

### 5.2.1. Artemisinin-based combination therapy

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#### Clinical Question/ PICO

<b>Population:</b>	Patients with uncomplicated <i>P. falciparum</i> malaria (malaria-endemic settings in Africa)
<b>Intervention:</b>	Dihydroartemisinin + piperaquine once daily for 3 days
<b>Comparator:</b>	Artemether + lumefantrine twice daily for 3 days

Outcome Timeframe	Study results and measurements	Comparator Artemether + lumefantrine	Intervention Dihydroartemi sinin + piperazine	Certainty of the Evidence (Quality of evidence)	Plain language summary
Treatment failure - PCR unadjusted <sup>1</sup> 28 days	Relative risk 0.34 (CI 95% 0.3 – 0.39) Based on data from 6,200 participants in 9 studies. (Randomized controlled)	<b>230</b> per 1000  Difference:	<b>78</b> per 1000  <b>152 fewer per 1000</b> ( CI 95% 161 fewer – 140 fewer )	<b>High</b> <sup>2</sup>	
Treatment failure - PCR adjusted <sup>3</sup> 28 days	Relative risk 0.42 (CI 95% 0.29 – 0.62) Based on data from 5,417 participants in 9 studies. (Randomized controlled)	<b>30</b> per 1000  Difference:	<b>13</b> per 1000  <b>17 fewer per 1000</b> ( CI 95% 21 fewer – 11 fewer )	<b>High</b> <sup>4</sup>	
Treatment failure - PCR unadjusted <sup>5</sup> 63 days	Relative risk 0.71 (CI 95% 0.65 – 0.78) Based on data from 3,200 participants in 2 studies. (Randomized controlled)	<b>450</b> per 1000  Difference:	<b>320</b> per 1000  <b>130 fewer per 1000</b> ( CI 95% 157 fewer – 99 fewer )	<b>High</b> <sup>6</sup>	
Treatment failure - PCR adjusted <sup>7</sup> 63 days	Relative risk 0.72 (CI 95% 0.5 – 1.04) Based on data from 2,097 participants in 2 studies. (Randomized controlled)	<b>60</b> per 1000  Difference:	<b>43</b> per 1000  <b>17 fewer per 1000</b> ( CI 95% 30 fewer – 2 more )	<b>High</b> <sup>8</sup>	

1. PCR unadjusted

2. **Risk of Bias: no serious.** No serious risk of bias: Trials generally have little risk of bias. Exclusion of studies with high or unclear risk for selection bias or detection bias did not change the result.. **Inconsistency: no serious.** No serious inconsistency: All the trials had similar results, and statistical heterogeneity was low.. **Indirectness: no serious.** No serious indirectness: The trials were conducted in different transmission settings in east, west and southern Africa. Most studies were limited to children.. **Imprecision: no serious.** No serious imprecision: The 95% CI implies appreciable benefit, and the meta-analysis is adequately powered to detect this result.. **Publication bias: no serious.**

3. PCR adjusted

4. **Risk of Bias: no serious.** No serious risk of bias: Trials generally have little risk of bias. Exclusion of studies with high or unclear risk for selection bias or detection bias did not change the result.. **Inconsistency: no serious.** No serious inconsistency: All the trials had similar results, and statistical heterogeneity was low.. **Indirectness: no serious.** No serious indirectness: The trials were conducted in different transmission settings in east, west and southern Africa. Most studies were limited to children.. **Imprecision: no serious.** No serious imprecision: Although there is a benefit in favour of dihydroartemisinin + piperazine, the PCR-adjusted treatment failure rate was < 5% with both drugs.. **Publication bias: no serious.**

5. PCR unadjusted

6. **Risk of Bias: no serious.** No serious risk of bias: Trials generally have little risk of bias. Exclusion of studies with high

or unclear risk for selection bias or detection bias did not change the result.. **Inconsistency: no serious.** No serious inconsistency: At this time, there is inconsistency between trials; both show a benefit with dihydroartemisinin + piperazine, but the size of the benefit differs.. **Indirectness: no serious.** No serious indirectness: The trials were conducted in different transmission settings in east, west and southern Africa. Most studies were limited to children.. **Imprecision: no serious.** No serious imprecision: The 95% CI implies appreciable benefit, and the meta-analysis is adequately powered to detect this result.. **Publication bias: no serious.**

7. PCR adjusted

8. **Risk of Bias: no serious.** No serious risk of bias: Trials generally have little risk of bias. Exclusion of studies with high or unclear risk for selection bias or detection bias did not change the result.. **Inconsistency: no serious.** No serious inconsistency: The treatment failure rate with dihydroartemisinin + piperazine was < 5% in both trials.. **Indirectness: no serious.** No serious indirectness: The trials were conducted in different transmission settings in east, west and southern Africa. Most studies were limited to children.. **Imprecision: no serious.** No serious imprecision: Both ACTs performed well in these two trials, with low rates of treatment failure.. **Publication bias: no serious.**

### Clinical Question/ PICO

**Population:** Patients with uncomplicated *P. falciparum* malaria (malaria-endemic settings in Africa)  
**Intervention:** Dihydroartemisinin + piperazine once daily for 3 days  
**Comparator:** Artesunate + mefloquine once daily for 3 days

Outcome Timeframe	Study results and measurements	Comparator Artesunate + mefloquine	Intervention Dihydroartemi sinin + piperazine	Certainty of the Evidence (Quality of evidence)	Plain language summary
Treatment failure - PCR unadjusted <sup>1</sup> 28 days	Relative risk 1.02 (CI 95% 0.28 – 3.72) Based on data from 3,487 participants in 8 studies. (Randomized controlled)	<b>20</b> per 1000  Difference:	<b>20</b> per 1000  <b>0 fewer per 1000</b> ( CI 95% 14 fewer – 54 more )	<b>High</b> Due to serious inconsistency <sup>2</sup>	
Treatment failure - PCR adjusted <sup>3</sup> 28 days	Relative risk 0.41 (CI 95% 0.21 – 0.8) Based on data from 3,467 participants in 8 studies. (Randomized controlled)	<b>10</b> per 1000  Difference:	<b>4</b> per 1000  <b>6 fewer per 1000</b> ( CI 95% 8 fewer – 2 fewer )	<b>High</b> Due to serious inconsistency <sup>4</sup>	
Treatment failure - PCR unadjusted <sup>5</sup> 63 days	Relative risk 0.84 (CI 95% 0.69 – 1.03) Based on data from 2,715 participants in 5 studies. (Randomized controlled)	<b>120</b> per 1000  Difference:	<b>101</b> per 1000  <b>19 fewer per 1000</b> ( CI 95% 37 fewer – 4 more )	<b>Moderate</b> Due to serious inconsistency <sup>6</sup>	
Treatment failure - PCR adjusted <sup>7</sup> 63 days	Relative risk 0.5 (CI 95% 0.3 – 0.84) Based on data from 2,500 participants in 5 studies. (Randomized	<b>30</b> per 1000  Difference:	<b>15</b> per 1000  <b>15 fewer per</b>	<b>High</b> Due to serious inconsistency <sup>8</sup>	

Outcome Timeframe	Study results and measurements	Comparator Artesunate + mefloquine	Intervention Dihydroartemisinin + piperazine	Certainty of the Evidence (Quality of evidence)	Plain language summary
	controlled)		1000 ( CI 95% 21 fewer – 5 fewer )		

## 1. PCR unadjusted

2. **Risk of Bias: no serious.** No serious risk of bias: Trials generally have little risk of selection or detection bias. Exclusion of trials with high or unclear risk of bias did not change the result.. **Inconsistency: serious.** Downgraded by 1 for serious inconsistency: in six trials, very few recurrences of parasitaemia were found in both groups. Two trials conducted mainly in areas in Thailand with multi-drug resistance showed increased risks for recurrent parasitaemia with artesunate + mefloquine.. **Indirectness: no serious.** No serious indirectness: The trials were conducted in adults and children in Cambodia, India, the Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam.. **Imprecision: no serious.** No serious imprecision: Overall, no significant difference between treatments; however, dihydroartemisinin + piperazine may be superior where *P. falciparum* is resistant to mefloquine.. **Publication bias: no serious.**

## 3. PCR adjusted

4. **Risk of Bias: no serious.** No serious risk of bias: Trials generally have little risk of selection or detection bias. Exclusion of trials with high or unclear risk of bias did not change the result.. **Inconsistency: serious.** Downgraded by 1 for serious inconsistency: in six trials, very few recurrences of parasitaemia were found in both groups. Two trials conducted mainly in areas in Thailand with multi-drug resistance showed increased risks for recurrent parasitaemia with artesunate + mefloquine.. **Indirectness: no serious.** No serious indirectness: The trials were conducted in adults and children in Cambodia, India, the Lao People's Democratic Republic, Myanmar, Thailand and Viet Nam.. **Imprecision: no serious.** No serious imprecision: Overall, a statistically significant benefit with dihydroartemisinin + piperazine, although the benefit may be present only where there is resistance to mefloquine.. **Publication bias: no serious.**

## 5. PCR unadjusted

6. **Risk of Bias: no serious.** No serious risk of bias: Trials generally have little risk of selection or detection bias. Exclusion of trials with high or unclear risk of bias did not change the result.. **Inconsistency: serious.** Downgraded by 1 for serious inconsistency: of the five trials, one in Thailand in 2005 showed a statistically significant benefit with dihydroartemisinin + piperazine, one in Myanmar in 2009 showed a benefit with dihydroartemisinin + piperazine, and three found no difference.. **Indirectness: no serious.** No serious indirectness: The trials were conducted in adults and children in Cambodia, India, the Lao People's Democratic Republic, Myanmar and Thailand.. **Imprecision: no serious.** No serious imprecision: Overall, no significant difference between treatments. Although some trials found statistically significant differences, these may not be clinically important.. **Publication bias: no serious.**

## 7. PCR adjusted

8. **Risk of Bias: no serious.** No serious risk of bias: Trials generally have little risk of selection or detection bias. Exclusion of trials with high or unclear risk of bias did not change the result.. **Inconsistency: serious.** Downgraded by 1 for serious inconsistency: Slight variation among trials, only one showing a statistically significant benefit with dihydroartemisinin + piperazine.. **Indirectness: no serious.** No serious indirectness: The trials were conducted in adults and children in Cambodia, India, the Lao People's Democratic Republic, Myanmar and Thailand.. **Imprecision: no serious.** No serious imprecision: Overall, no significant difference between treatments. Although some trials found statistically significant differences, these may not be clinically important.. **Publication bias: no serious.**

## Clinical Question/ PICO

<b>Population:</b>	Patients with uncomplicated <i>P. falciparum</i> malaria (malaria-endemic settings in Africa)
<b>Intervention:</b>	Dihydroartemisinin + piperazine
<b>Comparator:</b>	Artemether + lumefantrine

Outcome Timeframe	Study results and measurements	Comparator Artemether + lumefantrine	Intervention Dihydroartemi sinin + piperaquine	Certainty of the Evidence (Quality of evidence)	Plain language summary
Serious adverse events (including deaths)	Based on data from 7,022 participants in 8 studies. (Randomized controlled)	<b>6</b> per 1000  Difference:	<b>10</b> per 1000  <b>4 more per 1000</b> CI 95%	<b>Moderate</b> Due to serious imprecision <sup>1</sup>	
Early vomiting	Relative risk Based on data from 2,695 participants in 3 studies. (Randomized controlled)	<b>20</b> per 1000  Difference:	<b>30</b> per 1000  <b>10 more per 1000</b> CI 95% 0 fewer —	<b>Moderate</b> Due to serious risk of bias <sup>2</sup>	
Vomiting	Relative risk Based on data from 6,761 participants in 9 studies. (Randomized controlled)	<b>90</b> per 1000  Difference:	<b>90</b> per 1000  <b>0 fewer per 1000</b> CI 95%	<b>Moderate</b> Due to serious risk of bias <sup>3</sup>	
Nausea	Relative risk Based on data from 547 participants in 2 studies. (Randomized controlled)	<b>20</b> per 1000  Difference:	<b>20</b> per 1000  <b>0 fewer per 1000</b> CI 95%	<b>Low</b> Due to serious risk of bias and serious imprecision <sup>4</sup>	
Diarrhoea	Relative risk Based on data from 4,889 participants in 7 studies. (Randomized controlled)	<b>120</b> per 1000  Difference:	<b>120</b> per 1000  <b>0 fewer per 1000</b> CI 95%	<b>Moderate</b> Due to serious risk of bias <sup>5</sup>	
Abdominal pain	Relative risk Based on data from 911 participants in 5 studies. (Randomized controlled)	<b>190</b> per 1000  Difference:	<b>160</b> per 1000  <b>30 fewer per 1000</b> CI 95% 0 fewer —	<b>Low</b> Due to serious risk of bias and serious imprecision <sup>6</sup>	
Anorexia	Relative risk Based on data from 3,834 participants in 5 studies. (Randomized controlled)	<b>150</b> per 1000  Difference:	<b>140</b> per 1000  <b>10 fewer per 1000</b> CI 95% 0 fewer —	<b>Moderate</b> Due to serious risk of bias <sup>7</sup>	

Outcome Timeframe	Study results and measurements	Comparator Artemether + lumefantrine	Intervention Dihydroartemi sinin + piperazine	Certainty of the Evidence (Quality of evidence)	Plain language summary
Headache	Relative risk  Based on data from 309 participants in 2 studies. (Randomized controlled)	<b>270</b> per 1000  Difference:	<b>330</b> per 1000  <b>60 more per 1000</b> CI 95% 0 fewer —	<b>Low</b> Due to serious risk of bias and serious imprecision <sup>8</sup>	
Sleeplessness	Relative risk  Based on data from 547 participants in 2 studies. (Randomized controlled)	<b>10</b> per 1000  Difference:	<b>30</b> per 1000  <b>20 more per 1000</b> CI 95% 0 fewer —	<b>Low</b> Due to serious risk of bias and serious imprecision <sup>9</sup>	
Dizziness	Relative risk  Based on data from 547 participants in 2 studies. (Randomized controlled)	<b>30</b> per 1000  Difference:	<b>40</b> per 1000  <b>10 more per 1000</b> CI 95% 0 fewer —	<b>Low</b> Due to serious risk of bias and serious imprecision <sup>10</sup>	
Sleepiness	Relative risk  Based on data from 384 participants in 1 studies. (Randomized controlled)	<b>0</b> per 1000  Difference:	<b>0</b> per 1000  <b>0 fewer per 1000</b> CI 95%	<b>Low</b> Due to serious risk of bias and serious imprecision <sup>11</sup>	
Weakness	Relative risk  Based on data from 1,812 participants in 5 studies. (Randomized controlled)	<b>170</b> per 1000  Difference:	<b>180</b> per 1000  <b>10 more per 1000</b> CI 95% 0 fewer —	<b>Moderate</b> Due to serious risk of bias <sup>12</sup>	
Cough	Relative risk  Based on data from 4,342 participants in 5 studies. (Randomized controlled)	<b>420</b> per 1000  Difference:	<b>420</b> per 1000  <b>0 fewer per 1000</b> CI 95% 0 fewer —	<b>Moderate</b> Due to serious risk of bias <sup>13</sup>	
Coryza	Relative risk  Based on data from 832 participants in 2 studies. (Randomized controlled)	<b>680</b> per 1000  Difference:	<b>660</b> per 1000  <b>20 fewer per 1000</b> CI 95% 0 fewer —	<b>Low</b> Due to serious imprecision <sup>14</sup>	

Outcome Timeframe	Study results and measurements	Comparator Artemether + lumefantrine	Intervention Dihydroartemi sinin + piperazine	Certainty of the Evidence (Quality of evidence)	Plain language summary
Prolonged QT interval (adverse event)	Relative risk Based on data from 1,548 participants in 1 studies. (Randomized controlled)	<b>30</b> per 1000 Difference:	<b>20</b> per 1000 <b>10 fewer per 1000</b> CI 95% 0 fewer —	<b>Low</b> Due to serious imprecision and serious risk of bias <sup>15</sup>	
Prolonged QT interval (Bazett correction)	Relative risk Based on data from 1,548 participants in 1 studies. (Randomized controlled)	<b>70</b> per 1000 Difference:	<b>90</b> per 1000 <b>20 more per 1000</b> CI 95% 0 fewer —	<b>Low</b> Due to serious imprecision and serious risk of bias <sup>16</sup>	
Prolonged QT interval (Fridericia correction)	Relative risk Based on data from 1,548 participants in 1 studies. (Randomized controlled)	<b>0</b> per 1000 Difference:	<b>0</b> per 1000 <b>0 fewer per 1000</b> CI 95%	<b>Low</b> Due to serious risk of bias and serious imprecision <sup>17</sup>	
Pruritus	Relative risk Based on data from 2,033 participants in 5 studies. (Randomized controlled)	<b>20</b> per 1000 Difference:	<b>40</b> per 1000 <b>20 more per 1000</b> CI 95% 0 fewer —	<b>Moderate</b> Due to serious risk of bias <sup>18</sup>	
Facial oedema	Relative risk Based on data from 384 participants in 1 studies. (Randomized controlled)	<b>0</b> per 1000 Difference:	<b>0</b> per 1000 <b>0 fewer per 1000</b> CI 95%	<b>Low</b> Due to serious risk of bias and serious imprecision <sup>19</sup>	

- Risk of Bias: no serious.** No serious risk of bias: All but one of the trials were open label; however, we did not downgrade for this outcome.. **Inconsistency: no serious.** No serious inconsistency: The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** No serious indirectness: The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: serious.** Downgraded by 1 for serious imprecision: No statistically significant difference was detected between treatments; however the sample size does not exclude the possibility of rare but clinically important differences..
- Risk of Bias: serious.** Downgraded by 1 for risk of bias: The majority of trials were open label.. **Inconsistency: no serious.** No serious inconsistency: The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** No serious indirectness: The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: no serious.** No serious imprecision: No effect found, and the CIs around the absolute effects exclude clinically important differences..
- Risk of Bias: serious.** Downgraded by 1 for risk of bias: The majority of trials were open label.. **Inconsistency: no serious.** No serious inconsistency: The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** No serious indirectness: The trials were conducted mainly in children in Africa; few trials in Asia or in adults..

**Imprecision: no serious.** No serious imprecision: No effect found, and the CIs around the absolute effects exclude clinically important differences..

4. **Risk of Bias: serious.** Downgraded by 1 for risk of bias: The majority of trials were open label.. **Inconsistency: no serious.** No serious inconsistency: The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** No serious indirectness: The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: serious.** Downgraded by 1 for serious imprecision: There are limited data..

5. **Risk of Bias: serious.** Downgraded by 1 for risk of bias: The majority of trials were open label.. **Inconsistency: no serious.** No serious inconsistency: The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** No serious indirectness: The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: no serious.** No serious imprecision: No effect found, and the CIs around the absolute effects exclude clinically important differences..

6. **Risk of Bias: serious.** Downgraded by 1 for risk of bias: The majority of trials were open label.. **Inconsistency: no serious.** No serious inconsistency: The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** No serious indirectness: The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: serious.** Downgraded by 1 for serious imprecision: The result does not reach statistical significance..

7. **Risk of Bias: serious.** Downgraded by 1 for risk of bias: The majority of trials were open label.. **Inconsistency: no serious.** No serious inconsistency: The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** No serious indirectness: The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: no serious.** No serious imprecision: No effect found, and the CIs around the absolute effects exclude clinically important differences..

8. **Risk of Bias: serious.** Downgraded by 1 for risk of bias: The majority of trials were open label.. **Inconsistency: no serious.** No serious inconsistency: The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** No serious indirectness: The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: serious.** Downgraded by 1 for serious imprecision: The result does not reach statistical significance..

9. **Risk of Bias: serious.** Downgraded by 1 for risk of bias: The majority of trials were open label.. **Inconsistency: no serious.** No serious inconsistency: The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** No serious indirectness: The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: serious.** Downgraded by 1 for serious imprecision: There are limited data..

10. **Risk of Bias: serious.** Downgraded by 1 for risk of bias: The majority of trials were open label.. **Indirectness: no serious.** No serious indirectness: The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: serious.** Downgraded by 1 for serious imprecision: There are limited data..

11. **Risk of Bias: serious.** Downgraded by 1 for risk of bias: The majority of trials were open label.. **Inconsistency: no serious.** No serious inconsistency: The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** No serious indirectness: The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: serious.** Downgraded by 1 for serious imprecision: There are limited data..

12. **Risk of Bias: serious.** Downgraded by 1 for risk of bias: The majority of trials were open label.. **Inconsistency: no serious.** No serious inconsistency: The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** No serious indirectness: The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: no serious.** No serious imprecision: No effect found, and the CIs around the absolute effects exclude clinically important differences..

13. **Risk of Bias: serious.** Downgraded by 1 for risk of bias: The majority of trials were open label.. **Inconsistency: no serious.** No serious inconsistency: The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** No serious indirectness: The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: no serious.** No serious imprecision: No effect found, and the CIs around the absolute effects exclude clinically important differences..

14. **Risk of Bias: no serious.** No serious risk of bias: All but one of the trials were open label; however, we did not downgrade for this outcome.. **Inconsistency: no serious.** No serious inconsistency: The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** No serious indirectness: The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: serious.** Downgraded by 1 for serious imprecision: The result does not reach statistical significance..

15. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: This trial was unblinded. Only a few of the recorded prolonged QT intervals were registered as adverse events, which removed the statistical significance. The reasons for this are unclear.. **Indirectness: no serious.** No serious indirectness: This single trial was conducted in children in Burkina Faso, Kenya, Mozambique, Uganda and Zambia.. **Imprecision: serious.** Downgraded by 1 for serious imprecision: The result does not reach statistical significance..

16. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: This trial was unblinded. Only a few of the recorded prolonged QT intervals were registered as adverse events, which removed the statistical significance. The reasons for



this are unclear.. **Indirectness: no serious.** No serious indirectness: This single trial was conducted in children in Burkina Faso, Kenya, Mozambique, Uganda and Zambia.. **Imprecision: serious.** Downgraded by 1 for serious imprecision: The result does not reach statistical significance..

17. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: This trial was unblinded. Only a few of the recorded prolonged QT intervals were registered as adverse events, which removed the statistical significance. The reasons for this are unclear.. **Indirectness: no serious.** No serious indirectness: This single trial was conducted in children in Burkina Faso, Kenya, Mozambique, Uganda and Zambia.. **Imprecision: serious.** Downgraded by 1 for serious imprecision: The result does not reach statistical significance..

18. **Risk of Bias: serious.** Downgraded by 1 for risk of bias: The majority of trials were open label.. **Inconsistency: no serious.** No serious inconsistency: The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** No serious indirectness: The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: no serious.** No serious imprecision: No effect found, and the CIs around the absolute effects exclude clinically important differences..

19. **Risk of Bias: serious.** Downgraded by 1 for risk of bias: The majority of trials were open label.. **Inconsistency: no serious.** No serious inconsistency: The finding is consistent across all trials. Statistical heterogeneity is low.. **Indirectness: no serious.** No serious indirectness: The trials were conducted mainly in children in Africa; few trials in Asia or in adults.. **Imprecision: serious.** Downgraded by 1 for serious imprecision: There are limited data..

### Clinical Question/ PICO

**Population:** Patients with uncomplicated *P. falciparum* malaria (malaria-endemic settings in Africa)  
**Intervention:** Dihydroartemisinin + piperazine  
**Comparator:** Artesunate + mefloquine

Outcome Timeframe	Study results and measurements	Comparator Artesunate + mefloquine	Intervention Dihydroartemi sinin + piperazine	Certainty of the Evidence (Quality of evidence)	Plain language summary
Serious adverse events (including deaths)	Based on data from 3,522 participants in 8 studies. (Randomized controlled)	<b>8</b> per 1000  Difference:	<b>9</b> per 1000  <b>1 more per 1000</b> CI 95%	<b>Moderate</b> Due to serious imprecision <sup>1</sup>	
Nausea	Relative risk Based on data from 4,531 participants in 9 studies. (Randomized controlled)	<b>20</b> per 1000  Difference:	<b>14</b> per 1000  <b>6 fewer per 1000</b> CI 95%	<b>Moderate</b> Due to serious risk of bias <sup>2</sup>	
Early vomiting	Relative risk Based on data from 4,114 participants in 9 studies. (Randomized controlled)	<b>7</b> per 1000  Difference:	<b>6</b> per 1000  <b>1 fewer per 1000</b> CI 95%	<b>Moderate</b> Due to serious risk of bias <sup>3</sup>	
Vomiting	Relative risk Based on data from	<b>13</b> per 1000	<b>8</b> per 1000	<b>Moderate</b> Due to serious risk of bias <sup>4</sup>	

Outcome Timeframe	Study results and measurements	Comparator Artesunate + mefloquine	Intervention Dihydroartemi sinin + piperazine	Certainty of the Evidence (Quality of evidence)	Plain language summary
	2,744 participants in 5 studies. (Randomized controlled)	Difference:	<b>5 fewer per 1000</b> CI 95%		
<b>Anorexia</b>	Relative risk Based on data from 3,497 participants in 6 studies. (Randomized controlled)	<b>15</b> per 1000	<b>13</b> per 1000	<b>Low</b> Due to serious risk of bias and serious imprecision <sup>5</sup>	
		Difference:	<b>2 fewer per 1000</b> CI 95%		
<b>Diarrhoea</b>	Relative risk Based on data from 2,217 participants in 5 studies. (Randomized controlled)	<b>6</b> per 1000	<b>8</b> per 1000	<b>Moderate</b> Due to serious risk of bias <sup>6</sup>	
		Difference:	<b>2 more per 1000</b> CI 95%		
<b>Abdominal pain</b>	Relative risk Based on data from 3,887 participants in 7 studies. (Randomized controlled)	<b>11</b> per 1000	<b>11</b> per 1000	<b>Moderate</b> Due to serious risk of bias <sup>7</sup>	
		Difference:	<b>0 fewer per 1000</b> CI 95%		
<b>Headache</b>	Relative risk Based on data from 2,039 participants in 4 studies. (Randomized controlled)	<b>12</b> per 1000	<b>10</b> per 1000	<b>Low</b> Due to serious risk of bias and serious inconsistency <sup>8</sup>	
		Difference:	<b>2 fewer per 1000</b> CI 95%		
<b>Dizziness</b>	Relative risk Based on data from 4,531 participants in 9 studies. (Randomized controlled)	<b>36</b> per 1000	<b>26</b> per 1000	<b>Moderate</b> Due to serious risk of bias <sup>9</sup>	
		Difference:	<b>10 fewer per 1000</b> CI 95%		
<b>Sleeplessness</b>	Relative risk Based on data from 2,551 participants in 6 studies. (Randomized controlled)	<b>21</b> per 1000	<b>10</b> per 1000	<b>Moderate</b> Due to serious risk of bias <sup>10</sup>	
		Difference:	<b>11 fewer per 1000</b> CI 95%		
<b>Fatigue</b>	Relative risk Based on data from 872 participants in 2 studies. (Randomized controlled)	<b>8</b> per 1000	<b>3</b> per 1000	<b>Low</b> Due to serious risk of bias and serious indirectness <sup>11</sup>	
		Difference:	<b>5 fewer per 1000</b> CI 95%		

Outcome Timeframe	Study results and measurements	Comparator Artesunate + mefloquine	Intervention Dihydroartemi sinin + piperaquine	Certainty of the Evidence (Quality of evidence)	Plain language summary
Nightmares	Relative risk Based on data from 220 participants in 1 studies. (Randomized controlled)	<b>10</b> per 1000 Difference:	<b>1</b> per 1000 <b>9 fewer per 1000</b> CI 95%	<b>Low</b> Due to serious risk of bias and serious indirectness <sup>12</sup>	
Anxiety	Relative risk Based on data from 522 participants in 1 studies. (Randomized controlled)	<b>11</b> per 1000 Difference:	<b>1</b> per 1000 <b>10 fewer per 1000</b> CI 95%	<b>Low</b> Due to serious risk of bias and serious indirectness <sup>13</sup>	
Blurred vision	Relative risk Based on data from 464 participants in 1 studies. (Randomized controlled)	<b>9</b> per 1000 Difference:	<b>4</b> per 1000 <b>5 fewer per 1000</b> CI 95%	<b>Low</b> Due to serious risk of bias and serious indirectness <sup>14</sup>	
Tinnitus	Relative risk Based on data from 220 participants in 1 studies. (Randomized controlled)	<b>9</b> per 1000 Difference:	<b>4</b> per 1000 <b>5 fewer per 1000</b> CI 95%	<b>Low</b> Due to serious risk of bias and serious indirectness <sup>15</sup>	
Palpitations	Relative risk Based on data from 1,175 participants in 3 studies. (Randomized controlled)	<b>18</b> per 1000 Difference:	<b>11</b> per 1000 <b>7 fewer per 1000</b> CI 95%	<b>Moderate</b> Due to serious risk of bias <sup>16</sup>	
Cough	Relative risk Based on data from 1,148 participants in 1 studies. (Randomized controlled)	<b>10</b> per 1000 Difference:	<b>8</b> per 1000 <b>2 fewer per 1000</b> CI 95%	<b>Low</b> Due to serious risk of bias and serious imprecision <sup>17</sup>	
Dyspnoea	Relative risk Based on data from 220 participants in 1 studies. (Randomized controlled)	<b>9</b> per 1000 Difference:	<b>3</b> per 1000 <b>6 fewer per 1000</b> CI 95%	<b>Low</b> Due to serious risk of bias and serious imprecision <sup>18</sup>	
Prolonged QT interval (adverse event)	Relative risk Based on data from 1,148 participants in 1 studies. (Randomized controlled)	<b>4</b> per 1000 Difference:	<b>5</b> per 1000 <b>1 more per 1000</b> CI 95%	<b>Low</b> Due to serious risk of bias and serious imprecision <sup>19</sup>	

Outcome Timeframe	Study results and measurements	Comparator Artesunate + mefloquine	Intervention Dihydroartemisinin + piperaquine	Certainty of the Evidence (Quality of evidence)	Plain language summary
Prolonged QT interval (Bazett correction)	Relative risk Based on data from 1,148 participants in 1 studies. (Randomized controlled)	<b>4</b> per 1000 Difference:	<b>9</b> per 1000 <b>5 more per 1000</b> CI 95%	<b>Low</b> Due to serious risk of bias and serious imprecision <sup>20</sup>	
Prolonged QT interval (Fridericia correction)	Relative risk Based on data from 1,148 participants in 1 studies. (Randomized controlled)	<b>5</b> per 1000 Difference:	<b>4</b> per 1000 <b>1 fewer per 1000</b> CI 95%	<b>Low</b> Due to serious risk of bias and serious imprecision <sup>21</sup>	
Arthralgia	Relative risk Based on data from 1,148 participants in 1 studies. (Randomized controlled)	<b>6</b> per 1000 Difference:	<b>5</b> per 1000 <b>1 fewer per 1000</b> CI 95%	<b>Moderate</b> Due to serious risk of bias <sup>22</sup>	
Myalgia	Relative risk Based on data from 1,148 participants in 1 studies. (Randomized controlled)	<b>6</b> per 1000 Difference:	<b>6</b> per 1000 <b>0 fewer per 1000</b> CI 95%	<b>Moderate</b> Due to serious risk of bias <sup>23</sup>	
Urticaria	Relative risk Based on data from 719 participants in 2 studies. (Randomized controlled)	<b>2</b> per 1000 Difference:	<b>1</b> per 1000 <b>1 fewer per 1000</b> CI 95%	<b>Low</b> Due to serious risk of bias and serious imprecision <sup>24</sup>	
Pruritus	Relative risk Based on data from 872 participants in 2 studies. (Randomized controlled)	<b>3</b> per 1000 Difference:	<b>2</b> per 1000 <b>1 fewer per 1000</b> CI 95%	<b>Low</b> Due to serious risk of bias and serious imprecision <sup>25</sup>	
Rash	Relative risk Based on data from 220 participants in 1 studies. (Randomized controlled)	<b>1</b> per 1000 Difference:	<b>0</b> per 1000 <b>1 fewer per 1000</b> CI 95%	<b>Low</b> Due to serious risk of bias and serious imprecision <sup>26</sup>	

1. **Risk of Bias: no serious.** No serious risk of bias: Only eight of the 11 reports made any comment on serious adverse events. None of these eight trials was blinded. . **Inconsistency: no serious.** No serious inconsistency: None of the eight trials found statistically significant differences.. **Indirectness: no serious.** No serious indirectness: These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: serious.** Downgraded by 1 for imprecision: These trials do not exclude the possibility of rare but clinically important adverse effects..

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2. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** No serious inconsistency: This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: no serious.** No serious indirectness: These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** No serious imprecision: The result is statistically significant, and the meta-analysis has adequate power to detect this effect..
  3. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** No serious inconsistency: None of the eight trials found statistically significant differences.. **Indirectness: no serious.** No serious indirectness: These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** No serious imprecision: The 95% CI around the absolute effect is narrow and excludes clinically important differences..
  4. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** No serious inconsistency: This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: no serious.** No serious indirectness: These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** No serious imprecision: The result is statistically significant, and the meta-analysis has adequate power to detect this effect..
  5. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** No serious inconsistency: This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: no serious.** No serious indirectness: These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: serious.** Downgraded by 1 for serious imprecision: This result does not reach statistical significance..
  6. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** No serious inconsistency: This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: no serious.** No serious indirectness: These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** No serious imprecision: The result is statistically significant, and the meta-analysis has adequate power to detect this effect..
  7. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** No serious inconsistency: This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: no serious.** No serious indirectness: These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** No serious imprecision: No difference was found between treatments, and the sample is large enough for detection of any differences..
  8. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: serious.** Downgraded by 1 for serious inconsistency: There is moderate heterogeneity among trials.. **Indirectness: no serious.** No serious indirectness: These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** No serious imprecision: The result is statistically significant, and the meta-analysis has adequate power to detect this effect..
  9. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** No serious inconsistency: This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: no serious.** No serious indirectness: These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** No serious imprecision: The result is statistically significant, and the meta-analysis has adequate power to detect this effect..
  10. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** No serious inconsistency: This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: no serious.** No serious indirectness: These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** No serious imprecision: The result is statistically significant, and the meta-analysis has adequate power to detect this effect..
  11. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** No serious inconsistency: This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: serious.** Downgraded by 1 for serious indirectness: Only two trials assessed this outcome.. **Imprecision: no serious.**
  12. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** **Indirectness: serious.** Downgraded by 1 for serious indirectness: Only two trials assessed this outcome.. **Imprecision: no serious.**
  13. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** **Indirectness: serious.** Downgraded by 1 for serious indirectness: Only two trials assessed this outcome.. **Imprecision: no serious.**
  14. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** **Indirectness: serious.** Downgraded by 1 for serious indirectness: Only two trials assessed this outcome.. **Imprecision: no**

serious.

15. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** **Indirectness: serious.** Downgraded by 1 for serious indirectness: Only two trials assessed this outcome.. **Imprecision: no serious.**

16. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** No serious inconsistency: This finding was consistent across trials, with no significant statistical heterogeneity.. **Indirectness: no serious.** No serious indirectness: These trials included both adults and children and were conducted in Asia and South America.. **Imprecision: no serious.** No serious imprecision: The result is statistically significant, and the meta-analysis has adequate power to detect this effect..

17. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** **Indirectness: no serious.** **Imprecision: serious.** Downgraded by 1 for serious imprecision: This result does not reach statistical significance..

18. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** **Indirectness: no serious.** **Imprecision: serious.** Downgraded by 1 for imprecision: Limited data available, and the result is not statistically significant..

19. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: This trial is unblinded. Only a few of the recorded prolonged QT intervals were registered as adverse events, which removed the statistical significance. The reasons for this are unclear.. **Inconsistency: no serious.** **Indirectness: no serious.** No serious indirectness: This single large trial was conducted in adults and children in India, the Lao People's Democratic Republic and Thailand.. **Imprecision: serious.** Downgraded by 1 for serious imprecision: This result does not reach statistical significance..

20. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** **Indirectness: no serious.** No serious indirectness: This single large trial was conducted in adults and children in India, the Lao People's Democratic Republic and Thailand.. **Imprecision: serious.** Downgraded by 1 for serious imprecision: This result does not reach statistical significance..

21. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** **Indirectness: no serious.** No serious indirectness: This single large trial was conducted in adults and children in India, the Lao People's Democratic Republic and Thailand.. **Imprecision: serious.** Downgraded by 1 for serious imprecision: This result does not reach statistical significance..

22. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label. Downgraded by 1 for serious risk of bias: This trial is unblinded. Only a few of the recorded prolonged QT intervals were registered as adverse events, which removed the statistical significance. The reasons for this are unclear. 15 . **Inconsistency: no serious.** **Indirectness: no serious.** **Imprecision: no serious.** No serious imprecision: No difference was found between treatments, and the sample is large enough for detection of any differences..

23. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label. Downgraded by 1 for serious risk of bias: This trial is unblinded. Only a few of the recorded prolonged QT intervals were registered as adverse events, which removed the statistical significance. The reasons for this are unclear.. **Inconsistency: no serious.** **Indirectness: no serious.** **Imprecision: no serious.** No serious imprecision: No difference was found between treatments, and the sample is large enough for detection of any differences..

24. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** **Indirectness: no serious.** **Imprecision: serious.** Downgraded by 1 for imprecision: Limited data available, and the result is not statistically significant..

25. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** **Indirectness: no serious.** **Imprecision: serious.** Downgraded by 1 for imprecision: Limited data available, and the result is not statistically significant..

26. **Risk of Bias: serious.** Downgraded by 1 for serious risk of bias: All trials were open label.. **Inconsistency: no serious.** **Indirectness: no serious.** **Imprecision: serious.** Downgraded by 1 for imprecision: Limited data available, and the result is not statistically significant..

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## Clinical Question/ PICO

<b>Population:</b>	Adults and children with uncomplicated falciparum malaria (malaria-endemic areas in Africa and Asia)
<b>Intervention:</b>	Artesunate + pyronaridine once daily for 3 days
<b>Comparator:</b>	Artemether + lumefantrine twice daily for 3 days

Outcome Timeframe	Study results and measurements	Comparator Artemether + lumefantrine	Intervention Artesunate + pyronaridine	Certainty of the Evidence (Quality of evidence)	Plain language summary
Treatment failure on day 28 (PCR-unadjusted)	Relative risk 0.6 (CI 95% 0.4 – 0.9) Based on data from 1,720 participants in 2 studies. (Randomized controlled)	<b>70</b> per 1000  Difference:	<b>42</b> per 1000  <b>28 fewer per 1000</b> ( CI 95% 42 fewer – 7 fewer )	<b>Moderate</b> Due to serious indirectness <sup>1</sup>	
Treatment failure on day 28 (PCR-adjusted)	Relative risk 1.69 (CI 95% 0.56 – 5.1) Based on data from 1,650 participants in 2 studies. (Randomized controlled)	<b>10</b> per 1000  Difference:	<b>17</b> per 1000  <b>7 more per 1000</b> ( CI 95% 4 fewer – 41 more )	<b>Moderate</b> Due to serious indirectness <sup>2</sup>	
Treatment failure on day 42 (PCR-unadjusted)	Relative risk 0.85 (CI 95% 0.53 – 1.36) Based on data from 1,691 participants in 2 studies. (Randomized controlled)	<b>170</b> per 1000  Difference:	<b>145</b> per 1000  <b>25 fewer per 1000</b> ( CI 95% 80 fewer – 61 more )	<b>Moderate</b> Due to serious indirectness <sup>3</sup>	
Treatment failure on day 42 (PCR-adjusted)	Relative risk 1.53 (CI 95% 0.73 – 3.19) Based on data from 1,472 participants in 2 studies. (Randomized controlled)	<b>20</b> per 1000  Difference:	<b>31</b> per 1000  <b>11 more per 1000</b> ( CI 95% 5 fewer – 44 more )	<b>Low</b> Due to serious indirectness and serious inconsistency <sup>4</sup>	

1. **Risk of Bias: no serious.** Both studies were well conducted with low risk of bias. **Inconsistency: no serious.** The trend was towards benefit with artesunate + pyronaridine in both trials but reached statistical significance in only one. **Indirectness: serious.** The two trials were conducted in children aged 3 months–12 years in study sites in Africa and Asia. In both trials, only 152 children aged < 5 years received artesunate + pyronaridine, and only 115 children in total were randomized to artesunate + pyronaridine in Asia. Further, adequately powered studies in children in Africa and adults and children in Asia would be needed to generalize this result. **Imprecision: no serious.** The result is statistically significant and the meta-analysis is adequately powered; however, these multi-centred trials are underpowered to show equivalence at country level. Not downgraded.

2. **Risk of Bias: no serious.** Both studies were well conducted with low risk of bias. **Inconsistency: no serious.** The trend was towards benefit with artesunate + pyronaridine in both trials but reached statistical significance in only one. **Indirectness: serious.** The two trials were conducted in children aged 3 months–12 years in study sites in Africa and Asia. In both trials, only 152 children aged < 5 years received artesunate + pyronaridine, and only 115 children in total were randomized to artesunate + pyronaridine in Asia. Further, adequately powered studies in children in Africa and adults and children in Asia would be needed to generalize this result. **Imprecision: no serious.** No substantial difference found between the two ACTs; however, these multi-centred trials are underpowered to show equivalence at country level. Not downgraded.

3. **Risk of Bias: no serious.** Both studies were well conducted with low risk of bias. **Inconsistency: no serious.** The trend was towards benefit with artesunate + pyronaridine in both trials but reached statistical significance in only one. **Indirectness: serious.** The two trials were conducted in children aged 3 months–12 years in study sites in Africa and

Asia. In both trials, only 152 children aged < 5 years received artesunate + pyronaridine, and only 115 children in total were randomized to artesunate + pyronaridine in Asia. Further, adequately powered studies in children in Africa and adults and children in Asia would be needed to generalize this result. **Imprecision: no serious.** No substantial difference found between the two ACTs; however, these multi-centred trials are underpowered to show equivalence at country level. Not downgraded.

4. **Risk of Bias: no serious.** Both studies were well conducted with low risk of bias. **Inconsistency: serious.** Although statistical heterogeneity was low, PCR-adjusted treatment failure was > 5% in the one study with children aged < 5 years. **Indirectness: serious.** The two trials were conducted in children aged 3 months–12 years in study sites in Africa and Asia. In both trials, only 152 children aged < 5 years received artesunate + pyronaridine, and only 115 children in total were randomized to artesunate + pyronaridine in Asia. Further, adequately powered studies in children in Africa and adults and children in Asia would be needed to generalize this result. **Imprecision: no serious.** No substantial difference found between the two ACTs; however, these multi-centred trials are underpowered to show equivalence at country level. Not downgraded.

### Clinical Question/ PICO

<b>Population:</b>	People with uncomplicated falciparum malaria (malaria-endemic areas in Africa and Asia)
<b>Intervention:</b>	Artesunate + pyronaridine once daily for 3 days
<b>Comparator:</b>	Artesunate + mefloquine once daily for 3 days

Outcome Timeframe	Study results and measurements	Comparator Artesunate + mefloquine	Intervention Artesunate + pyronaridine	Certainty of the Evidence (Quality of evidence)	Plain language summary
Treatment failure on day 28 (PCR-unadjusted)	Relative risk 0.35 (CI 95% 0.17 – 0.73) Based on data from 1,200 participants in 1 studies. (Randomized controlled)	40 per 1000  Difference:	14 per 1000  26 fewer per 1000 ( CI 95% 33 fewer – 11 fewer )	Moderate Due to serious indirectness <sup>1</sup>	
Treatment failure on day 28 (PCR-adjusted)	Relative risk 0.38 (CI 95% 0.14 – 1.02) Based on data from 1,187 participants in 1 studies. (Randomized controlled)	20 per 1000  Difference:	8 per 1000  12 fewer per 1000 ( CI 95% 17 fewer – 0 fewer )	Moderate Due to serious indirectness <sup>2</sup>	
Treatment failure on day 42 (PCR-unadjusted)	Relative risk 0.86 (CI 95% 0.57 – 1.31) Based on data from 1,146 participants in 1 studies. (Randomized controlled)	80 per 1000  Difference:	69 per 1000  11 fewer per 1000 ( CI 95% 34 fewer – 25 more )	Moderate Due to serious indirectness <sup>3</sup>	
Treatment failure on day	Relative risk 1.64 (CI 95% 0.89 – 3)	40 per 1000	66 per 1000	Low Due to serious	



Outcome Timeframe	Study results and measurements	Comparator Artesunate + mefloquine	Intervention Artesunate + pyronaridine	Certainty of the Evidence (Quality of evidence)	Plain language summary
42 (PCR-adjusted)	Based on data from 1,116 participants in 1 studies. (Randomized controlled)	Difference:	<b>26 more per 1000</b> ( CI 95% 4 fewer – 80 more )	indirectness <sup>4</sup>	

- Risk of Bias: no serious.** This study was well conducted with low risk of bias. **Inconsistency: no serious.** Not applicable, as only one trial. **Indirectness: serious.** Of the 1271 children and adults aged > 5 years enrolled in this study, 81.3% (1033) were enrolled and treated in study sites in Asia (Cambodia, India, Thailand, Viet Nam) and only 18.7% (237) in Africa (Burkina Faso, Côte d'Ivoire, United Republic of Tanzania). Further studies in African children are necessary to generalize this result. **Imprecision: no serious.** The result is statistically significant, and the meta-analysis is adequately powered; however, this multi-centred trial is underpowered to show equivalence at country level. Not downgraded.
- Risk of Bias: no serious.** This study was well conducted with low risk of bias. **Inconsistency: no serious.** Not applicable, as only one trial. **Indirectness: serious.** Of the 1271 children and adults aged > 5 years enrolled in this study, 81.3% (1033) were enrolled and treated in study sites in Asia (Cambodia, India, Thailand, Viet Nam) and only 18.7% (237) in Africa (Burkina Faso, Côte d'Ivoire, United Republic of Tanzania). Further studies in African children are necessary to generalize this result. **Imprecision: no serious.** No clinically important differences found between ACTs; however, this multi-centred trial is underpowered to show equivalence at country level. Not downgraded.
- Risk of Bias: no serious.** This study was well conducted with low risk of bias. **Inconsistency: no serious.** Not applicable, as only one trial. **Indirectness: serious.** Of the 1271 children and adults aged > 5 years enrolled in this study, 81.3% (1033) were enrolled and treated in study sites in Asia (Cambodia, India, Thailand, Viet Nam) and only 18.7% (237) in Africa (Burkina Faso, Côte d'Ivoire, United Republic of Tanzania). Further studies in African children are necessary to generalize this result. **Imprecision: no serious.** No clinically important differences found between ACTs; however, this multi-centred trial is underpowered to show equivalence at country level. Not downgraded.
- Risk of Bias: no serious.** This study was well conducted with low risk of bias. **Inconsistency: no serious.** Not applicable, as only one trial. **Indirectness: serious.** Of the 1271 children and adults aged > 5 years enrolled in this study, 81.3% (1033) were enrolled and treated in study sites in Asia (Cambodia, India, Thailand, Viet Nam) and only 18.7% (237) in Africa (Burkina Faso, Côte d'Ivoire, United Republic of Tanzania). Further studies in African children are necessary to generalize this result. **Imprecision: no serious.** No clinically important differences found between ACTs; however, this multi-centred trial is underpowered to show equivalence at country level. Not downgraded.

### Clinical Question/ PICO

- Population:** People with uncomplicated falciparum malaria (high- and low-transmission settings for P. falciparum and P. vivax malaria)
- Intervention:** Pyronaridine alone or with an artemisinin derivative
- Comparator:** Another antimalarial drug

Outcome Timeframe	Study results and measurements	Comparator Comparator antimalarial	Intervention Pyronaridine alone or with artesunate	Certainty of the Evidence (Quality of evidence)	Plain language summary
Elevated alanine aminotransaminase activity (Grade 3, 4 toxicity)	Relative risk 4.17 (CI 95% 1.38 – 12.61) Based on data from 3,523 participants in 4 studies. (Randomized controlled)	<b>2</b> per 1000	<b>8</b> per 1000	Moderate Due to serious indirectness <sup>1</sup>	
		Difference:	<b>6 more per 1000</b> ( CI 95% 1 more – 23 more )		

Outcome Timeframe	Study results and measurements	Comparator Comparator antimalarial	Intervention Pyronaridine alone or with artesunate	Certainty of the Evidence (Quality of evidence)	Plain language summary
Elevated aspartate aminotransferase activity (Grade 3, 4 toxicity)	Relative risk 4.08 (CI 95% 1.17 – 14.26) Based on data from 3,528 participants in 4 studies. (Randomized controlled)	<b>2</b> per 1000  Difference:	<b>8</b> per 1000  <b>6 more per 1000</b> ( CI 95% 0 fewer – 27 more )	<b>Moderate</b> Due to serious indirectness <sup>2</sup>	
Elevated alkaline phosphatase activity (Grade 3, 4 toxicity)	Relative risk 0.62 (CI 95% 0.15 – 2.51) Based on data from 2,606 participants in 3 studies. (Randomized controlled)	<b>2</b> per 1000  Difference:	<b>1</b> per 1000  <b>1 fewer per 1000</b> ( CI 95% 2 fewer – 3 more )	<b>Moderate</b> Due to serious indirectness <sup>3</sup>	
Elevated bilirubin (Grade 3, 4 toxicity)	Relative risk 1.92 (CI 95% 0.59 – 6.24) Based on data from 3,067 participants in 3 studies. (Randomized controlled)	<b>3</b> per 1000  Difference:	<b>6</b> per 1000  <b>3 more per 1000</b> ( CI 95% 1 fewer – 16 more )	<b>Low</b> Due to serious indirectness and serious imprecision <sup>4</sup>	

1. **Risk of Bias: no serious.** The studies were well conducted, although the data analysis was not clearly independent of the drug manufacturer in three of the studies. **Inconsistency: no serious.** Statistical heterogeneity was low. **Indirectness: serious.** Only 232 children aged < 5 years were included in these trials. **Imprecision: no serious.** The 95% CI is wide, and there are few events. Larger trials would be necessary for the group to have full confidence in this result, but it was not downgraded.

2. **Risk of Bias: no serious.** The studies were well conducted, although the data analysis was not clearly independent of the drug manufacturer in three of the studies. **Inconsistency: no serious.** Statistical heterogeneity was low. **Indirectness: serious.** Only 232 children aged < 5 years were included in these trials. **Imprecision: no serious.** The 95% CI is wide, and there are few events. Larger trials would be necessary for the group to have full confidence in this result, but it was not downgraded.

3. **Risk of Bias: no serious.** The studies were well conducted, although the data analysis was not clearly independent of the drug manufacturer in three of the studies. **Inconsistency: no serious.** Statistical heterogeneity was low. **Indirectness: serious.** Only 232 children aged < 5 years were included in these trials. **Imprecision: no serious.** The 95% CI is narrow and probably excludes clinically important differences.

4. **Risk of Bias: no serious.** The studies were well conducted, although the data analysis was not clearly independent of the drug manufacturer in three of the studies. **Inconsistency: no serious.** Statistical heterogeneity was low. **Indirectness: serious.** Only 232 children aged < 5 years were included in these trials. **Imprecision: serious.** The 95% CI is wide and includes no difference in clinically important effects.

## Clinical Question/ PICO

**Population:** Adults and children with uncomplicated *P. falciparum* malaria (malaria-endemic settings)  
**Intervention:** Artemisinin + naphthoquine; 1-day course  
**Comparator:** Artemether + lumefantrine twice daily for 3 days

Outcome Timeframe	Study results and measurements	Comparator Artemether + lumefantrine	Intervention Artemisinin + naphthoquine	Certainty of the Evidence (Quality of evidence)	Plain language summary
Treatment failure on day 28 (PCR-unadjusted)	Relative risk 1.54 (CI 95% 0.27 – 8.96) Based on data from 297 participants in 2 studies. (Randomized controlled)	<b>10</b> per 1000  Difference:	<b>15</b> per 1000  <b>5 more per 1000</b> ( CI 95% 7 fewer – 80 more )	<b>Very low</b> Due to serious indirectness and very serious imprecision <sup>1</sup>	
Treatment failure on day 28 (PCR-adjusted)	Relative risk 3.25 (CI 95% 0.13 – 78.69) Based on data from 295 participants in 2 studies. (Randomized controlled)	<b>0</b> per 1000  Difference:	<b>0</b> per 1000  <b>0 fewer per 1000</b> ( CI 95% 0 fewer – 0 fewer )	<b>Very low</b> Due to serious indirectness and very serious imprecision <sup>2</sup>	
Fever clearance: fever on day 2	Relative risk 5.9 (CI 95% 0.73 – 47.6) Based on data from 123 participants in 1 studies. (Randomized controlled)	<b>20</b> per 1000  Difference:	<b>118</b> per 1000  <b>98 more per 1000</b> ( CI 95% 5 fewer – 932 more )	<b>Very low</b> Due to serious indirectness and very serious imprecision <sup>3</sup>	
Parasite clearance: parasitaemia on day 2	Relative risk 0.15 (CI 95% 0.01 – 2.92) Based on data from 297 participants in 2 studies. (Randomized controlled)	<b>20</b> per 1000  Difference:	<b>3</b> per 1000  <b>17 fewer per 1000</b> ( CI 95% 20 fewer – 38 more )	<b>Very low</b> Due to serious indirectness and very serious imprecision <sup>4</sup>	
Gametocytaemia on day 7	Relative risk 1.97 (CI 95% 0.18 – 21.14) Based on data from 123 participants in 1 studies. (Randomized controlled)	<b>20</b> per 1000  Difference:	<b>39</b> per 1000  <b>19 more per 1000</b> ( CI 95% 16 fewer – 403 more )	<b>Very low</b> Due to serious indirectness and very serious imprecision <sup>5</sup>	

1. **Risk of Bias: no serious.** One study adequately concealed allocation and thus had a low risk of selection bias. In the other study, the process of randomization and allocation concealment was unclear. **Inconsistency: no serious.** Statistical heterogeneity was low. **Indirectness: serious.** Only two studies, in Benin and Cote d'Ivoire, evaluated this comparison. Further studies in additional settings are required before this result can be generalized. **Imprecision: very serious.**

Demonstration of non-inferiority at 95% efficacy would require a sample size of 472. Both trials are significantly underpowered.

2. **Risk of Bias: no serious.** One study adequately concealed allocation and thus had a low risk of selection bias. In the other study, the process of randomization and allocation concealment was unclear. **Inconsistency: no serious.** Statistical heterogeneity was low. **Indirectness: serious.** Only two studies, in Benin and Cote d'Ivoire, evaluated this comparison. Further studies in additional settings are required before this result can be generalized. **Imprecision: very serious.** Demonstration of non-inferiority at 95% efficacy would require a sample size of 472. Both trials are significantly underpowered.

3. **Risk of Bias: no serious.** This study adequately concealed allocation and thus had a low risk of selection bias. **Indirectness: serious.** Study in Cote d'Ivoire. Further studies in additional settings are required before this result can be generalized. **Imprecision: very serious.** This trial was small and the result has a very wide 95% confidence interval, including appreciable benefit and harm.

4. **Risk of Bias: no serious.** One study adequately concealed allocation and thus had a low risk of selection bias. In the other study, the process of randomization and allocation concealment was unclear. **Inconsistency: no serious.** Statistical heterogeneity was low. **Indirectness: serious.** Only two studies, in Benin and Cote d'Ivoire, evaluated this comparison. Further studies in additional settings are required before this result can be generalized. **Imprecision: very serious.** The result has a very wide 95% confidence interval, including appreciable benefit and harm.

5. **Risk of Bias: no serious.** This study adequately concealed allocation and thus had a low risk of selection bias. **Indirectness: serious.** Study in Cote d'Ivoire. Further studies in additional settings are required before this result can be generalized. **Imprecision: very serious.** This trial was small and the result has a very wide 95% confidence interval, including appreciable benefit and harm.

## Clinical Question/ PICO

<b>Population:</b>	Adults and children with uncomplicated <i>P. falciparum</i> malaria (malaria-endemic settings)
<b>Intervention:</b>	Artemisinin + naphthoquine; 1-day course
<b>Comparator:</b>	Dihydroartemisinin + piperaquine; 3-day course

Outcome Timeframe	Study results and measurements	Comparator Dihydroartemi sinin + piperaquine	Intervention Artemisinin + naphthoquine	Certainty of the Evidence (Quality of evidence)	Plain language summary
Treatment failure on day 28 (PCR- unadjusted)	Relative risk Based on data from 143 participants in 1 studies. (Randomized controlled)	0 per 1000	0 per 1000 CI 95% 0 fewer –	Very low Due to serious indirectness and very serious imprecision <sup>1</sup>	
Treatment failure on day 28 (PCR- adjusted)	Relative risk Based on data from 143 participants in 1 studies. (Randomized controlled)	0 per 1000	0 per 1000 CI 95% 0 fewer –	Very low Due to serious indirectness and very serious imprecision <sup>2</sup>	
Treatment failure on day 42 (PCR- unadjusted)	Relative risk 0.91 (CI 95% 0.13 – 6.26) Based on data from 143 participants in 1 studies. (Randomized controlled)	30 per 1000 Difference:	27 per 1000 3 fewer per 1000 (CI 95% 26	Very low Due to serious indirectness and very serious imprecision <sup>3</sup>	

Outcome Timeframe	Study results and measurements	Comparator Dihydroartemi sinin + piperazine	Intervention Artemisinin + naphthoquine	Certainty of the Evidence (Quality of evidence)	Plain language summary
Treatment failure on day 42 (PCR- adjusted)	Relative risk 0.19 (CI 95% 0.01 – 3.82) Based on data from 141 participants in 1 studies. (Randomized controlled)	30 per 1000  Difference:	fewer – 158 more )  6 per 1000  24 fewer per 1000 ( CI 95% 30 fewer – 85 more )	Very low Due to serious indirectness and very serious imprecision <sup>4</sup>	
Fever clearance: fever on day 2	Relative risk  Based on data from 144 participants in 1 studies. (Randomized controlled)	0 per 1000	0 per 1000  CI 95%	Very low Due to serious indirectness and very serious imprecision <sup>5</sup>	
Parasite clearance: parasitaemia on day 2	Relative risk 6.29 (CI 95% 0.33 – 119.69) Based on data from 144 participants in 1 studies. (Randomized controlled)	0 per 1000	40 per 1000  CI 95%	Very low Due to serious indirectness and very serious imprecision <sup>6</sup>	
Gametocytaemi a: on day 7	Relative risk 1.38 (CI 95% 0.52 – 3.7) Based on data from 144 participants in 1 studies. (Randomized controlled)	80 per 1000  Difference:	110 per 1000  30 more per 1000 ( CI 95% 38 fewer – 216 more )	Very low Due to serious indirectness and very serious imprecision <sup>7</sup>	

- Risk of Bias: no serious.** Although the description of the randomization procedure is vague, this trial is probably at low risk of selection bias. **Indirectness: serious.** This comparison has been evaluated in only a single setting. Further studies in additional settings are required before this result can be generalized. **Imprecision: very serious.** Demonstration of non-inferiority at 95% efficacy would require a sample size of 472. This trial is significantly underpowered.
- Risk of Bias: no serious.** Although the description of the randomization procedure is vague, this trial is probably at low risk of selection bias. **Indirectness: serious.** This comparison has been evaluated in only a single setting. Further studies in additional settings are required before this result can be generalized. **Imprecision: very serious.** Demonstration of non-inferiority at 95% efficacy would require a sample size of 472. This trial is significantly underpowered.
- Risk of Bias: no serious.** Although the description of the randomization procedure is vague, this trial is probably at low risk of selection bias. **Indirectness: serious.** This comparison has been evaluated in only a single setting. Further studies in additional settings are required before this result can be generalized. **Imprecision: very serious.** Demonstration of non-inferiority at 95% efficacy would require a sample size of 472. This trial is significantly underpowered.
- Risk of Bias: no serious.** Although the description of the randomization procedure is vague, this trial is probably at low risk of selection bias. **Indirectness: serious.** This comparison has been evaluated in only a single setting. Further studies in additional settings are required before this result can be generalized. **Imprecision: very serious.** Demonstration of non-inferiority at 95% efficacy would require a sample size of 472. This trial is significantly underpowered.
- Risk of Bias: no serious.** Although the description of the randomization procedure is vague, this trial is probably at

low risk of selection bias. **Indirectness: serious.** This comparison has been evaluated in only a single setting. Further studies in additional settings are required before this result can be generalized. **Imprecision: very serious.** This trial is small. No participants in either group had fever on day 2.

6. **Risk of Bias: no serious.** Although the description of the randomization procedure is vague, this trial is probably at low risk of selection bias. **Indirectness: serious.** This comparison has been evaluated in only a single setting. Further studies in additional settings are required before this result can be generalized. **Imprecision: very serious.** The result has a very wide 95% confidence interval, including appreciable benefit and harm.

7. **Risk of Bias: no serious.** Although the description of the randomization procedure is vague, this trial is probably at low risk of selection bias. **Indirectness: serious.** This comparison has been evaluated in only a single setting. Further studies in additional settings are required before this result can be generalized. **Imprecision: very serious.** The result has a very wide 95% confidence interval, including appreciable benefit and harm.