M-H,Fixed 95% CI |
|-------------------|---------------|-------------|-----------------------------|-------------------------|
| **1. Arthralgia** |               |             |                             |                         |
| Hale 2003         | 0/46          | 3/94        |                             |                         |
| **Subtotal (95% CI)** | **46** | **94**     | **100.0 %**                  | **0.29 [0.02, 5.48]** |
| Total events: 0 (Mefloquine), 3 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 0.83 (P = 0.41) | | | | |
| **2. Back pain** |               |             |                             |                         |
| Hale 2003         | 0/46          | 10/94       |                             |                         |
| **Subtotal (95% CI)** | **46** | **94**     | **100.0 %**                  | **0.10 [0.01, 1.61]** |
| Total events: 0 (Mefloquine), 10 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 1.63 (P = 0.10) | | | | |
| **3. Blurred vision** |               |             |                             |                         |
| Salako 1992 (1)   | 0/107         | 2/101       |                             |                         |
| **Subtotal (95% CI)** | **107** | **101**    | **100.0 %**                  | **0.19 [0.01, 3.89]** |
| Total events: 0 (Mefloquine), 2 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 1.08 (P = 0.28) | | | | |
| **4. Cough** |               |             |                             |                         |
| Nosten 1994       | 56/102        | 61/100      |                             |                         |
| **Subtotal (95% CI)** | **102** | **100**    | **100.0 %**                  | **0.90 [0.71, 1.14]** |
| Total events: 56 (Mefloquine), 61 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 0.88 (P = 0.38) | | | | |
| **5. Constipation** |               |             |                             |                         |
| Nosten 1994       | 32/102        | 41/100      |                             |                         |
| **Subtotal (95% CI)** | **102** | **100**    | **100.0 %**                  | **0.77 [0.53, 1.11]** |
| Total events: 32 (Mefloquine), 41 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 1.41 (P = 0.16) | | | | |
| **6. Decreased appetite** |               |             |                             |                         |
| Nosten 1994 (2)   | 82/102        | 73/100      |                             |                         |
| **Subtotal (95% CI)** | **102** | **100**    | **100.0 %**                  | **1.10 [0.95, 1.28]** |
| Total events: 82 (Mefloquine), 73 (Control) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 1.41 (P = 0.16) | | | | |

(Continued...)
| Study or subgroup | Mefloquine | Control | Risk Ratio | Weight | Risk Ratio |
|------------------|------------|---------|------------|--------|------------|
|                  | n/N        | n/N     |            |        |            |
| Total events:    | 82 (Mefloquine), 73 (Control) |          |            |        |            |
| Heterogeneity:   | not applicable |          |            |        |            |
| Test for overall effect: | Z = 1.24 (P = 0.22) |          |            |        |            |
| Falls            | Nosten 1994 | 53/102  | 48/100     | 100.0% | 1.08 [0.82, 1.43] |
| Subtotal (95% CI)| 102        | 100     |            | 100.0% | 1.08 [0.82, 1.43] |
| Total events:    | 53 (Mefloquine), 48 (Control) |          |            |        |            |
| Heterogeneity:   | not applicable |          |            |        |            |
| Test for overall effect: | Z = 0.56 (P = 0.57) |          |            |        |            |
| Fatigue          | Vuurman 1996 | 2/22    | 2/20       | 100.0% | 0.91 [0.14, 5.86] |
| Subtotal (95% CI)| 22         | 20      |            | 100.0% | 0.91 [0.14, 5.86] |
| Total events:    | 2 (Mefloquine), 2 (Control) |          |            |        |            |
| Heterogeneity:   | not applicable |          |            |        |            |
| Test for overall effect: | Z = 0.10 (P = 0.92) |          |            |        |            |
| Gastritis        | Hale 2003   | 1/46    | 2/94       | 100.0% | 1.02 [0.10, 10.98] |
| Subtotal (95% CI)| 46         | 94      |            | 100.0% | 1.02 [0.10, 10.98] |
| Total events:    | 1 (Mefloquine), 2 (Control) |          |            |        |            |
| Heterogeneity:   | not applicable |          |            |        |            |
| Test for overall effect: | Z = 0.02 (P = 0.99) |          |            |        |            |
| Myalgia          | Hale 2003   | 3/46    | 4/94       | 100.0% | 1.53 [0.36, 6.57] |
| Subtotal (95% CI)| 46         | 94      |            | 100.0% | 1.53 [0.36, 6.57] |
| Total events:    | 3 (Mefloquine), 4 (Control) |          |            |        |            |
| Heterogeneity:   | not applicable |          |            |        |            |
| Test for overall effect: | Z = 0.58 (P = 0.57) |          |            |        |            |
| Rash             | Hale 2003   | 1/46    | 7/94       | 100.0% | 0.29 [0.04, 2.30] |
| Subtotal (95% CI)| 46         | 94      |            | 100.0% | 0.29 [0.04, 2.30] |
| Total events:    | 1 (Mefloquine), 7 (Control) |          |            |        |            |
| Heterogeneity:   | not applicable |          |            |        |            |
| Test for overall effect: | Z = 1.17 (P = 0.24) |          |            |        |            |
| Respiratory tract infection | Hale 2003 | 9/46    | 7/94       | 100.0% | 2.63 [1.04, 6.61] |
| Subtotal (95% CI)| 46         | 94      |            | 100.0% | 2.63 [1.04, 6.61] |
| Total events:    | 9 (Mefloquine), 7 (Control) |          |            |        |            |
| Heterogeneity:   | not applicable |          |            |        |            |
| Test for overall effect: | Z = 2.05 (P = 0.040) |          |            |        |            |
| Sore throat      | Hale 2003   | 1/46    | 6/94       | 100.0% | 0.34 [0.04, 2.75] |
| Study or subgroup | Mefloquine | Control | Risk Ratio (M-H,Fixed) 95% CI | Weight | Risk Ratio (M-H,Fixed) 95% CI |
|------------------|------------|---------|-----------------------------|--------|-----------------------------|
| **Subtotal (95% CI)** | 46 | 94 | | 100.0 % | 0.34 [0.04, 2.75] |
| Total events: 1 (Mefloquine), 6 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: $Z = 1.01$ ($P = 0.31$) | | | | | |
| 14 Unsteadiness | | | | | |
| Nosten 1994 | 39/102 | 36/100 | | 100.0 % | 1.06 [0.74, 1.52] |
| **Subtotal (95% CI)** | 102 | 100 | | 100.0 % | 1.06 [0.74, 1.52] |
| Total events: 39 (Mefloquine), 36 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: $Z = 0.33$ ($P = 0.74$) | | | | | |
| 15 Weakness | | | | | |
| Nosten 1994 | 93/102 | 86/100 | | 100.0 % | 1.06 [0.96, 1.17] |
| **Subtotal (95% CI)** | 102 | 100 | | 100.0 % | 1.06 [0.96, 1.17] |
| Total events: 93 (Mefloquine), 86 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: $Z = 1.15$ ($P = 0.25$) | | | | | |

1. Salako 1992. 'Blurred sight'
2. Nosten 1994. 'Anorexia'
Analysis 1.20. Comparison 1 Mefloquine versus placebo/non users, Outcome 20 Other adverse effects (cohort studies).

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 1 Mefloquine versus placebo/non users

Outcome: 20 Other adverse effects (cohort studies)

| Study or subgroup | Mefloquine | Non-users | Risk Ratio | Weight | Risk Ratio |
|------------------|------------|-----------|------------|--------|------------|
|                  | n/N        | n/N       | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| 1 Agitation      | 27/394     | 22/340    | 1.06 [ 0.61, 1.82 ] | 100.0 % | 1.06 [ 0.61, 1.82 ] |
| Subtotal (95% CI)| 394        | 340       | 100.0 % | 1.06 [ 0.61, 1.82 ] |
|                  |            |           | Subtotal (95% CI) 394 340 |        |                     |
|                  |            |           | Heterogeneity: not applicable |        |                     |
|                  |            |           | Test for overall effect: Z = 0.21 (P = 0.84) |        |                     |
| 2 Altered spatial perception | Petersen 2000 | 23/809 0/161 | 9.40 [ 0.57, 153.97 ] | 100.0 % | 9.40 [ 0.57, 153.97 ] |
| Subtotal (95% CI)| 809        | 161       | 100.0 % | 9.40 [ 0.57, 153.97 ] |
|                  |            |           | Subtotal (95% CI) 809 161 |        |                     |
|                  |            |           | Heterogeneity: not applicable |        |                     |
|                  |            |           | Test for overall effect: Z = 0.12 (P = 0.12) |        |                     |
| 3 Confusion      | van Riemsdijk 1997 | 7/394 9/340 | 0.67 [ 0.25, 1.78 ] | 100.0 % | 0.67 [ 0.25, 1.78 ] |
| Subtotal (95% CI)| 394        | 340       | 100.0 % | 0.67 [ 0.25, 1.78 ] |
|                  |            |           | Subtotal (95% CI) 394 340 |        |                     |
|                  |            |           | Heterogeneity: not applicable |        |                     |
|                  |            |           | Test for overall effect: Z = 0.42 (P = 0.42) |        |                     |
| 4 Loss of appetite | Petersen 2000 (1) | 72/809 16/161 | 0.90 [ 0.54, 1.50 ] | 100.0 % | 0.90 [ 0.54, 1.50 ] |
| Subtotal (95% CI)| 809        | 161       | 100.0 % | 0.90 [ 0.54, 1.50 ] |
|                  |            |           | Subtotal (95% CI) 809 161 |        |                     |
|                  |            |           | Heterogeneity: not applicable |        |                     |
|                  |            |           | Test for overall effect: Z = 0.42 (P = 0.67) |        |                     |
| 5 Mouth ulcers   | Petersen 2000 | 25/809 5/161 | 1.00 [ 0.39, 2.56 ] | 100.0 % | 1.00 [ 0.39, 2.56 ] |
| Subtotal (95% CI)| 809        | 161       | 100.0 % | 1.00 [ 0.39, 2.56 ] |
|                  |            |           | Subtotal (95% CI) 809 161 |        |                     |
|                  |            |           | Heterogeneity: not applicable |        |                     |
|                  |            |           | Test for overall effect: Z = 0.01 (P = 0.99) |        |                     |
| 6 Palpitations   | Hoebe 1997 | 4/104 0/93 | 8.06 [ 0.44, 147.68 ] | 100.0 % | 8.06 [ 0.44, 147.68 ] |
| Subtotal (95% CI)| 104        | 93        | 100.0 % | 8.06 [ 0.44, 147.68 ] |

(Continued ...)

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

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Study or subgroup & Mefloquine & Non-users & Risk Ratio & Weight & Risk Ratio & Weight
\hline
Total events: 4 (Mefloquine), 0 (Non-users) \\
Heterogeneity: not applicable \\
Test for overall effect: Z = 1.41 (P = 0.16) \\
7 Tingling \\
Petersen 2000 & 29/809 & 3/161 & 100.0 % & 1.92 [0.59, 6.24] & \\
\textbf{Subtotal (95% CI)} & 809 & 161 & 100.0 % & 1.92 [0.59, 6.24] & \\
Total events: 29 (Mefloquine), 3 (Non-users) \\
Heterogeneity: not applicable \\
Test for overall effect: Z = 1.09 (P = 0.28) \\
Test for subgroup differences: Chi$^2$ = 6.44, df = 6 (P = 0.38), I$^2$ = 7%

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

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 2 Mefloquine versus doxycycline

**Outcome:** 1 Clinical cases of malaria (RCTs)

| Study or subgroup | Mefloquine | Doxycycline | Risk Ratio | Weight | Risk Ratio | Weight |
|-------------------|------------|-------------|------------|--------|------------|--------|
| Arthur 1990 (1)   | 0/134      | 0/119       |            |        | Not estimable |        |
| Ohrt 1997 (2)     | 0/61       | 1/62        |            |        | 43.5 %      | 0.34 [0.01, 8.16] |
| Schlagenhauf 2003 (3) | 0/153     | 0/153       |            |        | Not estimable |        |
| Weiss 1995 (4)    | 4/30       | 2/32        |            |        | 56.5 %      | 2.13 [0.42, 10.81] |
| **Total (95% CI)** | 378        | 366         | 100.0 %    | 1.35 [0.35, 5.19] |
Analysis 2.2. Comparison 2 Mefloquine versus doxycycline, Outcome 2 Serious adverse events or effects (all studies).

Review: Mefloquine for preventing malaria during travel to endemic areas
Comparison: 2 Mefloquine versus doxycycline
Outcome: 2 Serious adverse events or effects (all studies)

| Study or subgroup | Mefloquine | Doxycycline | Rm | Weight |
|-------------------|------------|-------------|----|--------|
| **Subtotal (95% CI)** | 348 | 334 | 100.0 % | 0.34 [ 0.01, 8.16 ] |
| Total events: 0 (Mefloquine), 1 (Doxycycline) |

Heterogeneity: not applicable
Test for overall effect: Z = 0.67 (P = 0.50)

**Cohort studies (adverse effects)**

| Study or subgroup | Mefloquine | Doxycycline | Rm | Weight |
|-------------------|------------|-------------|----|--------|
| **Subtotal (95% CI)** | 2125 | 1597 | 100.0 % | 1.53 [ 0.23, 10.24 ] |
| Total events: 19 (Mefloquine), 10 (Doxycycline) |

Heterogeneity: Tau² = 1.32; Chi² = 2.86, df = 1 (P = 0.09); I² =65%
Test for overall effect: Z = 0.43 (P = 0.66)
Test for subgroup differences: Chi² = 0.63, df = 1 (P = 0.43), I² =0.0%

(1) Arthur 1990: Non-immune soldiers. Mefloquine dose 250mg weekly
(2) Oht 1997. 'Largely non-immune' Indonesian soldiers. Mefloquine dose 250mg weekly
(3) Schlagenhauf 2003: Short term international travellers. Mefloquine dose 250mg weekly
(4) Weiss 1995. Kenyan children, semi-immune. Mefloquine dose 125mg weekly.
### Analysis 2.3. Comparison 2 Mefloquine versus doxycycline, Outcome 3 Discontinuations due to adverse effects (all studies).

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 2 Mefloquine versus doxycycline

Outcome: 3 Discontinuations due to adverse effects (all studies)

| Study or subgroup | Mefloquine | Doxycycline | Risk Ratio M-H| Random, 95% CI | Weight |
|-------------------|------------|-------------|---------------|----------------|--------|
|                   | n/N        | n/N         |               |                |        |
| **1 RCTs**        |            |             |               |                |        |
| Arthur 1990       | 0/134      | 0/119       |               |                |        |
| Ohrt 1997         | 1/61       | 1/62        |               |                |        |
| Schlagenhaufer 2003 | 6/156     | 5/169       |               |                |        |
| Weiss 1995        | 1/30       | 2/32        |               |                |        |
| **Subtotal (95% CI)** | 381       | 382         |               |                | 100.0% |
|                   |            |             |               | 1.08 [0.41, 2.87] |        |
| **Total events:** | 8 (Mefloquine), 8 (Doxycycline) | | | | |
| Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.45, df = 2 (P = 0.80); I^2 = 0.0% |
| Test for overall effect: Z = 0.15 (P = 0.88)

| Study or subgroup | Mefloquine | Doxycycline | Risk Ratio M-H| Random, 95% CI | Weight |
|-------------------|------------|-------------|---------------|----------------|--------|
|                   | n/N        | n/N         |               |                |        |
| **2 Cohort studies** |            |             |               |                |        |
| Korhonen 2007     | 370/1612   | 88/708      |               |                |        |
| Napoletano 2007   | 66/548     | 4/33        |               |                |        |
| Philips 1996      | 18/285     | 22/383      |               |                |        |
| Saunders 2015     | 23/596     | 196/2011    |               |                |        |
| Schwartz 1999     | 0/25       | 1/19        |               |                |        |
| Shamiss 1996      | 0/13       | 1/28        |               |                |        |
| Sharafeldin 2010  | 8/40       | 1/11        |               |                |        |
| Stoney 2016       | 0/11       | 0/18        |               |                |        |
| Tan 2017          | 365/2973   | 64/828      |               |                |        |
| Tuck 2016         | 2/13       | 1/20        |               |                |        |
| **Subtotal (95% CI)** | 6116      | 4049        |               |                | 100.0% |
|                   |            |             |               | 0.92 [0.54, 1.55] |        |
| **Total events:** | 852 (Mefloquine), 378 (Doxycycline) | | | | |
| Heterogeneity: Tau^2 = 0.37; Chi^2 = 54.51, df = 8 (P<0.0001); I^2 = 85% |
| Test for overall effect: Z = 0.32 (P = 0.75)
| Test for subgroup differences: Chi^2 = 0.08, df = 1 (P = 0.77), I^2 = 0.0%

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

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

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 2 Mefloquine versus doxycycline

**Outcome:** 4 Nausea (all studies)

| Study or subgroup  | Mefloquine | Doxycycline | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|-------------|------------|--------|------------|
|                   | n/N        | n/N         | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| 1 Cohort studies (adverse effects) |            |            |             |        |            |
| Shamiss 1996      | 2/13       | 0/28        | 0.2 % 10.36 [ 0.53, 201.60 ] |        |            |
| Sonmez 2005 (1)   | 7/228      | 41/506      | 12.7 % 0.38 [ 0.17, 0.83 ] |        |            |
| Kerhonen 2007     | 165/1453   | 102/308     | 83.8 % 0.34 [ 0.28, 0.42 ] |        |            |
| Cunningham 2014 (2) | 2/49     | 7/65        | 3.0 % 0.38 [ 0.08, 1.75 ] |        |            |
| Tuck 2016         | 1/13       | 1/20        | 0.4 % 1.54 [ 0.11, 22.49 ] |        |            |
| **Subtotal (95% CI)** | **1756**  | **927**     | **100.0 % 0.37 [ 0.30, 0.45 ]** |        |            |
|                   |            |            |             |        |            |
| 2 RCTs (adverse events) |            |            |             |        |            |
| Ohrt 1997         | 8/61       | 3/62        | 100.0 % 2.71 [ 0.75, 9.74 ] |        |            |
| **Subtotal (95% CI)** | **61**    | **62**      | **100.0 % 2.71 [ 0.75, 9.74 ]** |        |            |
|                   |            |            |             |        |            |
| 3 Cohort studies (adverse events) |            |            |             |        |            |
| Philips 1996 (3)  | 43/285     | 36/383      | 100.0 % 1.61 [ 1.06, 2.43 ] |        |            |
| **Subtotal (95% CI)** | **285**   | **383**     | **100.0 % 1.61 [ 1.06, 2.43 ]** |        |            |

Total events: 177 (Mefloquine), 151 (Doxycycline)

Heterogeneity: Chi² = 6.40, df = 4 (P = 0.17); I² =38%

Test for overall effect: Z = 9.38 (P < 0.00001)

(1) Sonmez 2005: Data from the second week of the study

(2) Cunningham 2014: Includes ‘nausea’, ‘nauseous’ and ‘feeling sick’

(3) Philips 1996. Reported in the original paper as ‘nausea/vomiting’
### Analysis 2.5. Comparison 2 Mefloquine versus doxycycline, Outcome 5 Vomiting (all studies).

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 2 Mefloquine versus doxycycline

**Outcome:** 5 Vomiting (all studies)

| Study or subgroup | Mefloquine | Doxycycline | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|-------------|------------|--------|------------|
|                   | n/N        | n/N         | M-H,Fixed 95% CI |        | M-H,Fixed 95% CI |
| Cohort studies (adverse effects) |           |             |            |        |             |
| Sonmez 2005 (1)   | 0/228      | 10/506      | 4.7 %      | 0.11  | [ 0.01, 1.79 ] |
| Korhonen 2007     | 28/1453    | 38/308      | 44.9 %     | 0.16  | [ 0.10, 0.25 ] |
| Cunningham 2014   | 0/49       | 1/65        | 0.9 %      | 0.44  | [ 0.02, 10.57 ] |
| Saunders 2015     | 9/564      | 151/1898    | 49.5 %     | 0.20  | [ 0.10, 0.39 ] |
| **Subtotal (95% CI)** | **2294**   | **2777**    |            | **100.0 %** | **0.18 [ 0.12, 0.27 ]** |
| RCTs (adverse events) |           |             |            |        |             |
| Ohrt 1997         | 2/61       | 1/62        |            | **100.0 %** | **2.03 [ 0.19, 21.84 ]** |
| **Subtotal (95% CI)** | **61**     | **62**      |            | **100.0 %** | **2.03 [ 0.19, 21.84 ]** |

*Total events: 37 (Mefloquine), 200 (Doxycycline)*

Heterogeneity: $\chi^2 = 0.87$, $df = 3$ ($P = 0.83$); $I^2 = 0.0$

Test for overall effect: $Z = 8.10$ ($P < 0.00001$)

Heterogeneity: not applicable

Test for overall effect: $Z = 0.59$ ($P = 0.56$)

Test for subgroup differences: $\chi^2 = 3.91$, $df = 1$ ($P = 0.05$), $I^2 = 74$

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(1) Sonmez 2005. Data from the second week of the study
Analysis 2.6. Comparison 2 Mefloquine versus doxycycline, Outcome 6 Abdominal pain (all studies).

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 2 Mefloquine versus doxycycline

Outcome: 6 Abdominal pain (all studies)

| Study or subgroup | Mefloquine | Doxycycline | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|-------------|------------|--------|------------|
|                   | n/N        | n/N         | H/Random,95% CI |        | H/Random,95% CI |
| Overall weighted mean |          |             |            |        |             |
| 1 Cohort studies (adverse effects) | | | | | |
| Shamiss 1996      | 3/13       | 7/28        | 35.7 %     | 0.92 [0.28, 3.01] | |
| Sonmez 2005 (1)   | 0/228      | 30/506      | 14.8 %     | 0.04 [0.00, 0.59] | |
| Korhonen 2007     | 54/1453    | 45/308      | 49.5 %     | 0.25 [0.17, 0.37] | |
| Tuck 2016         | 0/13       | 0/20        |            | Not estimable | |
| **Subtotal (95% CI)** | **1707** | **862**    | **100.0 %** | **0.30 [0.09, 1.07]** | |
| 2 RCTs (adverse events) | | | | | |
| Ohrt 1997         | 13/61      | 8/62        |            | 1.65 [0.74, 3.70] | |
| **Subtotal (95% CI)** | **61**   | **62**     | **100.0 %** | **1.65 [0.74, 3.70]** | |
| 3 Cohort studies (adverse events) | | | | | |
| Philips 1996      | 30/285     | 30/383      |            | 1.34 [0.83, 2.18] | |
| **Subtotal (95% CI)** | **285**  | **383**    | **100.0 %** | **1.34 [0.83, 2.18]** | |

Total events: 57 (Mefloquine), 82 (Doxycycline)
Heterogeneity: \( T^2 = 0.81; \ Chi^2 = 6.76, df = 2 (P = 0.03); I^2 = 70\%
Test for overall effect: Z = 1.85 (P = 0.065)

Test for subgroup differences: \( Chi^2 = 5.34, df = 2 (P = 0.07), I^2 = 63\%

(1) Sonmez 2005. Data from the second week of the study
Analysis 2.7. Comparison 2 Mefloquine versus doxycycline, Outcome 7 Diarrhoea (all studies).

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 2 Mefloquine versus doxycycline

Outcome: 7 Diarrhoea (all studies)

| Study or subgroup | Mefloquine | Doxycycline | Risk Ratio | Weight |
|------------------|------------|-------------|------------|--------|
|                  | n/N        | n/N         | M-H, Random, 95% CI |        |
| M-H, Random, 95% CI |            |             |            |        |
| 1 Cohort studies (adverse effects) |            |             |            |        |
| Sonmez 2005 (1)  | 4/228      | 108/506     | 24.6 % 0.08 [0.03, 0.22] | 4.6 % |
| Korhonen 2007    | 45/1453    | 12/308      | 29.1 % 0.79 [0.43, 1.48] | 7.8 % |
| Cunningham 2014  | 0/49       | 2/65        | 7.8 % 0.26 [0.01, 5.38] | 7.8 % |
| Saunders 2015    | 22/564     | 311/1898    | 31.1 % 0.24 [0.16, 0.36] | 31.1 % |
| Tuck 2016        | 0/13       | 1/20        | 7.4 % 0.50 [0.02, 11.42] | 7.4 % |
| Subtotal (95% CI)| 2307       | 2797        | 100.0 % 0.28 [0.11, 0.73] | 100.0 % |
| Total events: 71 (Mefloquine), 434 (Doxycycline) |            |             |            |        |
| Heterogeneity: Tau² = 0.73; Chi² = 18.74, df = 4 (P = 0.00088); I² =79% |            |             |            |        |
| Test for overall effect: Z = 2.61 (P = 0.0090) |            |             |            |        |
| 2 RCTs (adverse events) |            |             |            |        |
| Arthur 1990      | 64/134     | 58/119      | 95.5 % 0.98 [0.76, 1.27] | 95.5 % |
| Ohrt 1997        | 7/61       | 4/62        | 45.5 % 1.78 [0.55, 5.77] | 45.5 % |
| Subtotal (95% CI)| 195        | 181         | 100.0 % 1.01 [0.78, 1.29] | 100.0 % |
| Total events: 71 (Mefloquine), 62 (Doxycycline) |            |             |            |        |
| Heterogeneity: Tau² = 0.0; Chi² = 1 (P = 0.32); I² =0.0% |            |             |            |        |
| Test for overall effect: Z = 0.05 (P = 0.96) |            |             |            |        |
| 3 Cohort studies (adverse events) |            |             |            |        |
| Philips 1996     | 24/285     | 9/383       | 100.0 % 3.58 [1.69, 7.59] | 100.0 % |
| Subtotal (95% CI)| 285        | 383         | 100.0 % 3.58 [1.69, 7.59] | 100.0 % |
| Total events: 24 (Mefloquine), 9 (Doxycycline) |            |             |            |        |
| Heterogeneity: not applicable |            |             |            |        |
| Test for overall effect: Z = 3.33 (P = 0.00086) |            |             |            |        |
| Test for subgroup differences: Chi² = 17.73, df = 2 (P = 0.00), I² =89% |            |             |            |        |

(1) Sonmez 2005. Data from the second week of the study
Analysis 2.8. Comparison 2 Mefloquine versus doxycycline, Outcome 8 Dyspepsia (all studies).

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 2 Mefloquine versus doxycycline

Outcome: 8 Dyspepsia (all studies)

| Study or subgroup | Mefloquine | Doxycycline | Risk Ratio Mefloquine | Weight | Risk Ratio Doxycycline |
|-------------------|------------|-------------|-----------------------|--------|------------------------|
|                   | n/N        | n/N         | Risk Ratio M-H,Random,95% CI |        | Risk Ratio M-H,Random,95% CI |
| 1. Cohort studies (adverse effects) | | | | | |
| Sonmez 2005 (1) | 5/228 | 61/506 | 0.18 [0.07, 0.45] | 25.2 % | 0.18 [0.07, 0.45] |
| Korhonen 2007 (2) | 1/1453 | 6/308 | 0.04 [0.00, 0.29] | 13.5 % | 0.04 [0.00, 0.29] |
| Cunningham 2014 (3) | 3/49 | 11/65 | 0.36 [0.11, 1.23] | 21.7 % | 0.36 [0.11, 1.23] |
| Saunders 2015 (4) | 57/564 | 259/1898 | 0.74 [0.56, 0.97] | 30.6 % | 0.74 [0.56, 0.97] |
| Tuck 2016 | 0/13 | 3/20 | 0.21 [0.01, 3.84] | 9.0 % | 0.21 [0.01, 3.84] |

Subtotal (95% CI) 2307 2797 100.0 % 0.26 [0.09, 0.74]

Total events: 66 (Mefloquine), 340 (Doxycycline)

Heterogeneity: Tau² = 0.88; χ² = 17.70, df = 4 (P = 0.001); I² = 77%

Test for overall effect: Z = 2.54 (P = 0.011)

Test for subgroup differences: Not applicable

(1) Sonmez 2005. Data from the second week of the study

(2) Korhonen 2007. Reported in the original paper as ‘heartburn’

(3) Cunningham 2014. Reported in the original paper as ‘indigestion’

(4) Saunders 2015. Reported in the original paper as ‘heartburn/dyspepsia’
### Analysis 2.9. Comparison 2 Mefloquine versus doxycycline, Outcome 9 Headache (all studies).

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 2 Mefloquine versus doxycycline

Outcome: 9 Headache (all studies)

| Study or subgroup | Mefloquine | Doxycycline | Risk Ratio M-H (95% CI) | Weight |
|------------------|------------|-------------|------------------------|--------|
|                   | n/N        | n/N         |                        |        |
| 1 Cohort studies (adverse effects) |            |             |                        |        |
| Sonmez 2005 (1)  | 2/228      | 11/506      | 0.40 [0.09, 1.81]      | 20.0%  |
| Korhonen 2007    | 100/1453   | 15/308      | 1.41 [0.83, 2.40]      | 40.5%  |
| Cunningham 2014  | 0/49       | 3/65        | 0.19 [0.01, 3.57]      | 7.5%   |
| Landman 2015     | 23/380     | 6/304       | 3.07 [1.26, 7.44]      | 32.0%  |
| Stoney 2016      | 0/11       | 0/18        | Not estimable          |        |
| **Subtotal (95% CI)** | 2121       | 1201        | 1.21 [0.50, 2.92]      | 100.0% |

Total events: 125 (Mefloquine), 35 (Doxycycline)
Heterogeneity: $I^2 = 60\%$
Test for overall effect: $Z = 0.43$ ($P = 0.67$)

2 RCTs (adverse events)

| Study or subgroup | Mefloquine | Doxycycline | Risk Ratio M-H (95% CI) | Weight |
|------------------|------------|-------------|------------------------|--------|
|                   | n/N        | n/N         |                        |        |
| Ohrt 1997         | 25/61      | 11/62       | 2.31 [1.25, 4.27]      | 100.0% |
| **Subtotal (95% CI)** | 61         | 62          | 2.31 [1.25, 4.27]      | 100.0% |

Total events: 25 (Mefloquine), 11 (Doxycycline)
Heterogeneity: not applicable
Test for overall effect: $Z = 2.67$ ($P = 0.0076$)

3 Cohort studies (adverse events)

| Study or subgroup | Mefloquine | Doxycycline | Risk Ratio M-H (95% CI) | Weight |
|------------------|------------|-------------|------------------------|--------|
|                   | n/N        | n/N         |                        |        |
| Philips 1996      | 31/285     | 17/383      | 2.45 [1.38, 4.34]      | 100.0% |
| **Subtotal (95% CI)** | 285        | 383         | 2.45 [1.38, 4.34]      | 100.0% |

Total events: 31 (Mefloquine), 17 (Doxycycline)
Heterogeneity: not applicable
Test for overall effect: $Z = 3.08$ ($P = 0.0021$)
Test for subgroup differences: $Chi^2 = 1.87$, df = 2 ($P = 0.39$), I² = 0.0%

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(1) Sonmez 2005. Data from the second week of the study

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

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

Review: Mefloquine for preventing malaria during travel to endemic areas
Comparison: 2 Mefloquine versus doxycycline
Outcome: 10 Dizziness (all studies)

| Study or subgroup | Mefloquine | Doxycycline | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|------------------|------------|-------------|-------------------------------|--------|-------------------------------|
| n/N              | n/N        |             |                               |        |                               |
| 1 Cohort studies (adverse effects) | | | | | |
| Shamiss 1996     | 2/13       | 0/28        | 13.2 % 10.36 [0.53, 201.60 ] |        |                               |
| Korhonen 2007    | 189/1453   | 22/308      | 33.6 % 1.82 [1.19, 2.78 ]    |        |                               |
| Cunningham 2014 (1) | 1/49    | 0/65        | 12.1 % 3.96 [0.16, 95.17 ]   |        |                               |
| Landman 2015 (2) | 52/380     | 3/304       | 27.8 % 13.87 [4.37, 43.97 ]  |        |                               |
| Tuck 2016       | 0/13       | 2/20        | 13.3 % 0.30 [0.02, 5.79 ]    |        |                               |
| **Subtotal (95% CI)** | **1908** | **725**     | **100.0 % 3.49 [0.88, 13.75 ]** | | |
| 2 RCTs (adverse events) | | | | | |
| Ohrt 1997       | 18/61      | 6/62        | 100.0 % 3.05 [1.30, 7.16 ]   |        |                               |
| **Subtotal (95% CI)** | **61** | **62**      | **100.0 % 3.05 [1.30, 7.16 ]** | | |
| 3 Cohort studies (adverse events) | | | | | |
| Philips 1996    | 41/285     | 23/383      | 100.0 % 2.40 [1.47, 3.90 ]   |        |                               |
| **Subtotal (95% CI)** | **285** | **383**     | **100.0 % 2.40 [1.47, 3.90 ]** | | |
| 4 Retrospective healthcare record analysis (adverse events) | | | | | |
| Eick-Cost 2017 (3) | 608/36538 | 7834/318421 | 100.0 % 0.68 [0.62, 0.73 ]  |        |                               |
| **Subtotal (95% CI)** | **36538** | **318421** | **100.0 % 0.68 [0.62, 0.73 ]** | | |
| Total events: 244 (Mefloquine), 27 (Doxycycline) | | | | | |
| Heterogeneity: Tau^2 = 1.41; Chi^2 = 14.26, df = 4 (P = 0.01); I^2 =72% |
| Test for overall effect: Z = 1.78 (P = 0.074) |
| Total events: 18 (Mefloquine), 6 (Doxycycline) |
| Heterogeneity: not applicable |
| Test for overall effect: Z = 2.56 (P = 0.010) |
| Total events: 41 (Mefloquine), 23 (Doxycycline) |
| Heterogeneity: not applicable |
| Test for overall effect: Z = 3.52 (P = 0.00044) |
| Total events: 608 (Mefloquine), 7834 (Doxycycline) |
| Heterogeneity: not applicable |
| Test for overall effect: Z = 9.37 (P < 0.00001) |
| Test for subgroup differences: Chi^2 = 41.66, df = 3 (P = 0.00), I^2 =93% |
(1) Cunningham 2014. Reported in the original paper as ‘feeling of vertigo’
(2) Landman 2015. Reported in the original paper as ‘dizziness/vertigo’
(3) Eck-Cost 2017. ‘Vertigo’

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

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 2 Mefloquine versus doxycycline

**Outcome:** 11 Abnormal dreams (all studies)

| Study or subgroup | Mefloquine | Doxycycline | Risk Ratio M-H Randolph 95% CI | Weight | Risk Ratio M-H Randolph 95% CI |
|-------------------|------------|-------------|--------------------------------|--------|-------------------------------|
| 1 Cohort studies (adverse effects) | | | | | |
| Korhonen 2007 (1) | 775/1453 | 12/308 | 39.9 % 13.69 [ 7.85, 23.89 ] | 39.9 % 13.69 [ 7.85, 23.89 ] |
| Cunningham 2014 (2) | 5/49 | 3/65 | 24.7 % 2.21 [ 0.55, 8.81 ] | 24.7 % 2.21 [ 0.55, 8.81 ] |
| Landman 2015 (3) | 173/380 | 6/304 | 35.4 % 23.07 [ 10.37, 51.33 ] | 35.4 % 23.07 [ 10.37, 51.33 ] |
| Stoney 2016 (4) | 0/11 | 0/18 | Not estimable | Not estimable |
| **Subtotal (95% CI)** | 1893 | 695 | 100.0 % 10.49 [ 3.79, 29.10 ] | 100.0 % 10.49 [ 3.79, 29.10 ] |

Total events: 953 (Mefloquine), 21 (Doxycycline)

Heterogeneity: $\tau^2 = 0.60$, $\chi^2 = 8.53$, df = 2 ($P = 0.01$); $I^2 = 77$

Test for overall effect: $Z = 4.52$ ($P < 0.00001$)

2 RCTs (adverse events)

| Ohrt 1997 (5) | 1/61 | 1/62 | 100.0 % 1.02 [ 0.07, 15.89 ] | 100.0 % 1.02 [ 0.07, 15.89 ] |
| **Subtotal (95% CI)** | 61 | 62 | 100.0 % 1.02 [ 0.07, 15.89 ] | 100.0 % 1.02 [ 0.07, 15.89 ] |

Total events: 1 (Mefloquine), 1 (Doxycycline)

Heterogeneity: not applicable

Test for overall effect: $Z = 0.01$ ($P = 0.99$)

3 Cohort studies (adverse events)

| Philips 1996 | 29/285 | 9/383 | 100.0 % 4.33 [ 2.08, 9.00 ] | 100.0 % 4.33 [ 2.08, 9.00 ] |
| **Subtotal (95% CI)** | 285 | 383 | 100.0 % 4.33 [ 2.08, 9.00 ] | 100.0 % 4.33 [ 2.08, 9.00 ] |

Total events: 29 (Mefloquine), 9 (Doxycycline)

Heterogeneity: not applicable

Test for overall effect: $Z = 3.92$ ($P = 0.000087$)

Test for subgroup differences: $\chi^2 = 3.40$, df = 2 ($P = 0.18$), $I^2 = 41$%
(1) Korhonen 2007. Reported in the original paper as ‘strange dreams’
(2) Cunningham 2014. Reported in the original paper as ‘unpleasant dreams’
(3) Landman 2015. Reported in the original paper as ‘nightmares/vivid dreams’
(4) Stoney 2016. Reported in the original paper as ‘intense nightmares’
(5) Ohrt 1997. Referred to in the original paper as ‘dreams’

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

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 2 Mefloquine versus doxycycline

**Outcome:** 12 Insomnia (all studies)

| Study or subgroup | Mefloquine | Doxycycline | Risk Ratio $\text{M-H, Random, 95\% CI}$ | Weight | Risk Ratio $\text{M-H, Random, 95\% CI}$ |
|-------------------|------------|-------------|----------------------------------------|--------|----------------------------------------|
| Sonmez 2005 (1)   | 0/228      | 14/506      | 12.7 % 0.08 [ 0.00, 1.27 ]             |        |                                         |
| Korhonen 2007     | 49/453     | 8/308       | 32.6 % 13.01 [ 6.54, 25.88 ]           |        |                                         |
| Landman 2015      | 94/380     | 8/304       | 32.4 % 9.40 [ 4.64, 19.04 ]            |        |                                         |
| Tuck 2016         | 3/13       | 2/20        | 22.2 % 2.31 [ 0.44, 11.98 ]            |        |                                         |
| **Subtotal (95\% CI)** | **2074** | **1138** |                                         | 100.0 % | 4.14 [ 1.19, 14.44 ] |

Total events: 588 (Mefloquine), 32 (Doxycycline)

Heterogeneity: $\tau^2 = 1.12; \chi^2 = 14.82, \text{df} = 3 (P = 0.002); I^2 = 80\%$

Test for overall effect: $Z = 2.23 (P = 0.026)$

2 RCTs (adverse events)

| Study or subgroup | Mefloquine | Doxycycline | Risk Ratio $\text{M-H, Random, 95\% CI}$ | Weight | Risk Ratio $\text{M-H, Random, 95\% CI}$ |
|-------------------|------------|-------------|----------------------------------------|--------|----------------------------------------|
| Ohrt 1997         | 8/61       | 4/62        | 100.0 % 2.03 [ 0.65, 6.40 ]            |        |                                         |
| **Subtotal (95\% CI)** | **61** | **62** |                                         | 100.0 % | 2.03 [ 0.65, 6.40 ] |

Total events: 8 (Mefloquine), 4 (Doxycycline)

Heterogeneity: not applicable

Test for overall effect: $Z = 1.21 (P = 0.23)$

3 Cohort studies (adverse events)

| Study or subgroup | Mefloquine | Doxycycline | Risk Ratio $\text{M-H, Random, 95\% CI}$ | Weight | Risk Ratio $\text{M-H, Random, 95\% CI}$ |
|-------------------|------------|-------------|----------------------------------------|--------|----------------------------------------|
| Philips 1996      | 27/285     | 8/383       | 100.0 % 4.54 [ 2.09, 9.83 ]            |        |                                         |
| **Subtotal (95\% CI)** | **285** | **383** |                                         | 100.0 % | 4.54 [ 2.09, 9.83 ] |

Total events: 27 (Mefloquine), 8 (Doxycycline)

Heterogeneity: not applicable

(Continued...)

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

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

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 2 Mefloquine versus doxycycline

**Outcome:** 13 Anxiety (all studies)

| Study or subgroup | Mefloquine | Doxycycline | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|-------------------|------------|-------------|-----------------------------|--------|-----------------------------|
| **1 Cohort studies (adverse effects)** | | | | | |
| Korhonen 2007 | 380/1453 | 4/308 | 52.4 | 20.14 [ 7.58, 53.52 ] |
| Cunningham 2014 (1) | 1/49 | 0/65 | 3.4 | 3.96 [ 0.16, 95.17 ] |
| Landman 2015 | 104/380 | 5/304 | 44.1 | 16.64 [ 6.87, 40.30 ] |
| **Subtotal (95% CI)** | **1882** | **677** | **100.0 %** | **18.04 [ 9.32, 34.93 ]** |

Total events: 485 (Mefloquine), 9 (Doxycycline)

Heterogeneity: Chi^2 = 0.95, df = 2 (P = 0.62); I^2 =0.0%

Test for overall effect: Z = 8.58 (P < 0.00001)

2 Cohort studies (adverse events)

| Study or subgroup | Mefloquine | Doxycycline | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|-------------------|------------|-------------|-----------------------------|--------|-----------------------------|
| Philips 1996 | 13/285 | 2/383 | 100.0 | 8.74 [ 1.99, 38.40 ] |
| **Subtotal (95% CI)** | **285** | **383** | **100.0 %** | **8.74 [ 1.99, 38.40 ]** |

Total events: 245 (Mefloquine), 11 (Doxycycline)

Heterogeneity: Chi^2 = 0.05, df = 1 (P = 0.82); I^2 =0.0%

Test for overall effect: Z = 0.32 (P = 0.75)

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

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 2 Mefloquine versus doxycycline

Outcome: 14 Depressed mood (all studies)

| Study or subgroup | Mefloquine n/N | Doxycycline n/N | Risk Ratio M-H,Fixed 95% CI | Weight |
|-------------------|----------------|-----------------|-----------------------------|--------|
| 1 Cohort studies (adverse events) | | | | |
| Korhonen 2007 (1) | 208/1453 | 3/308 | 52.7% | 14.70 [4.73, 45.64] |
| Landman 2015 (2) | 39/380 | 4/304 | 47.3% | 7.80 [2.82, 21.59] |
| **Subtotal (95% CI)** | **1833** | **612** | **100.0%** | **11.43 [5.21, 25.07]** |
| Total events: 247 (Mefloquine), 7 (Doxycycline) | | | | |
| Heterogeneity: Ch² = 0.73, df = 1 (P = 0.39); I² = 0.0% | | | | |
| Test for subgroup differences: Ch² = 6.08 (P < 0.00001) | | | | |
| 2 Cohort studies (adverse events) | | | | |
| Philips 1996 (3) | 14/285 | 3/383 | 100.0% | 6.27 [1.82, 21.62] |

(Continued...)

(1) Cunningham 2014. Reported in the original paper as 'anxiety attack'

(2) Eick-Cost 2017. Reported in the original paper as 'anxiety disorders'
### Study or subgroup

| Mefloquine | Doxycycline | Risk Ratio | Weight |
|------------|-------------|------------|--------|
| n/N        | n/N         | M-H,Fixed,95% CI | M-H,Fixed,95% CI |
| Subtotal (95% CI) | 285 | 383 | 100.0 % | 6.27 [ 1.82, 21.62 ] |
| Total events: 14 (Mefloquine), 3 (Doxycycline) |  |  |  |  |
| Heterogeneity: not applicable |  |  |  |  |
| Test for overall effect: Z = 2.91 (P = 0.0036) |  |  |  |  |
| 3 Retrospective healthcare record analysis (adverse events) |  |  |  |  |
| Meier 2004 | 53/16491 | 14/4574 | 1.2 % | 1.05 [ 0.58, 1.89 ] |
| Eick-Cost 2017 (4) | 541/36538 | 8640/318421 | 98.8 % | 0.55 [ 0.50, 0.59 ] |
| Subtotal (95% CI) | 53029 | 322995 | 100.0 % | 0.55 [ 0.51, 0.60 ] |
| Total events: 594 (Mefloquine), 8654 (Doxycycline) |  |  |  |  |
| Heterogeneity: Chi² = 4.66, df = 1 (P = 0.03); I² =79% |  |  |  |  |
| Test for overall effect: Z = 13.67 (P < 0.00001) |  |  |  |  |
| Test for subgroup differences: Chi² = 70.92, df = 2 (P = 0.00), I² =97% |  |  |  |  |

(1) Korhonen 2007. Reported in the original paper as ‘depression’
(2) Landman 2015. Reported in the original paper as ‘depression’
(3) Philips 1996. Reported in the original paper as ‘mood change’
(4) Eick-Cost 2017. Reported in the original paper as ‘depressive disorders’
Analysis 2.15. Comparison 2 Mefloquine versus doxycycline, Outcome 15 Abnormal thoughts and perceptions.

Review: Mefloquine for preventing malaria during travel to endemic areas
Comparison: 2 Mefloquine versus doxycycline
Outcome: 15 Abnormal thoughts and perceptions

| Study or subgroup | Mefloquine | Doxycycline | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|------------------|------------|-------------|----------------------------|--------|---------------------------|
| Cohort studies (adverse effects) | | | | | |
| Korhonen 2007 (1) | 9/1453 | 0/308 | 59.8 % | 4.04 [0.24, 69.19] |
| Landman 2015 (2) | 6/380 | 0/304 | 40.2 % | 10.41 [0.59, 184.00] |
| Subtotal (95% CI) | 1833 | 612 | 100.0 % | 6.60 [0.92, 47.20] |
| Total events: 15 (Mefloquine), 0 (Doxycycline) | | | | |
| Retrospective healthcare record analyses (adverse events) | | | | | |
| Meier 2004 (3) | 4/16491 | 0/4574 | 1.0 % | 2.50 [0.13, 46.36] |
| Eick-Cost 2017 (4) | 17/36538 | 381/318421 | 99.0 % | 0.39 [0.24, 0.63] |
| Subtotal (95% CI) | 53029 | 322995 | 100.0 % | 0.41 [0.26, 0.66] |
| Total events: 21 (Mefloquine), 381 (Doxycycline) | | | | |

Heterogeneity: Chi^2 = 0.21, df = 1 (P = 0.65); I^2 = 0.0%
Test for overall effect: Z = 1.88 (P = 0.06)
Test for subgroup differences: Chi^2 = 7.25, df = 1 (P = 0.01), I^2 = 86%

(1) Korhonen 2007. Reported in the original paper as ‘hallucinations’ or ‘went crazy’
(2) Landman 2015. Reported in the original paper as ‘psychosis’
(3) Meier 2004. Reported in the original paper as ‘psychosis’
(4) Eick-Cost 2017. Reported in the original paper as ‘psychosis’. Hallucinations were reported separately.
## Analysis 2.16. Comparison 2 Mefloquine versus doxycycline, Outcome 16 Pruritis (all studies).

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 2 Mefloquine versus doxycycline

**Outcome:** 16 Pruritis (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 |
|-------------------|----------------|----------------|-----------------------------|--------|-----------------------------|
| **1 Cohort studies (adverse effects)** | | | | | |
| Korhonen 2007 (1) | 42/1453 | 17/308 | 0.52 [0.30, 0.91] | 100.0% | |
| Tuck 2016 | 0/13 | 0/20 | Not estimable | | |
| **Subtotal (95% CI)** | 1466 | 328 | 0.52 [0.30, 0.91] | 100.0% | |
| **Total events:** | 42 (Mefloquine), 17 (Doxycycline) | | | | |
| **Heterogeneity:** | not applicable | | | | |
| **Test for overall effect:** | Z = 2.31 (P = 0.021) | | | | |
| **2 Cohort studies (adverse events)** | | | | | |
| Philips 1996 (2) | 10/285 | 5/383 | 2.69 [0.93, 7.78] | 100.0% | |
| **Subtotal (95% CI)** | 285 | 383 | 2.69 [0.93, 7.78] | 100.0% | |
| **Total events:** | 10 (Mefloquine), 5 (Doxycycline) | | | | |
| **Heterogeneity:** | not applicable | | | | |
| **Test for overall effect:** | Z = 1.82 (P = 0.068) | | | | |
| **Test for subgroup differences:** | Chi² = 7.18, df = 1 (P = 0.001), I² = 86% | | | | |

(1) Korhonen 2007. Reported in the original paper as 'itchy skin'

(2) Philips 1996. Reported in the original paper as 'itching'
## Analysis 2.17. Comparison 2 Mefloquine versus doxycycline, Outcome 17 Photosensitivity (all studies).

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 2 Mefloquine versus doxycycline

Outcome: 17 Photosensitivity (all studies)

| Study or subgroup | Mefloquine | Doxycycline | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|-------------|------------|--------|------------|
|                   | n/N        | n/N         | M-H,Fixed,95% CI |         | M-H,Fixed,95% CI |
| 1 Cohort studies (adverse effects) |             |             |             |        |             |
| Korhonen 2007     | 34/1453    | 95/308      | 0.08 [ 0.05, 0.11 ] | 97.1 % |             |
| Cunningham 2014 (1) | 0/49       | 5/65        | 0.12 [ 0.01, 2.12 ] | 2.9 % |             |
| **Subtotal (95% CI)** | **1502** | **373**     | **100.0 %** | **0.08 [ 0.05, 0.11 ]** |             |
| Total events: 34 (Mefloquine), 100 (Doxycycline) |             |             |             |        |             |
| Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² =0.0% |             |             |             |        |             |
| Test for overall effect: Z = 13.46 (P < 0.00001) |             |             |             |        |             |
| 2 Cohort studies (adverse events) |             |             |             |        |             |
| Philips 1996 (2)  | 0/285      | 22/383      | 0.03 [ 0.00, 0.49 ] | 100.0 % |             |
| **Subtotal (95% CI)** | **285** | **383**     | **100.0 %** | **0.03 [ 0.00, 0.49 ]** |             |
| Total events: 0 (Mefloquine), 22 (Doxycycline) |             |             |             |        |             |
| Heterogeneity: not applicable |             |             |             |        |             |
| Test for overall effect: Z = 2.46 (P = 0.014) |             |             |             |        |             |
| Test for subgroup differences: Chi² = 0.44, df = 1 (P = 0.51), I² =0.0% |             |             |             |        |             |

(1) Cunningham 2014. Reported in the original paper as ‘skin sensitivity’

(2) Philips 1996. Reported in the original paper as ‘red skin’
Analysis 2.18. Comparison 2 Mefloquine versus doxycycline, Outcome 18 Yeast infection (all studies).

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 2 Mefloquine versus doxycycline

Outcome: 18 Yeast infection (all studies)

| Study or subgroup | Mefloquine | Doxycycline | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|-------------|------------|--------|------------|
|                   | n/N        | n/N         | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| 1 Cohort studies (adverse effects) |            |            |            |        |            |
| Korhonen 2007     | 22/1453    | 49/308      | 100.0 %    | 0.10   | [ 0.06, 0.16 ] |
| Subtotal (95% CI) | 1453       | 308         | 100.0 %    | 0.10   | [ 0.06, 0.16 ] |
| Total events: 22 (Mefloquine), 49 (Doxycycline) |            |            |            |        |            |
| Heterogeneity: not applicable |            |            |            |        |            |
| Test for overall effect: Z = 9.45 (P < 0.00001) |            |            |            |        |            |
| 2 Cohort studies (adverse events) |            |            |            |        |            |
| Philips 1996      | 3/171      | 17/183      | 100.0 %    | 0.19   | [ 0.06, 0.63 ] |
| Subtotal (95% CI) | 171        | 183         | 100.0 %    | 0.19   | [ 0.06, 0.63 ] |
| Total events: 3 (Mefloquine), 17 (Doxycycline) |            |            |            |        |            |
| Heterogeneity: not applicable |            |            |            |        |            |
| Test for overall effect: Z = 2.70 (P = 0.0069) |            |            |            |        |            |
| Test for subgroup differences: Chi² = 1.06, df = 1 (P = 0.30), I² =6% |            |            |            |        |            |

(1) Philips 1996. Reported in the original paper as ‘vaginal itch’, the analysis of vaginal itch was limited to females.
### Analysis 2.19. Comparison 2 Mefloquine versus doxycycline, Outcome 19 Visual impairment (all studies).

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 2 Mefloquine versus doxycycline

**Outcome:** 19 Visual impairment (all studies)

| Study or subgroup       | Mefloquine | Doxycycline | Risk Ratio M-H,Fixed 95% CI | Weight | Risk Ratio M-H,Fixed 95% CI |
|------------------------|------------|-------------|-----------------------------|--------|-----------------------------|
| Cohort studies (adverse effects) |            |             |                             |        |                             |
| Korhonen 2007 (1)      | 164/1453   | 14/308      | 2.48 [1.46, 4.23]           | 94.7%  |                             |
| Cunningham 2014        | 0/49       | 1/65        | 0.44 [0.02, 10.57]          | 5.3%   |                             |
| **Subtotal (95% CI)**   | 1502       | 373         | 2.37 [1.41, 3.99]           | 100.0% |                             |

Total events: 164 (Mefloquine), 15 (Doxycycline)

Heterogeneity: $\chi^2 = 1.11$, df = 1 ($P = 0.29$); $I^2 = 10\%$

Test for overall effect: $Z = 3.26$ ($P = 0.0011$)

Test for subgroup differences: Not applicable

(1) Korhonen 2007. Reported in the original paper as 'visual disturbance'
### Analysis 2.20. Comparison 2 Mefloquine versus doxycycline, Outcome 20 Other adverse effects (cohort studies).

**Review:** Mefloquine for preventing malaria during travel to endemic areas  
**Comparison:** 2 Mefloquine versus doxycycline  
**Outcome:** 20 Other adverse effects (cohort studies)

| Study or subgroup | Mefloquine | Doxycycline | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|-------------|------------|--------|------------|
| **n/N**           | n/N        | M-H,Fixed,95% CI | M-H,Fixed,95% CI |        |           |
| Alopecia          | 1/49       | 0/65        | 2.1 %      | 3.96 [ 0.16, 95.17 ] |           |
| Cunningham 2014 (1) | 1/49       | 0/65        | 2.1 %      | 3.96 [ 0.16, 95.17 ] |           |
| Korhonen 2007 (2) | 194/1453   | 12/308      | 97.9 %     | 3.43 [ 1.94, 6.06 ] |           |
| **Subtotal (95% CI)** | **1502**    | **373**     |            | **100.0 %** | **3.44 [ 1.96, 6.03 ]** |
| **Total events:** |           |             | 195 (Mefloquine), 12 (Doxycycline) |        |           |
| **Heterogeneity:** | Chi² = 0.01, df = 1 (P = 0.93); I² =0.0% | | | | |
| **Test for overall effect:** | Z = 4.31 (P = 0.000016) | | | | |
| Asthenia           | 69/1453    | 8/308       | 100.0 %    | 1.83 [ 0.89, 3.76 ] |           |
| Korhonen 2007 (3) | 69/1453    | 8/308       | 100.0 %    | 1.83 [ 0.89, 3.76 ] |           |
| **Subtotal (95% CI)** | **1453**    | **308**     |            | **100.0 %** | **1.83 [ 0.89, 3.76 ]** |
| **Total events:** |           |             | 69 (Mefloquine), 8 (Doxycycline) |        |           |
| **Heterogeneity:** | not applicable | | | | |
| **Test for overall effect:** | Z = 1.64 (P = 0.10) | | | | |
| Balance disorder   | 122/1453   | 9/308       | 100.0 %    | 2.87 [ 1.48, 5.59 ] |           |
| Korhonen 2007 (4) | 122/1453   | 9/308       | 100.0 %    | 2.87 [ 1.48, 5.59 ] |           |
| **Subtotal (95% CI)** | **1453**    | **308**     |            | **100.0 %** | **2.87 [ 1.48, 5.59 ]** |
| **Total events:** |           |             | 122 (Mefloquine), 9 (Doxycycline) |        |           |
| **Heterogeneity:** | not applicable | | | | |
| **Test for overall effect:** | Z = 3.11 (P = 0.0019) | | | | |
| Decreased appetite | 5/228      | 9/506       | 100.0 %    | 1.23 [ 0.42, 3.64 ] |           |
| Sonmez 2005 (5)   | 5/228      | 9/506       | 100.0 %    | 1.23 [ 0.42, 3.64 ] |           |
| **Subtotal (95% CI)** | **228**     | **506**     |            | **100.0 %** | **1.23 [ 0.42, 3.64 ]** |
| **Total events:** |           |             | 5 (Mefloquine), 9 (Doxycycline) |        |           |
| **Heterogeneity:** | not applicable | | | | |
| **Test for overall effect:** | Z = 0.38 (P = 0.70) | | | | |
| Fatigue            | 0/13       | 5/28        | 64.2 %     | 0.19 [ 0.01, 3.17 ] |           |
| Shamiss 1996      | 0/13       | 5/28        | 64.2 %     | 0.19 [ 0.01, 3.17 ] |           |
| Tuck 2016 (6)     | 0/13       | 2/20        | 35.8 %     | 0.30 [ 0.02, 5.79 ] |           |
| **Subtotal (95% CI)** | **26**      | **48**      |            | **100.0 %** | **0.23 [ 0.03, 1.77 ]** |
| **Total events:** |           |             | 0 (Mefloquine), 7 (Doxycycline) |        |           |
| **Heterogeneity:** | Chi² = 0.05, df = 1 (P = 0.82); I² =0.0% | | | | |
| **Test for overall effect:** | Z = 1.41 (P = 0.16) | | | | |

(Continued...)

**Mefloquine for preventing malaria during travel to endemic areas (Review)**  
Copyright © 2017 The Authors. Cochrane Database of Systematic Reviews published by John Wiley & Sons, Ltd. on behalf of The Cochrane Collaboration.
| Study or subgroup | Mefloquine | Doxycycline | Risk Ratio | Weight | Risk Ratio |
|------------------|------------|-------------|------------|--------|------------|
|                  | n/N        | n/N         | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| 6 Hypoaesthesia  | 22/1453    | 1/308       | 59.8 % | 4.66 [ 0.63, 34.47 ] |
| Korhonen 2007 (7)|            |             |          |        |             |
| Landman 2015 (8) | 27/380     | 1/304       | 40.2 % | 21.60 [ 2.95, 158.05 ] |
| **Subtotal (95% CI)** | **1833** | **612** | **100.0 %** | **11.48 [ 3.01, 43.70 ]** |
|                  |            |             |          |        |             |
| 7 Malaise        | 5/228      | 39/506      | 100.0 % | 0.28 [ 0.11, 0.71 ] |
| Sonmez 2005 (9)  |            |             |          |        |             |
| **Subtotal (95% CI)** | **228** | **506** | **100.0 %** | **0.28 [ 0.11, 0.71 ]** |
|                  |            |             |          |        |             |
| 8 Mouth ulcers   | 0/13       | 1/20        | 100.0 % | 0.50 [ 0.02, 11.42 ] |
| Tuck 2016        |            |             |          |        |             |
| **Subtotal (95% CI)** | **13** | **20** | **100.0 %** | **0.50 [ 0.02, 11.42 ]** |
|                  |            |             |          |        |             |
| 9 Palpitations   | 6/1453     | 0/308       | 100.0 % | 2.76 [ 0.16, 48.91 ] |
| Korhonen 2007 (7)|            |             |          |        |             |
| **Subtotal (95% CI)** | **1453** | **308** | **100.0 %** | **2.76 [ 0.16, 48.91 ]** |
|                  |            |             |          |        |             |
| 10 Tinnitus      | 4/380      | 0/304       | 100.0 % | 7.20 [ 0.39, 133.30 ] |
| Landman 2015 (8) |            |             |          |        |             |
| **Subtotal (95% CI)** | **380** | **304** | **100.0 %** | **7.20 [ 0.39, 133.30 ]** |

Heterogeneity: Chi² = 1.17, df = 1 (P = 0.28); I² = 14%
Analysis 2.21. Comparison 2 Mefloquine versus doxycycline, Outcome 21 Other adverse events (RCTs).

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 2 Mefloquine versus doxycycline

Outcome: 21 Other adverse events (RCTs)

| Study or subgroup | Mefloquine | Doxycycline | Risk Ratio | Weight |
|-------------------|------------|-------------|------------|--------|
|                   | n/N        | n/N         | M-H,Fixed,95% CI |        |
| Constipation      |            |             |             |        |
| Ohrt 1997         | 2/61       | 1/62        | 100.0 %     | 2.03 [ 0.19, 21.84 ] |
| **Subtotal (95% CI)** | 61 | 62 | 100.0 % | 2.03 [ 0.19, 21.84 ] |
| Total events:     | 2 (Mefloquine), 1 (Doxycycline) |
| Heterogeneity:    | not applicable |
| Test for overall effect: Z = 0.59 (P = 0.56) |
| Cough             |            |             |             |        |
| Ohrt 1997         | 11/61      | 21/62       | 100.0 %     | 0.53 [ 0.28, 1.01 ] |
| **Subtotal (95% CI)** | 61 | 62 | 100.0 % | 0.53 [ 0.28, 1.01 ] |
| Total events:     | 11 (Mefloquine), 21 (Doxycycline) |
| Heterogeneity:    | not applicable |
| Test for overall effect: Z = 1.94 (P = 0.053) |
| Decreased appetite|            |             |             |        |
| Ohrt 1997 (1)     | 14/61      | 4/62        | 100.0 %     | 3.56 [ 1.24, 10.20 ] |
| **Subtotal (95% CI)** | 61 | 62 | 100.0 % | 3.56 [ 1.24, 10.20 ] |
| Total events:     | 14 (Mefloquine), 4 (Doxycycline) |

Favours mefloquine Favours doxycycline

(Continued . . .)
| Study or subgroup | Mefloquine | Doxycycline | Risk Ratio | Weight | Risk Ratio |
|------------------|------------|-------------|------------|--------|------------|
|                  | n/N        | n/N         | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 2.36 (P = 0.018) | | | | | |
| 4 Malaise | | | | | |
| Ohrt 1997 | 14/61 | 7/62 | | | |
| Subtotal (95% CI) | 61 | 62 | | 100.0 % | 2.03 [ 0.88, 4.69 ] |
| Total events: 14 (Mefloquine), 7 (Doxycycline) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 1.66 (P = 0.096) | | | | | |
| 5 Palpitations | | | | | |
| Ohrt 1997 | 2/61 | 1/62 | | | |
| Subtotal (95% CI) | 61 | 62 | | 100.0 % | 2.03 [ 0.19, 21.84 ] |
| Total events: 2 (Mefloquine), 1 (Doxycycline) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.59 (P = 0.56) | | | | | |
| 6 Pyrexia | | | | | |
| Ohrt 1997 (2) | 14/61 | 5/62 | | | |
| Subtotal (95% CI) | 61 | 62 | | 100.0 % | 2.85 [ 1.09, 7.42 ] |
| Total events: 14 (Mefloquine), 5 (Doxycycline) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 2.14 (P = 0.032) | | | | | |
| 7 Sexual dysfunction | | | | | |
| Ohrt 1997 | 3/61 | 1/62 | | | |
| Subtotal (95% CI) | 61 | 62 | | 100.0 % | 3.05 [ 0.33, 28.51 ] |
| Total events: 3 (Mefloquine), 1 (Doxycycline) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.98 (P = 0.33) | | | | | |
| 8 Somnolence | | | | | |
| Ohrt 1997 | 2/61 | 1/62 | | | |
| Subtotal (95% CI) | 61 | 62 | | 100.0 % | 2.03 [ 0.19, 21.84 ] |
| Total events: 2 (Mefloquine), 1 (Doxycycline) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.59 (P = 0.56) | | | | | |

(1) Ohrt 1997. Referred to in the original paper as 'anorexia'

(2) Ohrt 1997. Referred to in the original paper as 'fever'
### Analysis 2.22. Comparison 2 Mefloquine versus doxycycline, Outcome 22 Other adverse events (cohort studies).

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** Mefloquine versus doxycycline

**Outcome:** Other adverse events (cohort studies)

| Study or subgroup | Mefloquine | Doxycycline | Risk Ratio | Weight | Risk Ratio |
|------------------|------------|-------------|------------|--------|------------|
|                  | n/N        | n/N         | M-H,Fixed,95% CI | M-H,Fixed,95% CI |        |
| 1 Adjustment disorder | Eick-Cost 2017 1220/36538 24853/318421 | 24853/318421 | 100.0 % | 0.43 [ 0.40, 0.45 ] |
| Subtotal (95% CI) | 36538      | 318421      | 100.0 % | 0.43 [ 0.40, 0.45 ] |
| Total events: 1220 (Mefloquine), 24853 (Doxycycline) | Heterogeneity: not applicable | Test for overall effect: Z = 29.48 (P < 0.00001) |
| 2 Confusion | Eick-Cost 2017 1/36538 4/318421 | 4/318421 | 100.0 % | 2.18 [ 0.24, 19.49 ] |
| Subtotal (95% CI) | 36538      | 318421      | 100.0 % | 2.18 [ 0.24, 19.49 ] |
| Total events: 1 (Mefloquine), 4 (Doxycycline) | Heterogeneity: not applicable | Test for overall effect: Z = 0.70 (P = 0.49) |
| 3 Convulsions | Eick-Cost 2017 65/36538 973/318421 | 973/318421 | 100.0 % | 0.58 [ 0.45, 0.75 ] |
| Subtotal (95% CI) | 36538      | 318421      | 100.0 % | 0.58 [ 0.45, 0.75 ] |
| Total events: 65 (Mefloquine), 973 (Doxycycline) | Heterogeneity: not applicable | Test for overall effect: Z = 4.23 (P = 0.000024) |
| 4 Hallucinations | Eick-Cost 2017 5/36538 237/318421 | 237/318421 | 100.0 % | 0.18 [ 0.08, 0.45 ] |
| Subtotal (95% CI) | 36538      | 318421      | 100.0 % | 0.18 [ 0.08, 0.45 ] |
| Total events: 5 (Mefloquine), 237 (Doxycycline) | Heterogeneity: not applicable | Test for overall effect: Z = 3.75 (P = 0.00018) |
| 5 Paranoia | Eick-Cost 2017 2/36538 44/318421 | 44/318421 | 100.0 % | 0.40 [ 0.10, 1.63 ] |
| Subtotal (95% CI) | 36538      | 318421      | 100.0 % | 0.40 [ 0.10, 1.63 ] |
| Total events: 2 (Mefloquine), 44 (Doxycycline) | Heterogeneity: not applicable | Test for overall effect: Z = 1.28 (P = 0.20) |
| 6 Palpitations | Philips 1996 10/285 1/383 | 1/383 | 100.0 % | 13.44 [ 1.73, 104.38 ] |
| Subtotal (95% CI) | 285        | 383         | 100.0 % | 13.44 [ 1.73, 104.38 ] |

(Continued...)
| Study or subgroup | Mefloquine | Doxycycline | Risk Ratio | Weight | Risk Ratio |
|------------------|------------|-------------|------------|--------|------------|
|                  | n/N        | n/N         | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| Total events: 10 (Mefloquine), 1 (Doxycycline) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 2.48 (P = 0.013) | | | | | |
| 7 Panic attacks | | | | | |
| Meier 2004 | 15/16491 | 14574 | | | |
| Subtotal (95% CI) | 16491 | 4574 | 100.0 % | 4.16 [0.55, 31.49] | 4.16 [0.55, 31.49] |
| Total events: 15 (Mefloquine), 1 (Doxycycline) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 1.38 (P = 0.17) | | | | | |
| 8 PTSD | | | | | |
| Eick-Cost 2017 | 448/36538 | 6719/318421 | | | |
| Subtotal (95% CI) | 36538 | 318421 | 100.0 % | 0.58 [0.53, 0.64] | 0.58 [0.53, 0.64] |
| Total events: 448 (Mefloquine), 6719 (Doxycycline) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 11.20 (P < 0.00001) | | | | | |
| 9 Rash | | | | | |
| Philips 1996 | 9/285 | 10/383 | | | |
| Subtotal (95% CI) | 285 | 383 | 100.0 % | 1.21 [0.50, 2.94] | 1.21 [0.50, 2.94] |
| Total events: 9 (Mefloquine), 10 (Doxycycline) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.42 (P = 0.67) | | | | | |
| 10 Suicidal ideation | | | | | |
| Eick-Cost 2017 | 91/36538 | 2066/318421 | | | |
| Subtotal (95% CI) | 36538 | 318421 | 100.0 % | 0.38 [0.31, 0.47] | 0.38 [0.31, 0.47] |
| Total events: 91 (Mefloquine), 2066 (Doxycycline) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 8.95 (P < 0.00001) | | | | | |
| 11 Suicide | | | | | |
| Eick-Cost 2017 | 2/36538 | 15/318421 | | | |
| Meier 2004 | 2/16491 | 0/4574 | | | |
| Subtotal (95% CI) | 53029 | 322995 | 100.0 % | 1.16 [0.27, 5.08] | 1.16 [0.27, 5.08] |
| Total events: 4 (Mefloquine), 15 (Doxycycline) | | | | | |
| Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); P =0.0% | | | | | |
| Test for overall effect: Z = 0.28 (P = 0.78) | | | | | |
| 12 Tinnitus | | | | | |
| Eick-Cost 2017 | 707/36538 | 9416/318421 | | | |
| Subtotal (95% CI) | 36538 | 318421 | 100.0 % | 0.65 [0.61, 0.71] | 0.65 [0.61, 0.71] |
| Total events: 707 (Mefloquine), 9416 (Doxycycline) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 10.99 (P < 0.00001) | | | | | |

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

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

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 2 Mefloquine versus doxycycline

**Outcome:** 23 Adherence (cohort 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 |
|------------------|----------------|----------------|-----------------------------|--------|-----------------------------|
| 1 Adherence during travel | | | | | |
| Cunningham 2014 (1) | 12/49 | 24/65 | 0.7 % 0.66 [0.37, 1.19] | 0.045 | |
| Goodyer 2011 (2) | 21/30 | 29/70 | 0.6 % 1.69 [1.17, 2.43] | 0.035 | |
| Korhonen 2007 (3) | 946/1453 | 115/308 | 6.3 % 1.74 [1.50, 2.02] | 0.035 | |
| Landman 2015 (4) | 231/380 | 206/304 | 7.6 % 1.74 [1.50, 2.02] | 0.035 | |
| Laver 2001 (5) | 163/184 | 38/48 | 2.0 % 1.12 [0.96, 1.31] | 0.035 | |
| Lavel 2001 (6) | 3430/3630 | 53/60 | 3.5 % 1.07 [0.98, 1.17] | 0.035 | |
| Philips 1996 (7) | 223/285 | 261/383 | 7.4 % 1.15 [1.05, 1.26] | 0.035 | |
| Saunders 2015 (8) | 477/536 | 870/1438 | 17.0 % 1.32 [1.25, 1.40] | 0.035 | |
| Shamiss 1996 (9) | 15/15 | 21/28 | 0.5 % 1.31 [1.04, 1.65] | 0.035 | |
| Sonmez 2005 (10) | 138/228 | 284/506 | 5.9 % 1.08 [0.95, 1.23] | 0.035 | |
| Tan 2017 (11) | 1691/2972 | 425/828 | 22.2 % 1.11 [1.03, 1.19] | 0.035 | |
| Terrell 2015 (12) | 891/938 | 695/752 | 25.8 % 1.03 [1.00, 1.05] | 0.035 | |
| Tuck 2016 (13) | 13/13 | 15/20 | 0.4 % 1.31 [0.99, 1.72] | 0.035 | |
| **Subtotal (95% CI)** | **10773** | **4810** | 100.0 % 1.15 [1.12, 1.18] | 0.035 | |

**Total events:** 8251 (Mefloquine), 3036 (Doxycycline)

**Heterogeneity:** Chi² = 162.08, df = 12 (P<0.00001); I² = 93%

**Test for overall effect:** Z = 10.12 (P < 0.00001)

2 Adherence in the post-travel period

| Study or subgroup | Mefloquine n/N | Doxycycline n/N | Risk Ratio M-H,Fixed 95% CI | Weight | Risk Ratio M-H,Fixed 95% CI |
|------------------|----------------|----------------|-----------------------------|--------|-----------------------------|
| Goodyer 2011 (14) | 15/30 | 19/70 | 5.5 % 1.84 [1.09, 3.11] | 0.035 | |
| Philips 1996 (15) | 154/285 | 205/383 | 84.8 % 1.01 [0.88, 1.16] | 0.035 | |
| Shamiss 1996 (16) | 13/15 | 21/28 | 7.1 % 1.16 [0.86, 1.55] | 0.035 | |
| Stoney 2016 (17) | 6/11 | 7/16 | 2.6 % 1.40 [0.64, 3.09] | 0.035 | |
| **Subtotal (95% CI)** | **341** | **499** | 100.0 % 1.08 [0.95, 1.22] | 0.035 | |

**Total events:** 188 (Mefloquine), 252 (Doxycycline)

(Continued . . .)
| Study or subgroup | Mefloquine | Doxycycline | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|-------------|------------|--------|------------|
| n/N n/N M-H,Fixed,95% CI | n/N M-H,Fixed,95% CI |
| Heterogeneity: Chi$^2$ = 5.47, df = 3 (P = 0.14); I$^2$ =45% Test for overall effect: Z = 1.13 (P = 0.26) Test for subgroup differences: Chi$^2$ = 1.02, df = 1 (P = 0.31), I$^2$ =2% |
| (1) Cunningham 2014. Reported taking prophylaxis >95% of the time |
| (2) Goodyer 2011. Defined as ‘proportion of travelers reporting taking all medication’ |
| (3) Karhonen 2007. Defined as participants who reported they ‘never’ missed doses |
| (4) Landman 2015. Defined as ‘PCVs reporting taking daily medications at any time each day or taking weekly medications with no more than 8 days between doses were defined as adherent’ |
| (5) Laver 2001. Defined as ‘full compliance, i.e., regular medication with no missed doses’ |
| (6) Lobel 2001. Defined as ‘uninterrupted use of antimalarial drugs during travel in Africa’ |
| (7) Philips 1996. Defined as ‘complete self-reported compliance’ |
| (8) Saunders 2015. Defined as doxycycline recipients reporting daily use, or mefloquine recipients reporting weekly use. |
| (9) Shamiss 1996. Defined as ‘compliance throughout operation’ |
| (10) Sonmez 2005. Defined as ‘always regular’ |
| (11) Tan 2017. ‘Taken as prescribed’ |
| (12) Terrell 2015. ‘Reported that they had taken their drugs as prescribed’ |
| (13) Tuck 2016. ‘Fully compliant’ |
| (14) Goodyer 2011. Reported as ‘took all drugs in the post-travel period’ |
| (15) Philips 1996. Reported as ‘reported completing the regimen’ |
| (16) Shamiss 1996. Reported as ‘compliance in post operation period’ |
| (17) Stoney 2016. Reported as ‘number adherent during post-prophylaxis period’ |

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

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

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 3 Mefloquine versus atovaquone-proguanil

Outcome: 1 Clinical cases of malaria (RCTs)

| Study or subgroup | Mefloquine | Atovaquone-proguanil | Odds Ratio | Weight | Odds Ratio |
|-------------------|------------|----------------------|------------|--------|------------|
|                   | n/N        | n/N                  | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| Overbosch 2001    | 0/483      | 0/493                | Not estimable |        | Not estimable |
| Schagenhauf 2003  | 0/153      | 0/164                | Not estimable |        | 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

Test for subgroup differences: Not applicable

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

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 3 Mefloquine versus atovaquone-proguanil

Outcome: 2 Serious adverse events or effects (all studies)

| Study or subgroup | Mefloquine | Atovaquone-proguanil | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|----------------------|------------|--------|------------|
|                   | n/N        | n/N                  | M-H,Fixed 95% CI |        | M-H,Fixed 95% CI |
| 1 Cohort studies  |            |                      |            |        |            |
| Andersson 2008    | 0/491      | 0/161                | Not estimable |        |            |
| Korhonen 2007 (1) | 15/1612    | 0/72                 | 100.0 %     | 1.40   | [ 0.08, 23.22 ] |
| Napoletano 2007   | 0/548      | 0/707                | Not estimable |        |            |
| **Total (95% CI)** | **2651** | **940**              | **100.0 %** | **1.40** | **[ 0.08, 23.22 ]** |

Total events: 15 (Mefloquine), 0 (Atovaquone-proguanil)

Heterogeneity: not applicable

Test for overall effect: Z = 0.24 (P = 0.81)

Test for subgroup differences: Not applicable

(1) Korhonen 2007. The denominator includes all participants who reported taking the drug at any time. Participants may contribute data more than once.
Analysis 3.3. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 3 Discontinuations due to adverse effects (all studies).

Review: Mefloquine for preventing malaria during travel to endemic areas
Comparison: 3 Mefloquine versus atovaquone-proguanil
Outcome: 3 Discontinuations due to adverse effects (all studies)

| Study or subgroup | Mefloquine | Atovaquone-proguanil | Risk Ratio M-H | Weight | Risk Ratio M-H |
|-------------------|------------|----------------------|----------------|--------|----------------|
|                   | n/N        | n/N                  |                |        |                |
| 1 RCTs            |            |                      |                |        |                |
| Overbosch 2001    | 24/483     | 6/493                | 4.08 [ 1.68, 9.90 ] | 49.2 % |                |
| Schlagenhauf 2003 | 6/156      | 3/166                | 2.13 [ 0.54, 8.36 ] | 20.6 % |                |
| van Riemsdijk 2002| 9/75       | 4/65                 | 1.95 [ 0.63, 6.04 ] | 30.2 % |                |
| **Subtotal (95% CI)** | **714** | **724** | **100.0 %** | **2.86 [ 1.53, 5.31 ]** |        |
| Total events: 39 (Mefloquine), 13 (Atovaquone-proguanil) |

Heterogeneity: Tau² = 0.0; Chi² = 1.25, df = 2 (P = 0.53); I² =0.0%
Test for overall effect: Z = 3.31 (P = 0.00093)

2 Cohort studies

| Study or subgroup | Mefloquine | Atovaquone-proguanil | Risk Ratio M-H | Weight | Risk Ratio M-H |
|-------------------|------------|----------------------|----------------|--------|----------------|
|                   | n/N        | n/N                  |                |        |                |
| Andersson 2008    | 40/488     | 4/121                | 2.48 [ 0.90, 6.80 ] | 11.2 % |                |
| Kato 2013         | 4/38       | 5/278                | 5.85 [ 1.64, 20.85 ] | 7.9 % |                |
| Korhonen 2007     | 370/1612   | 2/72                 | 8.26 [ 2.10, 32.50 ] | 7.0 % |                |
| Kuhner 2005       | 7/142      | 4/82                 | 1.01 [ 0.30, 3.35 ] | 8.7 % |                |
| Napoletano 2007   | 66/548     | 24/707               | 3.55 [ 2.25, 5.58 ] | 25.4 % |                |
| Sharafeldin 2010 (1) | 8/40 | 10/62              | 1.24 [ 0.54, 2.87 ] | 14.2 % |                |
| Stoney 2016       | 0/11       | 10/297               | 1.18 [ 0.07, 19.02 ] | 2.0 % |                |
| Tan 2017          | 365/2973   | 8/183                | 2.81 [ 1.42, 5.57 ] | 18.0 % |                |
| Tuck 2016         | 2/13       | 5/118                | 3.63 [ 0.78, 16.88 ] | 5.8 % |                |
| **Subtotal (95% CI)** | **5865** | **1920** | **100.0 %** | **2.73 [ 1.83, 4.08 ]** |        |
| Total events: 862 (Mefloquine), 72 (Atovaquone-proguanil) |

Heterogeneity: Tau² = 0.11; Chi² = 11.89, df = 8 (P = 0.16); I² =33%
Test for overall effect: Z = 4.90 (P < 0.00001)
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² =0.0%

(1) Sharafeldin 2010. Number of discontinuations due to adverse effects was unclear. ‘Shortage of tablets or simply forgetting to take the prophylaxis constituted the main reasons for stopping the use of atovaquone/proguanil’
**Analysis 3.4. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 4 Nausea (all studies).**

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 3 Mefloquine versus atovaquone-proguanil

Outcome: 4 Nausea (all studies)

| Study or subgroup | Mefloquine | Atovaquone-proguanil | Risk Ratio (M-H,Fixed,95% CI) | Weight | Risk Ratio (M-H,Fixed,95% CI) |
|-------------------|------------|----------------------|-------------------------------|--------|-------------------------------|
| 1 RCTs (adverse effects) | | | | | |
| Overbosch 2001 | 40/483 | 15/493 | 2.72 [1.52, 4.86] | 100.0 % | 2.72 [1.52, 4.86] |
| **Subtotal (95% CI)** | **483** | **493** | | | | 100.0 % | 2.72 [1.52, 4.86] |
| Total events: 40 (Mefloquine), 15 (Atovaquone-proguanil) |
| Heterogeneity: not applicable |
| Test for overall effect: Z = 3.38 (P = 0.00071) |
| 2 Cohort studies (adverse effects) | | | | | |
| Andersson 2008 (1) | 30/491 | 4/161 | 2.46 [0.88, 6.87] | 26.2 % | 2.46 [0.88, 6.87] |
| Cunningham 2014 | 2/49 | 1/182 | 7.43 [0.69, 80.24] | 1.8 % | 7.43 [0.69, 80.24] |
| Kato 2013 | 5/38 | 5/277 | 7.29 [2.21, 24.02] | 5.2 % | 7.29 [2.21, 24.02] |
| Korhonen 2007 | 165/1453 | 2/16 | 0.91 [0.25, 3.35] | 17.2 % | 0.91 [0.25, 3.35] |
| Kuhner 2005 | 19/142 | 5/82 | 2.19 [0.85, 5.66] | 27.6 % | 2.19 [0.85, 5.66] |
| Laverone 2006 | 65/444 | 2/43 | 3.15 [0.80, 12.41] | 15.9 % | 3.15 [0.80, 12.41] |
| Tuck 2016 | 1/13 | 7/118 | 1.30 [0.17, 9.73] | 6.0 % | 1.30 [0.17, 9.73] |
| **Subtotal (95% CI)** | **2630** | **879** | | | | 100.0 % | 2.50 [1.54, 4.06] |
| Total events: 287 (Mefloquine), 26 (Atovaquone-proguanil) |
| Heterogeneity: $\chi^2 = 6.80$, df = 6 (P = 0.34); $I^2 = 12\%$ |
| Test for overall effect: Z = 3.72 (P = 0.00020) |
| Test for subgroup differences: $\chi^2 = 0.05$, df = 1 (P = 0.83), $I^2 = 0.0\%$ |

(1) Andersson 2008. Reported in the original paper as ‘nausea/vomiting’
## Analysis 3.5. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 5 Vomiting (all studies).

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 3 Mefloquine versus atovaquone-proguanil

**Outcome:** 5 Vomiting (all studies)

| Study or subgroup | Mefloquine | Atovaquone-proguanil | Risk Ratio | Weight | Risk Ratio |
|------------------|------------|----------------------|------------|--------|------------|
|                  | n/N        | n/N                  |            |        |            |
|                  |            |                      | M-H,Random,95% CI |        | M-H,Random,95% CI |
| 1 RCTs (adverse effects) |           |                      |            |        |            |
| Overbosch 2001   | 9/483      | 7/493                | 100.0 %    | 1.31   | [0.49, 3.50] |
| Subtotal (95% CI) | 483        | 493                  | 100.0 %    | 1.31   | [0.49, 3.50] |
| Total events:    | 9 (Mefloquine), 7 (Atovaquone-proguanil) | | | | |
| Heterogeneity:   | not applicable | | | | |
| Test for overall effect: | Z = 0.54 (P = 0.59) | | | | |
| 2 Cohort studies (adverse effects) | | | | | |
| Korhonen 2007    | 28/1453    | 2/16                 | 38.7 %     | 0.15   | [0.04, 0.59] |
| Kuhner 2005      | 5/142      | 1/82                 | 30.5 %     | 2.89   | [0.34, 24.29] |
| Laverone 2006    | 6/444      | 1/43                 | 30.8 %     | 0.58   | [0.07, 4.72] |
| Subtotal (95% CI) | 2039       | 141                  | 100.0 %    | 0.57   | [0.08, 4.09] |
| Total events:    | 39 (Mefloquine), 4 (Atovaquone-proguanil) | | | | |
| Heterogeneity:   | Tau² = 2.16, Chi² = 6.93, df = 2 (P = 0.03); I² =71% | | | | |
| Test for overall effect: | Z = 0.56 (P = 0.57) | | | | |
| Test for subgroup differences: | Chi² = 0.56, df = 1 (P = 0.46), I² =0.0% | | | | |

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

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 3 Mefloquine versus atovaquone-proguanil

Outcome: 6 Abdominal pain (all studies)

| Study or subgroup | Mefloquine | Atovaquone-proguanil | Risk Ratio  | Weight | Risk Ratio  |
|-------------------|------------|----------------------|-------------|--------|-------------|
|                   | n/N        | n/N                  | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| I RCTs (adverse effects) |            |                      |              |        |             |
| Overbosch 2001    | 23/483     | 26/493               |              | 100.0 % | 0.90 [ 0.52, 1.56 ] |
| **Subtotal (95% CI)** | **483**   | **493**              |              | **100.0 %** | **0.90 [ 0.52, 1.56 ]** |
| Total events: 23 (Mefloquine), 26 (Atovaquone-proguanil) |
| Heterogeneity: not applicable |
| Test for overall effect: Z = 0.37 (P = 0.71) |
| 2 Cohort studies (adverse effects) |            |                      |              |        |             |
| Andersson 2008 (1) | 18/491     | 13/161               | 57.5 %      | 0.45 [ 0.23, 0.91 ] |
| Cunningham 2014   | 0/49       | 4/182                | 5.7 %       | 0.41 [ 0.02, 7.43 ] |
| Kato 2013         | 1/38       | 11/277               | 7.8 %       | 0.66 [ 0.09, 4.99 ] |
| Khorhen 2007      | 54/1453    | 0/16                 | 2.9 %       | 1.27 [ 0.08, 19.80 ] |
| Kuhner 2005       | 9/142      | 4/82                 | 14.9 %      | 1.30 [ 0.41, 4.09 ] |
| Laverone 2006 (2) | 9/444      | 1/43                 | 5.4 %       | 0.87 [ 0.11, 6.72 ] |
| Tuck 2016         | 0/13       | 9/118                | 5.9 %       | 0.45 [ 0.03, 7.28 ] |
| **Subtotal (95% CI)** | **2630**  | **879**              |              | **100.0 %** | **0.64 [ 0.38, 1.07 ]** |
| Total events: 91 (Mefloquine), 42 (Atovaquone-proguanil) |
| Heterogeneity: Chi² = 2.90, df = 6 (P = 0.82); I² =0.0% |
| Test for overall effect: Z = 1.71 (P = 0.087) |
| Test for subgroup differences: Chi² = 0.82, df = 1 (P = 0.37), I² =0.0% |

(1) Andersson 2008. Reported in the original paper as ‘stomach pain’

(2) Laverone 2006. Reported in the original paper as ‘stomachache’
**Analysis 3.7. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 7 Diarrhoea (all studies).**

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 3 Mefloquine versus atovaquone-proguanil

**Outcome:** 7 Diarrhoea (all studies)

| Study or subgroup | Mefloquine | Atovaquone-proguanil | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|----------------------|------------|--------|------------|
|                   | n/N        | n/N                  | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| 1 RCTs (adverse effects) |           |                      |            |        |             |
| Overbosch 2001    | 34/483     | 37/493               | 1.000 %    | 0.94   | [0.60, 1.47] |
| **Subtotal (95% CI)** | **483**   | **493**              |            | **0.94** | [0.60, 1.47] |
| Total events: 34 (Mefloquine), 37 (Atovaquone-proguanil) |
| Heterogeneity: not applicable |
| Test for overall effect: Z = 0.28 (P = 0.78) |
| 2 Cohort studies (adverse effects) |           |                      |            |        |             |
| Andersson 2008    | 23/491     | 6/161                | 24.5 %     | 1.26   | [0.52, 3.03] |
| Cunningham 2014   | 0/49       | 3/182                | 4.1 %      | 0.52   | [0.03, 9.96] |
| Kato 2013         | 1/38       | 14/277               | 9.2 %      | 0.52   | [0.07, 3.85] |
| Korhonien 2007    | 45/1453    | 1/116                | 5.4 %      | 0.50   | [0.07, 3.38] |
| Kuhner 2005       | 16/142     | 10/82                | 34.4 %     | 0.92   | [0.44, 1.94] |
| Laverone 2006     | 21/444     | 3/43                 | 14.8 %     | 0.68   | [0.21, 2.18] |
| Tuck 2016         | 0/13       | 13/118               | 7.7 %      | 0.31   | [0.02, 5.01] |
| **Subtotal (95% CI)** | **2630**  | **879**              |            | **0.85** | [0.53, 1.35] |
| Total events: 106 (Mefloquine), 50 (Atovaquone-proguanil) |
| Heterogeneity: Chi² = 2.09, df = 6 (P = 0.91); I² = 0.0% |
| Test for overall effect: Z = 0.70 (P = 0.48) |
| Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.75), I² = 0.0% |
Analysis 3.8. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 8 Mouth ulcers (all studies).

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 3 Mefloquine versus atovaquone-proguanil

Outcome: 8 Mouth ulcers (all studies)

| Study or subgroup | Mefloquine | Atovaquone-proguanil | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|----------------------|------------|--------|------------|
|                   | n/N        | n/N                  | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| 1 RCTs (adverse effects) |           |                      |            |        |            |
| Overbosch 2001    | 17/483     | 12/493               | 1.45 [ 0.70, 3.00 ] | 100.0 % | 1.45 [ 0.70, 3.00 ] |
| **Subtotal (95% CI)** | 483        | 493                  |            |        |            |
| Total events: 17 (Mefloquine), 12 (Atovaquone-proguanil) |
| Heterogeneity: not applicable |
| Test for overall effect: Z = 0.99 (P = 0.32) |
| 2 Cohort studies (adverse effects) |           |                      |            |        |            |
| Andersson 2008    | 3/491      | 11/161               | 0.09 [ 0.03, 0.32 ] | 82.7 % | 0.09 [ 0.03, 0.32 ] |
| Tuck 2016         | 0/13       | 16/118               | 0.26 [ 0.02, 4.06 ] | 17.3 % | 0.26 [ 0.02, 4.06 ] |
| **Subtotal (95% CI)** | 504        | 279                  |            |        |            |
| Total events: 3 (Mefloquine), 27 (Atovaquone-proguanil) |
| Heterogeneity: Chi² = 0.50, df = 1 (P = 0.48); I² =0.0% |
| Test for overall effect: Z = 3.64 (P = 0.00028) |
| Test for subgroup differences: Chi² = 12.98, df = 1 (P = 0.00), I² =92% |

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

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 3 Mefloquine versus atovaquone-proguanil

**Outcome:** 9 Headache (all studies)

| Study or subgroup | Mefloquine n/N | Atovaquone-proguanil n/N | Risk Ratio M-H,Fixed 95% CI | Weight |
|------------------|---------------|--------------------------|-----------------------------|--------|
| 1 RCTs (adverse effects) | | | | |
| Overbosch 2001 | 32/483 | 19/493 | 1.72 [ 0.99, 2.99 ] | 100.0 % |
| **Subtotal (95% CI)** | 483 | 493 | 1.72 [ 0.99, 2.99 ] | 100.0 % |
| **Total events:** Mefloquine 32, Atovaquone-proguanil 19 |
| Heterogeneity: not applicable |
| Test for overall effect: Z = 1.92 (P = 0.055) |

| 2 Cohort studies (adverse effects) | | | | |
| Andersen 2008 | 21/491 | 2/161 | 3.44 [ 0.82, 14.52 ] | 25.7 % |
| Cunningham 2014 | 0/49 | 3/182 | 12.8 % | 0.52 [ 0.03, 9.96 ] |
| Kata 2013 | 4/38 | 4/277 | 8.2 % | 7.29 [ 1.90, 27.94 ] |
| Korhonen 2007 | 100/1453 | 0/16 | 8.4 % | 2.35 [ 0.15, 36.30 ] |
| Kuhner 2005 | 8/142 | 2/82 | 21.7 % | 2.31 [ 0.50, 10.62 ] |
| Landman 2015 | 23/380 | 1/97 | 13.6 % | 5.87 [ 0.80, 42.94 ] |
| Laverone 2006 | 18/444 | 0/43 | 7.8 % | 3.66 [ 0.22, 59.68 ] |
| Stoney 2016 | 0/11 | 2/97 | 1.7 % | 4.97 [ 0.25, 97.88 ] |
| **Subtotal (95% CI)** | 3008 | 1155 | 3.42 [ 1.71, 6.82 ] | 100.0 % |
| **Total events:** Mefloquine 174, Atovaquone-proguanil 14 |
| Heterogeneity: Chi² = 3.45, df = 7 (P = 0.84); I² = 0.0% |
| Test for overall effect: Z = 3.49 (P = 0.00048) |
| Test for subgroup differences: Chi² = 2.32, df = 1 (P = 0.13), I² = 57% |
Analysis 3.10. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 10 Dizziness (all studies).

Review: Mefloquine for preventing malaria during travel to endemic areas
Comparison: 3 Mefloquine versus atovaquone-proguanil
Outcome: 10 Dizziness (all studies)

| Study or subgroup | Mefloquine | Atovaquone-proguanil | Risk Ratio | Weight | Risk Ratio |
|------------------|------------|----------------------|------------|---------|------------|
|                  | n/N        | n/N                  | M-H,Fixed 95% CI |         | M-H,Fixed 95% CI |
| Subtotal (95% CI)| 483        | 493                  | -           | 100.0%  | 3.99 [2.08, 7.64] |
| 1 RCTs (adverse effects) | | | | | |
| Overbosch 2001 (1) | 43/483 | 11/493 | - | 100.0% | 3.99 [2.08, 7.64] |
| Subtotal (95% CI) | 483 | 493 | - | 100.0% | 3.99 [2.08, 7.64] |
| Total events: 43 (Mefloquine), 11 (Atovaquone-proguanil) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 4.17 (P = 0.000030) | | | | |
| 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 | - | 4.3% | 1.86 [0.17, 20.06] |
| Kato 2013 | 3/38 | 8/277 | - | 9.7% | 2.73 [0.76, 9.86] |
| Korhonen 2007 | 189/1453 | 1/16 | - | 100.0% | 2.08 [0.31, 13.95] |
| Kuhner 2005 | 17/142 | 1/82 | - | 6.4% | 9.82 [1.33, 72.42] |
| Landman 2015 (2) | 52/380 | 0/97 | - | 4.0% | 27.01 [1.68, 433.65] |
| Laverone 2006 | 25/444 | 2/43 | - | 18.4% | 1.21 [0.30, 4.94] |
| Tuck 2016 | 0/13 | 1/118 | - | 1.6% | 2.83 [0.12, 66.27] |
| Subtotal (95% CI) | 3010 | 976 | - | 100.0% | 3.83 [2.23, 6.58] |
| Total events: 339 (Mefloquine), 21 (Atovaquone-proguanil) | | | | |
| Heterogeneity: Chi² = 6.88, df = 7 (P = 0.44); I² =0.0% | | | | |
| Test for overall effect: Z = 4.86 (P < 0.000001) | | | | |
| 3 Retrospective healthcare record analysis (adverse events) | | | | |
| Eick-Cost 2017 | 608/36538 | 174/12881 | - | 100.0% | 1.23 [1.04, 1.46] |
| Subtotal (95% CI) | 36538 | 12881 | - | 100.0% | 1.23 [1.04, 1.46] |
| Total events: 608 (Mefloquine), 174 (Atovaquone-proguanil) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 2.44 (P = 0.015) | | | | |
| Test for subgroup differences: Chi² = 25.29, df = 2 (P = 0.00), I² =92% | | | | |

(1) Overbosch 2001. Reported in the original paper as ‘dizziness or vertigo’
(2) Landman 2015. Reported in the original paper as ‘dizziness/vertigo’
Analysis 3.11. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 11 Abnormal dreams (all studies).

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 3 Mefloquine versus atovaquone-proguanil

Outcome: 11 Abnormal dreams (all studies)

| Study or subgroup | Mefloquine | Atovaquone-proguanil | Risk Ratio M: H Random, 95% CI | Weight |
|-------------------|------------|---------------------|-------------------------------|--------|
| n/N               | n/N        |                     |                               |        |
| Overbosch 2001 (1)| 66/483     | 33/493              | 2.04 [ 1.37, 3.04 ]           |        |
| Total events: 66 (Mefloquine), 33 (Atovaquone-proguanil) |
| Heterogeneity: not applicable |
| Test for overall effect: Z = 3.51 (P = 0.00045) |

| Study or subgroup | Mefloquine | Atovaquone-proguanil | Risk Ratio M: H Random, 95% CI | Weight |
|-------------------|------------|---------------------|-------------------------------|--------|
| n/N               | n/N        |                     |                               |        |
| Andersson 2008 (2)| 168/491    | 5/161               | 3.51 [ 1.91, 6.37 ]           |        |
| Cunningham 2014 (3)| 5/49       | 27/182              | 1.90 [ 0.69, 5.51 ]           |        |
| Korhonen 2007 (4)| 775/1453   | 0/16                | 18.13 [ 1.18, 278.37 ]        |        |
| Kuhner 2005       | 8/142      | 0/82                | 11.7 [ 0.69, 21.52 ]          |        |
| Landman 2015 (5)  | 173/380    | 2/97                | 11.5 [ 0.54, 25.26 ]          |        |
| Laverone 2006 (6) | 25/444     | 0/43                | 11.5 [ 0.31, 42.41 ]          |        |
| Stoney 2016 (7)   | 0/11       | 1/297               | 11.5 [ 0.36, 39.02 ]          |        |
| Total events: 1154 (Mefloquine), 35 (Atovaquone-proguanil) |
| Heterogeneity: Tau² = 2.55; Chi² = 31.02, df = 6 (P = 0.00003); I² = 81% |
| Test for overall effect: Z = 2.65 (P = 0.0080) |
| Test for subgroup differences: Chi² = 2.57, df = 1 (P = 0.11), I² = 61% |

(1) Overbosch 2001. Reported in the original paper as 'strange or vivid dreams'
(2) Andersson 2008. Reported in the original paper as 'nightmares'
(3) Cunningham 2014. Reported in the original paper as 'unpleasant dreams'
(4) Korhonen 2007. Reported in the original paper as 'strange dreams'
(5) Landman 2015. Reported in the original paper as 'nightmares/ vivid dreams'
(6) Laverone 2006. Reported in the original paper as 'nightmares'
(7) Stoney 2016. Reported in the original paper as 'intense nightmares'
### Analysis 3.12. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 12 Insomnia (all studies).

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 3 Mefloquine versus atovaquone-proguanil

**Outcome:** 12 Insomnia (all studies)

| Study or subgroup | Mefloquine n/N | Atovaquone-proguanil n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|-------------------|----------------|--------------------------|-----------------------------|--------|-----------------------------|
| 1 RCTs (adverse effects) |               |                          |                             |        |                             |
| Overbosch 2001    | 65/483         | 15/493                   | 4.42 [ 2.56, 7.64 ]         | 100.0% |                             |
| **Subtotal (95% CI)** | 483           | 493                      | 4.42 [ 2.56, 7.64 ]         | 100.0% |                             |
| Total events: 65 (Mefloquine), 15 (Atovaquone-proguanil) |               |                          |                             |        |                             |

**Heterogeneity:** not applicable

**Test for overall effect:** Z = 5.33 (P < 0.00001)

| 2 Cohort studies (adverse effects) |               |                          |                             |        |                             |
|-----------------------------------|----------------|--------------------------|-----------------------------|--------|-----------------------------|
| Andersson 2008 (1)                | 171/491        | 8/161                    | 54.8 % 7.01 [ 3.53, 13.92 ] | 1.1 % 14.58 [1.35, 156.96] |
| Cunningham 2014                   | 0/49           | 5/182                    | 10.7 % 0.33 [0.02, 5.92]    | 4.5 % 11.49 [0.75, 176.52] |
| Kato 2013                         | 2/38           | 1/277                    | 5.8 % 8.08 [1.08, 60.36]    | 4.5 % 12.00 [3.01, 47.82]  |
| Kehronen 2007                     | 491/1453       | 0/16                     | 4.5 % 4.58 [1.35, 156.96]   | 4.5 % 7.29 [4.37, 12.16]   |
| Kuhner 2005                       | 14/142         | 1/82                     | 1.1 % 14.58 [1.35, 156.96]  | 4.5 % 7.02 [0.44, 112.48]  |
| Landman 2015                      | 94/380         | 2/97                     | 1.1 % 14.58 [1.35, 156.96]  | 4.5 % 7.02 [0.44, 112.48]  |
| Laverone 2006                     | 35/444         | 0/43                     | 1.1 % 14.58 [1.35, 156.96]  | 4.5 % 7.02 [0.44, 112.48]  |
| Tuck 2016                         | 3/13           | 5/118                    | 1.1 % 14.58 [1.35, 156.96]  | 4.5 % 7.02 [0.44, 112.48]  |
| **Subtotal (95% CI)**             | 3010           | 976                      | 100.0% 7.29 [4.37, 12.16]   |        |                             |
| Total events: 810 (Mefloquine), 22 (Atovaquone-proguanil) |               |                          |                             |        |                             |

**Heterogeneity:** Chi² = 5.56, df = 7 (P = 0.59); I² = 0%

**Test for overall effect:** Z = 7.61 (P < 0.00001)

| 3 Retrospective healthcare record analysis (adverse events) |               |                          |                             |        |                             |
|------------------------------------------------------------|----------------|--------------------------|-----------------------------|--------|-----------------------------|
| Eick-Cost 2017                                              | 743/36538      | 212/12881                | 1.24 [1.06, 1.44]           | 100.0% |                             |
| **Subtotal (95% CI)**                                       | 36538          | 12881                    | 1.24 [1.06, 1.44]           | 100.0% |                             |
| Total events: 743 (Mefloquine), 212 (Atovaquone-proguanil) |               |                          |                             |        |                             |

**Heterogeneity:** not applicable

**Test for overall effect:** Z = 2.74 (P = 0.0061)

**Test for subgroup differences:** Chi² = 57.94; df = 2 (P = 0.00); I² = 97%

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(1) Andersson 2008. Reported in the original paper as ‘sleep disturbance’
### Analysis 3.13. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 13 Anxiety (all studies).

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 3 Mefloquine versus atovaquone-proguanil

**Outcome:** 13 Anxiety (all studies)

| Study or subgroup | Mefloquine | Atovaquone-proguanil | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|----------------------|------------|--------|------------|
|                   | n/N        | n/N                  | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| 1 RCTs (adverse effects) | | | | | |
| Overbosch 2001 | 18/483 | 3/493 | `<` | 100.0 % | 6.12 [1.82, 20.66] |
| **Subtotal (95% CI)** | 483 | 493 | `<` | 100.0 % | 6.12 [1.82, 20.66] |
| Total events: | 18 (Mefloquine), 3 (Atovaquone-proguanil) |
| Heterogeneity: not applicable |
| Test for overall effect: Z = 2.92 (P = 0.0035) |
| 2 Cohort studies (adverse effects) | | | | | |
| Cunningham 2014 | 1/49 | 1/182 | `<` | 7.7 % | 3.71 [0.24, 58.32] |
| Kerhonen 2007 | 380/1453 | 0/16 | `<` | 17.9 % | 8.90 [0.58, 136.71] |
| Landman 2015 | 104/380 | 2/97 | `<` | 57.8 % | 13.27 [3.34, 52.83] |
| Laverone 2006 (1) | 16/444 | 0/43 | `<` | 16.5 % | 3.26 [0.20, 53.46] |
| **Subtotal (95% CI)** | 2326 | 338 | `<` | 100.0 % | 10.10 [3.48, 29.32] |
| Total events: | 501 (Mefloquine), 3 (Atovaquone-proguanil) |
| Heterogeneity: Chi² = 1.29, df = 3 (P = 0.73); I² =0.0% |
| Test for overall effect: Z = 4.25 (P = 0.000021) |
| 3 Retrospective healthcare record analysis (adverse events) | | | | | |
| Eick-Cost 2017 (2) | 620/36538 | 142/12881 | `<` | 100.0 % | 1.54 [1.28, 1.85] |
| **Subtotal (95% CI)** | 36538 | 12881 | `<` | 100.0 % | 1.54 [1.28, 1.85] |
| Total events: | 620 (Mefloquine), 142 (Atovaquone-proguanil) |
| Heterogeneity: not applicable |
| Test for overall effect: Z = 4.66 (P < 0.00001) |
| Test for subgroup differences: Chi² = 16.12, df = 2 (P = 0.00), I² =88% |

(1) Laverone 2006. Reported in the original paper as 'anxiety disorder'

(2) Eick-Cost 2017. Report in the original paper as 'anxiety disorder'
### Analysis 3.14. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 14 Depressed mood (all studies).

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 3 Mefloquine versus atovaquone-proguanil

Outcome: 14 Depressed mood (all studies)

| Study or subgroup | Mefloquine | Atovaquone-proguanil | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|----------------------|------------|--------|-----------|
|                   | n/N        | n/N                  | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| 1 RCTs (adverse effects) | | | | | |
| Overbosch 2001 (1) | 17/483 | 3/493 | 100.0 % | 5.78 [ 1.71, 19.61 ] | |
| Subtotal (95% CI) | 483 | 493 | 100.0 % | 5.78 [ 1.71, 19.61 ] | |
| Total events: 17 (Mefloquine), 3 (Atovaquone-proguanil) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 2.82 (P = 0.0048) | | | | |
| 2 Cohort studies (adverse effects) | | | | |
| Andersson 2008 (2) | 82/491 | 2/161 | 33.1 % | 13.44 [ 3.34, 54.05 ] | |
| Kato 2013 (3) | 0/38 | 3/277 | 9.5 % | 1.02 [ 0.05, 19.34 ] | |
| Korhonen 2007 (4) | 208/1453 | 0/16 | 10.9 % | 4.88 [ 0.32, 75.03 ] | |
| Kuhner 2005 (5) | 13/142 | 2/82 | 27.9 % | 3.75 [ 0.87, 16.22 ] | |
| Landman 2015 (6) | 39/380 | 0/97 | 8.7 % | 20.32 [ 1.26, 327.69 ] | |
| Laverone 2006 (7) | 6/444 | 0/43 | 10.0 % | 1.29 [ 0.07, 22.44 ] | |
| Subtotal (95% CI) | 2948 | 676 | 100.0 % | 8.02 [ 3.56, 18.07 ] | |
| Total events: 348 (Mefloquine), 7 (Atovaquone-proguanil) | | | | |
| Heterogeneity: Chi^2 = 5.58, df = 5 (P = 0.35); I^2 =10% | | | | |
| Test for overall effect: Z = 5.03 (P < 0.00001) | | | | |
| 3 Retrospective healthcare record analysis (adverse events) | | | | |
| Eick-Cost 2017 (8) | 541/36538 | 99/12881 | 100.0 % | 1.93 [ 1.56, 2.38 ] | |
| Subtotal (95% CI) | 36538 | 12881 | 100.0 % | 1.93 [ 1.56, 2.38 ] | |
| Total events: 541 (Mefloquine), 99 (Atovaquone-proguanil) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 6.02 (P < 0.00001) | | | | |
| Test for subgroup differences: Chi^2 = 13.64, df = 2 (P = 0.00), I^2 =85% | | | | |
Analysis 3.15. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 15 Abnormal thoughts and perceptions (all studies).

Review: Mefloquine for preventing malaria during travel to endemic areas
Comparison: 3 Mefloquine versus atovaquone-proguanil
Outcome: 15 Abnormal thoughts and perceptions (all studies)

| Study or subgroup | Mefloquine | Atovaquone-proguanil | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|-------------------|------------|----------------------|-----------------------------|--------|-----------------------------|
| 1 Cohort studies (adverse effects) | | | | | |
| Korhonen 2007 (1) | 9/1453 | 0/16 | 36.7 % 0.22 [ 0.01, 3.67 ] | | |
| Landman 2015 (2) | 6/380 | 0/97 | 29.5 % 3.34 [ 0.19, 58.85 ] | | |
| Laverone 2006 (3) | 6/444 | 0/43 | 33.8 % 1.29 [ 0.07, 22.44 ] | | |
| Subtotal (95% CI) | 2277 | 156 | 100.0 % 1.50 [ 0.30, 7.42 ] | | |

Total events: 21 (Mefloquine), 0 (Atovaquone-proguanil)
Heterogeneity: $\chi^2 = 2.10$, df = 2 ($P = 0.35$); $I^2 = 5\%$
Test for overall effect: $Z = 0.50$ ($P = 0.62$)

2 Retrospective healthcare record analysis (adverse events)
| Eick-Cost 2017 (4) | 17/36538 | 2/12881 | 100.0 % 3.00 [ 0.69, 12.97 ] | | |
| Subtotal (95% CI) | 36538 | 12881 | 100.0 % 3.00 [ 0.69, 12.97 ] | | |

Total events: 17 (Mefloquine), 2 (Atovaquone-proguanil)
Heterogeneity: not applicable
Test for overall effect: $Z = 1.47$ ($P = 0.14$)
Test for subgroup differences: $\chi^2 = 0.39$, df = 1 ($P = 0.53$); $I^2 = 0\%$
### Analysis 3.16. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 16 Pruritis (all studies).

**Review:** Mefloquine for preventing malaria during travel to endemic areas  
**Comparison:** 3 Mefloquine versus atovaquone-proguanil  
**Outcome:** 16 Pruritis (all studies)

| Study or subgroup | Mefloquine | Atovaquone-proguanil | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|----------------------|------------|--------|------------|
|                   | n/N        | n/N                  | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| 1 RCTs (adverse effects) | | | | | |
| Overbosch 2001 (1) | 15/483 | 12/493 | 1.28 [0.60, 2.70] | 100.0 % | 1.28 [0.60, 2.70] |
| Subtotal (95% CI) | 483 | 493 | 100.0 % | 1.28 [0.60, 2.70] |
| Total events: | 15 (Mefloquine), 12 (Atovaquone-proguanil) | | | |
| Heterogeneity: | not applicable | | | |
| Test for overall effect: | $Z = 0.64 (P = 0.52)$ | | | |
| 2 Cohort studies (adverse effects) | | | | |
| Korhonen 2007 (2) | 42/1453 | 0/16 | 4.06 [0.21, 77.69] | 29.5 % | 4.06 [0.21, 77.69] |
| Kuhner 2005 | 3/142 | 0/82 | 4.06 [0.21, 77.69] | 29.5 % | 4.06 [0.21, 77.69] |
| Tuck 2016 | 0/13 | 2/118 | 1.70 [0.09, 33.65] | 24.5 % | 1.70 [0.09, 33.65] |
| Subtotal (95% CI) | 1608 | 216 | 100.0 % | 2.07 [0.40, 10.68] |
| Total events: | 45 (Mefloquine), 2 (Atovaquone-proguanil) | | | |
| Heterogeneity: | $\chi^2 = 0.49, df = 2 (P = 0.78); I^2 = 0.0%$ | | | |
| Test for overall effect: | $Z = 0.87 (P = 0.38)$ | | | |
| Test for subgroup differences: | $\chi^2 = 0.28, df = 1 (P = 0.60), I^2 = 0.0%$ | | | |

(1) Overbosch 2001. Reported in the original paper as ‘itching’  
(2) Korhonen 2007. Reported in the original paper as ‘itchy skin’
### Analysis 3.17. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 17 Visual impairment (all studies).

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 3 Mefloquine versus atovaquone-proguanil

**Outcome:** 17 Visual impairment (all studies)

| Study or subgroup | Mefloquine | Atovaquone-proguanil | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|----------------------|------------|--------|------------|
|                   | n/N        | n/N                  | M-H,Fixed, 95% CI |        | M-H,Fixed, 95% CI |
| 1 RCTs (adverse effects) |            |                      |            |        |            |
| Overbosch 2001 (1) | 16/483 | 8/493 | 100.0 % | 2.04 [ 0.88, 4.73 ] |            |
| **Subtotal (95% CI)** | **483** | **493** | **100.0 %** | **2.04 [ 0.88, 4.73 ]** |            |
| Total events: 16 (Mefloquine), 8 (Atovaquone-proguanil) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 1.67 (P = 0.096) | | | | | |
| 2 Cohort studies (adverse effects) | | | | | |
| Korhonen 2007 (2) | 164/1453 | 1/16 | 52.0 % | 1.81 [ 0.27, 12.11 ] | 1.17 [ 0.29, 4.72 ] |
| Laverone 2006 (3) | 5/444 | 1/43 | 48.0 % | 0.48 [ 0.06, 4.05 ] | 0.01 0.1 1 10 100 |
| **Subtotal (95% CI)** | **1897** | **59** | **100.0 %** | **1.17 [ 0.29, 4.72 ]** |            |
| Total events: 169 (Mefloquine), 2 (Atovaquone-proguanil) | | | | | |
| Heterogeneity: Chi² = 0.86, df = 1 (P = 0.35); I² =0.0% | | | | | |
| Test for overall effect: Z = 0.22 (P = 0.82) | | | | | |
| Test for subgroup differences: Chi² = 0.45, df = 1 (P = 0.50), I² =0.0% | | | | | |

(1) Overbosch 2001. Reported in the original paper as ‘visual difficulties’

(2) Korhonen 2007. Reported in the original paper as ‘visual disturbances’

(3) Laverone 2006. Reported in the original paper as ‘blurred vision’

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

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

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 3 Mefloquine versus atovaquone-proguanil

Outcome: 18 Other adverse effects (cohort studies)

| Study or subgroup | Mefloquine | Atovaquone-proguanil | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|----------------------|------------|--------|------------|
|                   | n/N        | n/N                  | M-H,Fixed 95% CI |        | M-H,Fixed 95% CI |
| **1 Allergic reaction** | 0/38       | 4/278                | 0.79 [0.04, 14.48] | 100.0 % | **0.79 [0.04, 14.48]** |
| **Subtotal (95% CI)** | **38**     | **278**              | **100.0 %** | **0.79 [0.04, 14.48]** |
| Total events: 0 (Mefloquine), 4 (Atovaquone-proguanil) |
| Heterogeneity: not applicable |
| Test for overall effect: Z = 0.16 (P = 0.88) |
| **2 Alopecia** | 194/1453 | 0/16                 | 4.55 [0.30, 70.01] | 100.0 % | **4.55 [0.30, 70.01]** |
| **Subtotal (95% CI)** | **1453**     | **16**              | **100.0 %** | **4.55 [0.30, 70.01]** |
| Total events: 194 (Mefloquine), 0 (Atovaquone-proguanil) |
| Heterogeneity: not applicable |
| Test for overall effect: Z = 1.09 (P = 0.28) |
| **3 Asthenia** | 69/1453 | 0/16                 | 1.63 [0.10, 25.18] | 52.1 % | **1.63 [0.10, 25.18]** |
| Laverone 2006 (3) | 10/444 | 0/43 | 2.08 [0.12, 34.84] | 47.9 % | **2.08 [0.12, 34.84]** |
| **Subtotal (95% CI)** | **1897**     | **59**              | **100.0 %** | **1.84 [0.26, 13.12]** |
| Total events: 79 (Mefloquine), 0 (Atovaquone-proguanil) |
| Heterogeneity: Chi² = 0.01, df = 1 (P = 0.90); I² =0.0% |
| Test for overall effect: Z = 0.61 (P = 0.54) |
| **4 Balance disorder** | 122/1453 | 0/16 | 2.86 [0.19, 44.19] | 100.0 % | **2.86 [0.19, 44.19]** |
| **Subtotal (95% CI)** | **1453**     | **16**              | **100.0 %** | **2.86 [0.19, 44.19]** |
| Total events: 122 (Mefloquine), 0 (Atovaquone-proguanil) |
| Heterogeneity: not applicable |
| Test for overall effect: Z = 0.75 (P = 0.45) |
| **5 Cough** | 3/491 | 2/161 | 0.49 [0.08, 2.92] | 100.0 % | **0.49 [0.08, 2.92]** |
| **Subtotal (95% CI)** | **491**     | **161**             | **100.0 %** | **0.49 [0.08, 2.92]** |
| Total events: 3 (Mefloquine), 2 (Atovaquone-proguanil) |
| Heterogeneity: not applicable |
| Test for overall effect: Z = 0.78 (P = 0.43) |

(Continued ...)
| Study or subgroup | Mefloquine n/N | Atovaquone-proguanil n/N | Risk Ratio M-H,Fixed 95% CI | Weight | Risk Ratio M-H,Fixed 95% CI |
|------------------|----------------|--------------------------|-----------------------------|--------|-----------------------------|
| Andersson 2008 (5) | 55/491 | 4/161 | 97.6 % | 79.6 % | 4.51 [ 1.66, 12.25 ] |
| Kühner 2005 (6) | 7/142 | 0/82 | 8.4 % | 8.1 % | 8.71 [ 0.50, 150.50 ] |
| Laverone 2006 (7) | 5/444 | 0/43 | 12.0 % | 12.0 % | 1.09 [ 0.06, 19.35 ] |
| **Subtotal (95% CI)** | **1077** | **286** | **100.0 %** | **100.0 %** | **4.45 [ 1.84, 10.77 ]** |
| Total events: 67 (Mefloquine), 4 (Atovaquone-proguanil) | | | | | |
| Heterogeneity: $\chi^2 = 1.13$, df = 2 ($P = 0.57$); $I^2 = 0.0\%$ | | | | | |
| Test for overall effect: $Z = 3.31$ ($P = 0.00094$) | | | | | |
| 7 Dyspepsia | | | | | |
| Cunningham 2014 (8) | 3/49 | 21/182 | 78.6 % | 78.6 % | 0.53 [ 0.17, 1.71 ] |
| Tuck 2016 (9) | 0/13 | 11/118 | 21.4 % | 21.4 % | 0.37 [ 0.02, 5.94 ] |
| **Subtotal (95% CI)** | **62** | **300** | **100.0 %** | **100.0 %** | **0.50 [ 0.17, 1.46 ]** |
| Total events: 3 (Mefloquine), 32 (Atovaquone-proguanil) | | | | | |
| Heterogeneity: $\chi^2 = 0.06$, df = 1 ($P = 0.81$); $I^2 = 0.0\%$ | | | | | |
| Test for overall effect: $Z = 1.27$ ($P = 0.20$) | | | | | |
| 8 Fatigue | | | | | |
| Laverone 2006 (10) | 26/444 | 0/43 | 74.2 % | 74.2 % | 5.24 [ 0.32, 84.52 ] |
| Tuck 2016 (11) | 0/13 | 1/118 | 25.8 % | 25.8 % | 2.83 [ 0.12, 66.27 ] |
| **Subtotal (95% CI)** | **457** | **161** | **100.0 %** | **100.0 %** | **4.62 [ 0.47, 45.56 ]** |
| Total events: 26 (Mefloquine), 1 (Atovaquone-proguanil) | | | | | |
| Heterogeneity: $\chi^2 = 0.10$, df = 1 ($P = 0.75$); $I^2 = 0.0\%$ | | | | | |
| Test for overall effect: $Z = 1.31$ ($P = 0.19$) | | | | | |
| 9 Hypoaesthesia | | | | | |
| Korhonen 2007 (12) | 21/1453 | 0/16 | 38.3 % | 38.3 % | 0.50 [ 0.03, 7.97 ] |
| Landman 2015 (13) | 27/380 | 1/97 | 61.7 % | 61.7 % | 6.89 [ 0.95, 50.09 ] |
| **Subtotal (95% CI)** | **1833** | **113** | **100.0 %** | **100.0 %** | **4.45 [ 0.93, 21.26 ]** |
| Total events: 48 (Mefloquine), 1 (Atovaquone-proguanil) | | | | | |
| Heterogeneity: $\chi^2 = 2.58$, df = 1 ($P = 0.11$); $I^2 = 61\%$ | | | | | |
| Test for overall effect: $Z = 1.87$ ($P = 0.062$) | | | | | |
| 10 Loss of appetite | | | | | |
| Andersson 2008 | 21/491 | 10/161 | 100.0 % | 100.0 % | 0.69 [ 0.33, 1.43 ] |
| **Subtotal (95% CI)** | **491** | **161** | **100.0 %** | **100.0 %** | **0.69 [ 0.33, 1.43 ]** |
| Total events: 21 (Mefloquine), 10 (Atovaquone-proguanil) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: $Z = 1.00$ ($P = 0.32$) | | | | | |
| 11 Muscle pain | | | | | |
| Andersson 2008 | 11/491 | 0/161 | 100.0 % | 100.0 % | 7.57 [ 0.45, 127.80 ] |
| **Subtotal (95% CI)** | **491** | **161** | **100.0 %** | **100.0 %** | **7.57 [ 0.45, 127.80 ]** |
| Total events: 11 (Mefloquine), 0 (Atovaquone-proguanil) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Study or subgroup | Mefloquine (n/N) | Atovaquone-proguanil (n/N) | Risk Ratio M-H,Fixed 95% CI | Weight | Risk Ratio M-H,Fixed 95% CI |
|------------------|-----------------|---------------------------|-----------------------------|--------|-----------------------------|
| Palpitations     |                 |                           |                             |        |                             |
| Korhonen 2007    | 6/1453          | 0/16                      | 39.1% 0.15 [0.01, 2.59]     |        |                             |
| Kuhner 2005      | 7/142           | 0/82                      | 25.0% 0.81 [0.05, 15.050]   |        |                             |
| Laverone 2006    | 15/444          | 0/43                      | 36.0% 3.07 [0.19, 50.36]    |        |                             |

**Subtotal (95% CI)** 2039 141 100.0% 3.34 [0.73, 15.26]

Total events: 28 (Mefloquine), 0 (Atovaquone-proguanil)
Heterogeneity: Chi² = 4.99, df = 2 (P = 0.08); I² = 60%
Test for overall effect: Z = 1.40 (P = 0.16)

| Sensitization   |                 |                           |                             |        |                             |
|-----------------|-----------------|---------------------------|-----------------------------|--------|-----------------------------|
| Cunningham 2014 | 0/49            | 4/182                     | 68.0% 0.41 [0.02, 7.43]     |        |                             |
| Laverone 2006   | 6/444           | 0/43                      | 32.0% 1.29 [0.07, 22.44]    |        |                             |

**Subtotal (95% CI)** 493 225 100.0% 0.69 [0.10, 4.92]

Total events: 6 (Mefloquine), 4 (Atovaquone-proguanil)
Heterogeneity: Chi² = 0.31, df = 1 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.37 (P = 0.71)

| Pyrexia         |                 |                           |                             |        |                             |
|-----------------|-----------------|---------------------------|-----------------------------|--------|-----------------------------|
| Andersson 2008  | 6/491           | 0/161                     | 100.0% 4.28 [0.24, 75.57]   |        |                             |

**Subtotal (95% CI)** 491 161 100.0% 4.28 [0.24, 75.57]

Total events: 6 (Mefloquine), 0 (Atovaquone-proguanil)
Heterogeneity: not applicable
Test for overall effect: Z = 0.99 (P = 0.32)

| Rash            |                 |                           |                             |        |                             |
|-----------------|-----------------|---------------------------|-----------------------------|--------|-----------------------------|
| Kuhner 2005     | 2/142           | 1/82                      | 58.2% 1.15 [0.11, 12.54]    |        |                             |
| Laverone 2006   | 3/444           | 0/43                      | 41.8% 0.69 [0.04, 13.18]    |        |                             |

**Subtotal (95% CI)** 586 125 100.0% 0.96 [0.15, 6.09]

Total events: 5 (Mefloquine), 1 (Atovaquone-proguanil)
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%
Test for overall effect: Z = 0.04 (P = 0.97)

| Restlessness    |                 |                           |                             |        |                             |
|-----------------|-----------------|---------------------------|-----------------------------|--------|-----------------------------|
| Laverone 2006   | 26/444          | 0/43                      | 100.0% 5.24 [0.32, 84.52]   |        |                             |

**Subtotal (95% CI)** 444 43 100.0% 5.24 [0.32, 84.52]

Total events: 26 (Mefloquine), 0 (Atovaquone-proguanil)
Heterogeneity: not applicable
Test for overall effect: Z = 1.17 (P = 0.24)

| Slight illness  |                 |                           |                             |        |                             |
|-----------------|-----------------|---------------------------|-----------------------------|--------|-----------------------------|
| Laverone 2006   | 29/444          | 0/43                      | 100.0% 5.83 [0.36, 93.84]   |        |                             |

Heterogeneity: not applicable
Test for overall effect: Z = 1.17 (P = 0.24)
| Study or subgroup | Mefloquine | Atovaquone-proguanil | Risk Ratio | Weight | Risk Ratio |
|------------------|------------|----------------------|------------|--------|------------|
|                  | n/N        | n/N                  | M-H, Fixed, 95% CI |        | M-H, Fixed, 95% CI |
| Subtotal (95% CI) | 444 | 43 | | 100.0 % | 5.83 [0.36, 93.84] |
| Total events: 29 (Mefloquine), 0 (Atovaquone-proguanil) | | | |
| Heterogeneity: not applicable | | | |
| Test for overall effect: Z = 1.24 (P = 0.21) | | | |
| 18 Somnolence | | | |
| Laverone 2006 (16) | 16/444 | 1/43 | 100.0 % | 1.55 [0.21, 11.40] |
| Subtotal (95% CI) | 444 | 43 | | 100.0 % | 1.55 [0.21, 11.40] |
| Total events: 16 (Mefloquine), 1 (Atovaquone-proguanil) | | | |
| Heterogeneity: not applicable | | | |
| Test for overall effect: Z = 0.43 (P = 0.67) | | | |
| 19 Tinnitus | | | |
| Landman 2015 | 4/380 | 0/97 | 100.0 % | 2.31 [0.13, 42.64] |
| Subtotal (95% CI) | 380 | 97 | | 100.0 % | 2.31 [0.13, 42.64] |
| Total events: 4 (Mefloquine), 0 (Atovaquone-proguanil) | | | |
| Heterogeneity: not applicable | | | |
| Test for overall effect: Z = 0.56 (P = 0.57) | | | |
| 20 Circulatory disorders | | | |
| Kuhner 2005 | 5/142 | 0/82 | 100.0 % | 6.38 [0.36, 114.01] |
| Subtotal (95% CI) | 142 | 82 | | 100.0 % | 6.38 [0.36, 114.01] |
| Total events: 5 (Mefloquine), 0 (Atovaquone-proguanil) | | | |
| Heterogeneity: not applicable | | | |
| Test for overall effect: Z = 1.26 (P = 0.21) | | | |
(1) Korhonen 2007. Reported in the original paper as ‘hair loss’
(2) Korhonen 2007. Reported in the original paper as ‘weakness’
(3) Laverone 2006. Reported in the original paper as ‘weakness’
(4) Korhonen 2007. Reported in the original paper as ‘unsteadiness’
(5) Andersson 2008. Reported in the original paper as ‘concentration difficulties’
(6) Kunher 2005. Reported in the original paper as ‘losing of concentration’
(7) Laverone 2006. Reported in the original paper as ‘mental confusion’
(8) Cunningham 2014. Reported in the original paper as ‘indigestion’
(9) Tuck 2016. Reported in the original paper as ‘indigestion’
(10) Laverone 2006. Reported in the original paper as ‘tiredness’
(11) Tuck 2016. Reported in the original paper as ‘lethargy’
(12) Korhonen 2007. Reported in the original paper as ‘limb numbness’
(13) Landman 2015. Reported in the original paper as ‘limb numbness’
(14) Cunningham 2014. Reported in the original paper as ‘skin sensitivity’
(15) Andersson 2008. Reported in the original paper as ‘fever’
(16) Laverone 2006. Reported in the original paper as ‘drowsiness’
### Analysis 3.19. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 19 Other adverse events (cohort studies).

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 3 Mefloquine versus atovaquone-proguanil

Outcome: 19 Other adverse events (cohort studies)

| Study or subgroup | Mefloquine | Atovaquone-proguanil | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|----------------------|------------|--------|------------|
|                   | n/N        | n/N                  | M-H,Fixed, 95% CI |        | M-H,Fixed, 95% CI |
| 1 Adjustment disorder | 1220/36538 | 244/12881             |             | 100.0% | 1.76 [1.54, 2.02] |
| **Subtotal (95% CI)** | **36538** | **12881**             |             | 100.0% | 1.76 [1.54, 2.02] |
| Total events: 1220 (Mefloquine), 244 (Atovaquone-proguanil) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 8.17 (P < 0.00001) | | | | | |
| 2 Confusion | 1/36538 | 0/12881 | 100.0% | 1.06 [0.04, 25.96] |
| **Subtotal (95% CI)** | **36538** | **12881** | 100.0% | 1.06 [0.04, 25.96] |
| Total events: 1 (Mefloquine), 0 (Atovaquone-proguanil) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.03 (P = 0.97) | | | | | |
| 3 Convulsions | 65/36538 | 17/12881 | 100.0% | 1.35 [0.79, 2.30] |
| **Subtotal (95% CI)** | **36538** | **12881** | 100.0% | 1.35 [0.79, 2.30] |
| Total events: 65 (Mefloquine), 17 (Atovaquone-proguanil) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 1.10 (P = 0.27) | | | | | |
| 4 Hallucinations | 5/36538 | 7/12881 | 100.0% | 0.25 [0.08, 0.79] |
| **Subtotal (95% CI)** | **36538** | **12881** | 100.0% | 0.25 [0.08, 0.79] |
| Total events: 5 (Mefloquine), 7 (Atovaquone-proguanil) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 2.36 (P = 0.018) | | | | | |
| 5 Paranoia | 2/36538 | 0/12881 | 100.0% | 1.76 [0.08, 36.72] |
| **Subtotal (95% CI)** | **36538** | **12881** | 100.0% | 1.76 [0.08, 36.72] |
| Total events: 2 (Mefloquine), 0 (Atovaquone-proguanil) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.37 (P = 0.71) | | | | | |
| 6 PTSD | 448/36538 | 63/12881 | 100.0% | 2.51 [1.93, 3.26] |

(Continued...)
### Study or subgroup

|          | Mefloquine | Atovaquone-proguanil | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|----------|------------|----------------------|-----------------------------|--------|-----------------------------|
| **Subtotal (95% CI)** | 36538 | 12881 | * 100.0 % 2.51 [1.93, 3.26] | |
| Total events: 448 (Mefloquine), 63 (Atovaquone-proguanil) | |
| Heterogeneity: not applicable | |
| Test for overall effect: Z = 6.85 (P < 0.00001) | |
| **7 Suicidal ideation** | | | | |
| Eick-Cost 2017 | 91/36538 | 19/12881 | 100.0 % 1.69 [1.03, 2.77] | |
| Total events: 91 (Mefloquine), 19 (Atovaquone-proguanil) | |
| Heterogeneity: not applicable | |
| Test for overall effect: Z = 2.08 (P = 0.038) | |
| **8 Suicide** | | | | |
| Eick-Cost 2017 | 2/36538 | 1/12881 | 100.0 % 0.71 [0.06, 7.78] | |
| Total events: 2 (Mefloquine), 1 (Atovaquone-proguanil) | |
| Heterogeneity: not applicable | |
| Test for overall effect: Z = 0.29 (P = 0.78) | |
| **9 Tinnitus** | | | | |
| Eick-Cost 2017 | 707/36538 | 175/12881 | 100.0 % 1.42 [1.21, 1.68] | |
| Total events: 707 (Mefloquine), 175 (Atovaquone-proguanil) | |
| Heterogeneity: not applicable | |
| Test for overall effect: Z = 4.22 (P = 0.000024) | |

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

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

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 3 Mefloquine versus atovaquone-proguanil

**Outcome:** 20 Adherence (RCTs)

| Study or subgroup     | Mefloquine | Atovaquone-proguanil | Risk Ratio M-H/Random, 95% CI | Weight | Risk Ratio M-H/Random, 95% CI |
|-----------------------|------------|----------------------|-------------------------------|--------|-------------------------------|
| van Riemsdijk 2002    | 54/58      | 60/61                | 100.0 % 0.95 [0.88, 1.02]    |        |                               |
| **Subtotal (95% CI)** | **58**     | **61**               | **100.0 % 0.95 [0.88, 1.02]** | **1**  |                               |
| Overbosch 2001; during travel | 444/477  | 465/489              | 100.0 % 0.98 [0.95, 1.01]    |        |                               |
| **Subtotal (95% CI)** | **477**    | **489**              | **100.0 % 0.98 [0.95, 1.01]** | **1**  |                               |
| Overbosch 2001; post-travel | 334/477  | 430/489              | 100.0 % 0.80 [0.74, 0.85]    |        |                               |
| **Subtotal (95% CI)** | **477**    | **489**              | **100.0 % 0.80 [0.74, 0.85]** | **1**  |                               |

Total events: 54 (Mefloquine), 60 (Atovaquone-proguanil)

Heterogeneity: not applicable

Test for overall effect: Z = 1.40 (P = 0.16)

Test for subgroup differences: Chi$^2$ = 29.61, df = 2 (P = 0.00001), I$^2$ = 93%
### Analysis 3.21. Comparison 3 Mefloquine versus atovaquone-proguanil, Outcome 21 Adherence (cohort studies).

**Review:** Mefloquine for preventing malaria during travel to endemic areas  
**Comparison:** Mefloquine versus atovaquone-proguanil  
**Outcome:** Adherence (cohort studies)

| Study or subgroup | Mefloquine | Atovaquone-proguanil | Risk Ratio M. H.Random, 95% CI | Weight | Risk Ratio M. H.Random, 95% CI |
|-------------------|------------|----------------------|------------------------------|--------|------------------------------|
| n/N               | n/N        |                      |                              |        |                              |
| During travel     |            |                      |                              |        |                              |
| Cunningham 2014 (1) | 12/49    | 40/182               | 9.2 % 1.11 [0.63, 1.96]       |        |                              |
| Goodyer 2011 (2)  | 21/30     | 56/84                | 16.9 % 1.05 [0.79, 1.39]      |        |                              |
| Korhonen 2007 (3) | 946/1453  | 8/16                 | 10.8 % 1.30 [0.80, 2.13]      |        |                              |
| Landman 2015 (4)  | 231/380   | 77/97                | 21.4 % 0.77 [0.67, 0.87]      |        |                              |
| Tan 2017 (5)      | 1691/2972 | 86/183               | 20.6 % 1.21 [1.03, 1.42]      |        |                              |
| Tuck 2016 (6)     | 13/13     | 93/118               | 21.2 % 1.23 [1.07, 1.41]      |        |                              |
| **Subtotal (95% CI)** | 4897     | 680                  | 100.0 % 1.08 [0.86, 1.34]     |        |                              |
| Total events      | 2914 (Mefloquine), 360 (Atovaquone-proguanil) |                          |                          |        |                              |
| Heterogeneity: Tau² = 0.06; Chi² = 31.62, df = 5 (P<0.00001); I² =84% | | | | |
| Test for overall effect: Z = 0.64 (P = 0.52) | | | | |
| 2 Post-travel     |            |                      |                              |        |                              |
| Goodyer 2011 (7)  | 15/30     | 46/84                | 64.3 % 0.91 [0.61, 1.37]      |        |                              |
| Stoney 2016 (8)   | 6/11      | 190/297              | 35.7 % 0.85 [0.49, 1.47]      |        |                              |
| **Subtotal (95% CI)** | 41       | 381                  | 100.0 % 0.89 [0.64, 1.23]     |        |                              |
| Total events      | 21 (Mefloquine), 236 (Atovaquone-proguanil) |                          |                          |        |                              |
| Heterogeneity: Tau² = 0.0; Chi² = 0.04, df = 1 (P = 0.84); I² =0.0% | | | | |
| Test for overall effect: Z = 0.69 (P = 0.49) | | | | |
| Test for subgroup differences: Chi² = 0.87, df = 1 (P = 0.35); I² =0.0% | | | | |

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Mefloquine for preventing malaria during travel to endemic areas (Review)  
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(1) Cunningham 2014. Defined as ‘travellers reporting >95% adherence’
(2) Goodyer 2011. Defined as ‘proportion of travelers reporting taking all medication’
(3) Korhonen 2007. Defined as ‘participants who reported they ‘never’ missed doses’
(4) Landman 2015. ‘PCVs reporting taking daily medications at any time each day or taking weekly medications with no more than 8 days between doses were defined as adherent’
(5) Tan 2017. ‘Taken as prescribed’
(6) Tuck 2016. ‘Fully compliant’
(7) Goodyer 2011. Defined as ‘proportion of travelers reporting taking all medication, post travel’
(8) Stoney 2016. Defined as ‘number adherent in the post-prophylaxis period’

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

Review: Mefloquine for preventing malaria during travel to endemic areas
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 (1)   | 38/145         | 53/77       | 0.38 [ 0.28, 0.52 ]         | 93.2 % |                             |
| Bunnag 1992 (2)     | 2/123          | 5/119       | 0.39 [ 0.08, 1.96 ]         | 6.8 %  |                             |
| Salako 1992 (3)     | 0/107          | 0/103       | Not estimable               |        |                             |
| Sossouhounto 1995 (4)| 0/103         | 0/100       | Not estimable               |        |                             |
| **Total (95% CI)**  | **478**        | **399**     | **0.38 [ 0.28, 0.52 ]**     | **100.0 %** |                             |

Total events: 40 (Mefloquine), 58 (Control)
Heterogeneity: $Chi^2 = 0.00$, df = 1 ($P = 0.98$); $I^2 = 0.0$
Test for overall effect: $Z = 6.08$ ($P < 0.00001$)
Test for subgroup differences: Not applicable

(1) Boudreau 1991. Population: Thai adults, semi-immune, mefloquine dose 500mg fortnightly.
(2) Bunnag 1992. Thai adult males, presumed semi-immune. Dose 250mg weekly for first 4 weeks, then 125mg weekly.
(3) Salako 1992. Nigerian adults, semi-immune. Dose 250mg weekly for first 4 weeks, then 125mg weekly.
(4) Sossouhounto 1995. Ivory coast adult males, semi-immune. Dose 250mg weekly for first 4 weeks, then 125mg weekly.
### Analysis 4.2. Comparison 4 Mefloquine versus chloroquine, Outcome 2 Serious adverse events or effects (all studies).

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 4 Mefloquine versus chloroquine

Outcome: 2 Serious adverse events or effects (all studies)

| Study or subgroup | Mefloquine | Chloroquine | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|-------------|------------|--------|------------|
|                   | n/N        | n/N         | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| **1 RCTs**        |            |             |            |        |             |
| Boudreau 1993 (1) | 1/46       | 0/78        |            | 35.9 % | 5.04 [0.21, 121.28] |
| Boudreau 1993     | 1/157      | 0/78        |            | 64.1 % | 1.50 [0.06, 36.40] |
| 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** | **100.0 %** | **2.77 [0.32, 23.85]** |
| **Total events:** | 2 (Mefloquine), 0 (Chloroquine) | | | | |
| Heterogeneity: Chi² = 0.28, df = 1 (P = 0.60); I² =0.0% |
| Test for overall effect: Z = 0.93 (P = 0.35) |
| **2 Cohort studies** | | | | | |
| Albright 2002     | 1/115      | 0/22        |            | 4.5 %  | 0.59 [0.03, 14.15] |
| Corominas 1997    | 1/1609     | 0/137       |            | 4.4 %  | 0.68 [0.03, 16.57] |
| Korhonen 2007     | 15/1612    | 4/832       |            | 28.3 % | 1.94 [0.64, 5.81] |
| Napoletano 2007   | 0/548      | 0/37        |            |        | Not estimable |
| Petersen 2000     | 5/809      | 2/1223      |            | 8.5 %  | 3.78 [0.74, 19.43] |
| Steffen 1993 (2)  | 7/52981  | 7/20332     |            | 54.3 % | 0.38 [0.13, 1.09] |
| **Subtotal (95% CI)** | **56674** | **22583** | **100.0 %** | **1.14 [0.62, 2.07]** |
| **Total events:** | 29 (Mefloquine), 13 (Chloroquine) | | | | |
| Heterogeneity: Chi² = 7.35, df = 4 (P = 0.12); I² =46% |
| Test for overall effect: Z = 0.41 (P = 0.68) |
| Test for subgroup differences: Chi² = 0.61, df = 1 (P = 0.43), I² =0.0% |

(1) Boudreau 1993, Mefloquine group received loading dose of 250mg daily for 3 days

(2) Steffen 1993, Reports of serious side effects were followed up locally (in Africa and Europe) for diagnosis and outcome. Includes all events possibly or probably related to the drugs
Analysis 4.3. Comparison 4 Mefloquine versus chloroquine, Outcome 3 Discontinuations due to adverse effects (all studies).

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 4 Mefloquine versus chloroquine

Outcome: 3 Discontinuations due to adverse effects (all studies)

| Study or subgroup | Mefloquine | Chloroquine | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|-------------|------------|--------|------------|
|                   | n/N        | n/N         | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| 1 RCTs            |            |             |            |        |            |
| Boudreau 1993     | 10/203     | 5/156       | 1.54 [ 0.54, 4.41 ] | 84.7 % |            |
| Bunnag 1992       | 2/116      | 1/112       | 1.93 [ 0.18, 21.00 ] | 15.3 % |            |
| Salako 1992       | 0/113      | 0/115       | Not estimable |        |            |
| **Subtotal (95% CI)** | **432** | **383** | **100.0 %** | **1.60 [ 0.61, 4.18 ]** | |
| Total events:     | 12 (Mefloquine), 6 (Chloroquine) | | | | |
| Heterogeneity:    | Chi² = 0.03, df = 1 (P = 0.86); I² =0.0% | | | | |
| Test for overall effect: | Z = 0.95 (P = 0.34) | | | | |
| 2 Cohort studies in short-term travellers | | | | | |
| Albright 2002     | 2/115      | 0/22        | 0.99 [ 0.05, 19.98 ] | 0.6 % |            |
| Corominas 1997    | 30/609     | 4/137       | 1.69 [ 0.60, 4.71 ] | 5.0 % |            |
| Hill 2000         | 0/102      | 3/374       | 0.52 [ 0.03, 9.99 ] | 1.2 % |            |
| Napoletano 2007   | 66/548     | 0/37        | 9.21 [ 0.58, 145.85 ] | 0.7 % |            |
| Steffen 1993      | 851/50053  | 64/3354     | 0.89 [ 0.69, 1.15 ] | 92.4 % |            |
| Stoney 2016       | 0/11       | 0/35        | Not estimable |        |            |
| **Subtotal (95% CI)** | **51438** | **3959** | **100.0 %** | **0.99 [ 0.78, 1.26 ]** | |
| Total events:     | 949 (Mefloquine), 71 (Chloroquine) | | | | |
| Heterogeneity:    | Chi² = 4.38, df = 4 (P = 0.36); I² =9% | | | | |
| Test for overall effect: | Z = 0.10 (P = 0.92) | | | | |
| 3 Cohort studies in longer term occupational travellers | | | | | |
| Korhonen 2007     | 370/1612   | 70/832      | 2.73 [ 2.14, 3.47 ] | 71.1 % |            |
| Tan 2017          | 365/2973   | 23/668      | 3.57 [ 2.36, 5.39 ] | 28.9 % |            |
| **Subtotal (95% CI)** | **4585** | **1500** | **100.0 %** | **2.97 [ 2.41, 3.66 ]** | |
| Total events:     | 735 (Mefloquine), 93 (Chloroquine) | | | | |
| Heterogeneity:    | Chi² = 1.23, df = 1 (P = 0.27); I² =19% | | | | |
| Test for overall effect: | Z = 10.15 (P < 0.00001) | | | | |
| Test for subgroup differences: | Chi² = 45.67, df = 2 (P = 0.00), I² =96% | | | | |
### Analysis 4.4.  Comparison 4 Mefloquine versus chloroquine, Outcome 4 Nausea (all studies).

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 4 Mefloquine versus chloroquine

**Outcome:** 4 Nausea (all studies)

| Study or subgroup | Mefloquine | Chloroquine | Risk Ratio M/H Random, 95% CI | Weight | Risk Ratio M/H Random, 95% CI |
|------------------|------------|-------------|-------------------------------|--------|-------------------------------|
|                  | n/N        | n/N         |                               |        |                               |
| 1. Cohort studies (adverse effects) | | | | | |
| Albright 2002    | 1/115      | 2/22        | 1.7 %                         | 1.7 %  | 0.10 [0.01, 1.01]            |
| Corominas 1997   | 15/609     | 0/137       | 1.2 %                         | 1.2 %  | 7.01 [0.42, 116.50]          |
| Korhonen 2007    | 165/1453   | 0/137       | 28.6 %                        | 28.6 % | 0.87 [0.69, 1.11]            |
| Laverone 2006    | 65/444     | 3/81        | 6.3 %                         | 6.3 %  | 3.95 [1.27, 12.27]           |
| Petersen 2000    | 130/809    | 89/684      | 29.1 %                        | 29.1 % | 1.56 [1.24, 1.96]            |
| Steffen 1993     | 6157/50053 | 362/3354    | 33.1 %                        | 33.1 % | 1.14 [1.03, 1.26]            |
| **Subtotal (95% CI)** | **53483** | **5501**    | **100.0 %**                   | **100.0 %** | **1.23 [0.89, 1.68]** |
| Total events: 6533 (Mefloquine), 582 (Chloroquine) | | | | | |
| Heterogeneity: Tau^2 = 0.08; Chi^2 = 22.34, df = 5 (P = 0.00045); I^2 = 78%  |
| Test for overall effect: Z = 1.27 (P = 0.20)  |
| 2 RCTs (adverse events) | | | | | |
| Boudreau 1993    | 22/157     | 10/78       | 67.8 %                        | 67.8 % | 1.09 [0.54, 2.19]            |
| Boudreau 1993 (1) | 5/46       | 10/78       | 32.2 %                        | 32.2 % | 0.85 [0.31, 2.33]            |
| **Subtotal (95% CI)** | **203** | **156**     | **100.0 %**                   | **100.0 %** | **1.01 [0.57, 1.79]** |
| Total events: 27 (Mefloquine), 20 (Chloroquine) | | | | | |
| Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.16, df = 1 (P = 0.68); I^2 = 0.0%  |
| Test for overall effect: Z = 0.02 (P = 0.98)  |

(1) Boudreau 1993. Mefloquine group received loading dose of 250mg daily for 3 days
### Analysis 4.5. Comparison 4 Mefloquine versus chloroquine, Outcome 5 Vomiting (all studies).

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 4 Mefloquine versus chloroquine

**Outcome:** 5 Vomiting (all studies)

| Study or subgroup | Mefloquine | Chloroquine | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|-------------|------------|--------|-----------|
|                   | n/N        | n/N         | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| 1 Cohort studies (adverse effects) |            |            |            |        |            |
| Albright 2002     | 3/115      | 2/22        | 4.0 %      | 0.29   | [ 0.05, 1.62 ] |
| Corominas 1997    | 8/609      | 0/137       | 1.0 %      | 3.85   | [ 0.22, 66.23 ] |
| Korhonen 2007     | 28/1453    | 6/684       | 9.7 %      | 2.20   | [ 0.09, 5.28 ] |
| Laverone 2006     | 6/444      | 0/81        | 1.0 %      | 2.40   | [ 0.14, 42.11 ] |
| Petersen 2000     | 53/809     | 89/1223     | 84.3 %     | 0.90   | [ 0.65, 1.25 ] |
| **Subtotal (95% CI)** | 3430       | 2147        |            | 100.0 % | 1.05 [ 0.78, 1.40 ] |
| Total events: 98 (Mefloquine), 97 (Chloroquine) |            |            |            |        |            |
| Heterogeneity: Ch² = 6.82, df = 4 (P = 0.15); I² = 41% |            |            |            |        |            |
| Test for overall effect: Z = 0.29 (P = 0.77) |            |            |            |        |            |
| 2 RCTs (adverse events) |            |            |            |        |            |
| Boudreau 1993     | 9/157      | 3/78        | 68.2 %     | 1.49   | [ 0.42, 5.35 ] |
| Boudreau 1993 (1) | 0/46       | 2/78        | 31.8 %     | 0.34   | [ 0.02, 6.85 ] |
| **Subtotal (95% CI)** | 203        | 156         |            | 100.0 % | 1.12 [ 0.36, 3.49 ] |
| Total events: 9 (Mefloquine), 5 (Chloroquine) |            |            |            |        |            |
| Heterogeneity: Ch² = 0.80, df = 1 (P = 0.37); I² = 0.0% |            |            |            |        |            |
| Test for overall effect: Z = 0.20 (P = 0.84) |            |            |            |        |            |

(1) Boudreau 1993. Mefloquine group received loading dose of 250mg daily for 3 days.
## Analysis 4.6. Comparison 4 Mefloquine versus chloroquine, Outcome 6 Abdominal pain (all studies).

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 4 Mefloquine versus chloroquine

**Outcome:** 6 Abdominal pain (all studies)

| Study or subgroup | Mefloquine | Chloroquine | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|-------------|------------|--------|------------|
|                   | n/N        | n/N         | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| **1 Cohort studies (adverse effects)** | | | | | |
| Corominas 1997    | 30/609     | 4/137       | 3.9 %      | 1.69 [0.60, 4.71] | |
| Korhonen 2007     | 54/1453    | 25/684      | 20.3 %     | 1.02 [0.64, 1.62] | |
| Laverone 2006     | 9/444      | 0/81        | 0.5 %      | 3.50 [0.21, 59.57] | |
| Petersen 2000     | 97/809     | 158/1223    | 75.3 %     | 0.93 [0.73, 1.18] | |
| **Subtotal (95% CI)** | **3315** | **2125** | 100.0 % | 0.99 [0.80, 1.22] | |
| **Total events:** | 190 (Mefloquine), 187 (Chloroquine) | | | | |
| Heterogeneity: Chi$^2$ = 2.09, df = 3 (P = 0.55); I$^2$ =0.0% | | | | | |
| Test for overall effect: Z = 0.11 (P = 0.91) | | | | | |
| **2 RCTs (adverse events)** | | | | | |
| Boudreau 1993 (1) | 5/46       | 8/78        | 32.1 %     | 1.06 [0.37, 3.05] | |
| Boudreau 1993    | 8/157      | 9/78        | 65.1 %     | 0.44 [0.18, 1.10] | |
| Salako 1992      | 1/107      | 0/103       | 2.8 %      | 2.89 [0.12, 70.11] | |
| **Subtotal (95% CI)** | **310** | **259** | 100.0 % | 0.71 [0.37, 1.36] | |
| **Total events:** | 14 (Mefloquine), 17 (Chloroquine) | | | | |
| Heterogeneity: Chi$^2$ = 2.33, df = 2 (P = 0.31); I$^2$ =14% | | | | | |
| Test for overall effect: Z = 1.04 (P = 0.30) | | | | | |

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(1) Boudreau 1993. Mefloquine group received loading dose of 250mg daily for 3 days
### Analysis 4.7. Comparison 4 Mefloquine versus chloroquine, Outcome 7 Diarrhoea (all studies).

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 4 Mefloquine versus chloroquine

**Outcome:** 7 Diarrhoea (all studies)

| Study or subgroup | Mefloquine | Chloroquine | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|------------------|------------|-------------|---------------------------|--------|---------------------------|
| n/N              | n/N        |             |                           |        |                           |
| **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      | 8.0 %                     | 0.88 [ 0.54, 1.44 ] | |
| Laverone 2006    | 21/444     | 2/81        | 0.8 %                     | 1.92 [ 0.46, 8.01 ] | |
| Petersen 2000    | 249/809    | 467/1223    | 90.6 %                    | 0.81 [ 0.71, 0.91 ] | |
| **Subtotal (95% CI)** | **3430** | **2147** | **100.0 %** | **0.84 [ 0.74, 0.95 ]** | |
| Total events: 339 (Mefloquine), 494 (Chloroquine) | | | | | |
| Heterogeneity: Chi² = 4.69, df = 4 (P = 0.32); I² = 15% | | | | | |
| Test for overall effect: Z = 2.85 (P = 0.0044) | | | | | |
| **2 RCTs (adverse events)** | | | | | |
| Boudreau 1993    | 11/157     | 10/78       | 63.5 %                    | 0.55 [ 0.24, 1.23 ] | |
| Boudreau 1993 (1) | 5/46       | 9/78        | 31.7 %                    | 0.94 [ 0.34, 2.64 ] | |
| Salako 1992      | 1/107      | 0/103       | 2.4 %                     | 2.89 [ 0.12, 70.11 ] | |
| Sossouhounto 1995 | 2/103     | 0/100       | 2.4 %                     | 4.86 [ 0.24, 99.90 ] | |
| **Subtotal (95% CI)** | **413** | **359** | **100.0 %** | **0.83 [ 0.46, 1.50 ]** | |
| Total events: 19 (Mefloquine), 19 (Chloroquine) | | | | | |
| Heterogeneity: Chi² = 2.98, df = 3 (P = 0.40); I² = 0.0% | | | | | |
| Test for overall effect: Z = 0.61 (P = 0.54) | | | | | |

(1) Boudreau 1993. Mefloquine group received loading dose of 250mg daily for 3 days
### Analysis 4.8. Comparison 4 Mefloquine versus chloroquine, Outcome 8 Headache (all studies).

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 4 Mefloquine versus chloroquine

**Outcome:** 8 Headache (all studies)

| Study or subgroup | Mefloquine | Chloroquine | Risk Ratio (Mefloquine | Weight | Risk Ratio (Chloroquine | Weight |
|------------------|------------|-------------|-----------------------|--------|-------------------------|--------|
|                  | n/N        | n/N         |                       |        |                         |        |
|                  |            |             |                       |        |                         |        |
| 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       | 4.8 %                 | 3.82   | [0.51, 28.49]           |        |
| Korhonen 2007    | 100/1453   | 7/8684      | 39.6 %                | 0.60   | [0.46, 0.80]            |        |
| Latorene 2006    | 18/444     | 1/81        | 4.8 %                 | 3.28   | [0.44, 24.26]           |        |
| Steffen 1993     | 3103/50053 | 215/3354    | 44.6 %                | 0.97   | [0.85, 1.11]            |        |
| Stoney 2016      | 0/11       | 0/35        | Not estimable         |        |                         |        |
| **Subtotal (95% CI)** | **52685** | **4313**    |                       | **100.0 %** | **0.84 [0.53, 1.34]** |        |
| Heterogeneity: Tau² = 0.12; Chi² = 14.15, df = 4 (P = 0.01); I² = 72% |
| Test for overall effect: Z = 0.72 (P = 0.47) |

| 2 RCTs (adverse events) | Mefloquine | Chloroquine | Risk Ratio (Mefloquine | Weight | Risk Ratio (Chloroquine | Weight |
|------------------------|------------|-------------|-----------------------|--------|-------------------------|--------|
|                       | n/N        | n/N         |                       |        |                         |        |
|                       |            |             |                       |        |                         |        |
| Boudreau 1993         | 35/157     | 20/78       | 63.8 %                | 0.87   | [0.54, 1.40]            |        |
| Boudreau 1993 (1)     | 11/46      | 19/78       | 34.8 %                | 0.98   | [0.51, 1.87]            |        |
| Salako 1992           | 0/107      | 1/103       | 1.4 %                 | 0.32   | [0.01, 7.79]            |        |
| Sossouhounto 1995     | 0/103      | 0/100       | Not estimable         |        |                         |        |
| **Subtotal (95% CI)** | **413**    | **359**     |                       | **100.0 %** | **0.89 [0.61, 1.31]** |        |
| Heterogeneity: Tau² = 0.00; Chi² = 4.99, df = 2 (P = 0.78); I² = 0.0% |
| Test for overall effect: Z = 0.58 (P = 0.57) |

- 0.01 0.1 1 10 100
  - Favours mefloquine
  - Favours chloroquine

(1) Boudreau 1993. Mefloquine group received loading dose of 250mg daily for 3 days
### Analysis 4.9. Comparison 4 Mefloquine versus chloroquine, Outcome 9 Dizziness (all studies).

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 4 Mefloquine versus chloroquine

**Outcome:** 9 Dizziness (all studies)

| Study or subgroup | Mefloquine | Chloroquine | Risk Ratio | Weight |
|------------------|------------|-------------|------------|--------|
|                  | n/N        | n/N         | M-H,Fixed,95% CI |        |
|                  |            |             |            |        |
| 1 Cohort studies (adverse effects) |            |             |            |        |
| Corominas 1997  | 33/609     | 9/137       | 3.1 % 0.82 [ 0.40, 1.68 ] |        |
| Korhonen 2007   | 189/1453   | 55/684      | 15.6 % 1.62 [ 1.22, 2.15 ] |        |
| Laverone 2006   | 25/444     | 1/81        | 0.4 % 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    | 69.7 % 1.43 [ 1.24, 1.66 ] |        |
| **Subtotal (95% CI)** | 53368 | 5479 | 100.0 % 1.51 [ 1.34, 1.70 ] |        |
|                  |            |             |            |        |
| Total events: 4139 (Mefloquine), 311 (Chloroquine) |            |             |            |        |

**Heterogeneity:** Chi² = 7.47, df = 4 (P = 0.11); I² =46%

**Test for overall effect:** Z = 6.88 (P < 0.00001)

| Study or subgroup | Mefloquine | Chloroquine | Risk Ratio | Weight |
|------------------|------------|-------------|------------|--------|
|                  | n/N        | n/N         | M-H,Fixed,95% CI |        |
|                  |            |             |            |        |
| 2 RCTs (adverse events) |            |             |            |        |
| Boudreau 1993   | 9/157      | 7/78        | 58.2 % 0.64 [ 0.25, 1.65 ] |        |
| Boudreau 1993 (1) | 4/46      | 7/78        | 32.3 % 0.97 [ 0.30, 3.13 ] |        |
| Salako 1992     | 0/107      | 1/103       | 9.5 % 0.32 [ 0.01, 7.79 ] |        |
| **Subtotal (95% CI)** | 310 | 259 | 100.0 % 0.72 [ 0.35, 1.46 ] |        |
|                  |            |             |            |        |
| Total events: 13 (Mefloquine), 15 (Chloroquine) |            |             |            |        |

**Heterogeneity:** Chi² = 0.55, df = 2 (P = 0.76); I² =0.0%

**Test for overall effect:** Z = 0.92 (P = 0.36)

(1) Boudreau 1993. Mefloquine group received loading dose of 250mg daily for 3 days.
### Analysis 4.10. Comparison 4 Mefloquine versus chloroquine, Outcome 10 Abnormal dreams (all studies).

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 4 Mefloquine versus chloroquine

Outcome: 10 Abnormal dreams (all studies)

| Study or subgroup | Mefloquine | Chloroquine | Risk Ratio | Weight |
|-------------------|------------|-------------|------------|--------|
|                   | n/N        | n/N         | M-H,Fixed,95% CI |        |
| 1 Cohort studies (adverse effects) | | | | |
| Albright 2002 (1) | 4/115 | 0/22 | 0.2 % | 1.78 [ 0.10, 32.02 ] |
| Korhonen 2007 (2) | 775/1453 | 306/684 | 99.6 % | 1.19 [ 1.08, 1.31 ] |
| Laverone 2006 (3) | 25/444 | 0/81 | 0.2 % | 9.40 [ 0.58, 152.84 ] |
| Stoney 2016 (4) | 0/11 | 0/35 | Not estimable | |
| **Subtotal (95% CI)** | **2023** | **822** | 100.0 % | 1.21 [ 1.10, 1.33 ] |

Total events: 804 (Mefloquine), 306 (Chloroquine)
Heterogeneity: Chi$^2$ = 2.24, df = 2 (P = 0.33); I$^2$ = 11%
Test for overall effect: Z = 3.87 (P = 0.00011)

2 RCTs (adverse events)

| Study or subgroup | Mefloquine | Chloroquine | Risk Ratio | Weight |
|-------------------|------------|-------------|------------|--------|
|                   | n/N        | n/N         | M-H,Fixed,95% CI |        |
| Boudreau 1993 (5) | 6/46 | 2/78 | 27.0 % | 5.09 [ 1.07, 24.17 ] |
| Boudreau 1993 | 11/157 | 3/78 | 73.0 % | 1.82 [ 0.52, 6.34 ] |
| **Subtotal (95% CI)** | **203** | **156** | 100.0 % | 2.70 [ 1.05, 6.95 ] |

Total events: 17 (Mefloquine), 5 (Chloroquine)
Heterogeneity: Chi$^2$ = 1.02, df = 1 (P = 0.31); I$^2$ = 2%
Test for overall effect: Z = 2.06 (P = 0.039)

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(1) Albright 2002. Reported in the original paper as ‘vivid dreams’

(2) Korhonen 2007. Reported in the original paper as ‘strange dreams’

(3) Laverone 2006. Reported in the original paper as ‘nightmares’

(4) Stoney 2016. Reported in the original paper as ‘intense nightmares’

(5) Boudreau 1993. Reported in the original paper as ‘dreams’. Mefloquine group received loading dose of 250mg daily for 3 days
### Analysis 4.11. Comparison 4 Mefloquine versus chloroquine, Outcome 11 Insomnia (all studies).

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 4 Mefloquine versus chloroquine

**Outcome:** 11 Insomnia (all studies)

| Study or subgroup | Mefloquine | Chloroquine | Risk Ratio | Weight | Risk Ratio |
|------------------|------------|-------------|------------|--------|------------|
|                  | n/N        | n/N         | H Random, 95% CI |        | H Random, 95% CI |
| 1. Cohort studies (adverse effects) | | | | | |
| Albright 2002 (1) | 1/115 | 1/22 | 8.5 % | 0.19 [0.01, 2.95] | |
| Corominas 1997 | 19/609 | 1/137 | 13.1 % | 4.27 [0.58, 31.66] | |
| Korhonen 2007 | 491/1453 | 83/684 | 34.9 % | 2.78 [2.25, 3.45] | |
| Laverone 2006 | 35/444 | 0/81 | 8.3 % | 13.08 [0.81, 211.16] | |
| Steffen 1993 | 2102/50053 | 151/3354 | 35.2 % | 0.93 [0.79, 1.10] | |
| **Subtotal (95% CI)** | 52674 | 4278 | 100.0 % | 1.81 [0.73, 4.51] | |

Total events: 2648 (Mefloquine), 236 (Chloroquine)
Heterogeneity: Tau² = 0.61; Chi² = 70.73, df = 4 (P<0.00001); I² = 94%
Test for overall effect: Z = 1.28 (P = 0.20)

2 RCTs (adverse events)

| Study or subgroup | Mefloquine | Chloroquine | Risk Ratio | Weight | Risk Ratio |
|------------------|------------|-------------|------------|--------|------------|
|                  | n/N        | n/N         | H Random, 95% CI |        | H Random, 95% CI |
| Boudreau 1993 (1) | 39/157 | 20/78 | 55.1 % | 0.97 [0.61, 1.54] | |
| Boudreau 1993 (2) | 17/46 | 19/78 | 44.9 % | 1.52 [0.88, 2.61] | |
| **Subtotal (95% CI)** | 203 | 156 | 100.0 % | 1.19 [0.76, 1.84] | |

Total events: 56 (Mefloquine), 39 (Chloroquine)
Heterogeneity: Tau² = 0.03; Chi² = 1.51, df = 1 (P = 0.22); I² = 34%
Test for overall effect: Z = 0.76 (P = 0.45)

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(1) Albright 2002. Reported in the original paper as 'changes in sleep'

(2) Boudreau 1993. Mefloquine group received loading dose of 250mg daily for 3 days
## Analysis 4.12. Comparison 4 Mefloquine versus chloroquine, Outcome 12 Anxiety (all studies).

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 4 Mefloquine versus chloroquine

**Outcome:** 12 Anxiety (all studies)

| Study or subgroup | Mefloquine | Chloroquine | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|-------------|------------|--------|------------|
|                   | n/N        | n/N         | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| Cohort studies (adverse effects) | | | | | |
| Corominas 1997 | 5/609 | 0/137 | 2.1 % | 2.49 [ 0.14, 44.74 ] | |
| Korhonen 2007 | 380/1453 | 28/684 | 95.8 % | 6.39 [ 4.40, 9.28 ] | |
| Laverone 2006 (1) | 16444 | 0/81 | 2.1 % | 6.08 [ 0.37, 100.36 ] | |
| **Subtotal (95% CI)** | **2506** | **902** | **100.0 %** | **6.30 [ 4.37, 9.09 ]** | |

Total events: 401 (Mefloquine), 28 (Chloroquine)

Heterogeneity: Chi² = 0.40, df = 2 (P = 0.82); I² =0.0%

Test for overall effect: Z = 9.85 (P < 0.00001)

(1) Laverone 2006. Reported in the original paper as ‘anxiety disorder’
### Analysis 4.13. Comparison 4 Mefloquine versus chloroquine, Outcome 13 Depressed mood (all studies).

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 4 Mefloquine versus chloroquine

Outcome: 13 Depressed mood (all studies)

| Study or subgroup | Mefloquine | Chloroquine | Risk Ratio M-H (Random, 95% CI) | Weight | Risk Ratio M-H (Random, 95% CI) |
|-------------------|------------|-------------|--------------------------------|--------|--------------------------------|
| n/N               | n/N        |             |                                |        |                                |
| 1 Cohort studies (adverse effects) | | | | | |
| Corominas 1997 (1) | 3/609 | 0/137 | 8.3 % | 1.58 [0.08, 30.48] |
| Korhonen 2007 (2) | 209/1461 | 17/684 | 27.5 % | 5.76 [3.54, 9.36] |
| Laverone 2006 (3) | 6/444 | 0/81 | 8.7 % | 2.40 [0.14, 42.11] |
| Petersen 2000 | 55/809 | 14/1223 | 26.8 % | 5.94 [3.33, 10.61] |
| Steffen 1993 (4) | 901/50053 | 47/3354 | 28.7 % | 1.28 [0.96, 1.72] |
| **Subtotal (95% CI)** | 53376 | 5479 | 100.0 % | 3.14 [1.15, 8.57] |

Total events: 1174 (Mefloquine), 78 (Chloroquine)

Heterogeneity: Tau² = 0.89; Chi² = 40.33, df = 4 (P<0.00001); I² = 90%

Test for overall effect: Z = 2.24 (P = 0.025)

(1) Corominas 1997. Reported in the original paper as 'depression'
(2) Korhonen 2007. Reported in the original paper as 'depression'
(3) Laverone 2006. Reported in the original paper as 'depression'
(4) Steffen 1993. Reported in the original paper as 'depression'
## Analysis 4.14. Comparison 4 Mefloquine versus chloroquine, Outcome 14 Abnormal thoughts and perceptions.

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 4 Mefloquine versus chloroquine

Outcome: 14 Abnormal thoughts and perceptions

| Study or subgroup | Mefloquine n/N | Chloroquine n/N | Risk Ratio M-H,Fixed 95% CI | Weight | Risk Ratio M-H,Fixed 95% CI |
|------------------|----------------|----------------|-----------------------------|--------|-----------------------------|
|                  | n/N            | n/N            |                             |        |                             |
| 1 Cohort studies (adverse effects) | | | | | |
| Albright 2002 (1) | 1/115          | 0/22           | 10.5 % 0.59 [0.03, 14.15]  |        |                             |
| Korpainen 2007 (2) | 9/1453         | 0/684          | 8.6 % 8.95 [0.52, 153.57]  |        |                             |
| Laverone 2006 (3) | 6/444          | 0/81           | 10.6 % 2.40 [0.14, 42.11]  |        |                             |
| Petersen 2000 (4) | 29/809         | 7/1223         | 70.3 % 6.26 [2.76, 14.23]  |        |                             |
| Subtotal (95% CI) | 2821           | 2010           | 100.0 % 5.49 [2.65, 11.35] |        |                             |

Total events: 45 (Mefloquine), 7 (Chloroquine)

Heterogeneity: Chi² = 2.42, df = 3 (P = 0.49); I² = 0.0%

Test for overall effect: Z = 4.59 (P < 0.00001)

(1) Albright 2002. Reported in the original paper as ‘hallucinations’

(2) Karhonen 2007. Reported in the original paper as ‘hallucinations’ or ‘went crazy’

(3) Laverone 2006. Reported in the original paper as ‘hallucinations’

(4) Petersen 2000. Reported in the original paper as ‘strange thoughts’
### Analysis 4.15. Comparison 4 Mefloquine versus chloroquine, Outcome 15 Pruritis (all studies).

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 4 Mefloquine versus chloroquine

**Outcome:** 15 Pruritis (all studies)

| Study or subgroup | Mefloquine | Chloroquine | Risk Ratio M-H Random 95% CI | Weight | Risk Ratio M-H Random 95% CI |
|-------------------|------------|-------------|-----------------------------|--------|-----------------------------|
|                   | n/N        | n/N         |                             |        |                             |
| 1 Cohort studies (adverse effects) | | | | | |
| Korhonen 2007 (1) | 42/1453 | 21/684 | 16.2 % 0.94 [0.56, 1.58] | 95% CI | 1.18 [0.94, 1.48] |
| Steffen 1993 | 1351/50053 | 773/3354 | 83.8 % | 0.28 [0.03, 2.93] |
| Subtotal (95% CI) | 51506 | 4038 | 100.0 % 1.13 [0.92, 1.40] | 95% CI | |
| Total events: 1393 (Mefloquine), 98 (Chloroquine) | | | | | |
| Heterogeneity: $\tau^2 = 0.0; \chi^2 = 1 (P = 0.44); I^2 =0.0\%$ | | | | | |
| Test for overall effect: Z = 1.19 (P = 0.24) | | | | | |
| 2 RCTs (adverse events) | | | | | |
| Salako 1992 (2) | 1/107 | 12/103 | 44.5 % 0.08 [0.01, 0.61] | 95% CI | 0.78 [0.21, 2.81] |
| Sossouhounto 1995 | 4/103 | 5/100 | 55.5 % | 0.28 [0.03, 2.93] |
| Subtotal (95% CI) | 210 | 203 | 100.0 % 0.28 [0.03, 2.93] | 95% CI | |
| Total events: 5 (Mefloquine), 17 (Chloroquine) | | | | | |
| Heterogeneity: $\tau^2 = 2.13; \chi^2 = 3.85, df = 1 (P = 0.05); I^2 =74\%$ | | | | | |
| Test for overall effect: Z = 1.06 (P = 0.29) | | | | | |

(1) Korhonen 2007. Reported in the original paper as 'itchy skin'

(2) Salako 1992. Reported in the original paper as 'pruritis/itching'
### Analysis 4.16. Comparison 4 Mefloquine versus chloroquine, Outcome 16 Visual impairment (all studies).

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 4 Mefloquine versus chloroquine

**Outcome:** 16 Visual impairment (all studies)

| Study or subgroup | Mefloquine | Chloroquine | Risk Ratio Mefloquine vs Chloroquine (95% CI) | Weight |
|-------------------|------------|-------------|----------------------------------------------|--------|
| n/N               | n/N        |             |                                              |        |
| M-H, Random, 95% CI |            |             |                                              |        |
| 1. Cohort studies (adverse effects) |            |             |                                              |        |
| Corominas 1997 (1) | 4/609      | 1/137       | 9.2% [0.10, 7.99]                            |        |
| Korhonen 2007 (2) | 164/1453   | 35/684      | 28.0% [1.55, 3.14]                          |        |
| Laverone 2006 (3) | 5/444      | 1/81        | 9.5% [0.11, 7.71]                            |        |
| Petersen 2000 (4) | 14/809     | 19/1223     | 24.3% [0.56, 2.21]                          |        |
| Steffen 1993 (5) | 1102/50053 | 117/3354    | 29.1% [0.52, 0.76]                          |        |
| **Subtotal (95% CI)** | **53368**  | **5479**    | **100.0%** [0.50, 2.44]                      |        |
| Total events: 1289 (Mefloquine), 173 (Chloroquine) |            |             |                                              |        |
| Heterogeneity: Tau² = 0.56; Chi² = 39.43, df = 4 (P<0.0001); I² = 90% |            |             |                                              |        |
| Test for overall effect: Z = 0.23 (P = 0.82) |            |             |                                              |        |
| 2. RCTs (adverse events) |            |             |                                              |        |
| Salako 1992 (6) | 0/107      | 3/103       | 100.0% [0.01, 2.63]                          |        |
| **Subtotal (95% CI)** | **107**    | **103**     | **100.0%** [0.01, 2.63]                      |        |
| Total events: 0 (Mefloquine), 3 (Chloroquine) |            |             |                                              |        |
| Heterogeneity: not applicable |            |             |                                              |        |
| Test for overall effect: Z = 1.32 (P = 0.19) |            |             |                                              |        |

(1) Corominas 1997. Reported in the original paper as 'loss of visual acuity'

(2) Korhonen 2007. Reported in the original paper as 'visual disturbance'

(3) Laverone 2006. Reported in the original paper as 'blurred vision'

(4) Petersen 2000. Reported in the original paper as 'blurred vision'

(5) Steffen 1993. Reported in the original paper as 'visual'

(6) Salako 1992. Reported in the original paper as 'blurred sight'

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

Review: Mefloquine for preventing malaria during travel to endemic areas
Comparison: 4 Mefloquine versus chloroquine
Outcome: 17 Vertigo (all studies)

| Study or subgroup | Mefloquine | Chloroquine | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|-------------|------------|--------|------------|
|                   | n/N        | n/N         | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| Cohort studies (adverse effects) | 2/609 | 0/137 | 1.13 [0.05, 23.43] | 100.0 % | 1.13 [0.05, 23.43] |
| Subtotal (95% CI) | 609 | 137 | 100.0 % | 1.13 [0.05, 23.43] |

Total events: 2 (Mefloquine), 0 (Chloroquine)
Heterogeneity: not applicable
Test for overall effect: Z = 0.08 (P = 0.94)
### Analysis 4.18. Comparison 4 Mefloquine versus chloroquine, Outcome 18 Cohort studies in travellers; prespecified adverse effects.

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 4 Mefloquine versus chloroquine

**Outcome:** 18 Cohort studies in travellers; prespecified adverse effects

| Study or subgroup | Mefloquine | Chloroquine | Risk Ratio | Weight | Risk Ratio |
|------------------|------------|-------------|------------|--------|------------|
|                  | n/N        | n/N         |            |        |            |
| 1 Vertigo        |            |             |            |        |            |
| Corominas 1997   | 2/609      | 0/137       |            |        | 1.13 [0.05, 23.43] |
| Subtotal (95% CI)| 609        | 137         | 100.0 %    |        | 1.13 [0.05, 23.43] |
|                  |            |             |            |        |            |
| 2 Nausea         |            |             |            |        |            |
| Albright 2002    | 1/115      | 2/22        |            |        | 0.10 [0.01, 1.01] |
| Corominas 1997   | 15/609     | 0/137       |            |        | 7.01 [0.42, 116.50] |
| Laverone 2006    | 65/444     | 3/81        |            |        | 3.95 [1.27, 12.27] |
| Petersen 2000    | 130/809    | 126/1223    |            |        | 1.56 [1.24, 1.96] |
| Steffen 1993     | 6157/50053 | 362/3354    |            |        | 1.14 [1.03, 1.26] |
| Subtotal (95% CI)| 52030      | 4817        | 100.0 %    |        | 1.42 [0.94, 2.13] |
|                  |            |             |            |        |            |
| 3 Vomiting       |            |             |            |        |            |
| Albright 2002    | 3/115      | 2/22        |            |        | 0.29 [0.05, 1.62] |
| Corominas 1997   | 8/609      | 0/137       |            |        | 3.85 [0.22, 66.23] |
| Laverone 2006    | 6/444      | 0/81        |            |        | 2.40 [0.14, 42.11] |
| Petersen 2000    | 53/809     | 89/1223     |            |        | 0.90 [0.65, 1.25] |
| Subtotal (95% CI)| 1977       | 1463        | 100.0 %    |        | 0.89 [0.55, 1.42] |
|                  |            |             |            |        |            |
| 4 Abdominal pain |            |             |            |        |            |
| Corominas 1997   | 30/609     | 4/137       |            |        | 1.69 [0.60, 4.71] |
| Laverone 2006    | 9/444      | 0/81        |            |        | 3.50 [0.21, 59.57] |
| Petersen 2000    | 97/809     | 158/1223    |            |        | 0.93 [0.73, 1.18] |

Heterogeneity: not applicable

Test for overall effect: Z = 0.08 (P = 0.94)

Heterogeneity: Tau^2 = 0.09; Chi^2 = 16.28, df = 4 (P = 0.003); I^2 = 75%

Test for overall effect: Z = 1.68 (P = 0.093)

Heterogeneity: Tau^2 = 0.04; Chi^2 = 3.16, df = 3 (P = 0.37); I^2 = 5%

Test for overall effect: Z = 0.50 (P = 0.61)

(Continued . . .)
| Study or subgroup | Mefloquine (n/N) | Chloroquine (n/N) | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|------------------|-----------------|------------------|-------------------------------|--------|-------------------------------|
| **Subtotal (95% CI)** | 1862 1441 | 100.0% 0.98 [0.74, 1.30] |
| Total events: 136 (Mefloquine), 162 (Chloroquine) | | | |
| Heterogeneity: Tau² = 0.01; Chi² = 2.06, df = 2 (P = 0.36); I² = 3% | | | |
| Test for overall effect: Z = 0.13 (P = 0.89) | | | |
| **Diarrhoea** | | | |
| Albright 2002 | 3/115 0/22 | 6.2% 1.39 [0.07, 25.97] | | | |
| Corominas 1997 | 21/609 1/137 | 12.0% 4.72 [0.64, 34.82] | | | |
| Laverone 2006 | 21/444 2/81 | 19.8% 1.92 [0.46, 8.01] | | | |
| Petersen 2000 | 249/809 467/1223 | 61.9% 0.81 [0.71, 0.91] | | | |
| **Subtotal (95% CI)** | 1977 1463 | 100.0% 1.22 [0.57, 2.64] | | | |
| Total events: 294 (Mefloquine), 470 (Chloroquine) | | | |
| Heterogeneity: Tau² = 0.24; Chi² = 4.59, df = 3 (P = 0.20); I² = 35% | | | |
| Test for overall effect: Z = 0.52 (P = 0.61) | | | |
| **Headache** | | | |
| Albright 2002 | 3/115 2/22 | 17.1% 0.29 [0.05, 1.62] | | | |
| Corominas 1997 | 17/609 1/137 | 13.7% 3.82 [0.51, 28.49] | | | |
| Laverone 2006 | 18/444 1/81 | 13.8% 3.28 [0.44, 24.26] | | | |
| Steffen 1993 | 3103/50053 215/3354 | 55.4% 0.97 [0.85, 1.11] | | | |
| Stoney 2016 | 0/11 0/35 | Not estimable | | | |
| **Subtotal (95% CI)** | 51232 3629 | 100.0% 1.12 [0.48, 2.65] | | | |
| Total events: 3141 (Mefloquine), 219 (Chloroquine) | | | |
| Heterogeneity: Tau² = 0.34; Chi² = 5.16, df = 3 (P = 0.04); I² = 42% | | | |
| Test for overall effect: Z = 0.27 (P = 0.79) | | | |
| **Dizziness** | | | |
| Corominas 1997 | 33/609 9/137 | 14.7% 0.82 [0.40, 1.68] | | | |
| Laverone 2006 | 25/444 1/81 | 25.0% 4.56 [0.63, 33.19] | | | |
| Petersen 2000 | 88/809 68/1223 | 35.7% 1.96 [1.44, 2.65] | | | |
| Steffen 1993 | 3804/50053 178/3354 | 47.1% 1.43 [1.24, 1.66] | | | |
| **Subtotal (95% CI)** | 51915 4795 | 100.0% 1.52 [1.10, 2.10] | | | |
| Total events: 3950 (Mefloquine), 256 (Chloroquine) | | | |
| Heterogeneity: Tau² = 0.05; Chi² = 7.23, df = 3 (P = 0.06); I² = 58% | | | |
| Test for overall effect: Z = 2.54 (P = 0.011) | | | |
| **Abnormal dreams** | | | |
| Albright 2002 (1) | 4/115 0/22 | 48.3% 1.78 [0.10, 32.02] | | | |
| Laverone 2006 (2) | 25/444 0/81 | 51.7% 9.40 [0.58, 152.84] | | | |
| Stoney 2016 (3) | 0/11 0/35 | Not estimable | | | |
| **Subtotal (95% CI)** | 570 138 | 100.0% 4.21 [0.57, 31.33] | | | |
| Study or subgroup | Mefloquine | Chloroquine | Risk Ratio M-H | Weight | Risk Ratio M-H |
|------------------|------------|-------------|----------------|--------|---------------|
|                  | n/N        | n/N         | 95% CI         |        | 95% CI        |
| **Total events:** |            |             |                |        |               |
| 9 Insomnia       | 29 (Mefloquine), 0 (Chloroquine) |             |                |        |               |
| Albright 2002 (4) | 1/115      | 1/22        | 16.1 % | 0.19 [0.01, 29.5] |
| Corominas 1997   | 19/609     | 1/137       | 23.0 % | 4.27 [0.58, 31.66] |
| Laverone 2006    | 35/444     | 0/81        | 15.8 % | 13.08 [0.81, 211.16] |
| Steffen 1993     | 2/102/50053| 1/135/3354  | 45.1 % | 0.93 [0.79, 1.10] |
| **Subtotal (95% CI)** | 51221      | 3594        | 100.0 % | 1.56 [0.40, 6.10] |
| 10 Anxiety       | 2157 (Mefloquine), 153 (Chloroquine) |             |                |        |               |
| Corominas 1997   | 5/609      | 0/137       | 48.5 % | 2.49 [0.14, 44.74] |
| Laverone 2006    | 16/444     | 0/81        | 51.5 % | 6.08 [0.37, 100.36] |
| **Subtotal (95% CI)** | 1053       | 218         | 100.0 % | 3.94 [0.53, 29.48] |
| 11 Depressed mood| 965 (Mefloquine), 61 (Chloroquine) |             |                |        |               |
| Corominas 1997 (6) | 3/609   | 0/137       | 11.7 % | 1.58 [0.08, 30.48] |
| Laverone 2006 (7) | 6/444    | 0/81        | 12.2 % | 2.40 [0.14, 42.11] |
| Petersen 2000    | 55/809    | 1/1223      | 36.8 % | 5.94 [3.33, 10.61] |
| Steffen 1993 (8) | 9/509     | 0/1223      | 39.3 % | 1.28 [0.96, 1.72] |
| **Subtotal (95% CI)** | 51915      | 4795        | 100.0 % | 2.49 [0.75, 8.31] |
| 12 Abnormal thoughts or perceptions | 36 (Mefloquine), 7 (Chloroquine) |             |                |        |               |
| Albright 2002 (9) | 1/115     | 0/22        | 9.9 % | 0.59 [0.03, 14.15] |
| Laverone 2006    | 6/444     | 0/81        | 11.8 % | 2.40 [0.14, 42.11] |
| Petersen 2000 (10) | 29/809  | 7/1223      | 78.1 % | 6.26 [2.76, 14.23] |
| **Subtotal (95% CI)** | 1368       | 1326        | 100.0 % | 4.42 [1.58, 12.40] |

**Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.74, df = 1 (P = 0.39); I^2 = 0.0%**

**Test for overall effect: Z = 1.41 (P = 0.16)**

| Study or subgroup | Mefloquine | Chloroquine | Risk Ratio M-H | Weight | Risk Ratio M-H |
|------------------|------------|-------------|----------------|--------|---------------|
|                  | n/N        | n/N         | 95% CI         |        | 95% CI        |
| 13 Pruritis      | 0.005      | 0.1         | 1.00           | 100.0% | 4.48 [1.58, 12.40] |
| Study or subgroup | Mefloquine n/N | Chloroquine n/N | Risk Ratio M-H Random, 95% CI | Weight |
|------------------|---------------|----------------|-------------------------------|--------|
| Steffen 1993     | 1351/50053    | 77/3354        | 1.18 [0.94, 1.48]             | 100.0% |

**Subtotal (95% CI)** 50053 3354 100.0% 1.18 [0.94, 1.48]

Total events: 1351 (Mefloquine), 77 (Chloroquine)

Heterogeneity: not applicable

Test for overall effect: Z = 1.40 (P = 0.16)

### 14 Visual impairment

| Study or subgroup | Mefloquine n/N | Chloroquine n/N | Risk Ratio M-H Random, 95% CI | Weight |
|------------------|---------------|----------------|-------------------------------|--------|
| Corominas 1997 (11) | 4/609 | 1/137 | 0.90 [0.10, 7.99] |
| Laverone 2006 (12) | 5/444 | 1/81 | 0.91 [0.11, 7.71] |
| Petersen 2000 (13) | 14/809 | 19/1223 | 1.11 [0.56, 2.21] |
| Steffen 1993 (14) | 1102/50053 | 117/3354 | 0.63 [0.52, 0.76] |

**Subtotal (95% CI)** 51915 4795 100.0% 0.66 [0.55, 0.79]

Total events: 1125 (Mefloquine), 138 (Chloroquine)

Heterogeneity: $\tau^2 = 0.0$, $\chi^2 = 2.64$, df = 3 (P = 0.45); I² = 0.0%

Test for overall effect: Z = 4.55 (P < 0.00001)

(1) Albright 2002. Reported in the original paper as ‘vivid dreams’
(2) Laverone 2006. Reported in the original paper as ‘nightmares’
(3) Stoney 2016. Reported in the original paper as ‘intense nightmares’
(4) Albright 2002. Reported in the original paper as ‘changes in sleep’
(5) Laverone 2006. Reported in the original paper as ‘anxiety disorder’
(6) Corominas 1997. Reported in the original paper as ‘depression’
(7) Laverone 2006. Reported in the original paper as ‘depression’
(8) Steffen 1993. Reported in the original paper as ‘depression’
(9) Albright 2002. Reported in the original paper as ‘hallucinations’
(10) Petersen 2000. Reported in the original paper as ‘strange thoughts’
(11) Corominas 1997. Reported in the original paper as ‘loss of visual acuity’
(12) Laverone 2006. Reported in the original paper as ‘blurred vision’
(13) Petersen 2000. Reported in the original paper as ‘blurred vision’
(14) Steffen 1993. Reported in the original paper as ‘visual’
### Analysis 4.19. Comparison 4 Mefloquine versus chloroquine, Outcome 19 Other adverse effects (cohort studies).

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 4 Mefloquine versus chloroquine

Outcome: 19 Other adverse effects (cohort studies)

| Study or subgroup | Mefloquine | Chloroquine | Risk Ratio | Weight | Risk Ratio |
|------------------|------------|-------------|------------|--------|------------|
|                  | n/N        | n/N         | M-H,Fixed,95% CI |        | M-H,Fixed,95% CI |
| 1. Altered spatial perception | | | | | |
| Petersen 2000 | 23/809 | 11/1223 | | | |
|                | 100.0 % | | | | |
| **Subtotal (95% CI)** | 809 | 1223 | | | |
| Total events: 23 (Mefloquine), 11 (Chloroquine) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 3.16 (P = 0.0016) | | | | | |
| 2. Alopecia | | | | | |
| Korhonen 2007 | 194/1453 | 54/684 | | | |
|                | 100.0 % | | | | |
| **Subtotal (95% CI)** | 1453 | 684 | | | |
| Total events: 194 (Mefloquine), 54 (Chloroquine) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 3.58 (P = 0.00034) | | | | | |
| 3. Asthenia | | | | | |
| Corominas 1997 | 5/609 | 1/137 | | | |
|                | 5.0 % | | | | |
| Korhonen 2007 (1) | 69/1453 | 22/684 | | | |
| Laverone 2006 (2) | 10/444 | 0/81 | | | |
|                | 92.4 % | | | | |
| **Subtotal (95% CI)** | 2506 | 902 | | | |
| Total events: 84 (Mefloquine), 23 (Chloroquine) | | | | | |
| Heterogeneity: Chi^2 = 0.51, df = 2 (P = 0.77); I^2 = 0.0% | | | | | |
| Test for overall effect: Z = 1.81 (P = 0.070) | | | | | |
| 4. Balance disorder | | | | | |
| Korhonen 2007 (3) | 122/1453 | 16/684 | | | |
|                | 100.0 % | | | | |
| **Subtotal (95% CI)** | 1453 | 684 | | | |
| Total events: 122 (Mefloquine), 16 (Chloroquine) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 4.88 (P < 0.00001) | | | | | |
| 5. Confusion | | | | | |
| Laverone 2006 (4) | 5/444 | 0/81 | | | |
|                | 100.0 % | | | | |
| **Subtotal (95% CI)** | 444 | 81 | | | |
| Total events: 5 (Mefloquine), 0 (Chloroquine) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.48 (P = 0.63) | | | | | |

(Continued...)

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

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| Study or subgroup | Mefloquine | Chloroquine | Risk Ratio | Weight |
|------------------|------------|-------------|------------|--------|
|                  | n/N        | n/N         | M-H,Fixed 95% CI |        |
| 6 Decreased appetite | 72/809     | 93/1223     | 100.0 % | 1.17 [ 0.87, 1.57 ] |
| **Subtotal (95% CI)** | **809** | **1223** | 100.0 % | 1.17 [ 0.87, 1.57 ] |
| Total events: 72 (Mefloquine), 93 (Chloroquine) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 1.05 (P = 0.30) | | | | |
| 7 Fatigue | | | | |
| Laverone 2006 (6) | 26/444 | 2/81 | 100.0 % | 2.37 [ 0.57, 9.80 ] |
| **Subtotal (95% CI)** | **444** | **81** | 100.0 % | 2.37 [ 0.57, 9.80 ] |
| Total events: 26 (Mefloquine), 2 (Chloroquine) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 1.19 (P = 0.23) | | | | |
| 8 Hypoaesthesia | | | | |
| Korhonen 2007 (7) | 21/1453 | 0/684 | 100.0 % | 20.26 [ 1.23, 333.93 ] |
| **Subtotal (95% CI)** | **1453** | **684** | 100.0 % | 20.26 [ 1.23, 333.93 ] |
| Total events: 21 (Mefloquine), 0 (Chloroquine) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 2.10 (P = 0.035) | | | | |
| 9 Irritability | | | | |
| Corominas 1997 (8) | 10/609 | 0/137 | 100.0 % | 4.75 [ 0.28, 80.59 ] |
| **Subtotal (95% CI)** | **609** | **137** | 100.0 % | 4.75 [ 0.28, 80.59 ] |
| Total events: 10 (Mefloquine), 0 (Chloroquine) | | | | |
| Heterogeneity: not applicable | | | | |
| Test for overall effect: Z = 1.08 (P = 0.28) | | | | |
| 10 Mouth ulcers | | | | |
| Petersen 2000 | 25/809 | 33/1223 | 34.2 % | 1.15 [ 0.69, 1.91 ] |
| Steffen 1993 | 601/50053 | 27/3354 | 65.8 % | 1.49 [ 1.02, 2.19 ] |
| **Subtotal (95% CI)** | **50862** | **4577** | 100.0 % | 1.37 [ 1.01, 1.87 ] |
| Total events: 626 (Mefloquine), 60 (Chloroquine) | | | | |
| Heterogeneity: Chi$^2$ = 0.66, df = 1 (P = 0.42); I$^2$ = 0.0% | | | | |
| Test for overall effect: Z = 2.02 (P = 0.044) | | | | |
| 11 Paresthesia | | | | |
| Corominas 1997 | 1/609 | 0/137 | 5.1 % | 0.68 [ 0.03, 16.57 ] |
| Petersen 2000 (9) | 29/809 | 19/1223 | 94.9 % | 2.31 [ 1.30, 4.09 ] |
| **Subtotal (95% CI)** | **1418** | **1360** | 100.0 % | 2.22 [ 1.27, 3.89 ] |
| Total events: 30 (Mefloquine), 19 (Chloroquine) | | | | |
| Heterogeneity: Chi$^2$ = 0.55, df = 1 (P = 0.46); I$^2$ = 0.0% | | | | |
| Test for overall effect: Z = 2.80 (P = 0.0051) | | | | |
| 12 Palpitations | | | | |
| Corominas 1997 | 5/609 | 0/137 | 34.9 % | 2.49 [ 0.14, 44.74 ] |
| 0.005 0.1 1 10 200 |
| Favours mefloquine | Favours chloroquine |
| (Continued . . .) |
| Study or subgroup | Mefloquine | Chloroquine | Risk Ratio Weight | Risk Ratio |
|------------------|------------|-------------|------------------|------------|
|                  | n/N        | n/N         | M-H Fixed, 95% CI| M-H Fixed, 95% CI |
| Korhonen 2007    | 6/1453     | 0/684       |                 | 29.1% 6.12 [0.35, 108.56] |
| Laverone 2006    | 15/444     | 0/81        |                 | 36.1% 5.71 [0.35, 94.53] |
| **Subtotal (95% CI)** | **2506** | **902** | **100.0% 4.71 [0.91, 24.26]** |
|                  |            |             |                 |            |
| Total events: 26 (Mefloquine), 0 (Chloroquine) |            |             |                 |            |
| Heterogeneity: Chi² = 0.24, df = 2 (P = 0.89); I² = 0.0% |            |             |                 |            |
| Test for overall effect: Z = 1.85 (P = 0.064) |            |             |                 |            |
| 13 Photosensitization |            |             |                 |            |
| Korhonen 2007    | 34/1453    | 19/684      |                 | 96.8% 0.84 [0.48, 1.47] |
| Laverone 2006    | 6/444      | 0/81        |                 | 3.2% 2.40 [0.14, 42.11] |
| **Subtotal (95% CI)** | **1897** | **765** | **100.0% 0.89 [0.52, 1.53]** |
| Total events: 40 (Mefloquine), 19 (Chloroquine) |            |             |                 |            |
| Heterogeneity: Chi² = 0.50, df = 1 (P = 0.48); I² = 0.0% |            |             |                 |            |
| Test for overall effect: Z = 0.41 (P = 0.68) |            |             |                 |            |
| 14 Restlessness |            |             |                 |            |
| Laverone 2006    | 26/444     | 1/81        |                 | 100.0% 4.74 [0.65, 34.46] |
| **Subtotal (95% CI)** | **444** | **81** | **100.0% 4.74 [0.65, 34.46]** |
| Total events: 26 (Mefloquine), 1 (Chloroquine) |            |             |                 |            |
| Heterogeneity: not applicable |            |             |                 |            |
| Test for overall effect: Z = 1.54 (P = 0.12) |            |             |                 |            |
| 15 Slight illness |            |             |                 |            |
| Laverone 2006    | 29/444     | 2/81        |                 | 100.0% 2.65 [0.64, 10.87] |
| **Subtotal (95% CI)** | **444** | **81** | **100.0% 2.65 [0.64, 10.87]** |
| Total events: 29 (Mefloquine), 2 (Chloroquine) |            |             |                 |            |
| Heterogeneity: not applicable |            |             |                 |            |
| Test for overall effect: Z = 1.35 (P = 0.18) |            |             |                 |            |
| 16 Somnolence    |            |             |                 |            |
| Laverone 2006 (10) | 16/444    | 0/81        |                 | 100.0% 6.08 [0.37, 100.36] |
| **Subtotal (95% CI)** | **444** | **81** | **100.0% 6.08 [0.37, 100.36]** |
| Total events: 16 (Mefloquine), 0 (Chloroquine) |            |             |                 |            |
| Heterogeneity: not applicable |            |             |                 |            |
| Test for overall effect: Z = 1.26 (P = 0.21) |            |             |                 |            |
| 17 Yeast infection |            |             |                 |            |
| Korhonen 2007    | 22/1453    | 9/684       |                 | 100.0% 1.15 [0.53, 2.49] |
| **Subtotal (95% CI)** | **1453** | **684** | **100.0% 1.15 [0.53, 2.49]** |
| Total events: 22 (Mefloquine), 9 (Chloroquine) |            |             |                 |            |
| Heterogeneity: not applicable |            |             |                 |            |
| Test for overall effect: Z = 0.36 (P = 0.72) |            |             |                 |            |
(1) Korhonen 2007. Reported in the original paper as ‘weakness’
(2) Laverone 2006. Reported in the original paper as ‘weakness’
(3) Korhonen 2007. Reported in the original paper as ‘unsteadiness’
(4) Laverone 2006. Reported in the original paper as ‘mental confusion’
(5) Petersen 2000. Reported in the original paper as ‘loss of appetite’
(6) Laverone 2006. Reported in the original paper as ‘tiredness’
(7) Korhonen 2007. Reported in the original paper as ‘limb numbness’
(8) Coreminas 1997. Reported in the original paper as ‘irritability’
(9) Petersen 2000. Reported in the original paper as ‘tingling’
(10) Laverone 2006. Reported in the original paper as ‘drowsiness’

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

Review: Mefloquine for preventing malaria during travel to endemic areas
Comparison: 4 Mefloquine versus chloroquine
Outcome: 20 Other adverse events (RCTs)

| Study or subgroup | Mefloquine | Chloroquine | Risk Ratio | Weight |
|-------------------|------------|-------------|------------|--------|
|                   | n/N        | n/N         | M-H,Fixed,95% CI |          |
| Abdominal distension | 2/46 | 1/78 | 35.7 % | 3.39 [ 0.32, 36.37 ] |
| Boudreau 1993 (1) | 6/157 | 1/78 | 64.3 % | 2.98 [ 0.37, 24.33 ] |
| Subtotal (95% CI) | 203 | 156 | 100.0 % | 3.13 [ 0.64, 15.27 ] |
| Anger | 2/157 | 3/78 | 68.2 % | 0.33 [ 0.06, 1.94 ] |
| Boudreau 1993 | 0/46 | 2/78 | 31.8 % | 0.34 [ 0.02, 6.85 ] |
| Subtotal (95% CI) | 203 | 156 | 100.0 % | 0.33 [ 0.07, 1.55 ] |

Test for overall effect: Z = 1.41 (P = 0.16)
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0.0%

(Continued ... )
| Study or subgroup | Mefloquine n/N | Chloroquine n/N | Risk Ratio | Weight n/N | Risk Ratio |
|------------------|---------------|----------------|------------|------------|------------|
| **3 Disturbance in attention** | 1/46 | 1/78 | 35.7 % | 1.70 [ 0.11, 26.46 ] |  
| Boudreau 1993 (2) | 1/46 | 1/78 | 35.7 % | 1.70 [ 0.11, 26.46 ] |  
| Boudreau 1993 (3) | 8/157 | 1/78 | 64.3 % | 3.97 [ 0.51, 31.22 ] |  
| **Subtotal (95% CI)** | 203 | 156 | 100.0 % | 3.16 [ 0.61, 16.47 ] |  
| **Total events:** | 9 (Mefloquine), 2 (Chloroquine) | Heterogeneity: Ch^2 = 0.24, df = 1 (P = 0.62); P =0.0% | Test for overall effect: Z = 1.37 (P = 0.17) |  
| **4 Irritability** | 4/46 | 4/78 | 35.7 % | 1.70 [ 0.45, 6.46 ] |  
| Boudreau 1993 | 4/46 | 4/78 | 35.7 % | 1.70 [ 0.45, 6.46 ] |  
| Boudreau 1993 | 6/157 | 4/78 | 64.3 % | 0.75 [ 0.22, 2.56 ] |  
| **Subtotal (95% CI)** | 203 | 156 | 100.0 % | 1.08 [ 0.45, 2.64 ] |  
| **Total events:** | 10 (Mefloquine), 8 (Chloroquine) | Heterogeneity: Ch^2 = 0.78, df = 1 (P = 0.38); P =0.0% | Test for overall effect: Z = 0.18 (P = 0.86) |  
| **5 Loss of appetite** | 5/157 | 3/78 | 73.0 % | 0.83 [ 0.20, 3.38 ] |  
| Boudreau 1993 | 5/157 | 3/78 | 73.0 % | 0.83 [ 0.20, 3.38 ] |  
| Boudreau 1993 (4) | 2/46 | 2/78 | 27.0 % | 1.70 [ 0.25, 11.63 ] |  
| **Subtotal (95% CI)** | 203 | 156 | 100.0 % | 1.06 [ 0.35, 3.25 ] |  
| **Total events:** | 7 (Mefloquine), 5 (Chloroquine) | Heterogeneity: Ch^2 = 0.35, df = 1 (P = 0.56); P =0.0% | Test for overall effect: Z = 0.11 (P = 0.92) |  
| **6 Malaise** | 3/103 | 1/100 | 100.0 % | 0.32 [ 0.01, 7.85 ] |  
| Sossouhounto 1995 | 0/103 | 1/100 | 100.0 % | 0.32 [ 0.01, 7.85 ] |  
| **Subtotal (95% CI)** | 103 | 100 | 100.0 % | 0.32 [ 0.01, 7.85 ] |  
| **Total events:** | 0 (Mefloquine), 1 (Chloroquine) | Heterogeneity: not applicable | Test for overall effect: Z = 0.69 (P = 0.49) |  
| **7 Mood altered** | 2/46 | 1/78 | 21.7 % | 3.39 [ 0.32, 36.37 ] |  
| Boudreau 1993 (5) | 2/46 | 1/78 | 21.7 % | 3.39 [ 0.32, 36.37 ] |  
| Boudreau 1993 | 2/157 | 2/78 | 78.3 % | 0.50 [ 0.07, 3.46 ] |  
| **Subtotal (95% CI)** | 203 | 156 | 100.0 % | 1.13 [ 0.29, 4.34 ] |  
| **Total events:** | 4 (Mefloquine), 3 (Chloroquine) | Heterogeneity: Ch^2 = 1.51, df = 1 (P = 0.22); P =34% | Test for overall effect: Z = 0.17 (P = 0.86) |  

(1) Boudreau 1993. Mefloquine loading dose group (250mg daily for 3 days)
(2) Boudreau 1993. 'Concentration difficulties' Mefloquine loading dose group (250mg daily for 3 days)
(3) Boudreau 1993. 'concentration difficulties'
(4) Boudreau 1993. Reported in the original paper as 'anorexia'
(5) Boudreau 1993. Reported in the original paper as 'moodiness'
Analysis 4.21. Comparison 4 Mefloquine versus chloroquine, Outcome 21 Pregnancy related outcomes (RCTs).

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: 4 Mefloquine versus chloroquine

Outcome: 21 Pregnancy related outcomes (RCTs)

| Study or subgroup | Mefloquine n/N | Chloroquine n/N | Risk Ratio M-H(Fixed,95% CI) | Weight % | Risk Ratio M-H(Fixed,95% CI) |
|------------------|----------------|----------------|-----------------------------|----------|-----------------------------|
| 1 Spontaneous abortions | 42.8 % 1.01 [0.32, 3.17] | | | | |
| Steketee 1996 5/466 7/661 | | | | | |
| Steketee 1996 (1) 4/466 10/741 | | | | | |
| Subtotal (95% CI) 932 1402 | 100.0 % 0.80 [0.36, 1.79] | | | | |
| Total events: 9 (Mefloquine), 17 (Chloroquine) | | | | | |
| Heterogeneity: Chi² = 0.32, df = 1 (P = 0.57); I² =0.0% | | | | | |
| Test for overall effect: Z = 0.55 (P = 0.58) | | | | | |
| 2 Still births | | | | | |
| Steketee 1996 19/466 29/661 | 54.4 % 0.93 [0.53, 1.64] | | | | |
| Steketee 1996 (2) 18/466 26/741 | 45.6 % 1.10 [0.61, 1.99] | | | | |
| Subtotal (95% CI) 932 1402 | 100.0 % 1.01 [0.67, 1.52] | | | | |
| Total events: 37 (Mefloquine), 55 (Chloroquine) | | | | | |
| Heterogeneity: Chi² = 0.16, df = 1 (P = 0.68); I² =0.0% | | | | | |
| Test for overall effect: Z = 0.04 (P = 0.97) | | | | | |
| 3 Congenital malformations | | | | | |
| Steketee 1996 0/932 0/1402 | | | | | |
| Subtotal (95% CI) 932 1402 | Not estimable | | | | |
| Total events: 0 (Mefloquine), 0 (Chloroquine) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |
| Test for subgroup differences: Chi² = 0.26, df = 1 (P = 0.61), I² =0.0% | | | | | |

(1) Steketee 1996. Chloroquine loading dose group (25mg of base/kg given as a divided dose over 2 days)

(2) Steketee 1996. Chloroquine loading dose group (25mg of base/kg given as a divided dose over 2 days)
### Analysis 4.22. Comparison 4 Mefloquine versus chloroquine, Outcome 22 Adherence (cohort studies).

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 4 Mefloquine versus chloroquine

**Outcome:** 22 Adherence (cohort studies)

| Study or subgroup | Mefloquine | Chloroquine | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|-------------|------------|--------|------------|
|                   | n/N        | n/N         |            |        |            |
| 1 Short-term travellers |
| Hill 2000 (1)     | 90/103     | 314/382     | 1.06 [0.97, 1.16] | 44.6 % |
| Laver 2001 (2)    | 163/184    | 34/40       | 1.04 [0.91, 1.20] | 31.7 % |
| Rietz 2002 (3)    | 65/92      | 42/51       | 0.86 [0.71, 1.03] | 23.7 % |
| **Subtotal (95% CI)** | **379**    | **473**     | 1.00 [0.90, 1.13] |        |
| Total events: 318 (Mefloquine), 390 (Chloroquine) |
| Heterogeneity: Tau² = 0.01; Ch² = 4.51, df = 2 (P = 0.10); I² = 56% |
| Test for overall effect: Z = 0.07 (P = 0.95) |
| 2 Short-term travellers: after return |
| Stoney 2016 (4)   | 6/11       | 19/35       | 1.00 [0.54, 1.87] | 100.0 % |
| **Subtotal (95% CI)** | **11**     | **35**      | 1.00 [0.54, 1.87] |        |
| Total events: 6 (Mefloquine), 19 (Chloroquine) |
| Heterogeneity: not applicable |
| Test for overall effect: Z = 0.02 (P = 0.99) |
| 3 Longer-term occupational travellers |
| Korhonen 2007 (5) | 946/1453   | 233/684     | 1.91 [1.71, 2.14] | 54.4 % |
| Tan 2017 (6)      | 1691/2972  | 177/668     | 2.15 [1.89, 2.45] | 45.6 % |
| **Subtotal (95% CI)** | **4425**   | **1352**    | 2.02 [1.80, 2.26] |        |
| Total events: 2637 (Mefloquine), 410 (Chloroquine) |
| Heterogeneity: Tau² = 0.00; Ch² = 1.82, df = 1 (P = 0.18); I² = 45% |
| Test for overall effect: Z = 1.96 (P < 0.0001) |
| Test for subgroup differences: Ch² = 72.01, df = 2 (P = 0.000), I² = 97% |

(1) Hill 2000. Defined as filled prescription, taken the prescribed number of doses before, during and following their trip

(2) Laver 2001. Defined as 'full compliance, i.e. regular medication with no missed doses'

(3) Rietz 2002. Defined as 'took them as prescribed during the whole journey and even after their return'

(4) Stoney 2016. Defined as 'number adherent in the post-prophylaxis period'

(5) Korhonen 2007. Defined as 'reported never missing the drug during their time in service.'

(6) Tan 2017. 'Taken as prescribed'
## Analysis 5.1. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 1 Nausea; effects.

Review: Mefloquine for preventing malaria during travel to endemic areas

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

Outcome: 1 Nausea; effects

| Study or subgroup | Mefloquine | Control | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|-------------------|------------|---------|----------------------------|--------|----------------------------|
| 1 RCTs            |            |         |                            |        |                            |
| Overbosch 2001 (1)| 40/483     | 15/493  | 100.0 % 2.72 [ 1.52, 4.86 ]|        |                            |
| Subtotal (95% CI)| 483        | 493     | 100.0 % 2.72 [ 1.52, 4.86 ]|        |                            |

Total events: 40 (Mefloquine), 15 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 3.38 (P = 0.00071)

2 Cohort studies

| Study or subgroup | Mefloquine | Control | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|-------------------|------------|---------|----------------------------|--------|----------------------------|
| Andersson 2008 (2)| 30/491     | 4/161   | 10.5 % 2.46 [ 0.88, 6.87 ]  |        |                            |
| Corominas 1997 (3)| 15/609     | 0/137   | 4.9 % 7.01 [ 0.42, 116.50 ] |        |                            |
| Cunningham 2014 (4)| 2/49       | 8/247   | 8.7 % 1.26 [ 0.28, 5.76 ]   |        |                            |
| Kata 2013 (5)     | 5/38       | 5/277   | 9.9 % 7.29 [ 2.21, 24.02 ]  |        |                            |
| Karhonen 2007 (6) | 165/1453   | 104/324 | 12.7 % 0.35 [ 0.29, 0.44 ]  |        |                            |
| Kuhner 2005 (7)   | 19/142     | 5/82    | 10.8 % 2.19 [ 0.85, 5.66 ]  |        |                            |
| Laverone 2006 (8) | 65/444     | 2/43    | 9.2 % 3.15 [ 0.80, 12.41 ]  |        |                            |
| Philips 1996 (9)  | 43/285     | 36/383  | 12.4 % 1.61 [ 1.06, 2.43 ]  |        |                            |
| Shamiss 1996 (10)| 2/13       | 0/28    | 4.5 % 10.36 [ 0.53, 20.60 ] |        |                            |
| Sonmez 2005 (11) | 7/228      | 41/506  | 11.4 % 0.38 [ 0.17, 0.83 ]  |        |                            |
| Tuck 2016        | 1/13       | 1/20    | 5.1 % 1.54 [ 0.11, 22.49 ]  |        |                            |

Subtotal (95% CI) 3765 2208 100.0 % 1.72 [ 0.78, 3.77 ]

Total events: 354 (Mefloquine), 206 (Control)

Heterogeneity: Tau² = 1.26; Ch² = 96.35, df = 10 (P<0.00001); I² =90%

Test for overall effect: Z = 1.35 (P = 0.18)

Test for subgroup differences: Ch² = 0.85, df = 1 (P = 0.36), I² =0.0%
Analysis 5.2. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 2 Abdominal pain; effects.

Review: Mefloquine for preventing malaria during travel to endemic areas

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

Outcome: 2 Abdominal pain; effects

| Study or subgroup | Mefloquine | Control | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|---------|------------|--------|------------|
|                   | n/N        | n/N     | RR         |        |            |
|                   | n/N        | n/N     | M-H Random | 95% CI |            |
| 1 RCTs            |            |         |            |        |            |
| Overbosch 2001 (1)| 23/483     | 26/493  | 100.0 %    | 0.90 [0.52, 1.56] |
| Subtotal (95% CI) | 483        | 493     | 100.0 %    | 0.90 [0.52, 1.56] |
|                  |            |         |            |        |            |
| 2 Cohort studies |            |         |            |        |            |
| Anderson 2008 (2)| 18/491     | 13/161  | 22.3 %     | 0.45 [0.23, 0.91] |
| Cunningham 2014 (3)| 0/49 | 4/182 | 3.6 %     | 0.41 [0.02, 7.43] |
| Kato 2013 (4)    | 1/38       | 11/277  | 6.7 %     | 0.66 [0.09, 4.99] |
| Karhonen 2007 (5)| 54/1453    | 45/324  | 28.5 %    | 0.27 [0.18, 0.39] |
| Study or subgroup | Mefloquine | Control | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|------------------|------------|---------|-------------------------------|--------|-------------------------------|
| Kuhner 2005 (6)  | 9/142      | 4/82    | 14.5 % 1.30 [0.41, 4.09]      | 14.5 % | 1.30 [0.41, 4.09]             |
| Laverone 2006 (7)| 9/444      | 1/43    | 6.6 % 0.87 [0.11, 6.72]       | 6.6 %  | 0.87 [0.11, 6.72]            |
| Shamiss 1996 (8) | 3/13       | 7/28    | 14.0 % 0.92 [0.28, 3.01]      | 14.0 % | 0.92 [0.28, 3.01]            |
| Sonmez 2005 (9)  | 0/228      | 30/506  | 3.9 % 0.04 [0.00, 0.59]       | 3.9 %  | 0.04 [0.00, 0.59]            |
| Tuck 2016        | 0/13       | 0/20    | Not estimable                 |        |                               |
| **Subtotal (95% CI)** | **2871** | **1623** | 100.0 % 0.49 [0.27, 0.87]     | 100.0 %| 0.49 [0.27, 0.87]            |

Total events: 94 (Mefloquine), 115 (Control)
Heterogeneity: Tau² = 0.28; Chi² = 13.88, df = 7 (P = 0.05); I² = 50%
Test for overall effect: Z = 2.42 (P = 0.016)
Test for subgroup differences: Chi² = 2.31, df = 1 (P = 0.13), I² = 57%

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(1) Overbosch 2001. Mefloquine versus atovaquone-proguanil recipients
(2) Andersson 2008. Mefloquine versus atovaquone-proguanil recipients
(3) Cunningham 2014. Mefloquine versus atovaquone-proguanil and doxycycline recipients
(4) Kato 2013. Mefloquine versus atovaquone-proguanil recipients
(5) Korhonen 2007. Mefloquine versus atovaquone-proguanil and doxycycline recipients
(6) Kuhner 2005. Mefloquine versus atovaquone-proguanil recipients
(7) Laverone 2006. Mefloquine versus atovaquone-proguanil recipients
(8) Shamiss 1996. Mefloquine versus doxycycline recipients
(9) Sonmez 2005. Mefloquine versus doxycycline recipients
### Analysis 5.3. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 3 Diarrhoea; effects.

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 5 Mefloquine versus currently used regimens; by study design

**Outcome:** 3 Diarrhoea; effects

| Study or subgroup | Mefloquine | Control | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|------------------|------------|---------|-------------------------------|--------|-------------------------------|
| 1 RCTs           |            |         |                               |        |                               |
| Overbosch 2001 (1) | 34/483    | 37/493  | 100.0 % 0.94 [0.60, 1.47]     |        |                               |
| **Subtotal (95% CI)** | **483** | **493** | **100.0 % 0.94 [0.60, 1.47]** |        |                               |
| Total events: 34 (Mefloquine), 37 (Control) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 0.28 (P = 0.78) | | | | | |
| 2 Cohort studies |            |         |                               |        |                               |
| Andersson 2008 (2) | 23/491     | 6/161   | 11.7 % 1.26 [0.52, 3.03]      |        |                               |
| Cunningham 2014 (3) | 0/49       | 5/247   | 4.8 % 0.45 [0.03, 8.03]       |        |                               |
| Kato 2013 (4) | 1/38       | 14/277  | 7.2 % 0.52 [0.07, 3.85]       |        |                               |
| Karhonan 2007 (5) | 45/1453    | 13/324  | 12.7 % 0.77 [0.42, 1.41]      |        |                               |
| Kuhner 2005 (6) | 16/142     | 10/82   | 12.2 % 0.92 [0.44, 1.94]      |        |                               |
| Laverone 2006 (7) | 21/444     | 3/43    | 10.5 % 0.68 [0.21, 2.18]      |        |                               |
| Philips 1996 (8) | 24/285     | 9/383   | 12.2 % 3.58 [1.69, 7.59]      |        |                               |
| Saunders 2015 (9) | 22/564     | 31/1898 | 13.2 % 0.24 [0.16, 0.36]      |        |                               |
| Sonmez 2005 (10) | 4/228      | 108/506 | 11.3 % 0.08 [0.03, 0.22]      |        |                               |
| Tuck 2016 | 0/13       | 1/20    | 4.3 % 0.50 [0.02, 11.42]      |        |                               |
| **Subtotal (95% CI)** | **3707** | **3941** | **100.0 % 0.61 [0.28, 1.34]** |        |                               |
| Total events: 156 (Mefloquine), 480 (Control) | | | | | |
| Heterogeneity: Tau² = 1.16, Chi² = 63.94, df = 9 (P<0.0000); I² =86% | | | | | |
| Test for overall effect: Z = 1.22 (P = 0.22) | | | | | |
| Test for subgroup differences: Chi² = 0.84, df = 1 (P = 0.36), I² =0.0% | | | | | |

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

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

Review: Mefloquine for preventing malaria during travel to endemic areas

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

Outcome: 4 Headache; effects

| Study or subgroup | Mefloquine | Control | Risk Ratio M-H | Weight | Risk Ratio M-H |
|------------------|------------|---------|---------------|--------|---------------|
|                  | n/N        | n/N     |               |        |               |
| 1 RCTs           |            |         |               |        |               |
| Overbosch 2001 (1) | 32/483   | 19/493  | 1.72 [0.99, 2.99] | 100.0 % |               |
| Subtotal (95% CI) | 483       | 493     | 1.72 [0.99, 2.99] | 100.0 % |               |
| Total events: 32 (Mefloquine), 19 (Control) |
| Heterogeneity: not applicable |
| Test for overall effect: Z = 1.92 (P = 0.055) |

2 Cohort studies

|                  | n/N        | n/N     |               |        |               |
| Andersen 2008 (2) | 21/491   | 2/161   | 11.0 %        | 3.44 [0.82, 14.52] |               |
| Cunningham 2014 (3) | 0/49     | 6/247   | 3.7 %         | 0.38 [0.02, 6.66] |               |
| Kato 2013 (4)     | 4/38     | 4/227   | 12.0 %        | 7.29 [1.90, 27.94] |               |
| Korhonen 2007 (5) | 100/1453 | 15/324  | 25.8 %        | 1.49 [0.88, 2.52] |               |
| Kuhner 2005 (6)   | 8/142    | 2/82    | 10.1 %        | 2.31 [0.50, 10.62] |               |

(Continued...)

Mefloquine for preventing malaria during travel to endemic areas (Review)
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| Study or subgroup | Mefloquine n/N | Control n/N | Risk Ratio M-H, Random, 95% CI | Weight |
|------------------|---------------|-------------|-----------------------------|-------|
| Landman 2015 (7) | 23/380        | 7/401       | 19.6 % 3.47 [1.51, 7.99]     |       |
| Laverone 2006 (8)| 18/444        | 0/43        | 3.9 % 3.66 [0.22, 59.68]     |       |
| Sonmez 2005 (9) | 2/228         | 11/506      | 10.4 % 0.40 [0.09, 1.81]     |       |
| Stoney 2016 (10)| 0/11          | 2/315       | 3.4 % 5.27 [0.27, 103.81]    |       |
| **Subtotal (95% CI)** | **3236**       | **2356**   | **100.0 % 2.19 [1.22, 3.93]** |       |

Total events: 176 (Mefloquine), 49 (Control)

Heterogeneity: Tau^2 = 0.27; Chi^2 = 13.36, df = 8 (P = 0.10); I^2 = 40%

Test for overall effect: Z = 2.62 (P = 0.0087)

Test for subgroup differences: Chi^2 = 0.34, df = 1 (P = 0.56), I^2 = 0.0%

(1) Overbosch 2001. Mefloquine versus atovaquone-proguanil recipients
(2) Andersson 2008. Mefloquine versus atovaquone-proguanil recipients
(3) Cunningham 2014. Mefloquine versus atovaquone-proguanil and doxycycline recipients
(4) Kato 2013. Mefloquine versus atovaquone-proguanil recipients
(5) Karhonen 2007. Mefloquine versus atovaquone-proguanil and doxycycline recipients
(6) Kühner 2005. Mefloquine versus atovaquone-proguanil recipients
(7) Landman 2015. Mefloquine versus atovaquone-proguanil and doxycycline recipients
(8) Laverone 2006. Mefloquine versus atovaquone-proguanil and chloroquine recipients
(9) Sonmez 2005. Mefloquine versus doxycycline recipients
(10) Stoney 2016. Mefloquine versus atovaquone-proguanil, chloroquine and doxycycline recipients
### Analysis 5.5. Comparison of Mefloquine versus currently used regimens; by study design, Outcome 5. Dizziness; effects.

Review: Mefloquine for preventing malaria during travel to endemic areas

Comparison: Mefloquine versus currently used regimens; by study design

Outcome: Dizziness; effects

| Study or subgroup | Mefloquine | Control | Risk Ratio M-H Random 95% CI | Weight | Risk Ratio M-H Random 95% CI |
|-------------------|------------|---------|-------------------------------|--------|-------------------------------|
| **1 RCTs**        |            |         |                               |        |                               |
| Overbosch 2001 (1)| 43/483     | 11/493  | 3.99 [2.08, 7.64]             | 100.0% |                               |
| **Subtotal (95% CI)** | 483       | 493     |                               | 100.0% | 3.99 [2.08, 7.64]             |
| Total events: 43 (Mefloquine), 11 (Control) |
| Heterogeneity: not applicable |
| Test for overall effect: Z = 4.17 (P = 0.000030) |
| **2 Cohort studies** |            |         |                               |        |                               |
| Andersson 2008 (2)| 52/491     | 6/161   | 17.3% 2.84 [1.24, 6.49]       |        |                               |
| Cunningham 2014 (3)| 1/49      | 2/247   | 6.2% 2.52 [0.23, 27.25]       |        |                               |
| Kata 2013 (4)     | 3/38       | 8/277   | 12.8% 2.73 [0.76, 9.86]       |        |                               |
| Karhonen 2007 (5) | 189/1453   | 23/234  | 21.1% 1.83 [1.21, 2.78]       |        |                               |
| Kuhner 2005 (6)   | 17/142     | 1/82    | 7.9% 9.82 [1.33, 72.42]       |        |                               |
| Landman 2015 (7)  | 52/380     | 3/401   | 14.0% 18.29 [5.76, 58.07]     |        |                               |
| Laverene 2006 (8) | 25/444     | 2/43    | 11.8% 1.21 [0.30, 4.94]       |        |                               |
| Shamiss 1996 (9)  | 2/13       | 0/28    | 4.4% 10.36 [0.53, 201.60]     |        |                               |
| Tuck 2016         | 0/13       | 2/20    | 4.4% 0.30 [0.02, 5.79]        |        |                               |
| **Subtotal (95% CI)** | 3023       | 1583    |                               | 100.0% | 3.17 [1.58, 6.35]             |
| Total events: 341 (Mefloquine), 47 (Control) |
| Heterogeneity: τ² = 0.55; χ² = 20.61, df = 8 (P = 0.01); I² = 61% |
| Test for overall effect: Z = 3.26 (P = 0.0011) |
| Test for subgroup differences: χ² = 0.22, df = 1 (P = 0.64), I² = 0.0% |
Analysis 5.6. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 6 Abnormal dreams; effects.

Review: Mefloquine for preventing malaria during travel to endemic areas

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

Outcome: 6 Abnormal dreams; effects

| Study or subgroup | Mefloquine | Control | Risk Ratio M-H, Random, 95% CI | Weight % | Risk Ratio M-H, Random, 95% CI |
|-------------------|------------|---------|-------------------------------|---------|-------------------------------|
| Overbosch 2001 (1)| 66/483     | 33/493  | 2.04 [1.37, 3.04]              | 100.0   | 2.04 [1.37, 3.04]              |
| Total events: 66 (Mefloquine), 33 (Control) |
| Heterogeneity: not applicable |
| Test for overall effect: Z = 3.51 (P = 0.00045) |
| 2 Cohort studies |
| Andersson 2008 (2) | 168/491 | 5/161 | 18.4 % | 11.02 [4.61, 26.34] |
| Cunningham 2014 (3) | 5/49 | 30/247 | 18.2 % | 0.84 [0.34, 2.06] |
| Korhonen 2007 (4) | 775/1453 | 12/324 | 19.8 % | 14.40 [8.25, 25.14] |
| Kuhner 2005 (5) | 8/142 | 0/82 | 8.4 % | 9.87 [0.58, 168.77] |
| Landman 2015 (6) | 173/380 | 8/401 | 19.2 % | 22.82 [11.39, 45.71] |
| Laverone 2006 (7) | 15/444 | 0/43 | 8.6 % | 3.07 [0.19, 50.36] |

0.005 0.1 1 10 200
Favours mefloquine Favours other regime

(Continued...)
| Study or subgroup | Mefloquine | Control | Risk Ratio | Weight | Risk Ratio |
|------------------|------------|---------|------------|--------|------------|
|                  | n/N        | n/N     | M-H, Random, 95% CI |        | M-H, Random, 95% CI |
| Stoney 2016 (8)  | 0/11       | 1/315   | 7.4 % 8.78 [0.38, 204.48] |        |            |
| **Subtotal (95% CI)** | **2970** | **1573** | **100.0 % 7.30 [2.51, 21.18]** |        |            |
|                  |            |         |            |        |            |
|                  |            |         | Test for overall effect: Z = 3.66 (P = 0.00026) |        |            |
|                  |            |         | Test for subgroup differences: Chi² = 4.82, df = 1 (P = 0.03), I² = 79% |        |            |
|                  |            |         | Heterogeneity: Tau² = 1.41; Chi² = 38.64, df = 6 (P<0.00001); I² = 84% |        |            |

(1) Overbosch 2001. Mefloquine versus atovaquone-proguanil recipients
(2) Andersson 2008. Mefloquine versus atovaquone-proguanil recipients
(3) Cunningham 2014. Mefloquine versus atovaquone-proguanil and doxycycline participants
(4) Korhonen 2007. Mefloquine versus atovaquone-proguanil and doxycycline recipients
(5) Kühner 2005. Mefloquine versus atovaquone-proguanil recipients
(6) Landman 2015. Mefloquine versus atovaquone-proguanil and doxycycline recipients
(7) Laverone 2006. Mefloquine versus atovaquone-proguanil and chloroquine recipients
(8) Stoney 2016. Mefloquine versus atovaquone-proguanil, chloroquine and doxycycline recipients
### Analysis 5.7. Comparison of Mefloquine versus currently used regimens; by study design, Outcome 7: Insomnia; effects.

Review: Mefloquine for preventing malaria during travel to endemic areas.

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

Outcome: 7 Insomnia; 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 |
|-------------------|----------------|-------------|-------------------------------|--------|-------------------------------|
| 1 RCTs            |                |             |                               |        |                               |
| Overbosch 2001 (1) | 65/483         | 15/493      |                               |        |                               |
| Subtotal (95% CI) | 483            | 493         |                               |        |                               |
| Total events:     | 65 (Mefloquine) | 15 (Control) |                               |        |                               |

Heterogeneity: not applicable

Test for overall effect: Z = 5.33 (P < 0.00001)

2 Cohort studies

| Study or subgroup | Mefloquine n/N | Control n/N | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|-------------------|----------------|-------------|-------------------------------|--------|-------------------------------|
| Andersson 2008 (2) | 171/491        | 8/161       |                               |        |                               |
| Cunningham 2014 (3) | 0/49           | 5/247       |                               |        |                               |
| Kata 2013 (4)      | 2/38           | 1/277       |                               |        |                               |
| Karhonen 2007 (5)  | 491/1453       | 8/324       |                               |        |                               |
| Kuhner 2005 (6)    | 14/42          | 1/82        |                               |        |                               |
| Landman 2015 (7)   | 94/380         | 10/401      |                               |        |                               |
| Laverone 2006 (8)  | 35/444         | 0/43        |                               |        |                               |
| Sonmez 2005 (9)    | 0/228          | 14/506      |                               |        |                               |
| Tuck 2016          | 3/13           | 2/20        |                               |        |                               |
| Subtotal (95% CI)  | 3238           | 2061        |                               |        |                               |

Total events: 810 (Mefloquine), 15 (Control)

Heterogeneity: $\tau^2 = 0.52; \chi^2 = 19.74, df = 8 (P = 0.01); I^2 = 59\%$

Test for overall effect: Z = 4.88 (P < 0.00001)

Test for subgroup differences: $\chi^2 = 0.31, df = 1 (P = 0.57), I^2 = 0.0\%$

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Favours Mefloquine  Favours other regime

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

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

Review: Mefloquine for preventing malaria during travel to endemic areas

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

Outcome: 8 Anxiety; effects

| Study or subgroup | Mefloquine | Control | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|-------------------|------------|---------|-------------------------------|--------|-------------------------------|
|                   | n/N        | n/N     |                              |        |                               |
| 1 RCTs            |            |         |                               |        |                               |
| Overbosch 2001 (1)| 18/483     | 3/493   | 100.0 % 6.12 [ 1.82, 20.66 ] |        |                               |
| Subtotal (95% CI) | 483        | 493     | 100.0 % 6.12 [ 1.82, 20.66 ] |        |                               |
|                   |            |         |                               |        |                               |
|                   |            |         |                               |        |                               |
| 2 Cohort studies  |            |         |                               |        |                               |
| Cunningham 2014 (2)| 2/98      | 1/247   | 5.6 % 5.04 [ 0.46, 54.96 ]    |        |                               |
| Korhonen 2007 (3) | 380/1453   | 4/324   | 33.6 % 21.18 [ 7.97, 56.32 ]  |        |                               |
| Landman 2015 (4)  | 104/380    | 7/401   | 56.7 % 15.68 [ 7.39, 33.27 ]  |        |                               |
| Laverone 2006 (5) | 16/444     | 0/43    | 4.1 % 3.26 [ 0.20, 53.46 ]    |        |                               |
| Subtotal (95% CI) | 2375       | 1015    | 100.0 % 15.26 [ 8.66, 26.89 ] |        |                               |

Total events: 18 (Mefloquine), 3 (Control)
Heterogeneity: not applicable
Test for overall effect: Z = 2.92 (P = 0.0035)

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

#### Review: Mefloquine for preventing malaria during travel to endemic areas

#### Comparison: 5 Mefloquine versus currently used regimens; by study design

#### Outcome: 9 Depressed mood; effects

| Study or subgroup | Mefloquine | Control | Risk Ratio M-H, Random, 95% CI | Weight | Risk Ratio M-H, Random, 95% CI |
|-------------------|------------|---------|-----------------------------|--------|-----------------------------|
| n/N               | n/N        |         |                             |        |                             |
| 1 RCTs            |            |         |                             |        |                             |
| Overbosch 2001 (1) | 17/483 | 3/493   | 5.78 [1.71, 19.61]          | 100.0% | 5.78 [1.71, 19.61]          |
| Subtotal (95% CI) | 483       | 493     | 100.0%                      | 5.78   | 5.78 [1.71, 19.61]          |
| Total events: 17 (Mefloquine), 3 (Control) |            |         |                             |        |                             |
| Heterogeneity: not applicable |            |         |                             |        |                             |
| Test for overall effect: Z = 2.82 (P = 0.0048) |            |         |                             |        |                             |
| 2 Cohort studies |            |         |                             |        |                             |
| Andersson 2008 (2) | 82/491 | 2/161   | 13.44 [3.34, 54.05]         | 18.8%  | 13.44 [3.34, 54.05]         |
| Kato 2013 (3)     | 0/38      | 3/277   | 1.02 [0.05, 19.34]          | 5.5%   | 1.02 [0.05, 19.34]          |

(Continued . . .)
| Study or subgroup | Mefloquine | Control | Risk Ratio | Weight | Risk Ratio |
|------------------|------------|---------|------------|--------|------------|
|                  | n/N       | n/N     | M-H,Random |       | M-H,Random |
| Korhonen 2007 (4) | 208/1453  | 3/324   | 24.6 %     | 15.46  | [4.98, 48.02] |
| Kuhner 2005 (5)   | 13/142    | 2/82    | 17.5 %     | 3.75   | [0.87, 16.22] |
| Landman 2015 (6)  | 39/380    | 4/401   | 27.8 %     | 10.29  | [3.71, 28.52] |
| Laverone 2006 (7) | 6/444     | 0/43    | 5.8 %      | 1.29   | [0.07, 22.44] |
| Subtotal (95% CI) | 2948      | 1288    | 100.0 %    | 7.82   | [3.79, 16.12] |

Total events: 348 (Mefloquine), 14 (Control)

Heterogeneity: Tau² = 0.22; Chi² = 6.92, df = 5 (P = 0.23); I² = 28%

Test for overall effect: Z = 5.57 (P < 0.00001)

Test for subgroup differences: Chi² = 0.17, df = 1 (P = 0.68), I² = 0.0%

(1) Overbosch 2001. Mefloquine versus atovaquone-proguanil recipients
(2) Andersson 2008. Mefloquine versus atovaquone-proguanil recipients
(3) Kato 2013. Mefloquine versus atovaquone-proguanil recipients
(4) Korhonen 2007. Mefloquine versus atovaquone-proguanil and doxycycline recipients
(5) Kuhner 2005. Mefloquine versus atovaquone-proguanil recipients
(6) Landman 2015. Mefloquine versus atovaquone-proguanil and doxycycline recipients
(7) Laverone 2006. Mefloquine versus atovaquone-proguanil recipients

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

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

Review: Mefloquine for preventing malaria during travel to endemic areas

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

Outcome: 10 Abnormal thoughts or perceptions; effects

| Study or subgroup | Mefloquine | Control | Risk Ratio [M/H] Random, 95% CI | Weight | Mefloquine | Control | Risk Ratio [M/H] Random, 95% CI |
|-------------------|------------|---------|---------------------------------|--------|------------|---------|---------------------------------|
| 1 Cohort studies  |            |         |                                 |        |            |         |                                 |
| Korhonen 2007 (1) | 9/1453     | 0/324   | 33.7% 1.00 [0.25, 72.78]        | 4.20   | 0.00       | 0.00    | 100.0% 4.20 [0.81, 21.87]       |
| Landman 2015 (2)  | 6/380      | 0/401   | 33.0% 13.72 [0.78, 242.65]      | 0.00   | 0.00       | 0.00    | 100.0% 1.29 [0.07, 22.44]       |
| Laverone 2006 (3) | 6/444      | 0/43    | 33.3% 1.29 [0.07, 22.44]        | 0.00   | 0.00       | 0.00    | 100.0% 1.29 [0.07, 22.44]       |
| Subtotal (95% CI)| 2277/768   |         | 100.0% 4.20 [0.81, 21.87]       |        |            |         |                                 |

Total events: 21 (Mefloquine), 0 (Control)
Heterogeneity: τ² = 0.0; χ² = 1.36, df = 2 (P = 0.51); I² = 0.0%
Test for overall effect: Z = 1.70 (P = 0.088)
Test for subgroup differences: Not applicable

(1) Korhonen 2007. Mefloquine versus atovaquone-proguanil and doxycycline recipients
(2) Landman 2015. Mefloquine versus atovaquone-proguanil and doxycycline recipients
(3) Laverone 2006. Mefloquine versus atovaquone-proguanil recipients
Analysis 5.11. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 11 Pruritis; effects.

Review: Mefloquine for preventing malaria during travel to endemic areas

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

Outcome: 11 Pruritis; effects

| Study or subgroup | Mefloquine | Control | Risk Ratio | Weight | Risk Ratio |
|-------------------|------------|---------|------------|--------|------------|
|                   | n/N        | n/N     | (M-H, Random, 95% CI) |        | (M-H, Random, 95% CI) |
| 1 RCTs            |            |         |             |        |             |
| Overbosch 2001 (1) | 15/483     | 12/493  | 100.0% 1.28 [0.60, 2.70] |        |             |
| Subtotal (95% CI) | 483        | 493     | 100.0% 1.28 [0.60, 2.70] |        |             |
| Total events:     | 15 (Mefloquine), 12 (Control) |        |        |        |
| Heterogeneity:    | not applicable |        |        |        |
| Test for overall effect: | Z = 0.64 (P = 0.52) |        |        |        |
| 2 Cohort studies  |            |         |             |        |             |
| Korhonen 2007 (2) | 42/1453     | 17/324  | 76.5% 0.55 [0.32, 0.96] |        |             |
| Kuhner 2005 (3)   | 3/142       | 0/82    | 23.5% 4.06 [0.21, 77.69] |        |             |
| Tuck 2016         | 0/13        | 0/20    | Not estimable |        |             |
| Subtotal (95% CI) | 1608        | 426     | 100.0% 0.88 [0.16, 4.76] |        |             |
| Total events:     | 45 (Mefloquine), 17 (Control) |        |        |        |
| Heterogeneity:    | Tau² = 0.89; Chi² = 1.76, df = 1 (P = 0.18); I² = 43% |        |        |        |
| Test for overall effect: | Z = 0.15 (P = 0.88) |        |        |        |
| Test for subgroup differences: | Chi² = 0.15, df = 1 (P = 0.69), I² = 0.0% |        |        |        |

(1) Overbosch 2001. Mefloquine versus atovaquone-proguanil recipients

(2) Korhonen 2007. Mefloquine versus atovaquone-proguanil and doxycycline recipients

(3) Kuhner 2005. Mefloquine versus atovaquone-proguanil recipients
## Analysis 5.12. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 12 Visual impairment; effects.

Review: Mefloquine for preventing malaria during travel to endemic areas

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

Outcome: 12 Visual impairment; effects

| Study or subgroup | Mefloquine | Control | Risk Ratio | Weight | Risk Ratio |
|------------------|------------|---------|------------|--------|------------|
|                  | n/N        | n/N     | n/N        |        | n/N        |
|                  |           |         |            |        |            |
| I RCTs           |            |         |            |        |            |
| Overbosch 2001 (1) | 16/483     | 8/493   |            |        |            |
|                  | 100.0 %    | 2.04 [0.88, 4.73] |
| Subtotal (95% CI) | 483        | 493     | 100.0 %    | 2.04   | 0.88, 4.73 |
| Total events:    | 16 (Mefloquine), 8 (Control) |        |            |        |            |
| Heterogeneity:   | not applicable |        |            |        |            |
| Test for overall effect: | Z = 1.67 (P = 0.096) | |
| 2 Cohort studies |            |         |            |        |            |
| Cunningham 2014 (2) | 0/49       | 1/247   |            |        |            |
| Korhonen 2007 (3) | 164/1453   | 15/324  |            |        |            |
| Laverone 2006 (4) | 5/444      | 1/43    |            |        |            |
| Subtotal (95% CI) | 1946       | 614     | 100.0 %    | 2.06   | 1.05, 4.02 |
| Total events:    | 169 (Mefloquine), 17 (Control) |        |            |        |            |
| Heterogeneity:   | Tau² = 0.07; Chi² = 2.15, df = 2 (P = 0.34); I² =7% |        |            |        |            |
| Test for overall effect: | Z = 2.12 (P = 0.034) | |
| Test for subgroup differences: | Chi² = 0.00, df = 1 (P = 0.99), I² =0.0% | |

(1) Overbosch 2001. Mefloquine versus atovaquone-proguanil recipients
(2) Cunningham 2014. Mefloquine versus atovaquone-proguanil and doxycycline recipients
(3) Korhonen 2007. Mefloquine versus atovaquone-proguanil and doxycycline recipients
(4) Laverone 2006. Mefloquine versus atovaquone-proguanil recipients
**Analysis 5.13. Comparison 5 Mefloquine versus currently used regimens; by study design, Outcome 13 Adherence; during travel.**

**Review:** Mefloquine for preventing malaria during travel to endemic areas

**Comparison:** 5 Mefloquine versus currently used regimens; by study design

**Outcome:** 13 Adherence; during travel

| Study or subgroup | Mefloquine | Atovaquone-proguanil | Risk Ratio M-H Random, 95% CI | Weight | Risk Ratio M-H Random, 95% CI |
|-------------------|------------|----------------------|-------------------------------|--------|-------------------------------|
| 1 RCTs            | n/N        | n/N                  |                               |        |                               |
| van Riemsdijk 2002 (1) | 54/58     | 60/61                |                               | 100.0 % | 0.95 [ 0.88, 1.02 ]          |
| **Subtotal (95% CI)** | 58        | 61                   |                               | 100.0 % | 0.95 [ 0.88, 1.02 ]          |
| Total events: 54 (Mefloquine), 60 (Atovaquone-proguanil) | | | | | |
| Heterogeneity: not applicable | | | | | |
| Test for overall effect: Z = 1.40 (P = 0.16) | | | | | |
| 2 Cohort studies | | | | | |
| Cunningham 2014 (2)          | 12/49      | 64/247               |                               | 3.3 %  | 0.95 [ 0.55, 1.61 ]          |
| Goodyer 2011 (3)             | 21/30      | 85/154               |                               | 6.9 %  | 1.27 [ 0.96, 1.67 ]          |
| Korhonen 2007 (4)           | 946/1453   | 123/324              |                               | 9.6 %  | 1.72 [ 1.48, 1.98 ]          |
| Landman 2015 (5)            | 231/380    | 283/403              |                               | 10.3 % | 0.87 [ 0.78, 0.96 ]          |
| Laver 2001 (6)              | 163/184    | 38/48                |                               | 9.4 %  | 1.12 [ 0.96, 1.31 ]          |
| Lobel 2001 (7)              | 3430/3630  | 53/60                |                               | 10.5 % | 1.07 [ 0.98, 1.17 ]          |
| Philips 1996 (8)            | 223/285    | 261/383              |                               | 10.5 % | 1.15 [ 1.05, 1.26 ]          |
| Saunders 2015 (9)           | 477/596    | 870/1438             |                               | 10.9 % | 1.32 [ 1.25, 1.40 ]          |
| Shamiss 1996 (10)           | 15/15      | 21/28                |                               | 7.7 %  | 1.31 [ 1.04, 1.65 ]          |
| Sonmez 2005 (11)            | 138/228    | 284/506              |                               | 9.8 %  | 1.08 [ 0.95, 1.23 ]          |
| Terrell 2015 (12)           | 891/938    | 695/752              |                               | 11.1 % | 1.03 [ 1.00, 1.05 ]          |
| **Subtotal (95% CI)**       | 7788       | 4343                 |                               | 100.0 % | 1.16 [ 1.03, 1.30 ]          |
| Total events: 6547 (Mefloquine), 2777 (Atovaquone-proguanil) | | | | | |
| Heterogeneity: Tau2 = 0.03; Chi2 = 166.53, df = 10 (P<0.0000); I² = 94% | | | | | |
| Test for overall effect: Z = 2.44 (P = 0.015) | | | | | |
| Test for subgroup differences: Chi2 = 7.87, df = 1 (P = 0.01), I² = 87% | | | | | |

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

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

Review: Mefloquine for preventing malaria during travel to endemic areas

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

Outcome: 14 Adherence; after return

| Study or subgroup | Mefloquine | Atovaquone-proguanil | Risk Ratio M-H Random 95% CI | Weight | Risk Ratio M-H Random 95% CI |
|------------------|------------|----------------------|-----------------------------|--------|-----------------------------|
|                  | n/N        | n/N                 |                             |        |                             |
| 1 Cohort studies |            |                      |                             |        |                             |
| Goodyer 2011 (1) | 15/30      | 65/154               | 8.7 %                       | 1.18 [0.79, 1.77] |
| Philips 1996 (2) | 154/285    | 205/383              | 70.0 %                      | 1.01 [0.88, 1.16] |
| Shamiss 1996 (3) | 13/15      | 21/28                | 16.6 %                      | 1.16 [0.86, 1.55] |
| Stoney 2016 (4)  | 6/11       | 197/315              | 4.7 %                       | 0.87 [0.51, 1.51] |
| Subtotal (95% CI)| 341        | 880                  | 100.0 %                     | 1.04 [0.92, 1.17] |

Total events: 188 (Mefloquine), 488 (Atovaquone-proguanil)
Heterogeneity: Tau² = 0.0; Chi² = 1.51, df = 3 (P = 0.68); I² = 0.0%
Test for overall effect: Z = 0.64 (P = 0.52)
Test for subgroup differences: Not applicable

van Riemsdijk 2002. Information about adherence was obtained by reference to the subjects diary cards and counts of returned study medication.
Cunningham 2014. Mefloquine versus atovaquone-proguanil and doxycycline users
Goodyer 2011. Mefloquine versus atovaquone-proguanil and doxycycline users
Karhonen 2007. Mefloquine versus atovaquone-proguanil and doxycycline users
Landman 2015. Mefloquine versus atovaquone-proguanil and doxycycline users
Laver 2001. Mefloquine versus doxycycline users
Lobel 2001. Mefloquine versus doxycycline users
Philips 1996. Mefloquine versus doxycycline users
Saunders 2015. Mefloquine versus doxycycline users
Shamiss 1996. Mefloquine versus doxycycline users
Sonmez 2005. Mefloquine versus doxycycline users
Terrell 2015. Mefloquine versus doxycycline users

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

Table 1. Risk of bias assessment methods for cohort studies

| Bias                      | Authors’ judgement           | Support for judgement                                                                 |
|---------------------------|------------------------------|--------------------------------------------------------------------------------------|
| **Confounding**           | Low risk                     | We used the following criteria:                                                       |
|                           | Moderate risk                | Low risk: identified confounders were measured and were balanced across groups (age,| |
|                           | Serious risk                 | sex, destination and duration of travel)                                              |
|                           | Critical risk                | Moderate risk: identified confounders were measured and not balanced across groups, or|
|                           | No information               | 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                     | 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% |
|                           | Moderate risk                |                                                                                      |
|                           | Serious risk                 |                                                                                      |
|                           | Critical risk                |                                                                                      |
|                           | No information               |                                                                                      |
| **Measurement of interventions** | Low risk                     | We used the following criteria:                                                       |
|                           | Moderate risk                | 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 |
|                           | Serious risk                 | Moderate risk: the prescription was provided by a travel clinic which also performed the study but no information regarding switches and discontinuations was |
|                           | Critical risk                | No information                                                                         |
|                           | No information               |                                                                                      |
Table 1. Risk of bias assessment methods for cohort studies (Continued)

| Category                                      | Low risk | Moderate risk | Serious risk | Critical risk | No information |
|-----------------------------------------------|----------|---------------|--------------|---------------|----------------|
| Departures from intended interventions       |          |               |              |               |                |
| 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                                 |          |               |              |               |                |
| 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                      |          |               |              |               |                |
| 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             |          |               |              |               |                |
| 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                                         |          |               |              |               |                |
| 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**                                                            |              |                                                                                                                                           |
| Were harms pre-defined using standardised or precise definitions?         | Adequate     | 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 |
|                                                                           | Inadequate   |                                                                                                                                           |
|                                                                           | Unclear      |                                                                                                                                           |
| Was ascertainment technique adequately described?                         | Adequate     | We classified as 'adequate' if the study reported methods used to ascertain complications, including who ascertained, timing, and methods used |
|                                                                           | Inadequate   |                                                                                                                                           |
|                                                                           | Unclear      |                                                                                                                                           |
| Was monitoring active or passive?                                         | Active       | We classified monitoring as 'active' when authors reviewed participants at set time points during treatment and enquired about symptoms       |
|                                                                           | Passive      |                                                                                                                                           |
|                                                                           | Unclear      |                                                                                                                                           |
| Was data collection prospective or retrospective?                         | Prospective  | We classified as 'prospective' if data collection occurred during treatment, or 'retrospective' if data collection occurred following treatment |
|                                                                           | Retrospective|                                                                                                                                           |
|                                                                           | Unclear      |                                                                                                                                           |
| **For laboratory investigations or other tests**                          |              |                                                                                                                                           |
| Was the number and timing of tests adequate?                              | Adequate     | We classified the number and timing of tests as 'adequate', when tests were taken at baseline and at least one time point during prophylaxis |
|                                                                           | Inadequate   |                                                                                                                                           |
|                                                                           | Unclear      |                                                                                                                                           |

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 | 339 | 250 mg weekly for first 4 weeks, then | Placebo | Various in endemic area (monitored) | Thai-Burma border | Not mentioned |
| Study | Characteristics | Placebo | Duration | Location | Notes |
|-------|-----------------|---------|----------|----------|-------|
| Pearlman 1980 | Burma border (presumed semi-immune) | 125 mg weekly until delivery | 26 weeks | Thailand | Chloroquine resistant \textit{Plasmodium falciparum} |
| Santos 1993 | Thai residents aged 10 to 60 years (semi-immune) | 180 mg tablet weekly, 360 mg tablet weekly, 360 mg every 2 weeks with appropriate adjustments for children | 17 weeks | Brazil | \textit{Plasmodium falciparum} resistant to chloroquine and "high prevalence of multi-resistant \textit{Plasmodium falciparum} transmission" |
| Sossouhounto 1995 | Brazilian civilians and soldiers aged 12 to 55 years (semi-immune) | 500 mg every 4 weeks, 250 mg every 2 weeks | 20 weeks | Ivory Coast | Not mentioned |
| Ohrt 1997 | Ivory Coast adult males (semi-immune) | 250 mg weekly for first 4 weeks, then 125 mg weekly | 'approximately weeks' 13 | Indonesia | Sulfadoxine-pyrimethamine and chloroquine resistance |
| Weiss 1995 | Indonesian soldiers ('largely' non-immune) | 250 mg weekly | Placebo, doxycycline | 11 weeks | Kenya | Not mentioned |
| Salako 1992 | Kenyan children (semi-immune) | 125 mg weekly | Placebo (multivitamin), doxycycline, primaquine | 24 weeks (trial duration) | Nigeria | "...at the time of the trial, chloroquine resistance was not a problem" |
### Table 3. Characteristics of included studies for efficacy (Continued)

| Study ID     | Participants                      | Number enrolled | Method of adverse event monitoring | Exclusions for psychiatric adverse effects | Trial duration | Source of funding |
|--------------|-----------------------------------|-----------------|------------------------------------|-------------------------------------------|----------------|-------------------|
| Hale 2003    | Ghanaian adults (semi-immune)     | 530             | Placebo                            | 12 weeks                                  | Ghana          | Not mentioned     |
| Arthur 1990  | USA soldiers (non-immune)         | 270             | Doxycycline                        | 8 weeks                                   | Thailand       | Local chloroquine resistance |
| Boudreau 1991| Thai adult males (semi-immune)    | 501             | Chloroquine                        | 14 weeks (trial duration)                 | Cambodia       | Local chloroquine resistance |
| Steketee 1996| Pregnant Malawian residents (semi-immune) | 4220         | 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    | Ghanaian 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 | None                                      | Various        | Government funding |
Table 4. Mefloquine versus placebo/no treatment; characteristics of included studies for safety  (Continued)

| Study (Year) | Participants | Number enrolled | Phase 2: weekly symptom questionnaire. Babies were assessed at birth and at 2 and 9 months | Method of adverse event monitoring | Factors influencing | Duration travel | Source of 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 with 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 | History of any serious psychiatric disorder; evidence of drug or alcohol abuse | 30 days             | Roche          |
| 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 | Duration travel | Source of funding |
|--------------|-----------------|-----------------------------------|----------------------|-----------------|------------------|

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

| Study ID     | Country | Travellers | Sample Size | Allocation Method | Drug Allocation | Duration | Funding Source |
|--------------|---------|------------|-------------|-------------------|-----------------|----------|----------------|
| Hoebe 1997  | Denmark | 300        | Telephone interview | Allocation based on guidelines and patient preference | Mean 3 weeks, range 1 to 9 weeks | Not mentioned |
| Petersen 2000| Denmark | 4154       | Participant self-reported questionnaire | Allocation based on guidelines and patient preference | Various, not specified | Not mentioned |
| Rietz 2002  | Sweden  | 491        | Participant self-reported questionnaire | Allocation based on guidelines and patient preference | “Most”, range 2 to 4 weeks | Not mentioned |
| van Riemsdijk 1997 | Denmark | 1501       | Participant self-reported questionnaire | Allocation based on guidelines and patient preference | Mean = 23 days | Not mentioned |
| Wells 2006  | USA     | 397,442    | Restrospective analysis of hospital records | No information available | Minimum month 1 | Government funding |

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

| Study ID    | Description of how adverse outcomes were defined and recorded¹ | Description of ascertainment technique² | Active or passive monitoring³ | 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 | Adequate | Active | Prospective |
| Study                | Reporting Quality | Data Collection | Study Design |
|---------------------|-------------------|-----------------|--------------|
| Nosten 1994         | Inadequate        | Adequate        | Active       |
| Comment: It is unclear what questions were included within the questionnaire and whether and how causality was assessed. ‘Serious’ adverse effects not defined | Prospective | |
| Ohrt 1997           | Inadequate        | Adequate        | Active       |
| Comment: No definition of adverse events or effects provided, it was unclear whether or how causality was assessed | Prospective | |
| Pearlman 1980       | Inadequate        | Inadequate      | Passive      |
| Comment: No definition of adverse events or effects was provided, it was unclear whether or how causality was assessed | Prospective | |
| Potasman 2002       | Inadequate        | Adequate        | Active       |
| Salako 1992         | Inadequate        | Adequate        | Active       |
| Santos 1993         | Inadequate        | Inadequate      | Active       |
| Schlagenhauf 1997   | Inadequate        | Adequate        | Active       |
Table 5. Mefloquine versus placebo/no treatment; quality of adverse events reporting (Continued)

| Study                      | Definitions & Detection | Causality | Collection | Study Design |
|----------------------------|--------------------------|-----------|------------|--------------|
| **Unclear whether or how causality was assessed** | | | | |
| **Sossouhounto 1995**      | Inadequate               | Unclear   | Passive    | Prospective  |
| **Vuurman 1996**           | Adequate                 | Unclear   | Active     | Prospective  |
| **Weiss 1995**             | Inadequate               | Adequate  | Active     | Prospective  |
| **Cohort studies**         |                          |           |            |              |
| **Hoebe 1997**             | Adequate                 | Adequate  | Active     | Retrospective |
| **Petersen 2000**          | Adequate                 | Adequate  | Active     | Retrospective |
| **Rietz 2002**             | Adequate                 | Adequate  | Active     | 'Filled in after their return' |
| **Steffen 1993**           | Adequate                 | Adequate  | Passive    | Unclear      |
| **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?
| Study ID       | Study design | Mefloquine users | Drug comparators |
|---------------|--------------|------------------|------------------|
|               | **Events/ participants** | **Description** | **Drug** | **Events/ participants** | **Description** |
| **Bunnag 1992** | RCT          | 0/116            | -             | Placebo | 1/121 | None provided |
| **Nosten 1994** | RCT          | 1/159 (women)    | One death      | Placebo | 0/152 (women) | One congenital malformation:
|               |              |                  | • Septic shock after an emergency caesarean section |              |                  | • anencephaly |
|               |              |                  | Four congenital malformations: |              |                  |   |
|               |              |                  | • Limb dysplasia (1 case) |              |                  |   |
|               |              |                  | • Ventricular septal defect (2 cases) |              |                  |   |
|               |              |                  | • Amniotic bands (1 case) |              |                  |   |
| **Sossouhounto 1995** | RCT | 0/103            | -             | Placebo | 1/96 | One death (not described) |
| **Ohrt 1997** | RCT          | 0/61             | -             | Placebo | 0/65 | - |
|               |              |                  | Doxycycline    | 1/62    | Acute hysteria¹ |
| **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” | Atovaquone-proguanil | 4/493 | “...infectious illnesses in 3 subjects and cerebral ischemia in 1 subject” |
### Table 6. Serious adverse events; mefloquine versus comparators (Continued)

| Studies reporting no serious events or effects | RCT | Cohort study |
|-----------------------------------------------|-----|--------------|
| **Salako 1992** | Placebo Chloroquine | 0/101 0/103 | - |
| **Arthur 1990** | Doxycycline | 0/119 | - |
| **Schlagenhauf 2003** | Doxycycline Atovaquone-proguanil | 0/153 0/164 | - |
| **Sonmez 2005** | Doxycycline | 0/506 | - |
| **Andersson 2008** | Atovaquone-proguanil | 0/161 | - |
| **Napoletano 2007** | Atovaquone-proguanil Chloroquine | 0/707 0/37 | - |
| **Sossouhounto 1995** | Chloroquine | 0/100 | - |

1 This trial described a potentially serious adverse event, but did not provide enough detail to meet our definition.
| Study ID     | Study design | Mefloquine users | Description | Drug comparators | Events/ participants | Description |
|-------------|--------------|------------------|-------------|-----------------|----------------------|-------------|
|             |              | Events/ participants | Description |                  |                      |             |
| Hoebe 1997  | Cohort study | 2/104            | Two "serious acute adverse reactions"¹ | No treatment | 0/93                 | -           |
|             |              |                  | • Depressed mood |                  |                      |             |
|             |              |                  | • Dizziness     |                  |                      |             |
| Petersen 2000 | Cohort study | 5/809            | 5 hospitalisations: | Chloroquine | 6/1223               | 2 hospitalisations: |
|             |              |                  | • Depressed mood |                  |                      | • Blurred vision, nausea, headache, general skin itching, paraesthesia |
|             |              |                  | • Depressed mood |                  |                      | • Depressed mood |
|             |              |                  | • Depressed mood, "strange thoughts" |                  |                      |             |
|             |              |                  | • Depressed mood, "strange thoughts", itching, vertigo |                  |                      |             |
|             |              |                  | • Vertigo, fever, mouth ulcers, diarrhoea |                  |                      |             |
| Korhonen 2007 | Cohort study | 15/1612          | 15 hospitalisations: | Doxycycline | 9/708                | 9 hospitalisations: |
|             |              |                  | • Dizziness (3) |                  |                      | • Gastrointestinal disturbance (6) |
|             |              |                  | • Heart palpitations (2) |                  |                      | • Photosensitivity (1), |
|             |              |                  | • Limb numbness (1) |                  |                      | • Coughing (1) |
|             |              |                  | • Abdominal pain (1) |                  |                      | • Anaemia (1) |
|             |              |                  | • Yeast infection (1) |                  |                      |             |
|             |              |                  | • Anxiety and depression (1) |                  |                      |             |
|             |              |                  | • Visual disturbance, photosensitivity |                  |                      |             |
### Table 7. Serious adverse effects; mefloquine versus comparators (Continued)

| Treatment                     | Serious adverse effects                                                                 | Hospitalisations | Notes                                      |
|-------------------------------|-----------------------------------------------------------------------------------------|-------------------|--------------------------------------------|
|                               | (1)  
|                               | • Passing out, extreme fatigue  
|                               | • “Went crazy”, anxiety, nausea, vomiting  
|                               | • “Psychotic reaction”, anxiety, abnormal dreams  
|                               | • Anxiety, abnormal dreams, insomnia, unsteadiness  
|                               | • Nausea, dizziness, blackout  | 0/72              | -                                          |
|                               | Atovaquone-proguanil                                                                   |                   |                                            |
|                               | (1)  
|                               | • Anxiety, abnormal dreams, insomnia, unsteadiness  
|                               | • Nausea, dizziness, visual disturbance, insomnia, abnormal dreams, unsteadiness, weakness  
|                               | • Abnormal dreams  
|                               | • Seizures  
|                               | • Abdominal pain, diarrhoea  | 4/832             | 4 hospitalisations:  
|                               | Chloroquine                                                                            |                   | Nausea, dizziness, visual disturbance, insomnia, abnormal dreams, unsteadiness, weakness  
|                               | (1)  
|                               | • Abnormal dreams  
|                               | • Seizures  
|                               | • Abdominal pain, diarrhoea  |                        |                                            |
| Philips 1996                  | Cohortstudy                                                                            | 4/285             | 3 hospitalisations with "either gastrointestinal or neurologic symptoms" and one seizure  
|                               | Doxycycline                                                                            | 1/383             | Severe oesophagitis  |
| Steketee 1996                 | RCT                                                                                   | 1/?               | One "neuropsychiatric side effect"  
|                               |                                                                                       |                   | Disorientation to time and place¹  
|                               | Chloroquine                                                                            | 0/?               | -                                          |
| Study                  | Design   | N     | Serious events, including:                                                                 | Comparator(s) | Events | N     |
|-----------------------|----------|-------|-------------------------------------------------------------------------------------------|---------------|--------|-------|
| Albright 2002         | Cohort   | 1/115 | One “serious side effect”¹<br>• Hallucinations                                             | Chloroquine   | 0/22   | -     |
| Corominas 1997        | Cohort   | 1/609 | One hospitalisation:<br>• Heart palpitations, convulsions, paraesthesia and vertigo       | Chloroquine   | 0/137  | -     |
| Steffen 1993          | Cohort   | 7/52981 | 7 hospitalisations, including:<br>• Seizures (2)<br>• Psychosis (2)<br>• Vertigo (1)<br>• 2 not characterised | Chloroquine   | 7/20332 | 7 hospitalisations. 'Includes':<br>• Seizures (2)<br>• Psychosis (1)<br>• 4 not characterised |
| Studies reporting no serious events or effects |          |       |                                                                                           |               | 0/94   | -     |
| Hale 2003             | RCT      | 0/46  | Nine serious adverse events in the trial (trial arm not specified)<br>“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       | 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 considered adverse events” | Doxycycline   | 0/153  | 0/164 |
Table 7. Serious adverse effects; mefloquine versus comparators  (Continued)

| Study ID       | Method of adverse event monitoring | Significant exclusions for psychiatric adverse effects | Duration of travel | Source of funding |
|---------------|-----------------------------------|-------------------------------------------------------|--------------------|-------------------|
| Sonmez 2005   | "No drug induced side effects necessitating emergency care were observed" | Doxycycline | 0/506 | - |
| Andersson 2008 | "No serious adverse events were recorded" | Atovaquone-proguanil | 0/161 | - |
| Napoletano 2007 | Records hospitalisations, and reports that none occurred in either group of participants | Atovaquone-proguanil Chloroquine | 0/707/0/37 | - |
| Sossouhounto 1995 | "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 | Method of adverse event monitoring | Significant exclusions for psychiatric adverse effects | Duration of travel | Source of funding |
|---------------|--------------|-----------------------------------|-------------------------------------------------------|--------------------|-------------------|
| Arthur 1990   | USA soldiers | Blood tests, stool samples. Interview with study personnel | None | 5 weeks | Not mentioned |
| Ohrt 1997     | Indonesian soldiers | Interview with study personnel. Exit questionnaire | " History of underlying illness" | 13 weeks | Pfizer and Roche |
| Schlagenhauf 2003 | Non-immune adult short-term | Participant self-reported | History of seizures or psychoses | 4 to 6 weeks | GlaxoSmithKline and Roche |
Table 8. Mefloquine versus doxycycline: characteristics of included studies for safety (Continued)

| Travellers                  | Questionnaire Method of adverse event monitoring Factors influencing drug allocation Duration of travel | Source of funding |
|-----------------------------|-------------------------------------------------------------------------------------------------------|-------------------|
| 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 soldiers 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 participant 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” |
| Lobel 2001                   | Adult short-term travellers 5626 | Participant self-reported questionnaire No information available < 5 weeks | “No financial interests to disclose” |
Table 8. Mefloquine versus doxycycline; characteristics of included studies for safety  *(Continued)*

| Study          | Population | Sample Size | Method of Collection | Follow-Up | Duration | Funding          |
|----------------|------------|-------------|----------------------|-----------|----------|------------------|
| Meier 2004     | UK adults enrolled in UK general practice 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: doxycycline After July 2002: mefloquine | A pprox. 6 months | Not mentioned |
Table 8. Mefloquine versus doxycycline; characteristics of included studies for safety (Continued)

| Study ID   | Country and study population | Participants | Study design | Allocation | Duration | Funding type |
|------------|------------------------------|--------------|--------------|------------|----------|--------------|
| 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 |
| 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 | Approx. 6 weeks | Not mentioned |

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

| Study ID     | Harms predefined¹ | Description of ascertainment technique² | Active or passive monitoring³ | 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 was unclear whether or how causality was assessed | Adequate | Active | Prospective |
| Schlagenhauf 2003 | Adequate | Adequate | Active | Prospective |
| Weiss 1995   | Inadequate: Comment: Each subject was visited daily at home by an assigned field worker, who | Adequate | Active | Prospective |
Table 9. Mefloquine versus doxycycline; quality of adverse event reporting  
(Continued)

| Study                  | Quality | Method | Cohort Structure | Notes                                                                 |
|------------------------|---------|--------|------------------|----------------------------------------------------------------------|
| Cunningham 2014        | Inadequate | Adequate | Passive | Unclear: questionnaire included a targeted list of side effects, including "other psychological problems". What was included within this was not defined |
| Eick-Cost 2017         | Adequate | Adequate | Passive | Prospective                                                        |
| Goodyer 2011           | Inadequate | Adequate | Active | Retrospective                                                      |
| Korhonen 2007          | Adequate | Adequate | Passive | Unclear: no information was provided regarding the timing of the questionnaire during treatment |
| Landman 2015           | Adequate | Adequate | Passive | Unclear: all participants were emailed the questionnaire at one time point, which occurred at varying points during the prophylactic regimen |
| Lobel 2001             | Inadequate | Adequate | Passive | Unclear: information was collected at the airport, when travellers should still have been taking the prophylactic regimen |
| Meier 2004             | Adequate | Adequate | Passive | Retrospective                                                      |
Table 9. Mefloquine versus doxycycline; quality of adverse event reporting  (Continued)

| Study            | Quality Assessment | Reporting Method | Study Design |
|------------------|--------------------|------------------|--------------|
| Napoletano 2007  | Unclear            | Adequate         | Active       | Retrospective |
| Comment: adverse events were categorised on a scale of one to four, but it is unclear whether and how causality was assessed |
| Philips 1996     | Inadequate         | Inadequate       | Active       | Retrospective |
| Comment: it was unclear what constituted a serious or severe event and insufficient information on the questions that travellers were asked |
| Comment: no details provided regarding abbreviated questionnaire |
| Saunders 2015    | Inadequate         | Adequate         | Passive      | Retrospective |
| Comment: insufficient information of the questions that travellers were asked |
| Schwartz 1999    | Inadequate         | Inadequate       | Unclear      | Unclear |
| Comment: see quote. Different methods of follow up for different forms of prophylaxis |
| Shamiss 1996     | Inadequate         | Inadequate       | Passive      | Unclear |
| Comment: see quote. Different methods of follow up for different forms of prophylaxis |
| Sharafeldin 2010 | Inadequate         | Inadequate       | Passive      | Retrospective |
| Comment: no information was provided on how adverse events were assessed |
| Comment: no mention of how adverse events were assessed |

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

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

| Study               | How information on adverse effects was sought | Were recorded in the questionnaire | Monitoring classed as ‘active’ if it occurred at set time points during treatment | Methodology |
|---------------------|-----------------------------------------------|-----------------------------------|--------------------------------------------------------------------------------|-------------|
| Sonmez 2005         | Inadequate                                    | Adequate                          | Active                                                                         | Prospective |
|                     | Comment: insufficient information provided on the questions that travellers were asked |                                   |                                                                                 |             |
| Stoney 2016         | Inadequate                                    | Inadequate                        | Active                                                                         | Prospective |
|                     | Comment: insufficient information provided on the questions that travellers were asked | No information is reported on how adverse events were ascertained |                                                                                 |             |
| Tan 2017            | Adequate                                      | Adequate                          | Active                                                                         | Retrospective |
| Terrell 2015        | Inadequate                                    | Adequate                          | Passive                                                                         | Unclear     |
|                     | Comment: The questionnaire approved by the MODREC included the 19 commonest adverse effects described in the manufacturers’ product documentation |                                     |                                                                                 |             |
|                     | Comment: adverse events listed in the questionnaires are not reported |                                     |                                                                                 |             |
| Tuck 2016           | Inadequate                                    | Adequate                          | Active                                                                         | Unclear     |
|                     | Comment: insufficient information provided on the questions that travellers were asked |                                     |                                                                                 |             |
| Waner 1999          | Inadequate                                    | Adequate                          | Passive                                                                         | Unclear     |
|                     | Comment: insufficient information provided on the questions that travellers were asked |                                     |                                                                                 |             |

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.
| 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 | "History of alcoholism, seizures, psychiatric disorders, severe neurological disorders" | Mean 19 days       | Government funding |
| **Non-randomized studies** |                                                   |                 |                                   |                                                       |                    |                   |
| Andersson 2008 | Swedish soldiers                                   | 609             | Participant self-reported questionnare | Mainly mefloquine, soldiers with contra-indications received atovaquone-proguanil | 6 months           | Not mentioned     |
| Belderok 2013 | Dutch short-term travellers                         | 945             | Participant self-reported questionnare (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 questionnare | Allocation based on guidelines and participant preference | 0-36 months        | Not mentioned     |
Table 10. Mefloquine versus atovaquone-proguanil; characteristics of included studies for safety  (Continued)

| Study            | Location/Limitation | Sample Size | Methodology | Allocation | Follow-up | Safety Considerations |
|------------------|---------------------|-------------|-------------|------------|-----------|-----------------------|
| Eick-Cost 2017   | USA soldiers        | 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 |
| 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 tovaquone-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 |
Table 10. Mefloquine versus atovaquone-proguanil; characteristics of included studies for safety (Continued)

| Study ID     | Country and Setting                                                                 | Sample Size | Study Design | Method of Assignment | Duration Range | Funding Information |
|--------------|-------------------------------------------------------------------------------------|-------------|--------------|----------------------|----------------|---------------------|
| 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 general practice research database                         | Not available | Incident cases of neuropsychiatric disorders during or after antimalarial drug use | No information available | Various, not specified | Roche |
| 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) | "No 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 | Description of ascertainment technique | Active or passive monitoring | 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
| Study                | Adverse Event Reporting | Data Collection | Adverse Event Reporting | Methodology | Comment: |
|---------------------|-------------------------|-----------------|-------------------------|-------------|---------|
| Andersson 2008      | Inadequate              | Inadequate      | Active                  | Unclear     | Insufficient information provided on the questions which soldiers were asked; different ascertainment technique used for one of the three groups, which is inadequately described |
| Cunningham 2014     | Inadequate              | Adequate        | Passive                 | Unclear     | Different ascertainment technique used for one of the three groups, which is inadequately described |
| Eick-Cost 2017      | Adequate                | Adequate        | Passive                 | Prospective | Data collection was prospective for 448/609 participants (LA04 and LA05), but retrospective for 161 participants (LA02) |
| Goodyer 2011        | Inadequate              | Adequate        | Active                  | Retrospective | Questionnaire included a targeted list of side effects, including "other psychological problems". What was included within this was not defined |
| Kato 2013           | Adequate                | Adequate        | Passive                 | Unclear     | Data collection was prospective for 448/609 participants (LA04 and LA05), but retrospective for 161 participants (LA02) |
| Korhonen 2007       | Adequate                | Adequate        | Passive                 | Unclear     | Data collection was prospective for 448/609 participants (LA04 and LA05), but retrospective for 161 participants (LA02) |
| Kuhner 2005         | Inadequate              | Adequate        | Active                  | Retrospective | Data collection was prospective for 448/609 participants (LA04 and LA05), but retrospective for 161 participants (LA02) |
| Landman 2015        | Adequate                | Adequate        | Passive                 | Unclear     | Data collection was prospective for 448/609 participants (LA04 and LA05), but retrospective for 161 participants (LA02) |
| Study          | Type of Surveillance | Causality Assessment | Period of Reporting |
|---------------|----------------------|----------------------|---------------------|
| Laverone 2006 | Adequate             | Passive              | Varying points during prophylactic regimen |
| Napoletano 2007 | Unclear              | Adequate             | Active              |
| Schneider 2013 | Adequate             | Adequate             | Passive             |
| Sharafeldin 2010 | Inadequate           | Inadequate           | Passive             |
| Stoney 2016   | Inadequate           | Inadequate           | Active              |
| Tan 2017      | Adequate             | Adequate             | Passive             |
| Tuck 2016     | Inadequate           | Adequate             | Active              |

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 |
|-------------|-----------------------------|-----------------|------------------------------------|-----------------------------------------------------|----------------|-------------------|
| **RCTs**    |                             |                 |                                    |                                                     |                |                   |
| 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 | "Medical history of psychiatric or neurological problems within the last 5 years" | 13 weeks       | Not mentioned     |
| Bunnag 1992  | Thai adult males            | 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 coast 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** | | | | | | |
| 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 |
| Corominas 1997 | Spanish short-term adult travellers | 1054 | Participant self-reported questionnaire | Allocation based on guidelines and participant preference | Maximum 6 weeks | Not mentioned |
| Study            | Type of Traveller                   | N     | Data Collection Method                              | Allocation Method                                      | Duration               | Financial Interest |
|------------------|-------------------------------------|-------|-----------------------------------------------------|--------------------------------------------------------|------------------------|--------------------|
| 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                                | Most < 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               |
Table 12. Mefloquine versus chloroquine; characteristics of included studies for safety (Continued)

| Study ID      | Country | Study Type                  | Sample Size | Data Collection Method                  | Allocation Method                      | Median Duration | Funding                      |
|--------------|---------|-----------------------------|-------------|-----------------------------------------|----------------------------------------|----------------|------------------------------|
| **Stoney 2016** | USA     | Short-term travellers       | 370         | Participant self-reported questionnaire | Allocation based on guidelines and participant preference | 13 days         | Government funding           |
| **Tan 2017**  |         | Peace Corps volunteers     | 8931        | Participant self-reported questionnaire | No information available               | Various, not specified | No dedicated funding        |
| **Wanner 1999** |         | Adult short-term travellers | 3051        | Participant self-reported questionnaire | No information available               | Approx. 6 weeks | “not funded by an external body” |

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

| Study ID      | Harms predefined¹ | Description of ascertainment technique² | Active or passive monitoring³ | Prospective or retrospective data collection? |
|---------------|-------------------|------------------------------------------|------------------------------|-----------------------------------------------|
| **RCTs**      |                   |                                          |                              |                                               |
| Boudreau 1991 | Adequate          | Adequate                                 | Active                       | Prospective                                   |
| Boudreau 1993 | Adequate          | Adequate                                 | Active                       | Prospective                                   |
| Bunnag 1992   | Inadequate        | Adequate                                 | Active                       | Prospective                                   |
|               | Adverse events    | Adequate                                 | Active                       |                                               |
|               | were defined      | Adequate                                 | Active                       |                                               |
|               | clinically, and   | Adequate                                 | Active                       |                                               |
|               | starting week 14, | Adequate                                 | Active                       |                                               |
|               | volunteers        | Adequate                                 | Active                       |                                               |
|               | reporting adverse | Adequate                                 | Active                       | Prospective                                   |
|               | events were       | Adequate                                 | Active                       |                                               |
|               | interviewed       | Adequate                                 | Active                       |                                               |
|               | by members of     | Adequate                                 | Active                       |                                               |
|               | the hospital team | Adequate                                 | Active                       |                                               |
| Salako 1992   | Inadequate        | Adequate                                 | Active                       | Prospective                                   |
|               | “Particular       | Adequate                                 | Active                       |                                               |
|               | attention was     | Adequate                                 | Active                       |                                               |
|               | paid to           | Adequate                                 | Active                       |                                               |
|               | complaints such   | Adequate                                 | Active                       |                                               |
|               | as fever, chills, | Adequate                                 | Active                       |                                               |
|               | malaise, nausea   | Adequate                                 | Active                       |                                               |
|               | and vomiting,     | Adequate                                 | Active                       |                                               |
|               | rashes and other  | Adequate                                 | Active                       |                                               |
|               | symptoms and      | Adequate                                 | Active                       |                                               |
|               | signs that could  | Adequate                                 | Active                       |                                               |
|               | be regarded as    | Adequate                                 | Active                       |                                               |
|               | adverse events.   | Adequate                                 | Active                       |                                               |
|               | Comment: no clear  | Adequate                                 | Active                       |                                               |
|               | definition of     | Adequate                                 | Active                       |                                               |
|               | adverse events    | Adequate                                 | Active                       |                                               |
|               | was provided      | Adequate                                 | Active                       |                                               |

Adverse events defined clinically, and starting week 14, volunteers reporting adverse events were interviewed by members of the hospital team.

Adverse events defined clinically, and starting week 14, volunteers reporting adverse events were interviewed by members of the hospital team.

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Adverse events defined clinically, and starting week 14, volunteers reporting adverse events were interviewed by members of the hospital team.
| Study                          | Reporting Quality | Adverse Event Reporting | Study Design | Study Period |
|-------------------------------|-------------------|-------------------------|--------------|--------------|
| Sossouhounto 1995            | Inadequate        | Unclear                 | Passive      | Prospective  |
|                              | “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” | |
| Steketee 1996                | Adequate          | Adequate                | Active       | Prospective  |
| Cohort studies               |                   |                         |              |              |
| Albright 2002                | Adequate          | Adequate                | Passive      | Retrospective |
| Corominas 1997               | Inadequate        | Adequate                | Active       | Retrospective |
|                              | Comment: insufficient information was provided about the questions that travellers were asked | | |
| Cunningham 2014             | Inadequate        | Adequate                | Passive      | Unclear      |
|                              | Comment: questionnaire included a targeted list of side effects, including "other psychological problems". What was included within this was not defined | | "questionnaire was performed while participants were still taking chemoprophylaxis medication, although 75% were non-compliant" |
| Hill 2000                    | Inadequate        | Adequate                | Active       | Retrospective |
|                              | Comment: insufficient information was provided about the questions that travellers were asked | | |
| Korhonen 2007                | Adequate          | Adequate                | Passive      | Unclear      |
|                              | Comment: No information was provided regarding the timing of the questionnaire during treatment | | |
| Laverone 2006                | Adequate          | Adequate                | Passive      | Retrospective |
| Lobel 2001                   | Inadequate        | Adequate                | Passive      | Unclear      |
|                              | “Travellers… were given a questionnaire that asked for... adverse health | | "information was collected at the airport, when travellers |
Table 13. Mefloquine versus chloroquine; quality of adverse events reporting  

| Study                  | Data Collection | Reporting | Data Acceptability | Monitoring | Methodology |
|------------------------|-----------------|-----------|--------------------|------------|-------------|
| **Napoletano 2007**    | Unclear         | Adequate  | Active             | Retrospective |
| Comment: adverse events were categorised on a scale of one to four, but it is unclear whether and how causality was assessed. | | | | |
| **Petersen 2000**      | Inadequate      | Adequate  | Active             | Retrospective |
| Comment: it was unclear whether the questionnaire implied causality to the drug regimen. | | | | |
| **Rietz 2002**         | Adequate        | Adequate  | Active             | Retrospective |
| **Steffen 1993**       | Adequate        | Adequate  | Passive            | |
| Comment: information was collected during the flight home, when travellers should still have been taking the prophylactic regimen. | | | | |
| **Stoney 2016**        | Inadequate      | Inadequate| Active             | Prospective |
| Comment: insufficient information provided on the questions that travellers were asked. | | | | |
| **Tan 2017**           | Adequate        | Adequate  | Active             | Retrospective |
| **Waner 1999**         | Inadequate      | Adequate  | Passive            | |
| Comment: insufficient information provided on the questions that travellers were asked. | | | | |

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

| Outcome                          | Mefloquine versus atovaquone-proguanil and doxycycline | Test for subgroup differences |
|----------------------------------|--------------------------------------------------------|------------------------------|
|                                  | Short- term travellers¹ | Longer- term travellers² |                               |
|                                  | 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 (0.15 to 2.71) 5 cohort studies (2428) | RR 0.57 (0.22 to 1.49) 4 cohort studies (5187) | P = 0.89                       |
| Headache                         | RR 2.39 (0.69 to 8.22) 5 cohort studies (2086) | RR 2.09 (1.10 to 3.95) 4 cohort studies (3506) | P = 0.85                       |
| Dizziness                        | RR 3.05 (1.15 to 8.12) 4 cohort studies (1067) | RR 3.84 (1.34 to 11.00) 4 cohort studies (3506) | P = 0.76                       |
| Abnormal dreams                  | RR 6.25 (1.16 to 33.67) 3 cohort studies (1037) | RR 7.62 (2.06 to 28.18) 4 cohort studies (3506) | P = 0.86                       |
| Insomnia                         | RR 3.09 (0.30 to 32.21) 4 cohort studies (1760) | RR 8.67 (4.73 to 15.89) 4 cohort studies (3506) | P = 0.40                       |
Table 14. Mefloquine versus currently used regimens; by duration of travel  
(Continued)

| Anxiety                  | RR 3.26 (0.20 to 53.46) | 1 cohort study (487) | RR 18.05 (9.75 to 33.42) | 3 cohort studies (2854) | P = 0.24  
|--------------------------|-------------------------|----------------------|---------------------------|-------------------------|-------  
| Depressed mood           | RR 2.52 (0.76 to 8.29)  | 3 cohort studies (1026) | RR 12.59 (6.47 to 24.49) | 3 cohort studies (3210) | P = 0.02  
| Abnormal thoughts and behaviours | RR 1.29 (0.07 to 22.44) | 1 cohort study (487) | RR 7.78 (1.12 to 54.06) | 2 cohort studies (2558) | P = 0.31  
| Adherence: during travel | RR 1.10 (1.03 to 1.18)  | 7 cohort studies (7241) | RR 1.20 (0.88 to 1.62) | 4 cohort studies (4890) | P = 0.61  
| 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

| Outcome                                      | Military¹ | Non-military² | 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  

Mefloquine for preventing malaria during travel to endemic areas (Review)  
Copyright © 2017 The Authors. Cochrane Database of Systematic Reviews published by John Wiley & Sons, Ltd. on behalf of The Cochrane Collaboration.
| Condition                  | RR (95% CI)                  | Studies | p-value |
|----------------------------|------------------------------|---------|---------|
| **Nausea**                 |                              |         |         |
|                           | RR 1.39 (0.36 to 5.36)       | 4 cohort studies (1578) | P = 0.26 |
|                           | RR 1.70 (0.60 to 4.81)       | 6 cohort studies (3767)  |         |
| **Abdominal pain**         |                              |         |         |
|                           | RR 0.43 (0.14 to 1.29)       | 4 cohort studies (1578)  | P = 0.72 |
|                           | RR 0.56 (0.23 to 1.35)       | 5 cohort studies (3099)  |         |
| **Diarrhoea**              |                              |         |         |
|                           | RR 0.30 (0.09 to 0.96)       | 4 cohort studies (3999)  | P = 0.07 |
|                           | RR 1.05 (0.54 to 2.06)       | 6 cohort studies (3767)  |         |
| **Headache**               |                              |         |         |
|                           | RR 1.19 (0.14 to 9.79)       | 2 cohort studies (1386)  | P = 0.51 |
|                           | RR 2.48 (1.40 to 4.40)       | 7 cohort studies (4206)  |         |
| **Dizziness**              |                              |         |         |
|                           | RR 2.95 (1.37 to 6.36)       | 3 cohort studies (844)   | P = 0.76 |
|                           | RR 3.58 (1.39 to 9.25)       | 6 cohort studies (3880)  |         |
| **Abnormal dreams**        |                              |         |         |
|                           | RR 11.02 (4.61 to 26.34)     | 1 cohort study (652)     | P = 0.53 |
|                           | RR 6.59 (1.74 to 25.00)      | 6 cohort studies (3891)  |         |
| **Insomnia**               |                              |         |         |
|                           | RR 2.34 (0.41 to 13.35)      | 3 cohort studies (1537)  | P = 0.11 |
|                           | RR 10.24 (6.26 to 16.76)     | 6 cohort studies (3880)  |         |
| **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)     | P = 0.39 |
|                           | RR 6.49 (2.66 to 15.85)      | 5 cohort studies (3584)  |         |
| **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)  | P = 0.85 |
|                           | RR 1.16 (0.99 to 1.35)       | 8 cohort studies (10785) |         |
| **Adherence: after return** |                              |         |         |
|                           | RR 1.16 (0.86 to 1.55)       | 1 cohort study (43)      | P = 0.44 |
|                           | RR 1.02 (0.89 to 1.16)       | 3 cohort studies (1178)  |         |
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    |
| 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    |

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
(Continued)

| 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 Register | Specialized Register | CENTRAL | MEDLINE | Embase | LILACS |
|------------|----------------|----------------------|---------|---------|--------|--------|
| 1          | malaria        | Malaria ti, ab, MeSH | Malaria ti, ab, MeSH | Malaria ti, ab, Emtree | malaria |
| 2          | Mefloquine OR Lariam | Antimalaria* ti, ab | Antimalaria* ti, ab | Antimalaria* ti, ab | Mefloquine OR Lariam |
| 3          | Prevent* OR prophyla* OR chemoprevent* OR chemopro- | 1 or 2 | 1 or 2 | 1 or 2 | Prevent* OR prophyla* OR chemoprevent* OR chemopro- |
(Continued)

| phyla* | 1 and 2 and 3 | Mefloquine ti, ab, MeSH | Mefloquine ti, ab, Emtree | 1 and 2 and 3 |
|--------|---------------|-------------------------|---------------------------|---------------|
| 4      |               |                         |                           |               |
| 5      | -             | Lariam ti, ab           | Lariam ti, ab             | -             |
| 6      | -             | 4 or 5                  | 4 or 5                    | -             |
| 7      | -             | Prevent* OR prophyla* OR chemoprevent* OR chemoprphylla* ti, ab | Prevent* OR prophyla* OR chemoprevent* OR chemoprphylla* ti, ab | -             |
| 8      | -             | 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<sup>1</sup>  
  2. Digit span backwards and forwards<sup>2</sup>  
  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 |
| Schlagenhaus 1997 | 23 (cross-over)     | Placebo (23, cross-over) | 1. POMS<sup>3</sup>,  
  2. ESQ<sup>4</sup>,  
  3. NES<sup>5</sup>,  
  4. Sleep assessment  
  5. ICA<sup>6</sup>  
  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 had a higher mean sway than placebo users but no differences were significant”

| Vuurman 1996 | 22 | Placebo (20) |
|-------------|----|--------------|
| 1. Critical flicker/fusion frequency | 2. Critical instability tracking tests | 3. Body sway |
| 4. Tests of driving performance | | |
| Critical flicker/fusion frequency: Reports no statistically significant differences between groups |
| Critical instability tracking tests: Reports no statistically significant differences between groups |
| Body sway: Reports no statistically significant differences between groups |
| Tests of driving performance: “[mefloquine] significantly improved road tracking performance on Day 4” |

1Symbol digit modalities test: a test of information processing speed.
2Digit 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.
3Profile 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.
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’.

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.

Instrument co-ordination analyser (ICA): This is a tool used in the selection of trainee pilots, and measures multiple task abilities. 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.

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.

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                                                                 |
|------------------|-------------------------|------------------------------------------------|-----------------------|----------------------------------------------------------------------------------|
| Schlagenhaus 2003 | 153                     | Atovaquone-proguanil (164), doxycycline (153) | 1. POMS¹ 2. Quality of life questionnaire² | 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. POMS¹ 2. NES³      | 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 |

¹Profile 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.

²Quality 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”)

³Neurobehavioral 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-
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

| 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
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.
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