South African National Essential Medicine List
Primary Health Care Medication Review Process
Component: Infections

TITLE: MALARIA PROPHYLAXIS: EVIDENCE REVIEW OF THE CLINICAL BENEFIT AND HARM

Date: 13 June 2021

Key findings

- The South African Malaria Elimination Committee reported an increase in malaria cases amongst migrant workers traveling home (mostly across borders in malaria-endemic areas), and motivated that malaria chemoprophylaxis be considered for inclusion on the National Essential Medicine List.
- There is no local susceptibility for malaria. However, local resistance to chloroquine and sulfadoxine-pyrimethamine precluded inclusion of these agents from the analysis. Currently, malaria chemoprophylaxis includes atovaquone-proguanil, doxycycline and mefloquine. Disconcertingly, mefloquine has recently been discontinued from the South African market.
- We conducted an evidence review for malaria chemoprophylaxis (mefloquine, atovaquone-proguanil or doxycycline) and one systematic review[8] and 4 RCTs[9-11] were identified.
- **Doxycycline:** A Kenyan study of children[11], 9-14 years, (n=169) that compared various agents against control was reviewed. Doxycycline (n=34) was shown to be 84% effective at preventing parasitaemia (95% CI 66 to 92%); NNT 4 (95% CI 3 to 10), *low certainty evidence;* and 91% effective at preventing clinical malaria (95% CI 61 to 98%) NNT 16 (95% CI 7 to 47), *low certainty evidence*. In this small RCT, mefloquine was also shown to be comparable to doxycycline in preventing asymptomatic (77%; 95% CI 55 to 88%) and symptomatic malaria (81%; 95% CI 44 to 93%), *low certainty evidence*
- **Mefloquine:** A systematic review by Tickell-Painter *et al.,* 2017[8], of 12 RCTs (n=1908) comparing mefloquine to placebo, showed that mefloquine was highly efficacious in reducing clinical cases of malaria (1.4% vs 21.0%; NNT 6, 95% CI 5 to 7; RR 0.09, 95% CI 0.04 to 0.19; I^2=53%), *low certainty evidence.*

  Overall, mefloquine also reduced cases of parasitaemia by 82% (9.8% vs 60.2%; NNT 2, 95% CI 1.7 to 2.3; RR 0.18, 95% CI 0.06 to 0.55; 3 RCTs; n=414; I^2=80%), *low certainty evidence.*

  And, substantially reduced the number of episodes of parasitaemia (8.4% vs 63.3%; NNT 2, 95% CI 1.6 to 2.1; RR 0.05, 95% CI 0.00 to 5.25; 2 RCTs; n=510; I^2=91%), *low certainty evidence.*

  Study heterogeneity was high, but the direction of the effect was consistent across all trials. Of note is that most study participants had a degree of immunity to malaria.

  Mefloquine was also shown to be comparable to doxycycline in preventing symptomatic malaria (4/378 vs 3/366; RR 1.35, 95% CI 0.35 to 5.1; 4 RCTs; n=744; I^2=3%), *low certainty evidence*.
- **Atovaquone-proguanil:** Tickell-Painter *et al.,* 2017[8] also reviewed efficacy of atovaquone-proguanil (n=657) compared to mefloquine (n=636), and reported no clinical cases of malaria with either agent in 2 RCTs, *low certainty evidence*. The authors concluded that *"the absolute risk of malaria during short-term travel appears low with all three established antimalarial agents".*
  Two later RCTs (Ling *et al.,* 2002[10], n=297; Soto *et al.,* 2006[9], n=144) that were not included in the systematic review confirms atovaquone-proguanil's protective efficacy against *Plasmodium falciparum*. The RCTs showed that atovaquone-proguanil reduced parasitaemia, by 96% and 100%, respectively; *low certainty evidence*.
- **Adverse effects:** Tickell-Painter *et al.,* 2017[8], reported that people were less likely to be non-adherent with atovaquone-proguanil compared to mefloquine due to adverse effects *(high-certainty evidence);* but equally as likely to be non-adherent as those taking doxycycline *(low-certainty evidence).*
  Mefloquine users experienced more abnormal dreams, insomnia, anxiety and depressed mood compared to atovaquone-proguanil users *(moderate-certainty evidence)* or doxycyline *(very low-certainty evidence).*
  Doxycycline users were more likely to have dyspepsia, photosensitivity, vomiting, and vaginal thrush *(very low-certainty evidence).*
- **Pregnancy:** General guidance is that pregnant women should avoid travel to malaria-endemic areas. When chemoprophylaxis is required, mefloquine is considered safe for use in the second and third trimesters of pregnancy[13] but globally, guidelines are increasingly recommending use in the first trimester. Doxycycline is avoided due to effects on skeletal development found in animal studies and there is a paucity of safety data in pregnancy for atovaquone-proguanil. However, mefloquine is not currently available on the South African market.
- **Children:** There is very limited RCT data in children.

PHC LEVEL ERC AND NEMLC RECOMMENDATION:					
Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	

Recommendation: The PHC/Adult Hospital Level Committee suggests that doxycycline be used as malaria chemoprophylaxis in non-pregnant adults.

Rationale: Available evidence shows that doxycycline reduces parasitemia and clinical malaria due to *P falciparum.* Furthermore, mefloquine is currently unavailable in South Africa, and atovaquone-proguanil is unaffordable.

Level of Evidence: Low certainty evidence

Review indicator: Price reduction of atovaquone-proguanil, availability of mefloquine

NEMLC MEETING OF 24 JUNE 2021:

NEMLC Recommendation: The NEMLC accepted the recommendation of doxycycline as malaria chemoprophylaxis as proposed by the PHC/Adult Hospital Level Committee, but included children ≥8 years of age[a].

Recommended dosing:

- *Non-pregnant adults:* Doxycycline oral, 100 mg daily, taken from 2 days prior to entering endemic area until 4 weeks after exiting the endemic area.
- *Children ≥ 8 years of age:* Doxycycline oral, 2.2 mg/kg/dose daily, taken from 2 days prior to entering endemic area until 4 weeks after exiting the endemic area.

Note: Pregnant women and children <8 years of age should avoid travelling to endemic areas. However, if this cannot be avoided, self-provided malaria chemoprophylaxis should be considered (as recommended by the National Department of Health Malaria Treatment Guidelines)

Monitoring and evaluation considerations

Research priorities

a. SAMF, 2020 edition

BACKGROUND

The World Health Organization recommends chemoprophylaxis for migrant workers and travellers, travelling to endemic malaria areas at no cost to the individual.[1] The National Guidelines for the Prevention of Malaria, South Africa (2018) supports South Africa's target for malaria elimination by 2020 and recommends various preventative measures for malaria, including chemoprophylaxis.[2]

The burden of malaria in South Africa, as reported by the South African Malaria Elimination Committee differs from other African regions. Other African regions report malaria cases mostly amongst children and pregnant woman, whilst in South Africa more than 70% cases are in adult males primarily imported from other countries. Those affected are mainly mobile populations who are usually uninsured and unable to access chemoprophylaxis before travel to endemic areas. [3,4]

The National Department of Health's strategic priorities are to (1) advance elimination in areas like KwaZulu Natal sub-districts and (2) reduce morbidity and mortality in Gauteng, where studies showed a malaria case fatality rate of 4% (which exceeds the WHO target of ≤ 0.5%). Due to the high malaria notification rates in Gauteng (a non-malaria endemic province in South Africa) the Gauteng Provincial Department of Health piloted public sector travel clinics, with the provision of malaria chemoprophylaxis to 327 travellers in the 2019/2020 financial year. [3,4]

Local resistance to chloroquine and sulfadoxine-pyrimethamine is common and these agents are currently not recommended as monotherapy for malaria chemoprophylaxis.[2] The currently recommended agents are mefloquine, atovaquone-proguanil and doxycycline which are registered in South Africa. However, mefloquine has recently been withdrawn from the South African market.

Malaria chemoprophylaxis for travellers to malaria-endemic areas is currently not included in the Primary Healthcare Standard Treatment Guidelines and Essential Medicines List. The purpose of this review is to interrogate the evidence (dosing, efficacy, safety and tolerability) for malaria chemoprophylaxis (mefloquine, atovaquone-proguanil or doxycycline) for adults, specifically migrant workers traveling to and from endemic areas outside and within South Africa.

INTRODUCTION

Malaria chemoprophylaxis works by blocking the development or reproduction of the malaria parasite at various stages in its life cycle. Preventative options for the dominant species, *P. Falciparum*, outlined in the National Guidelines for the Prevention of Malaria, South Africa (2018) include atovaquone-proguanil, doxycycline, mefloquine.[5]

Atovaquone 250mg combined with 100 mg proguanil hydrochloride is a fixed dose combination started one to two days before travel to the endemic area. Unlike doxycycline and mefloquine which should be continued for 4 weeks post travel, the atovaquone-proguanil combination can be discontinued a week after leaving an endemic area because atovaquone hydrochloride's mechanism of action is against the early liver stages of *P. falciparum*. However, despite publication of a good side effect profile, there is limited evidence for the use of atovaquone in high-risk groups such as pregnant women, children, and long-term travellers.[5]

Doxycycline is a blood schizontocide. Since these forms of the parasite are only present later in the malarial lifecycle, doxycycline must be continued for at least 4 weeks post travel to the malaria area. Areas of concern include its gastrointestinal tolerance, its contraindication in pregnancy and the side effect of photosensitivity. Doxycycline for malaria use is taken as a single daily dose of 100mg, starting one to two days before entering the endemic area, continuing daily while in the endemic area and only stopping the daily dose 4 weeks after leaving the endemic area.[5]

Mefloquine, which also acts on the malarial blood schizonts, offers a once weekly dosing advantage which encourages adherence[6]. Mefloquine is started 1 week before travel and like doxycycline is taken until 4 weeks after return from the malaria area. The agent can be used for long term travellers, pregnant women, breastfeeding women, small children weighing >5 kg and is a popular choice due to the dosing convenience. The recommended adult dose for chemoprophylaxis is 250 mg weekly as a single dose.[5]

Adverse events associated with malaria chemoprophylaxis, particularly neuropsychiatric side effects may affect adherence rates.

To reach a recommendation for the PHC STGs and EML, a review of the efficacy and safety profile is required for malaria prophylaxis.

QUESTION: Which Malaria Prophylaxis regimen should be recommended for travellers to malaria endemic areas in and outside South Africa?

METHODS

Eligibility criteria for review

Population: Children & Adults at risk of malaria

Intervention: Antimalarial agent used as prophylaxis [atovaquone-proguanil, doxycycline & mefloquine]

Comparators: Placebo, or no treatment, or alternative antimalarial

Outcomes: Malaria incidence, deaths, deaths due to malaria, safety

Study designs: Systematic Reviews and RCTs

Two reviewers (JN, MR) searched two electronic databases (Cochrane library and PubMed) on 17th and 19 February 2021, including systematic reviews and meta-analyses of randomised controlled trials (RCTs). We excluded observational studies, case reports, case series and narrative reviews. Publications were restricted to those published in English. The search strategy is shown in Appendix 1. One reviewer screened records and extracted data (MR). Screening of records was done independently and in duplicate (JN, MR), with disagreement resolved through discussion. Excluded studies with the rationale for exclusion are summarised in Table 1; whilst relevant study data were extracted in a narrative table of results (MR, TL). JN and PN reviewed the overall report.

The quality of evidence was assessed independently using the AMSTAR 2 tool[7] for systematic reviews (MR, JN, PN, TL).

RESULTS

Results of search

A search resulted in a total of 62 articles (Pubmed (n=53) and the Cochrane Library (n=9)). After the removal of 20 duplicates, 42 articles were reviewed for eligibility by two reviewers (JN, MR). One systematic review was selected. Of the remaining 41 articles 29 studies were excluded due to studies not meeting PICO or an update of the study being available. Of the remaining 13 records, 10 RCTs were excluded because the studies were included in the systematic review. Bibliographies of excluded systematic reviews were checked to ensure that no RCTs were missed. One RCT was identified and included, while a further 2 studies were excluded. After discussions, one RCT from the systematic review was extracted and elaborated on in the review. Therefore, 4 studies (1 systematic review[8] and 3 RCTs[9, 10, 11]) were included in this review.

Studies were excluded if they did not meet the eligibility criteria or were systematic reviews that included duplicate RCTs already included in other reviews. Table 1 summarises the studies excluded from the review. Table 2 reports the main characteristics and outcomes reported in the included systematic reviews and RCTs.

Description of the included studies

One systematic review and 3 RCTs were included in this review. Two of the 3 RCTs were not included in the systematic review, whilst the RCT of doxycycline was extracted from the systematic review to provide more information on doxycycline as an antimalarial agent. The study populations in the included studies included pregnant woman, travellers from endemic areas (male and female) and male soldiers. RCT evidence for children is very limited and this

topic has been deferred to the Paediatric Hospital Level Committee for further review. A description of the included studies follows.

Tickell-Painter *et al*., 2017[8] conducted a systematic review of 20 RCTs (n=11,470), 35 cohort studies (n=198,493) and 4 large retrospective analyses (n=800,652) of health records in adults (including pregnant woman and children).

The systematic review was considered to be of high quality (see the Amstar2 assessment in appendix 2).

MEFLOQUINE VS PLACEBO

Efficacy: Mefloquine was highly efficacious in reducing clinical cases of malaria [17/1179 (1.4%) vs 153/729 (21.0%); NNT 6 (95% CI 5 to 7); RR 0.09 (95% CI 0.04 to 0.19); I^2=53%], *low certainty evidence* (see figure 1).

Overall, mefloquine also reduced cases of parasitaemia by 82% [18/183 (9.8%) vs 139/231(60.2%); NNT 2 (95% CI 1.7 to 2.3); RR 0.18, 95% CI 0.06 to 0.55; 3 RCTs; n=414; I^2=80%], *low certainty evidence.*

Mefloquine also substantially reduced the number of episodes of parasitaemia [22/262 (8.4%) vs 157/248 (63.3%); NNT 2 (95% CI 1.6 to 2.1); RR 0.05, 95% CI 0.00 to 5.25; 2 RCTs; n=510; I^2=91%], *low certainty evidence.*

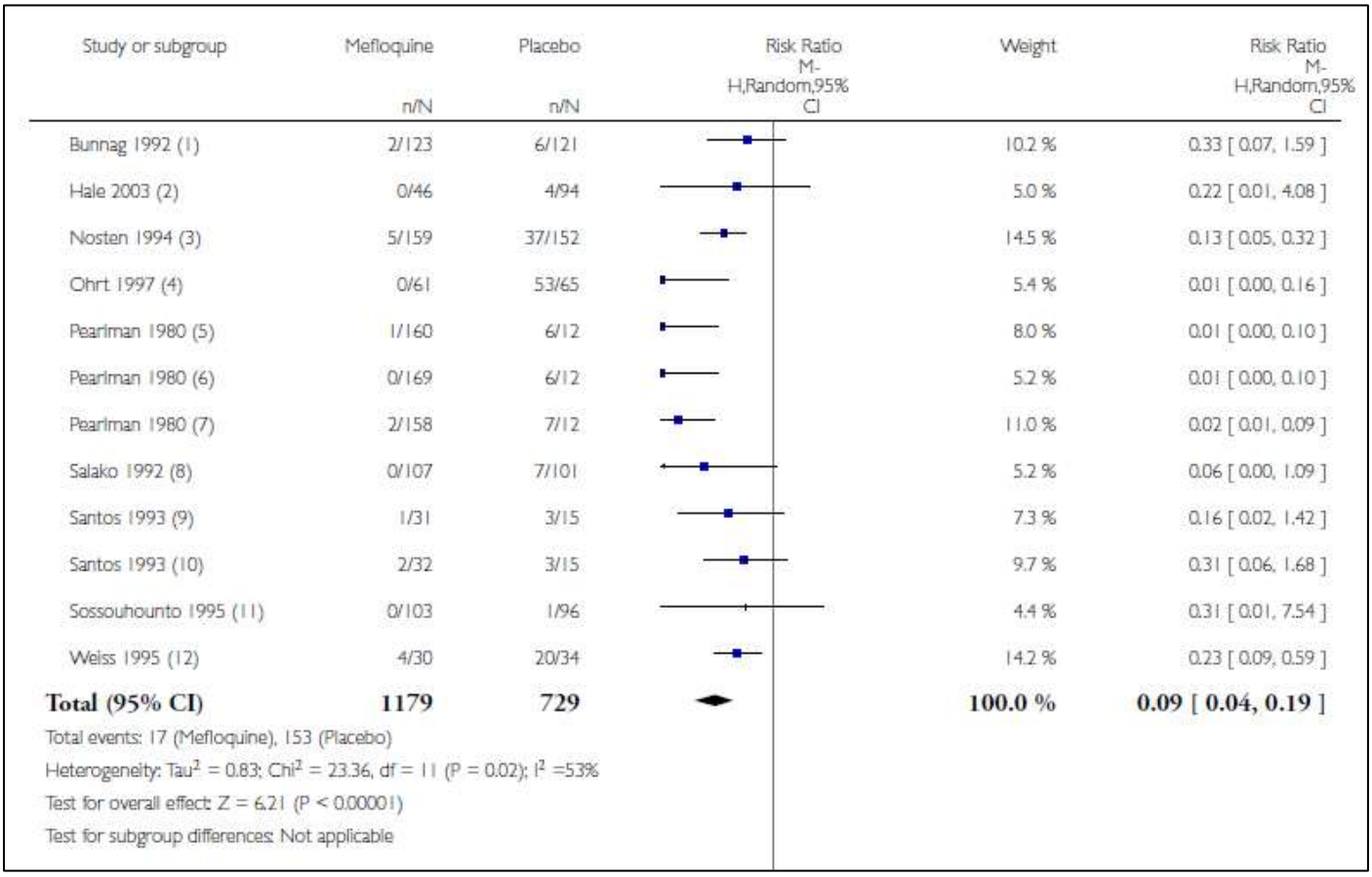

Figure 1: Forest plot of mefloquine vs placebo/non users for the outcome: clinical cases of malaria

Adverse events:

Seven serious adverse effects (n=5 psychological (depression) and n=2 neurological (dizziness)) was 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 cohort studies, n=1167). NNH=130 (95%CI: 75.0 to 497.75 for the mefloquine group).

- Nausea: Mefloquine users were more likely to experience nausea than those who took placebo (RR 1.35, 95% CI 1.05 to 1.73; 2 trials, n=244).
- Vomiting, abdominal pain or diarrhoea: No difference between groups. One RCT in pregnant women reported on both upper and lower abdominal pain.
- Neurological symptoms: Mefloquine users were no more likely to experience headache (RR 0.84, 95% CI 0.71 to 0.99; 5 trials, n=791) or dizziness (RR 1.03, 95% CI 0.90 to 1.17; 3 trials, n=452). Psychological symptoms: None of the RCTs reported on prespecified psychological symptoms.

- Other: No difference between groups for visual impairment and vertigo in RCTs. Respiratory tract infection reached statistical significance between groups in a single trial with few events (RR 2.63, 95%CI 1.04 to 6.61; 1 trial, n=140).
- Pregnancy outcomes: No difference for spontaneous abortions (RR 0.48, 95% CI 0.04 to 5.22; n=311), still births (RR 2.63, 95%CI 0.86 to 8.08; n=311) 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.

Discontinuation: Discontinuation due to adverse effects was low in both groups: 6/541 (1.1%) with mefloquine vs 4/583 (0.7%) with placebo (RR 1.64, 95% CI 0.55 to 4.88; 7 trials, n=1124).

MEFLOQUINE VS DOXYCYCLINE

Efficacy: Mefloquine shown to be comparable to doxycycline in preventing clinical malaria (4/378 vs 3/366 clinical cases; RR 1.35, 95% CI 0.35 to 5.1; 4 RCTs; n=744; I^2=3%), low certainty evidence. The RCT by Weiss et al (1995)[11], included in the analysis reported on episodes of parasitaemia in the semi-immune population, but there was no clear difference between the groups (RR 1.47, 95% CI 0.68 to 3.14; n=62). See figure 2, below.

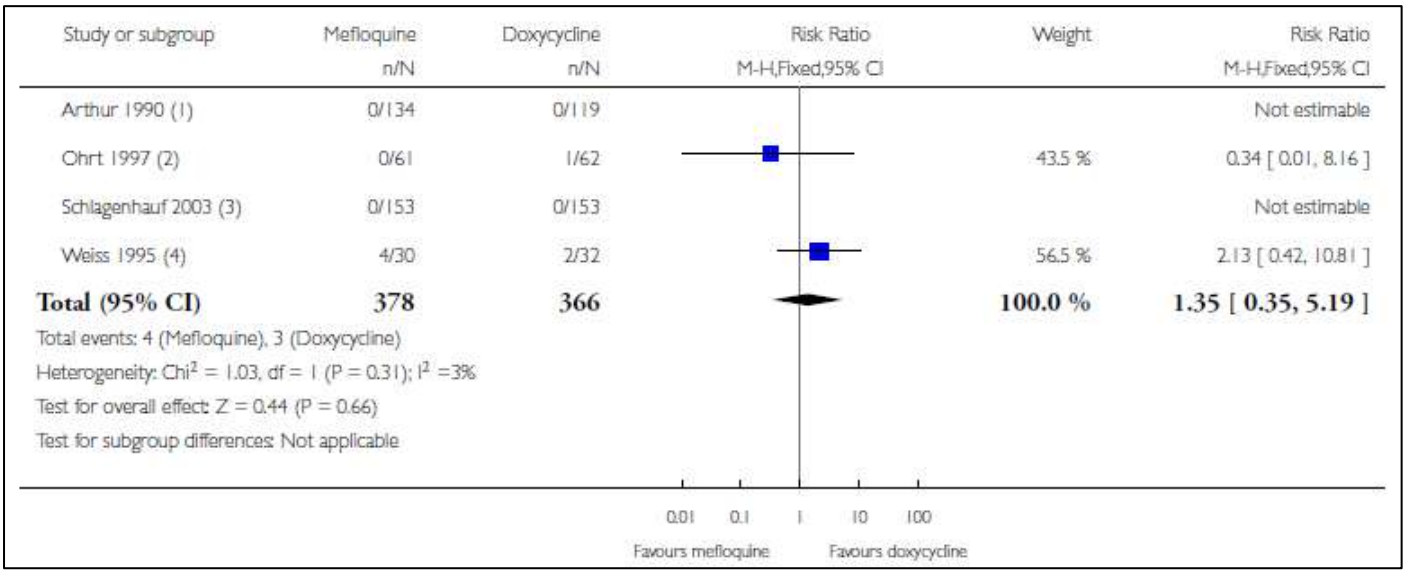

Figure 2: Forest plot of mefloquine vs doxycycline for the outcome: clinical cases of malaria.

Adverse events:
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, n=763; *low-certainty evidence*).

Safety data from 6 cohort studies in longer-term occupational travellers reporting on adverse effects, 1 RCT in military personnel and 1 cohort study in short-term travellers was analysed. Mefloquine users were reported to be more likely to report abnormal dreams (RR 10.49, 95% CI 3.79 to 29.10; 4 cohort studies, n= 2588 participants, *very low-certainty evidence*), insomnia (RR 4.14, 95% CI 1.19 to 14.44; 4 cohort studies, n= 3212, *very low-certainty evidence*), anxiety (RR 18.04, 95%CI 9.32 to 34.93; 3 cohort studies, n=2559 participants, *very low-certainty evidence*), and depressed mood (RR 11.43, 95% CI 5.21 to 25.07; 2 cohort studies, n=2445, *very low-certainty evidence*). However, the RCT in military personnel did not demonstrate a difference between groups in frequencies of abnormal dreams or insomnia.

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

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

MEFLOQUINE VS ATOVAQUONE-PROGUANIL

Efficacy: No clinical cases of malaria were recorded amongst 636 mefloquine users or 657 atovaquone-proguanil users (2 RCTs).

Adverse events: The mefloquine group was more likely to discontinue medication due to adverse effects vs atovaquone-proguanil (RR 2.86, 95% CI 1.53 to 5.31; 3 RCTs, n=1438, high certainty evidence) and there were few SAEs reported (15/2651 amongst mefloquine users and 0/940 amongst atovaquone-proguanil users).

Safety data from 1 RCT and 6 cohort studies were analysed. 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 (RR 2.72, 95% CI 1.52 to 4.86; n=976, *high-certainty evidence*) and dizziness (RR 3.99, 95% CI 2.08 to 7.64, *high-certainty evidence*).

Based on the available evidence, estimates of absolute effect sizes for mefloquine vs atovaquone-proguanil users were reported as 6% vs 2% for discontinuation of the drug, 13% vs 3% for insomnia, 14% vs 7% for abnormal dreams, 6% vs 1% for anxiety, and 6% vs 1% for depressed mood.

ATOVAQUONE-PROGUANIL VS PLACEBO

Two additional RCTs were reviewed, as they were not included in the systematic review:

- Soto *et al*., 2006[9] compared atovaquone/proguanil hydrochloride 250/100mg with placebo in a double-blind, RCT (n=180 male soldiers) in predominately *Plasmodium vivax* areas of Colombia, and
- Ling *et al*., 2002[10] conducted a randomized, double-blinded RCT (n=297) of migrants moving from non-endemic areas in Indonesia to endemic Papua about 26 months prior to the start of the study. Atovaquone/proguanil hydrochloride 250/100mg (n=148) was compared to placebo (n=149) per day for 20 weeks. Only 85/148 study participants from the atovaquone-proguanil and 124/149 from the placebo group, completed the study.

Efficacy:

- Soto *et al*., 2006[9] showed that of atovaquone-proguanil's protective efficacy for *Plasmodium falciparum* was 100%. No cases (0/120) of *Plasmodium falciparum* infection was reported with use of atovaquone-proguanil, whilst 2 case (2/60) occurred in the control arm.
- In the study by Ling *et al*., 2002[10] protective efficacy of atovaquone/proguanil against *Plasmodium falciparum* was shown to be 96% (95% CI, 72 to 99%) when compared to placebo – 1/150 cases reported in the atovaquone/proguanil group and 23/149 were reported in the placebo group. Malaria cases due to co-infection with both *Plasmodium vivax* and *Plasmodium falciparum* were also reported. The overall protective efficacy of atovaquone/proguanil against *Plasmodium falciparum* and *Plasmodium vivax* infection was reported to be 93% (95% CI, 77%–98%). The study was double-blinded and an ITT analysis was used; however, as attrition rate was >20%, being much higher in the atovaquone/proguanil than the placebo group, the evidence was considered of very low quality.

Adverse Events:

- *Serious Adverse Events:* Soto *et al*., 2006[9] reported no serious adverse. Ling *et al*., 2002[10] reported that four atovaquone-proguanil subjects had severe adverse effects (3 abdominal pain and 1 skin rash). However, the skin rash was considered potentially viral as 2 other non-study subjects in the same village had a similar occurrence.

- *Discontinuation of antimalarial*: Soto *et al*., 2006[9] had no subject discontinuing study medication because of adverse events. In the study by Ling *et al*., 2002[10],4 participants withdrew from the study due to adverse events (one in the atovaquone-proguanil group and 3 in the control group).
- *Common adverse events:* Soto *et al*., 2006[9] reported the following adverse events for atovaquone-proguanil vs placebo as*:* tinea infection (18% vs 28%), parasitic gastrointestinal infection (7% vs 5%), headache (7% vs 3%) and fever (5% vs 0%). In Ling *et al*., 2002[10], stomatitis and back pain appeared more frequently amongst atovaquone-proguanil recipients and abdominal pain and malaise occurred more frequently in the placebo group).

DOXYCYCLINE VS CONTROL

Weiss et al.[11] conducted a study on Kenyan children (9-14 years of age), n=169. It included several arms in two groups (weekly and daily prophylaxis groups). Following curative treatment, participants in the daily prophylaxis groups were randomised to doxycycline vs primaquine vs proguanil + weekly chloroquine vs weekly mefloquine + vitamin vs vitamin alone. Each were given for 11 weeks, with a 3-week subsequent follow-up period. For the purposes of comparison, the multivitamin tablet can be considered a placebo. Outcomes measured were parasitaemia, clinical malaria and side effects. Compared to vitamins (placebo), doxycycline was 84% effective (95% CI 66-92%) at preventing parasitaemia; NNT 4 95% CI 3 to 10), and 91% effective (95% CI 61 to 98%) at preventing clinical malaria; NNT 16 (95% CI 7 to 47). No significant differences in side effects between the vitamin group and the group receiving doxycycline.

LOCAL RESISTANCE PATTERNS

The South African Malaria Elimination Committee advised that local susceptibility is not collected for malaria. However, there is some concerning evidence for artemesinin resistance in some parts of Africa. Regarding prophylaxis, there is no indication that atovaquone/proguanil or doxycycline or mefloquine are facing resistance challenges. However, previous prophylaxis regimens (chloroquine and choroquine-proguanil) are no longer acceptable, based on resistance.[12]

PREGNANCY-RELATED OUTCOMES

All guidelines recommend that pregnant women should avoid not travel to malaria-endemic areas, however if this is unavoidable, mefloquine is the preferred option. Mefloquine is considered to be safe within the second and third trimesters of pregnancy and guidelines are increasingly recommending use in the first trimester. Mefloquine is also suitable for children who weigh more than 5 kg and breastfeeding mothers. Doxycycline has restrictions on its use during pregnancy due to effects on skeletal development found in animal studies. For atovaquone-proguanil, there is a paucity of safety data in pregnancy.

For serious pregnancy-related outcomes, Tickell-Painter *et al*. 2017[8] report on the findings from Nosten *et al*.[13] that reported 4 congenital malformations in the mefloquine study arm: 1 case of limb dysplasia, 2 cases of ventricular septal defect, and 1 case of amniotic bands (1 case) and one case of anencephaly in the placebo group. However, all were considered to be unrelated to mefloquine prophylaxis.

CONCLUSION

Available evidence shows that atovaquone-proguanil, doxycycline or mefloquine has comparable protective efficacy against *Plasmodium falciparum,* when compared to placebo. Discontinuation of therapy due to associated adverse events was more likely with mefloquine and doxycycline and less likely with atovaquone-proguanil. Mefloquine is associated with more neurological disorders (abnormal dreams, insomnia, anxiety and depressed mood), whilst doxycycline was reported to more likely be associated with dyspepsia, photosensitivity, vomiting, and vaginal thrush. Mefloquine is considered the safest option in pregnancy, but is currently not available in South Africa. Factors for consideration to determine the choice of antimalarial agent includes resistance patterns of the affected malaria-endemic area(s), associated adverse events and pill burden, that would impact patient adherence, and cost.

Reviewer(s): Ms T Leong, Dr R Reddy, Dr J Nel, Prof P Nyasulu.

Declaration of interests: TL (Essential Drugs Programme, National Department of Health), MR (Better Health Programme, South Africa), JN (Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand) and PN (Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University) have no conflicts to declare pertaining to this review.

Table 2: Excluded studies

No	Reference	Reason for Exclusion
1	González R et al. Mefloquine for preventing malaria in pregnant women. Cochrane Database Syst Rev. 2018 Mar 21;3(3):CD011444. Doi: 10.1002/14651858.CD011444.pub2. Update in: Cochrane Database Syst Rev. 2018 Nov 14;11:CD011444.	Duplicate /Update available
2	Rodrigo C, et al . Tafenoquine for primary and terminal prophylaxis of malaria in apparently healthy people: a systematic review. Trans R Soc Trop Med Hyg. 2019 Oct 11;113(10):579-586. Doi: 10.1093/trstmh/trz052.	Does Not Meet PICO
3	Tickell-Painter M, et al. Deaths and parasuicides associated with mefloquine chemoprophylaxis: A systematic review. Travel Med Infect Dis. 2017 Nov-Dec;20:5-14. Doi: 10.1016/j.tmaid.2017.10.011.	Case Reports and only 1 RCT included in the Cochrane Review
4	González et al. Mefloquine safety and tolerability in pregnancy: a systematic literature review. Malar J. 2014 Feb 28;13:75. Doi: 10.1186/1475-2875-13-75.	Of the relevant RCTs, these were included in Cochrane Review
5	Croft AM, Garner P. WITHDRAWN: Mefloquine for preventing malaria in non- immune adult travellers. Cochrane Database Syst Rev. 2008 Jan 23;2000(1):CD000138. Doi: 10.1002/14651858.CD000138.pub2. PMID: 18253969; PMCID: PMC6532714.	Withdrawn
6	Croft AM et al . Mefloquine for preventing malaria in non-immune adult travellers. Cochrane Database Syst Rev. 2000;(4):CD000138. Doi: 10.1002/14651858.CD000138. Update in: Cochrane Database Syst Rev. 2008;(1):CD000138.	Review Updated
7	Croft A et al . Mefloquine to prevent malaria: a systematic review of trials. BMJ. 1997 Nov 29;315(7120):1412-6. Doi: 10.1136/bmj.315.7120.1412. PMID: 9418088; PMCID: PMC2127902.	Articles included in Cochrane Review
8	Muanda FT et al. Antimalarial drugs for preventing malaria during pregnancy and the risk of low birth weight: a systematic review and meta-analysis of randomized and quasi-randomized trials. BMC Med. 2015 Aug 14;13:193. Doi:10.1186/s12916-015-0429-x.	Of 25 RCTS – 24 appear in one of the Cochrane Reviews. 1 Article was not relevant
9	Croft AM. Malaria: prevention in travellers. BMJ Clin Evid. 2010 Jul 12;2010:0903. PMID: 21418669; PMCID: PMC3217660.	Excluded - Duplicate RCTs included in this review.
10	Zhou LJ et al. Risk of drug resistance in *Plasmodium falciparum* malaria therapy-a systematic review and meta-analysis. Parasitol Res. 2017 Feb;116(2):781-788. Doi: 10.1007/s00436-016-5353-2.	Treatment / Does Not Meet PICO
11	Bitta MA et al . Antimalarial drugs and the prevalence of mental and neurological manifestations: A systematic review and meta-analysis. Wellcome Open Res. 2017 Jun 2;2:13. Doi: 10.12688/wellcomeopenres.10658.2.	Of the 50 articles included, some were included in the Cochrane Review, others were not applicable
12	Jacquerioz FA et al. Drugs for preventing malaria in travellers. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006491. Doi: 10.1002/14651858.CD006491.pub2. Update in: Cochrane Database Syst Rev. 2015;10:CD006491.	Update Available
13	Croft AM. Malaria: prevention in travellers. BMJ Clin Evid. 2007 Nov 29;2007:0903.	Duplicate /Update Available
14	Griffith KS et al . Treatment of malaria in the United States: a systematic review. JAMA. 2007 May 23;297(20):2264-77. Doi: 10.1001/jama.297.20.2264.	Malaria treatment
15	Frimpong A et al. Safety and effectiveness of antimalarial therapy in sickle cell disease: a systematic review and network meta-analysis. BMC Infect Dis. 2018 Dec 12;18(1):650. Doi: 10.1186/s12879-018-3556-0. PMID: 30541465; PMCID: PMC6292161.	Does Not Meet PICO requirements
16	Graves PM et al. Primaquine or other 8-aminoquinolines for reducing *Plasmodium falciparum* transmission. Cochrane Database Syst Rev. 2018 Feb 2;2(2):CD008152. Doi: 10.1002/14651858.CD008152.pub5. PMID: 29393511; PMCID: PMC5815493.	Does Not Meet PICO requirements
17	Kolifarhood G et al. Prophylactic efficacy of primaquine for preventing *Plasmodium falciparum* and *Plasmodium vivax* parasitaemia in travelers: A meta-analysis and systematic review. Travel Med Infect Dis. 2017 May-Jun;17:5-18. Doi: 10.1016/j.tmaid.2017.04.005. Epub 2017 Apr 24. PMID: 28450185.	Does Not Meet PICO requirements
18	Graves PM et al. Primaquine or other 8-aminoquinoline for reducing *Plasmodium falciparum* transmission. Cochrane Database Syst Rev. 2015 Feb 19;(2):CD008152. Doi: 10.1002/14651858.CD008152.pub4. Update in: Cochrane Database Syst Rev. 2018 Feb 02;2:CD008152. PMID: 25693791; PMCID: PMC4455224.	Does Not Meet PICO requirements
19	Graves PM et al. Primaquine for reducing *Plasmodium falciparum* transmission. Cochrane Database Syst Rev. 2012 Sep 12;(9):CD008152. Doi: 10.1002/14651858.CD008152.pub2. Update in: Cochrane Database Syst Rev. 2014;(6):CD008152. PMID: 22972117.	Does Not Meet PICO requirements
20	Graves et al. Primaquine or other 8-aminoquinoline for reducing *P. falciparum* transmission. Cochrane Database Syst Rev. 2014 Jun 30;(6):CD008152. Doi: 10.1002/14651858.CD008152.pub3. Update in: Cochrane Database Syst Rev. 2015;(2):CD008152. PMID: 24979199; PMCID: PMC4456193.	Does Not Meet PICO requirements
21	Jacquerioz FA et al. WITHDRAWN: Drugs for preventing malaria in travellers. Cochrane Database Syst Rev. 2015 Oct 5;(10):CD006491. Doi: 10.1002/14651858.CD006491.pub3. Update in: Cochrane Database Syst Rev. 2017 Oct 30;10 :CD006491. PMID: 26436859.	Paper Withdrawn
22	Hossain MS et al. The risk of Plasmodium vivax parasitaemia after *P. falciparum* malaria: An individual patient data meta- analysis from the WorldWide Antimalarial Resistance Network. PloS Med. 2020 Nov 19;17(11):e1003393. Doi: 10.1371/journal.pmed.1003393.	Does Not Meet PICO requirements
23	Garner P et al. A review of randomized controlled trials of routine antimalarial drug prophylaxis during pregnancy in endemic malarious areas. Bull World Health Organ. 1994;72(1):89-99.	Relevant papers included in the Cochrane Review
24	Goetze S et al. Phototoxicity of Doxycycline: A Systematic Review on Clinical Manifestations, Frequency, Cofactors, and Prevention. Skin Pharmacol Physiol. 2017;30(2):76-80.	Does Not Meet PICO requirements

No	Reference	Reason for Exclusion
25	Andrejko KL, et al. The safety of atovaquone-proguanil for the prevention and treatment of malariain pregnancy: A systematic review. Travel Med Infect Dis. 2019 Jan-Feb;27:20-26.	Not Relevant to Prophylaxis/ Does Not Meet PICO requirements
26	Savelkoel J et al. Abbreviated atovaquone-proguanil prophylaxis regimens in travellers after leaving malaria-endemic areas: A systematic review. Travel Med Infect Dis. 2018 Jan Feb;21:3-20.	Does not Meet PICO requirements
27	Staines HM et al. Clinical implications of Plasmodium resistance to atovaquone/proguanil: a systematic review and meta-analysis. J Antimicrob Chemother. 2018 Mar 1;73(3):581-595.	Treatment/ Does Not Meet PICO requirements
28	Nakato H et al. A systematic review and meta-analysis of the effectiveness and safety of atovaquone proguanil (Malarone) for chemoprophylaxis against malaria. J Antimicrob Chemother. 2007 Nov;60(5):929-36.	3 RCTs from this review that were not included in the Cochrane Reviews
29	Garner P et al. Drugs for preventing malaria in pregnant women. Cochrane Database Syst Rev. 2006 Oct 18;(4):CD000169.	Does Not Meet PICO requirements
30	Leoni S et al. The hyper-reactive malarial splenomegaly: a systematic review of the literature. Malar J. 2015 Apr 29;14:185.	Does Not Meet PICO requirements
31	Raquel González et al Mefloquine for preventing malaria in pregnant women. Cochrane Database Syst Rev. 2018 Mar 21;3(3):CD011444	Does Not Meet PICO requirements
32	Tickell-Painter M et al Mefloquine for preventing malaria during travel to endemic areas. Cochrane Database Syst Rev. 2017 Oct 30;10(10):CD006491.	Duplicate
33	Piero L Olliaro et al. Amodiaquine for treating malaria. Cochrane Database Syst Rev. 2000;(2):CD000016.	Does Not Meet PICO requirements
34	Oniyangi O et al. Malaria chemoprophylaxis in sickle cell disease. Cochrane Database Syst Rev. 2019 Nov 4;2019(11)	Does Not Meet PICO requirements
35	Gogtay N et al. Artemisinin-based combination therapy for treating uncomplicated Plasmodium vivax malaria. Cochrane Database Syst Rev. 2013 Oct 25;2013(10):CD008492.	Does Not Meet PICO requirements
36	Mathanga DP et al.Intermittent preventive treatment regimens for malaria in HIV-positive pregnant women. Cochrane Database Syst Rev. 2011 Oct 5;2011(10):CD006689.	Does Not Meet PICO requirements
37	Radeva-Petrova D et al Drugs for preventing malaria in pregnant women in endemic areas: any drug regimen versus placebo or no treatment. Cochrane Database Syst Rev. 2014 Oct 10;2014(10):CD000169.	Duplicate
38	Tomas Pantoja et al. Implementation strategies for health systems in low-income countries: an overview of systematic reviews.. Cochrane Database Syst Rev. 2017 Sep 12;9(9):CD011086.	Does Not Meet PICO requirements
39	Catherine Lees et al. Neonatal screening for sickle cell disease Intervention. Cochrane Database Syst Rev. 2000;(2):CD001913.	Does Not Meet PICO
40	Radeva-Petrova D et al. Drugs for preventing malaria in pregnant women in endemic areas: any drug regimen versus placebo or no treatment. Cochrane Database Syst Rev. 2014 Oct 10;2014(10):CD000169.	Only 1 paper relevant to PICO and was already included in Tickell-Painter Cochrane Review
41	Raquel González et al Mefloquine for preventing malaria in pregnant women. Cochrane Database Syst Rev. 2018 Mar 21;3(3):CD011444	Duplicate
42	Høgh B, et al - Malarone International Study Team. Atovaquone-proguanil versus chloroquine-proguanil for malaria prophylaxis in non-immune travellers: a randomised, double-blind study. Malarone International Study Team. Lancet. 2000 Dec 2;356(9245):1888-94.	Does Not Meet PICO requirements

RCT = Randomized Control Trial

Table 2: Characteristics of included studies

1) SYSTEMATIC REVIEW:

Citation	Study design	Population (n)	Treatment	Outcomes	Effect sizes	Comments
Tickell-Painter *et al.*, 2017[8]	Systematic Review: 20 RCTs, 35 cohort studies 4 large retrospective analyses of health records	Adults & children, including pregnant women. RCTs (n=11,470) Cohort studies (n=198,493) Retrospective Analyses (n=800,652) 9 RCTs excluded participants with a psychiatric history. 25 cohort studies choice of antimalarial based on medical history & personal preference	Mefloquine,250 mg once weekly in adults & equivalent dosing for children, vs placebo/ no intervention or alternative malaria chemoprophylaxis	**Efficacy:** Clinical cases of malaria **Safety:** • Adverse effects • Discontinuations due to adverse effects. • Adherence • Pregnancy-related outcomes: - adverse pregnancy outcomes - spontaneous abortions, stillbirths, congenital malformations.	**Efficacy:** <u>Mefloquine vs placebo:</u> • Developing malaria episode: o in the control arm varied from 1% to 82% (median 22%) & o 0% to 13% in the mefloquine group (median 1%). • Developing parasiteamia o 18/189 vs 139/231; NNT 11 (95% CI 8 to 19) <u>Mefloquine vs atovaquone-proguanil</u> o No clinical cases of malaria were recorded (2 RCTs, 636 mefloquine users; 657 atovaquone-proguanil users). **Doxycycline vs Mefloquine:** Similar numbers of participants were infected in both arms (3/366 doxycycline users vs 4 / 378 mefloquine users: RR 1.35, 95% CI 0.35 to 5.19; 4 trials, 744 participants) **<u>Safety:</u>** ***Mefloquine vs atovaquone-proguanil*** • Mefloquine grp more likely to: o discontinue medication due to AEs vs atovaquone-proguanil (RR 2.86, 95% CI 1.53 to 5.31; 3 RCTs, 1438 participants; NNT17 (95% CI 10 to 75) ***high-certainty evidence***). ▪ 15/2651 travellers) and 0 with atovaquone-proguanil (940 travellers). o more likely to report: ▪ abnormal dreams (RR 2.04, 95% CI 1.37 to 3.04, NNT 8 (95% CI 5 to 14) (***moderate-certainty evidence***), ▪ insomnia (RR 4.42, 95% CI 2.56 to 7.64, NNT 8 (95% CI 6 to 16) (***moderate-certainty evidence***), ▪ anxiety (RR 6.12, 95% CI 1.82 to 20.66, NNT 17 (95% CI 10 to 75) ***moderate-certainty evidence***), & ▪ depressed mood during travel (RR 5.78, 95% CI 1.71 to 19.61, NNT 17 (95% CI 10 to 75) ***moderate-certainty evidence***).	Systematic review of RCTs to determine efficacy and safety of various antimalarial agents. Observational studies were included in the safety review. Assessed as a high quality systematic review – see appendix 2 for the AMSTAR2 assessment. Included studies, though, were of low to very low quality.

Citation	Study design	Population (n)	Treatment	Outcomes	Effect sizes	Comments
					▪ nausea NNT 13 (95%CI 8 to 38) (**high-certainty evidence**) ▪ dizziness NNT 13 (95% CI 8 to 13) (***high-certainty evidence***). • **Absolute effect sizes: Mefloquine vs atovaquone-proguanil:** o 6% vs 2% - drug discontinuation o 13% vs 3% for insomnia o 14% vs 7% for abnormal dreams o 6% vs 1% for anxiety & o 6% vs 1% for depressed mood ***Doxycycline vs Mefloquine (Mefloquine RR reported)*** • No difference in serious adverse effects (***low-certainty evidence***) • No difference in discontinuations due to AEs (RR 1.08, 95% CI 0.41 to 2.87; 4 RCTs, 763 participants; ***low-certainty evidence***). • Doxycycline - less likely to report. Mefloquine RR reported o abnormal dreams (RR 10.49, 95% CI 3.79 to 29.10; 4 cohort studies, n=2588, ***very low-certainty evidence***), o insomnia (RR 4.14, 95% CI 1.19 to 14.44; 4 cohort studies, n=3212, ***very low-certainty evidence***), o anxiety (RR 18.04, 95% CI 9.32 to 34.93; 3 cohort studies, n=2559 ***very low-certainty evidence***), & o depressed mood (RR 11.43, 95% CI 5.21 to 25.07; 2 cohort studies, n=2445, ***very low-certainty evidence***). • Doxycycline more likely to report. Mefloquine RR reported o dyspepsia (RR 0.26, 95% CI 0.09 to 0.74; 5 cohort studies, n=5104, ***low certainty evidence***), o photosensitivity (RR 0.08, 95% CI 0.05 to 0.11; 2 cohort studies, n=1875, ***very low-certainty evidence***), o vomiting (RR 0.18, 95% CI 0.12 to 0.27; 4 cohort studies, n=5071) & o vaginal thrush (RR 0.10, 95% CI 0.06 to 0.16; 1 cohort study, n=1761, ***very low-certainty evidence***). • Based on the available evidence - **best estimates of absolute effect** - doxycycline vs mefloquine: o 2% vs 2% for discontinuation, o 3% vs 12% vs for insomnia,	

Citation	Study design	Population (n)	Treatment	Outcomes	Effect sizes	Comments
					○ 3% vs 31% for abnormal dreams, ○ 1% vs 18% for anxiety, ○ 1% vs 11% for depressed mood, ○ 14% vs 4% for dyspepsia, ○ 19% vs 2% for photosensitivity, ○ 5% vs 1% for vomiting, & ○ 16% vs 2% for vaginal thrush	

2) RANDOMISED CONTROLLED STUDIES:

• **ATOVAQUONE/PROGUANIL VS PLACEBO**						
Citation	**Study design**	**Population (n)**	**Treatment**	**Outcomes**	**Effect sizes**	**Comments**
Soto *et al*, 2006[9]	Phase IV, randomized, double blind, placebo-controlled single center trial	Colombia Non-immune Colombian soldiers, male, average age 19 years (17 to 27 years) Average weight 63 kg (48-81kg) 75% Hispanic & 25% black N=180 (120 atovaquone proguanil and 60 placebo)	250mg atovaquone + 100mg proguanil vs placebo One tablet daily with breakfast, from 1 day before entering the malaria endemic areas through 10–16 weeks of residence in the area and for 7 days after leaving the endemic areas Plasma sample was collected between weeks 5 and 7 and weeks 10 and 12, and if malaria exhibited, for determination drug concentrations	• Parasitemia Proportion who failed prophylaxis = number of subjects who failed/number of subjects treated Protective efficacy = 1– (proportion of atovaquone-proguanil failures/ proportion of placebo failures)	• n=24 unevaluable due to compliance issues, including n=1 atovaquone-proguanil subject (no detectable drug levels) who became infected -*P. vivax.* • 0/ 97 (100%) evaluable subjects who received atovaquone-proguanil parasitemic • 11/ 47 (23.4%) evaluable placebo subjects became infected with *P. vivax* and 2/47 (4.3%) infected with *Plasmodium falciparum*. • Protective efficacy of atovaquone-proguanil for all malaria and for *P. vivax* malaria was 100% (LL 95% CI =63%) and 100% (LL 95% CI = 58%), respectively (NNT 4, 95% CI 3 to 7) - and was 96% if the one case with undetectable blood levels was included. **<u>Adverse Events (AEs):</u>** • *Serious Adverse Events:* No SAEs reported. • *Discontinuation of antimalarial*: No subject discontinuing study medication because of adverse events. • *Common adverse events:* For atovaquone-proguanil vs placebo: tinea infection (18% vs 28%), parasitic gastrointestinal infection (7% vs 5%), headache (7% vs 3%) and fever (5% vs 0%).	Atovaquone-proguanil showed high protective efficacy compared to placebo. Small double-blinded RCT of very low certainty of evidence, with a very high attrition rate, restricted to male soldiers only.

Ling *et al*., 2002[10]	Randomized, double-blinded study	Individuals from non-endemicity (3 villages) in Indonesia who migrated to Papua (where malaria is endemic) ≤26 months before the study period
		
		N=297
		
		Aged 12–65 years and weighed 40 kg.
			3 distinct phases: (1) 17-day period of radical cure treatment, 20 weeks of prophylaxis, and 4 weeks of postprophylaxis follow up. Consisted of 1000mg of atovaquone and 400mg of proguanil hydrochloride (4 tablets, containing 250 mg of atovaquone and 100 mg of proguanil hydrochloride per tablet) given once daily with food for 3 days, followed by 2 primaquine phosphate tablets (15 mg primaquine per tablet) once daily for 14 days.
			
			After radical cure regimen, subjects randomized in 3:1 ratio to continue/ stop
			
			Subjects randomized to continue further randomized in a 1:1 ratio to receive 1 atovaquone-proguanil tablet or 1 placebo tablet daily for 20 weeks.
				Primary efficacy end point was the first occurrence of slide-proven *P. vivax* parasitemia.
				
				Secondary efficacy end point was first occurrence of slide proven *P. vivax* or *P. falciparum* parasitemia.
				
				% of efficacy was calculated as 100 x [1-(incidence density of malaria in atovaquone-proguanil recipients/incidence density of malaria in placebo recipients)].
				
				Adverse Events
					<u>Infection after the radical cure regimen:</u>
					• Malaria diagnosed in 40 subjects during the prophylaxis phase
					  ○ Parasitemia in 37 subjects in the placebo group
					  ▪ 14 cases due to *P. vivax* alone,
					  ▪ 21 due to *P. falciparum* alone, &
					  ▪ 2 due to *P. vivax–P. falciparum*
					  ○ Parasitemia in 3 subjects in atovaquone-proguanil group
					  ▪ 2 cases due to *P. vivax* alone &
					  ▪ 1 case due to *P. vivax–P. falciparum*.
					
					• The protective efficacy of atovaquone/proguanil:
					  ○ 84% (95% CI, 45%–95%) for *P. vivax,*
					  ○ 96% (95% CI, 71%–99%) for P. *falciparum, &*
					  ○ 93% (95% CI, 77%–98%) overall
					
					<u>During 4 weeks follow -up</u>
					• Parasitemia in:
					  ○ 5 subjects in the placebo group
					  ▪ n=3 *P. falciparum* &
					  ▪ n=2 *P. vivax* &
					  ○ 7 subjects in the atovaquone-proguanil group
					  ▪ n=2 *P. falciparum &*
					  ▪ *n*=5 *P vivax*
					
					<u>Adverse Events</u>
					• *Serious Adverse Events:* 4 SAEs - 3 abdominal pain and 1 skin rash (no causal effect with the skin rash SAE).
					• *Discontinuation of antimalarial*: 4 participants withdrew from the study due to adverse events (one in the atovaquone-proguanil group and 3 in the control group).
					• *Common adverse effects:* stomatitis and back pain appeared more frequently amongst atovaquone-proguanil recipients and abdominal pain and malaise occurred more frequently in the placebo group.)
						Atovaquone-proguanil showed high protective efficacy compared to placebo.
						
						Small double-blinded RCT, data analysed using ITT analysis.
						
						Very low certainty of evidence, with a very high attrition rate (that was not comparable between study gps).

<table>
<tr><th colspan="7">• DOXYCYCLINE VS PLACEBO</th></tr>
<tr><th>Citation</th><th>Study design</th><th>Population (n)</th><th>Treatment</th><th>Outcomes</th><th>Effect sizes</th><th>Comments</th></tr>
<tr>
<td>Weiss et al. 1995[11]</td>
<td>Randomised trial, slide readers and field workers were blinded.</td>
<td>Students from several villages in Saradidi Rural Health Program catchment area in Kenya. Ages 9-14.

N = 169</td>
<td>Curative treatment initially. Then (a) multivitamin tablet vs quinine on Mon, Wed, Fri for 12 weeks (“intermittent study”). Or (b) daily multivitamin vs daily doxycycline vs daily primaquine vs weekly mefloquine + daily multivitamin vs daily proguanil + weekly chloroquine (“daily study”) for 11 weeks.</td>
<td>Parasitaemia prevention efficacy

Clinical malaria prevention efficacy.</td>
<td>Parasitaemia prevention:
<table>
<tr><th>Regimen</th><th>Efficacy (95% CI)</th></tr>
<tr><td>Vitamin (n=34)</td><td>N/A</td></tr>
<tr><td>Primaquine (n=32)</td><td>85% (68-93%)</td></tr>
<tr><td>Doxycycline (n=32)</td><td>84% (66-92%); NNT 4 (3-10)</td></tr>
<tr><td>Mefloquine (n=30)</td><td>77% (55-88%)</td></tr>
<tr><td>Chloroquine + proguanil (n=37)</td><td>54% (25-72%)</td></tr>
</table>
Clinical malaria prevention
<table>
<tr><th>Regimen</th><th>Efficacy (95% CI)</th></tr>
<tr><td>Vitamin (n=34)</td><td>N/A</td></tr>
<tr><td>Primaquine (n=32)</td><td>83% (50-94%)</td></tr>
<tr><td>Doxycycline (n=32)</td><td>91% (61-98%); NNT 16 (7-17)</td></tr>
<tr><td>Mefloquine (n=30)</td><td>81% (44-93%)</td></tr>
<tr><td>Chloroquine + proguanil (n=37)</td><td>72% (35-88%)</td></tr>
</table>
Adverse events:
Mean number of symptoms per subject (doxycycline vs placebo)
• Headache 6.1 vs 7.0
• Fever 5.8 vs 5.3
• Diarrhea: 1 vs 1.2
• Stomach Pains: 8.3 vs 6.8
• Nausea: 4.9 vs 3.3</td>
<td>RCT was included in the systematic review by Tickell-Painter et al., 2017.

Small single-blinded RCT, comparing various antimalarials to control.

Random allocation of intervention/control, but allocation was likely not concealed.

Clinical malaria possibly over diagnosed (high pressure of malaria infection and symptoms may have been due to other diseases).

Potential participants with G6PD excluded.

Low certainty evidence as underpowered, single-blinded with possible selection and performance bias.</td>
</tr>
</table>

Appendix 1: Search strategy

Cochrane library *Search:* malaria prophylaxis in Cochrane Reviews **Records retrieved: 9 (3 Duplicates, 6 did not meet PICO)**
PUBMED *Search:* ("*plasmodium falciparum*"[All Fields]) AND ("primaquine"[All Fields]) **Filters:** Meta-Analysis, Systematic Review **Records retrieved: 52 (17 were duplicates, 35 did not meet PICO/incorrect study design/ update or duplicate or poor-quality design)**

Appendix 2: AMSTAR2 Assessment

Evaluating the methodological quality of the Tickell-Painter *et al.* (2017)[8] systematic review and meta-analysis using the AMSTAR 2 tool (Shea 2017[7]):

AMSTAR Assessments	
1. Research questions and inclusion criteria for the review included the components of PICO?	Yes
2. Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes
3. Review authors explained selection of the study designs for inclusion in the review?	Yes
4. Review authors used a comprehensive literature search strategy?	Yes
5. Review authors perform study selection and data extraction in duplicate?	Yes
6. Review authors provided a list of excluded studies and justify the exclusions?	Yes
7. Review authors described the included studies in adequate detail?	Yes
8. Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
9. Review authors reported on the sources of funding for the studies included in the review?	Yes
10. For meta-analyses, review authors used appropriate methods for statistical combination of results? (Random- vs fixed-effects)	n/a
11. For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis?	n/a
12. Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review?	Yes
13. Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes
14. For quantitative synthesis, review authors carried out an adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review?	No
15. Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

*Study authors explain that they were unable to assess publication bias using funnel plots due to high study heterogeneity.

Critical domains (2, 4, 7, 9)

Rating overall confidence in the results of the review

• *High:* No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest

• *Moderate:* More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review

• *Low:* One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest

• *Critically low*: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

(*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence).

OVERALL ASSESMENT: High quality

Appendix 3: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☒ Uncertain ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Systematic review by Tickell-Painter *et al.,* 2017[8], reviewed RCTs of low certainty evidence to determine the protective efficacy of antimalarial agents: mefloquine, atovaquone-proguanil and doxycycline.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☒ Moderate ☐ Small ☐ None ☐	Systematic review by Tickell-Painter *et al.,* 2017[8] showed comparable protective efficacy between mefloquine, atovaquone-proguanil and doxycycline. **Parasitaemia (*P. falciparum*):** Tickell-Painter *et al.,* 2017[8]: • Mefloquine vs placebo: 9.8% vs 60.2%; NNT 2, 95% CI 1.7 to 2.3; RR 0.18, 95% CI 0.06 to 0.55; 3 RCTs; n=414; I^2=80%), *low certainty evidence.* Soto et al., 2006 (n=144)[9]: • Atovaquone-proguanil vs placebo: atovaquone-proguanil was 100% effective in reducing parasitaemia; *low certainty evidence.* Weiss et al., 2011 (n=66)[11]: • Doxycycline vs placebo: 8/32 vs 34/34; NNT 4 (95% CI 3 to 10), *low certainty evidence* **Clinical cases of malaria (*P. falciparum*):** Tickell-Painter *et al.,* 2017[8]: • Mefloquine vs placebo: 1.4% vs 21.0%; NNT 6, 95% CI 5 to 7; RR 0.09, 95% CI 0.04 to 0.19; I^2=53%), *low certainty evidence.* • Mefloquine vs atovaquone-proguanil: no clinical cases of malaria with either agent in 2 RCTs, *low certainty evidence.* • Mefloquine vs doxycycline: 4/378 vs 3/366; RR 1.35, 95% CI 0.35 to 5.1; 4 RCTs; n=744; I2=3%, *low certainty evidence.* Weiss et al., 2011 (n=66)[11]: • Doxycycline vs placebo: 2/32 vs 20/30; NNT 16 (95% CI -47 to 7), *low certainty evidence*
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☒ Uncertain ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	• Tickell-Painter *et al.,* 2017[8], reported that people were less likely to be non-adherent with atovaquone-proguanil compared to mefloquine due to adverse effects *(high-certainty evidence);* but equally as likely to be non-adherent as those taking doxycycline *(low-certainty evidence).* • Mefloquine users experienced more abnormal dreams, insomnia, anxiety and depressed mood compared to atovaquone-proguanil users *(moderate-certainty evidence)* or doxycyline *(very low-certainty evidence).* • Doxycycline users were more likely to have dyspepsia, photosensitivity, vomiting, and vaginal thrush *(very low-certainty evidence).*
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** • Mefloquine: Large ☐ Moderate ☒ Small ☐ None ☐ • Atovaquone-proguanil: Large ☐ Moderate ☐ Small ☒ None ☐ • Doxycyline: Large ☐ Moderate ☒ Small ☐ None ☐	Refer to the evidence tables and narrative, above.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☒ Favours control ☐ Intervention = Control *or* Uncertain ☐	The interventions are protective against malaria, but mefloquine, atovaquone-proguanil and doxycycline have adverse-effects – mefloquine (neurological adverse effects) and doxycycline (gastrointestinal adverse effects), more so than atovaquone-proguanil.

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
FEASIBILITY	**Is implementation of this recommendation feasible?** Yes: x* No: Uncertain: *Except mefloquine, as discontinued, from the South African market.	• Doxycycline: Currently listed on the national EML, and Appears as effective as the alternatives, without more adverse effects. Registered, readily available and inexpensive. • Atovaquone-proguanil: SAHPRA–registered, but not included on the national EML. Affordability may be an issue (see below). • Mefloquine: SAHPRA–registered, but recently withdrawn from the South African market.
RESOURCE USE	**How large are the resource requirements?** More intensive: x Less intensive: Uncertain:	**Price/treatment course for 1 week trip for adults (average weight 70kg adult):**

	Doxycycline	Atovaquone-proguanil
Dose	Initiate 2 days before travel & continue for 4 weeks after	Initiate 2 days before travel & continue for 7 days after
Dosing	Daily	Daily
Doses / trip	1 week trip: 37 3-week trip: 51	1 week trip: 16 3-week trip: 30
Dose	100mg caps/tabs	250mg/100mg caps/tabs
Unit price	R0.30*	R19.68**
Cost / trip	1 week trip: R11.10 3-week trip: R15.30	1 week trip: R314.88 3-week trip: R590.40

* Average weighted price for doxycycline 100mg = R0.30 (contract circular HP02-2019AI, accessed 18 May 2021)
** 60% of SEP - SEP database, 30 December 2020 – accessed 16 April 2021

Estimated budget impact:
Assumptions:
1. Migrant workers travel solely between work and home, and not with their families.
2. Data on annual case-load received from SAMEC was used to estimate the number of travelers who would require malaria chemoprophylaxis.

Limitations:
1. Data on number of cases reported shared by SAMEC has not been validated and there may be under-reporting of malaria cases (no other data available to estimate the number of travelers who would require malaria chemoprophylaxis – thus, a sensitivity analysis was done as shown below).
2. Model does not consider impact of other malaria preventative measures.
3. Model does not factor in pregnant women or children.

Based on the annual case load report for 2019/2020 from SAMEC***, the estimated budget impact (+/-20% upper and lower limits) is as follows:

Total cases reported	20 959	
Medicine	Doxycycline (1 week trip)	Atovaquone-proguanil
Estimated budget impact		
- 1 week trip	R 232 650 (R186K to R279K)	R 6 599 570 (R5.2 mil to R7.9 mil)
- 4-week trip	R 320 670 (R257K to R385K)	R 12 374 200 (R9.9 mil to R14.85 mil)

*** NDoH data on file (60% of total cases were imported cases)

International benchmarking:

Medicine	Doxycycline 100mg cap/tab	Atovaquone-proguanil cap/tab
MSH Price - Median Price[1]	US$ 0.0192 (Buyer price)	US$ 4.1648 (Supplier: Durbin (PLC) UK - EXW)
ZAR[2]	R 0.28	R 64.83

[1]International Medical Products Price Guide (2015) available at: https://www.msh.org/resources/international-medical-products-price-guide (accessed 18 May 2021)
[2] OANDA currency converter – average for Nov 2020 to May 2021: US$: ZAR = 14.826 - available at: https://www1.oanda.com/currency/converter/ (accessed 18 May 2021)

WHO EML listing (2021):
Only doxycycline 100 mg (solid dosage form) is listed for chemoprophylaxis of *Plasmodium falciparum.*
https://list.essentialmeds.org/

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [x] Major [ ] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes [x] No [ ] Uncertain [ ]	The chemo- prophylactic options that have been reviewed, are recommended in guidelines. Dosing convenience and side effects may impact how much people value the different options. Mefloquine has shown an advantage in terms of once weekly dosing. However, it is not available in South Africa and is associated with neurological adverse effects. Atovaquone-proguanil, dosed daily, needs to be continued for a week after returning from endemic area while daily dosed doxycycline must be continued for 4 weeks, which might affect patient adherence. Despite a lack of local survey data, the Committee was of the opinion that malaria chemoprophylaxis would be acceptable by both clinicians/healthcare workers and patients.
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [x] Uncertain [ ]	Generally, equity would depend on access and capacity to deliver the intervention to public sector patients particularly migrant workers traveling to endemic areas, irrespective of South African resident status. Note that access to chemoprophylaxis for vulnerable populations (i.e., children and pregnant women) will be a challenge – doxycycline is contra-indicated in pregnant women and children<8 years of age[14] However, guidelines generally recommend that these vulnerable populations should avoid travelling to malaria-endemic areas.

Version	Date	Reviewer(s)	Recommendation and Rationale
First	14 June 2021	JN, PN, MR, TL	Doxycycline recommended for malaria chemoprophylaxis in children ≥ 8 years of age and in adults (excluding pregnancy), as available evidence shows that doxycycline reduces parasitemia and clinical malaria due to *P falciparum*. Mefloquine is currently unavailable in South Africa, and atovaquone-proguanil is currently unaffordable.

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