## 5.4. Treating uncomplicated malaria caused by P. vivax, P. ovale, P. malariae or P. knowlesi

### Clinical Question/ PICO

**Population:** Adults and children with uncomplicated P. vivax malaria (Malaria-endemic areas in which chloroquine is still effective for the first 28 days)

**Intervention:** Artemisinin-based combination therapy

**Comparator:** Chloroquine

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Chloroquine | **Intervention** ACT | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| **Remaining parasitaemia at 24 h** | Relative risk 0.42 (CI 95% 0.36 — 0.5) Based on data from 1,652 participants in 4 studies. (Randomized controlled) | 520 per 1000 Difference: | 218 per 1000 **302 fewer per 1000** ( CI 95% 333 fewer — 260 fewer ) | High [1] | |
| **Still febrile after 24 h** | Relative risk 0.55 (CI 95% 0.43 — 0.7) Based on data from 990 | 290 per 1000 | 160 per 1000 | Moderate Due to serious | |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Chloroquine | **Intervention**<br>ACT | **Certainty of the Evidence**<br>(Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| | participants in 2 studies. (Randomized controlled) | Difference: | **130 fewer per 1000**<br>( CI 95% 165 fewer — 87 fewer ) | inconsistency [2] | |
| **Effective treatment of blood-stage infection as assessed by recurrent parasitaemia before day 28** | Relative risk 0.58 (CI 95% 0.18 — 1.9) Based on data from 1,622 participants in 5 studies. (Randomized controlled) | 30<br>per 1000<br>Difference: | 17<br>per 1000<br>**13 fewer per 1000**<br>( CI 95% 25 fewer — 27 more ) | **High**<br>[3] | |
| **Post-treatment prophylaxis as assessed by recurrent parasitaemia between day 28 and day 42, 56 or 63 - with primaquine** | Relative risk 0.27 (CI 95% 0.08 — 0.94) Based on data from 376 participants in 1 studies. (Randomized controlled) | 60<br>per 1000<br>Difference: | 16<br>per 1000<br>**44 fewer per 1000**<br>( CI 95% 55 fewer — 4 fewer ) | **Low**<br>Due to serious indirectness and serious imprecision [4] | |
| **Post-treatment prophylaxis as assessed by recurrent parasitaemia between day 28 and day 42, 56 or 63 - without primaquine** | Relative risk 0.57 (CI 95% 0.4 — 0.82) Based on data from 1,066 participants in 3 studies. (Randomized controlled) | 400<br>per 1000<br>Difference: | 228<br>per 1000<br>**172 fewer per 1000**<br>( CI 95% 240 fewer — 72 fewer ) | **Moderate**<br>Due to serious indirectness [5] | |
| **Serious adverse events** | Relative risk 1 (CI 95% 0.14 — 7.04) Based on data from 1,775 participants in 5 studies. (Randomized controlled) | 0<br>per 1000<br>Difference: | 0<br>per 1000<br>**0 fewer per 1000**<br>( CI 95% 0 fewer — 0 fewer ) | **High**<br>[6] | |

1. **Risk of Bias: no serious.** Three studies adequately concealed allocation to be at low risk of selection bias. Removal of the remaining trials did not substantially change the result. **Inconsistency: no serious.** The findings of all the trials are consistent. **Indirectness: no serious.** The findings of these studies can reasonably be applied to other settings with similar transmission and resistance patterns. **Imprecision: no serious.** The studies show a clinically and statistically significant benefit of ACT.

**Publication bias: no serious.**

2. **Risk of Bias: no serious.** Three studies adequately concealed allocation to be at low risk of selection bias. Removal of the remaining trials did not substantially change the result. **Inconsistency: serious.** In one additional trial which could not be included in the meta-analysis, fever clearance was not significantly different between groups. **Indirectness: no serious.** The findings of these studies can reasonably be applied to other settings with similar transmission and resistance patterns. **Imprecision: no serious.** The studies show a clinically and statistically significant benefit of ACT.
3. **Risk of Bias: no serious.** Three studies adequately concealed allocation to be at low risk of selection bias. Removal of the remaining trials did not substantially change the result. **Inconsistency: no serious.** The findings of all the trials are consistent. **Indirectness: no serious.** The findings of these studies can reasonably be applied to other settings with similar transmission and resistance patterns. **Imprecision: no serious.** No clinically important difference between ACTs and chloroquine. Although the 95% CI around the relative effect is very wide, recurrent parasitaemia before day 28 and serious adverse events were very rare; consequently, the 95% CI around the absolute effect is very narrow.
4. **Indirectness: serious.** This study delayed primaquine until day 28; therefore, the course was not completed until day 42, the last day of the trial. The effect might not be present if primaquine is given in the usual way (on completion of 3 days of ACT). The period of follow-up was not long enough to fully assess this effect; the inevitable relapse might simply be delayed, rather than a reduction in clinical episodes. **Imprecision: serious.** Although the result is statistically significant, the 95% CI is wide and includes the possibility of no appreciable benefit.
5. **Inconsistency: no serious.** The findings of all the trials are consistent. **Indirectness: serious.** Both studies were conducted in Afghanistan where primaquine is not recommended because of a high prevalence of G6PD deficiency. The period of follow-up was not long enough to fully assess this effect; the inevitable relapse might simply be delayed, rather than a reduction in clinical episodes. **Imprecision: no serious.** The studies show a clinically and statistically significant benefit of ACT.
6. **Risk of Bias: no serious.** Three studies adequately concealed allocation to be at low risk of selection bias. Removal of the remaining trials did not substantially change the result. **Inconsistency: no serious.** The findings of all the trials are consistent. **Indirectness: no serious.** The findings of these studies can reasonably be applied to other settings with similar transmission and resistance patterns. **Imprecision: no serious.** No clinically important difference between ACTs and chloroquine. Although the 95% CI around the relative effect is very wide, recurrent parasitaemia before day 28 and serious adverse events were very rare; consequently, the 95% CI around the absolute effect is very narrow.

## Clinical Question/ PICO

**Population:** Adults and children with uncomplicated P. vivax malaria (Settings with high transmission of P. vivax (chloroquine resistance is also reported as high))

**Intervention:** Dihydroartemisinin + piperaquine

**Comparator:** Alternative ACTs

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Alternative ACT | **Intervention** Dihydroartemisinin + piperaquine | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| **Effective treatment of blood-stage parasites as assessed by recurrent parasitaemia before day 28** | Relative risk 0.2 (CI 95% 0.08 — 0.49) Based on data from 334 participants in 3 studies. (Randomized controlled) | 350 per 1000 Difference: | 70 per 1000 **280 fewer per 1000** ( CI 95% 322 fewer — 178 fewer ) | Moderate Due to serious inconsistency [1] | |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Alternative ACT | **Intervention** Dihydroartemisinin + piperaquine | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| **Post-treatment prophylaxis as assessed by recurrent parasitaemia between days 28 and 42 - with primaquine** | Relative risk 0.21 (CI 95% 0.1 — 0.46) Based on data from 179 participants in 2 studies. (Randomized controlled) | 340 per 1000<br>Difference: | 71 per 1000<br>**269 fewer per 1000** ( CI 95% 306 fewer — 184 fewer ) | **Low** Due to serious risk of bias and serious indirectness [2] | |
| **Post-treatment prophylaxis as assessed by recurrent parasitaemia between days 28 and 42 - without primaquine** | Relative risk 0.4 (CI 95% 0.14 — 1.1) Based on data from 66 participants in 1 studies. (Randomized controlled) | 330 per 1000<br>Difference: | 132 per 1000<br>**198 fewer per 1000** ( CI 95% 284 fewer — 33 more ) | **Very low** Due to serious risk of bias, serious indirectness and serious imprecision [3] | |

1. **Risk of Bias: no serious.** Allocation was adequately concealed in these studies, resulting in a low risk of bias. **Inconsistency: serious.** There was some clinical heterogeneity between trials. Dihydroartemisinin + piperaquine did not perform as well in Papua New Guinea as it has elsewhere; however, it was still superior to artemether + lumefantrine and artesunate+sulfadoxine–pyrimethamine. **Indirectness: no serious.** Studies included adults and children and were conducted in areas where transmission is high and chloroquine resistance is well documented. **Imprecision: no serious.** Both limits of the 95% CI suggest an appreciable clinical benefit with dihydroartemisinin + piperaquine.
2. **Risk of Bias: serious.** Losses to follow-up were high (> 20% at this time). **Inconsistency: no serious.** Statistical heterogeneity was low. **Indirectness: serious.** One trial delayed administration of primaquine until day 28; therefore, the course will not have been completed until the last day of the trial. The second trial offered unsupervised primaquine to all participants on completion of ACT. This reflects normal practice, but it is not clear how many participants completed their course. The period of follow-up was not long enough to fully assess this effect; the inevitable relapse might simply be delayed, rather than a reduction in clinical episodes.
3. **Risk of Bias: serious.** Losses to follow-up were high (> 20% at this time). **Indirectness: serious.** Only one study assessed this outcome. Recurrent parasitaemia was higher with all three ACTs than seen elsewhere, and the results are therefore not easily extrapolated to other sites. **Imprecision: serious.** The 95% CI of the effect estimate is wide and includes an important clinical benefit and no difference between treatments.

## Clinical Question/ PICO

**Population:** People with P. vivax malaria
**Intervention:** Primaquine (0.25 mg/kg bw) for 14 days plus chloroquine (25 mg/kg bw for 3 days)
**Comparator:** Chloroquine alone (25 mg/kg bw for 3 days)

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** No primaquine | **Intervention** Primaquine 14 days | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| **P. vivax relapse defined as reappearance of P. vivax parasitaemia > 30 days after starting primaquine** | Relative risk 0.6 (CI 95% 0.48 — 0.75) Based on data from 1,740 participants in 10 studies. (Randomized controlled) | 80 per 1000 Difference: | 48 per 1000 **32 fewer per 1000** ( CI 95% 42 fewer — 20 fewer ) | **High** [1] | |
| **Serious adverse events** | Based on data from: 1,740 participants in 10 studies. (Randomized controlled) | No adverse events reported in either group. Relative effect cannot be estimated. | | | |
| **Other adverse events** | Based on data from: 1,740 participants in 10 studies. (Randomized controlled) | No adverse events reported in either group. Relative effect cannot be estimated. | | | |

1. **Risk of Bias: no serious.** No serious study limitations: Three studies were at high risk of bias; however, they contributed only 15.5% weight to the pooled effect estimates, and their removal from the sensitivity analysis did not alter the results appreciably. **Inconsistency: no serious.** Results were consistent within subgroups based on duration of follow-up < 6 months or > 6 months and whether treatment was supervised or not; the I2 value for the pooled effect estimate from the 10 trials was 30%. **Indirectness: no serious.** The trials included children and were done in transmission settings and countries representative of the vivax malaria burden. The outcome used was the best estimate currently available in the absence of widely available validated molecular techniques to differentiate relapse from new infections. **Imprecision: no serious.** The upper and lower limits of the 95% CI of the pooled relative risk indicate appreciable benefit with chloroquine + primaquine for 14 days. The total number of events was < 300, but the total sample size was larger than the optimal information size, given the magnitude of risk reduction.

## Clinical Question/ PICO

**Population:** People with P. vivax malaria
**Intervention:** Primaquine (0.25 mg/kg bw) for 14 days plus chloroquine (25 mg/kg bw for 3 days)
**Comparator:** Primaquine (0.25 mg/kg bw) for 7 days plus chloroquine alone (25 mg/kg bw for 3 days)

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** 7 days primaquine | **Intervention** 14 days primaquine | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| **P. vivax relapse defined as reappearance of** | Relative risk 0.45 (CI 95% 0.25 — 0.81) Based on data from 126 | 420 per 1000 | 189 per 1000 | **Low** Due to serious indirectness and | |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** 7 days primaquine | **Intervention** 14 days primaquine | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| **P. vivax parasitaemia > 30 days after starting primaquine** | participants in 1 studies. (Randomized controlled) | Difference: | **231 fewer per 1000** ( CI 95% 315 fewer — 80 fewer ) | serious imprecision [1] | |
| **Severe adverse events** | Based on data from: 126 participants in 1 studies. (Randomized controlled) | No adverse events reported in either group. Relative effect cannot be estimated. | | | |
| **Other adverse events** | Based on data from: 126 participants in 1 studies. (Randomized controlled) | No adverse events reported in either group. Relative effect cannot be estimated. | | | |

1. **Indirectness: serious.** The trial authors did not include children < 15 years. Another trial in the same area by the same group of investigators immediately afterwards included children. The results for 3 days of primaquine versus 14 days of primaquine did not differ in children from that in adults. Duration of follow-up was 2 months. While this ensures detection of early relapse, it does not cover relapses after 2 months. The relapse rates at 6 months showed that most relapses occur by 2 months. The effects of 7 days of primaquine were assessed in only one trial. We therefore downgraded the evidence by 1. **Imprecision: serious.** Although the upper and lower limits of the 95% CI of the risk ratio in this trial showed statistically significant, clinically appreciable benefit with 14 days of primaquine over 7 days of primaquine, the total number of events was 38 and the sample size of the trial was 104. This is lower than the optimal information size. We downgraded the evidence by 1.

## Clinical Question/ PICO

**Population:** Malaria-endemic areas
**Intervention:** Chloroquine prophylaxis
**Comparator:** Placebo

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Placebo | **Intervention** Chloroquine prophylaxis | **Certainty of the Evidence** (Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| **Clinical malaria** | Relative risk | | CI 95% | | |
| **P. vivax parasitaemia** | Relative risk 0.02 (CI 95% 0 — 0.26) Based on data from 951 | **70** per 1000 | **1** per 1000 | **Moderate** Due to serious | |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Chloroquine prophylaxis | **Certainty of the Evidence**<br>(Quality of evidence) | **Plain language summary** |
|---|---|---|---|---|---|
| | participants in 1 studies. (Randomized controlled) | Difference: | **69 fewer per 1000**<br>( CI 95% 70 fewer — 52 fewer ) | imprecision [1] | |
| **Severe anaemia in third trimester** | Relative risk | | CI 95% | | |
| **Anaemia in third trimester** | Relative risk 0.95 (CI 95% 0.9 — 1.01)<br>Based on data from 951 participants in 1 studies. (Randomized controlled) | 509<br>per 1000<br>Difference: | 484<br>per 1000<br>**25 fewer per 1000**<br>( CI 95% 51 fewer — 5 more ) | **Moderate**<br>Due to serious imprecision [2] | |
| **Adverse events** | Relative risk | | CI 95% | | |

1. **Risk of Bias: no serious.** This study had a low risk of bias in all domains. **Indirectness: no serious.** This study was conducted in Thailand between 1998 and 2001. Chloroquine was administered as four tablets at enrolment, followed by two tablets once a week until delivery. **Imprecision: serious.** Although the intervention appeared to prevent all episodes of P. vivax malaria, there were few events, even in the control group.
2. **Risk of Bias: no serious.** This study had a low risk of bias in all domains. **Indirectness: no serious.** This study was conducted in Thailand between 1998 and 2001. Chloroquine was administered as four tablets at enrolment, followed by two tablets once a week until delivery. **Imprecision: serious.** The finding of a small clinical benefit did not reach statistical significance.