5.2.1. Artemisinin-based combination therapy

Clinical Question/ PICO

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

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

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 + piperaquine, 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 + piperaquine, 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 + piperaquine 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 + piperaquine once daily for 3 days
Comparator: Artesunate + mefloquine once daily for 3 days

Outcome Timeframe	**Study results and measurements**	**Comparator** Artesunate + mefloquine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Treatment failure - PCR unadjusted [1] 28 days	Relative risk 1.02 (CI 95% 0.28 — 3.72) Based on data from 3,487 patients in 8 studies. (Randomized controlled)	20 per 1000 Difference:	20 per 1000 **0 fewer per 1000** (CI 95% 14 fewer — 54 more)	**High** Due to serious inconsistency [2]	
Treatment failure - PCR adjusted [3] 28 days	Relative risk 0.41 (CI 95% 0.21 — 0.8) Based on data from 3,467 patients in 8 studies. (Randomized controlled)	10 per 1000 Difference:	4 per 1000 **6 fewer per 1000** (CI 95% 8 fewer — 2 fewer)	**High** Due to serious inconsistency [4]	
Treatment failure - PCR unadjusted [5]	Relative risk 0.84 (CI 95% 0.69 — 1.03) Based on data from 2,715 patients in 5	120 per 1000	101 per 1000	**Moderate** Due to serious inconsistency [6]	

Outcome Timeframe	**Study results and measurements**	**Comparator** Artesunate + mefloquine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
63 days	studies. (Randomized controlled)	Difference:	**19 fewer per 1000** (CI 95% 37 fewer — 4 more)		
Treatment failure - PCR adjusted [7] 63 days	Relative risk 0.5 (CI 95% 0.3 — 0.84) Based on data from 2,500 patients in 5 studies. (Randomized controlled)	30 per 1000 Difference:	15 per 1000 **15 fewer per 1000** (CI 95% 21 fewer — 5 fewer)	**High** Due to serious inconsistency [8]	

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 + piperaquine 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 + piperaquine, 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 + piperaquine, one in Myanmar in 2009 showed a benefit with dihydroartemisinin + piperaquine, 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 + piperaquine.. **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

Population: Patients with uncomplicated P. falciparum malaria (malaria-endemic settings in Africa)
Intervention: Dihydroartemisinin + piperaquine
Comparator: Artemether + lumefantrine

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

Outcome Timeframe	**Study results and measurements**	**Comparator** Artemether + lumefantrine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Anorexia	Relative risk Based on data from 3,834 patients in 5 studies. (Randomized controlled)	150 per 1000 Difference:	140 per 1000 **10 fewer per 1000** CI 95% 0 fewer –	Moderate Due to serious risk of bias [7]	
Headache	Relative risk Based on data from 309 patients in 2 studies. (Randomized controlled)	270 per 1000 Difference:	330 per 1000 **60 more per 1000** CI 95% 0 fewer –	Low Due to serious risk of bias and serious imprecision [8]	
Sleeplessness	Relative risk Based on data from 547 patients in 2 studies. (Randomized controlled)	10 per 1000 Difference:	30 per 1000 **20 more per 1000** CI 95% 0 fewer –	Low Due to serious risk of bias and serious imprecision [9]	
Dizziness	Relative risk Based on data from 547 patients in 2 studies. (Randomized controlled)	30 per 1000 Difference:	40 per 1000 **10 more per 1000** CI 95% 0 fewer –	Low Due to serious risk of bias and serious imprecision [10]	
Sleepiness	Relative risk Based on data from 384 patients in 1 studies. (Randomized controlled)	0 per 1000 Difference:	0 per 1000 **0 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious imprecision [11]	
Weakness	Relative risk Based on data from 1,812 patients in 5 studies. (Randomized controlled)	170 per 1000 Difference:	180 per 1000 **10 more per 1000** CI 95% 0 fewer –	Moderate Due to serious risk of bias [12]	
Cough	Relative risk Based on data from 4,342 patients in 5 studies. (Randomized controlled)	420 per 1000 Difference:	420 per 1000 **0 fewer per 1000** CI 95% 0 fewer –	Moderate Due to serious risk of bias [13]	

Outcome Timeframe	**Study results and measurements**	**Comparator** Artemether + lumefantrine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Coryza	Relative risk Based on data from 832 patients in 2 studies. (Randomized controlled)	680 per 1000 Difference:	660 per 1000 **20 fewer per 1000** CI 95% 0 fewer –	Low Due to serious imprecision [14]	
Prolonged QT interval (adverse event)	Relative risk Based on data from 1,548 patients in 1 studies. (Randomized controlled)	30 per 1000 Difference:	20 per 1000 **10 fewer per 1000** CI 95% 0 fewer –	Low Due to serious imprecision and serious risk of bias [15]	
Prolonged QT interval (Bazett correction)	Relative risk Based on data from 1,548 patients in 1 studies. (Randomized controlled)	70 per 1000 Difference:	90 per 1000 **20 more per 1000** CI 95% 0 fewer –	Low Due to serious imprecision and serious risk of bias [16]	
Prolonged QT interval (Fridericia correction)	Relative risk Based on data from 1,548 patients in 1 studies. (Randomized controlled)	0 per 1000 Difference:	0 per 1000 **0 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious imprecision [17]	
Pruritus	Relative risk Based on data from 2,033 patients in 5 studies. (Randomized controlled)	20 per 1000 Difference:	40 per 1000 **20 more per 1000** CI 95% 0 fewer –	Moderate Due to serious risk of bias [18]	
Facial oedema	Relative risk Based on data from 384 patients in 1 studies. (Randomized controlled)	0 per 1000 Difference:	0 per 1000 **0 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious imprecision [19]	

1. **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..

2. **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..
3. **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 + piperaquine
Comparator: Artesunate + mefloquine

Outcome Timeframe	**Study results and measurements**	**Comparator** Artesunate + mefloquine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Serious adverse events (including deaths)	Based on data from 3,522 patients in 8 studies. (Randomized controlled)	8 per 1000 Difference:	9 per 1000 **1 more per 1000** CI 95%	Moderate Due to serious imprecision [1]	
Nausea	Relative risk Based on data from 4,531 patients in 9 studies. (Randomized controlled)	20 per 1000 Difference:	14 per 1000 **6 fewer per 1000** CI 95%	Moderate Due to serious risk of bias [2]	
Early vomiting	Relative risk	7	6	Moderate Due to serious	

Outcome Timeframe	**Study results and measurements**	**Comparator** Artesunate + mefloquine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
	Based on data from 4,114 patients in 9 studies. (Randomized controlled)	per 1000 Difference:	per 1000 **1 fewer per 1000** CI 95%	risk of bias [3]	
Vomiting	Relative risk Based on data from 2,744 patients in 5 studies. (Randomized controlled)	13 per 1000 Difference:	8 per 1000 **5 fewer per 1000** CI 95%	Moderate Due to serious risk of bias [4]	
Anorexia	Relative risk Based on data from 3,497 patients in 6 studies. (Randomized controlled)	15 per 1000 Difference:	13 per 1000 **2 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious imprecision [5]	
Diarrhoea	Relative risk Based on data from 2,217 patients in 5 studies. (Randomized controlled)	6 per 1000 Difference:	8 per 1000 **2 more per 1000** CI 95%	Moderate Due to serious risk of bias [6]	
Abdominal pain	Relative risk Based on data from 3,887 patients in 7 studies. (Randomized controlled)	11 per 1000 Difference:	11 per 1000 **0 fewer per 1000** CI 95%	Moderate Due to serious risk of bias [7]	
Headache	Relative risk Based on data from 2,039 patients in 4 studies. (Randomized controlled)	12 per 1000 Difference:	10 per 1000 **2 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious inconsistency [8]	
Dizziness	Relative risk Based on data from 4,531 patients in 9 studies. (Randomized controlled)	36 per 1000 Difference:	26 per 1000 **10 fewer per 1000** CI 95%	Moderate Due to serious risk of bias [9]	
Sleeplessness	Relative risk Based on data from 2,551 patients in 6 studies. (Randomized controlled)	21 per 1000 Difference:	10 per 1000 **11 fewer per 1000** CI 95%	Moderate Due to serious risk of bias [10]	

Outcome Timeframe	**Study results and measurements**	**Comparator** Artesunate + mefloquine	**Intervention** Dihydroartemisinin + piperaquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Fatigue	Relative risk Based on data from 872 patients in 2 studies. (Randomized controlled)	8 per 1000 Difference:	3 per 1000 **5 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious indirectness [11]	
Nightmares	Relative risk Based on data from 220 patients in 1 studies. (Randomized controlled)	10 per 1000 Difference:	1 per 1000 **9 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious indirectness [12]	
Anxiety	Relative risk Based on data from 522 patients in 1 studies. (Randomized controlled)	11 per 1000 Difference:	1 per 1000 **10 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious indirectness [13]	
Blurred vision	Relative risk Based on data from 464 patients in 1 studies. (Randomized controlled)	9 per 1000 Difference:	4 per 1000 **5 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious indirectness [14]	
Tinnitus	Relative risk Based on data from 220 patients in 1 studies. (Randomized controlled)	9 per 1000 Difference:	4 per 1000 **5 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious indirectness [15]	
Palpitations	Relative risk Based on data from 1,175 patients in 3 studies. (Randomized controlled)	18 per 1000 Difference:	11 per 1000 **7 fewer per 1000** CI 95%	Moderate Due to serious risk of bias [16]	
Cough	Relative risk Based on data from 1,148 patients in 1 studies. (Randomized controlled)	10 per 1000 Difference:	8 per 1000 **2 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious imprecision [17]	
Dyspnoea	Relative risk Based on data from 220 patients in 1 studies. (Randomized controlled)	9 per 1000 Difference:	3 per 1000 **6 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious imprecision [18]	

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 (adverse event)	Relative risk Based on data from 1,148 patients in 1 studies. (Randomized controlled)	4 per 1000 Difference:	5 per 1000 **1 more per 1000** CI 95%	Low Due to serious risk of bias and serious imprecision [19]	
Prolonged QT interval (Bazett correction)	Relative risk Based on data from 1,148 patients in 1 studies. (Randomized controlled)	4 per 1000 Difference:	9 per 1000 **5 more per 1000** CI 95%	Low Due to serious risk of bias and serious imprecision [20]	
Prolonged QT interval (Fridericia correction)	Relative risk Based on data from 1,148 patients in 1 studies. (Randomized controlled)	5 per 1000 Difference:	4 per 1000 **1 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious imprecision [21]	
Arthralgia	Relative risk Based on data from 1,148 patients in 1 studies. (Randomized controlled)	6 per 1000 Difference:	5 per 1000 **1 fewer per 1000** CI 95%	Moderate Due to serious risk of bias [22]	
Myalgia	Relative risk Based on data from 1,148 patients in 1 studies. (Randomized controlled)	6 per 1000 Difference:	6 per 1000 **0 fewer per 1000** CI 95%	Moderate Due to serious risk of bias [23]	
Urticaria	Relative risk Based on data from 719 patients in 2 studies. (Randomized controlled)	2 per 1000 Difference:	1 per 1000 **1 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious imprecision [24]	
Pruritus	Relative risk Based on data from 872 patients in 2 studies. (Randomized controlled)	3 per 1000 Difference:	2 per 1000 **1 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious imprecision [25]	
Rash	Relative risk Based on data from 220 patients in 1 studies. (Randomized controlled)	1 per 1000 Difference:	0 per 1000 **1 fewer per 1000** CI 95%	Low Due to serious risk of bias and serious imprecision [26]	

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..
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..

Clinical Question/ PICO

Population: Adults and children with uncomplicated falciparum malaria (malaria-endemic areas in Africa and Asia)

Intervention: Artesunate + pyronaridine once daily for 3 days

Comparator: 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 patients in 2 studies. (Randomized controlled)	70 per 1000 Difference:	42 per 1000 **28 fewer per 1000** (CI 95% 42 fewer — 7 fewer)	Moderate Due to serious indirectness [1]	
Treatment failure on day 28 (PCR-adjusted)	Relative risk 1.69 (CI 95% 0.56 — 5.1) Based on data from 1,650 patients in 2 studies. (Randomized controlled)	10 per 1000 Difference:	17 per 1000 **7 more per 1000** (CI 95% 4 fewer — 41 more)	Moderate Due to serious indirectness [2]	
Treatment failure on day 42 (PCR-unadjusted)	Relative risk 0.85 (CI 95% 0.53 — 1.36) Based on data from 1,691 patients in 2 studies. (Randomized controlled)	170 per 1000 Difference:	145 per 1000 **25 fewer per 1000** (CI 95% 80 fewer — 61 more)	Moderate Due to serious indirectness [3]	
Treatment failure on day 42 (PCR-adjusted)	Relative risk 1.53 (CI 95% 0.73 — 3.19) Based on data from 1,472 patients in 2 studies. (Randomized controlled)	20 per 1000 Difference:	31 per 1000 **11 more per 1000** (CI 95% 5 fewer — 44 more)	Low Due to serious indirectness and serious inconsistency [4]	

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

Population: People with uncomplicated falciparum malaria (malaria-endemic areas in Africa and Asia)
Intervention: Artesunate + pyronaridine once daily for 3 days
Comparator: 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 patients 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 [1]	
Treatment failure on day 28 (PCR-adjusted)	Relative risk 0.38 (CI 95% 0.14 — 1.02) Based on data from 1,187 patients 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 [2]	
Treatment failure on day 42 (PCR-	Relative risk 0.86 (CI 95% 0.57 — 1.31) Based on data from	80 per 1000	69 per 1000	Moderate Due to serious indirectness [3]	

Outcome Timeframe	**Study results and measurements**	**Comparator** Artesunate + mefloquine	**Intervention** Artesunate + pyronaridine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
unadjusted)	1,146 patients in 1 studies. (Randomized controlled)	Difference:	**11 fewer per 1000** (CI 95% 34 fewer — 25 more)		
Treatment failure on day 42 (PCR-adjusted)	Relative risk 1.64 (CI 95% 0.89 — 3) Based on data from 1,116 patients in 1 studies. (Randomized controlled)	40 per 1000 Difference:	66 per 1000 **26 more per 1000** (CI 95% 4 fewer — 80 more)	**Low** Due to serious indirectness [4]	

1. **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.
2. **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.
3. **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.
4. **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 patients in 4 studies. (Randomized controlled)	2 per 1000 Difference:	8 per 1000 **6 more per 1000** (CI 95% 1 more — 23 more)	Moderate Due to serious indirectness [1]	
Elevated aspartate aminotransferase activity (Grade 3, 4 toxicity)	Relative risk 4.08 (CI 95% 1.17 — 14.26) Based on data from 3,528 patients in 4 studies. (Randomized controlled)	2 per 1000 Difference:	8 per 1000 **6 more per 1000** (CI 95% 0 fewer — 27 more)	Moderate Due to serious indirectness [2]	
Elevated alkaline phosphatase activity (Grade 3, 4 toxicity)	Relative risk 0.62 (CI 95% 0.15 — 2.51) Based on data from 2,606 patients in 3 studies. (Randomized controlled)	2 per 1000 Difference:	1 per 1000 **1 fewer per 1000** (CI 95% 2 fewer — 3 more)	Moderate Due to serious indirectness [3]	
Elevated bilirubin (Grade 3, 4 toxicity)	Relative risk 1.92 (CI 95% 0.59 — 6.24) Based on data from 3,067 patients in 3 studies. (Randomized controlled)	3 per 1000 Difference:	6 per 1000 **3 more per 1000** (CI 95% 1 fewer — 16 more)	Low Due to serious indirectness and serious imprecision [4]	

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 patients in 2 studies. (Randomized controlled)	10 per 1000 Difference:	15 per 1000 **5 more per 1000** (CI 95% 7 fewer — 80 more)	Very low Due to serious indirectness and very serious imprecision [1]	
Treatment failure on day 28 (PCR-adjusted)	Relative risk 3.25 (CI 95% 0.13 — 78.69) Based on data from 295 patients in 2 studies. (Randomized controlled)	0 per 1000 Difference:	0 per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 0 fewer)	Very low Due to serious indirectness and very serious imprecision [2]	
Fever clearance: fever on day 2	Relative risk 5.9 (CI 95% 0.73 — 47.6) Based on data from 123 patients in 1 studies. (Randomized controlled)	20 per 1000 Difference:	118 per 1000 **98 more per 1000** (CI 95% 5 fewer — 932 more)	Very low Due to serious indirectness and very serious imprecision [3]	
Parasite clearance: parasitaemia on day 2	Relative risk 0.15 (CI 95% 0.01 — 2.92) Based on data from 297 patients in 2 studies. (Randomized controlled)	20 per 1000 Difference:	3 per 1000 **17 fewer per 1000** (CI 95% 20 fewer — 38 more)	Very low Due to serious indirectness and very serious imprecision [4]	
Gametocytaemia on day 7	Relative risk 1.97 (CI 95% 0.18 — 21.14) Based on data from 123 patients in 1 studies. (Randomized controlled)	20 per 1000 Difference:	39 per 1000 **19 more per 1000** (CI 95% 16 fewer — 403 more)	Very low Due to serious indirectness and very serious imprecision [5]	

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

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

Outcome Timeframe	**Study results and measurements**	**Comparator** Dihydroartemisinin + 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 patients 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 [1]	
Treatment failure on day 28 (PCR-adjusted)	Relative risk Based on data from 143 patients 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 [2]	
Treatment failure on day 42 (PCR-unadjusted)	Relative risk 0.91 (CI 95% 0.13 — 6.26) Based on data from 143 patients in 1 studies. (Randomized controlled)	**30** per 1000 Difference:	**27** per 1000 **3 fewer per 1000** (CI 95% 26 fewer — 158 more)	**Very low** Due to serious indirectness and very serious imprecision [3]	
Treatment failure on day 42 (PCR-	Relative risk 0.19 (CI 95% 0.01 — 3.82) Based on data from 141	**30** per 1000	**6** per 1000	**Very low** Due to serious indirectness and	

Outcome Timeframe	**Study results and measurements**	**Comparator** Dihydroartemisinin + piperaquine	**Intervention** Artemisinin + naphthoquine	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
adjusted)	patients in 1 studies. (Randomized controlled)	Difference:	**24 fewer per 1000** (CI 95% 30 fewer — 85 more)	very serious imprecision [4]	
Fever clearance: fever on day 2	Relative risk Based on data from 144 patients in 1 studies. (Randomized controlled)	0 per 1000	0 per 1000 CI 95%	Very low Due to serious indirectness and very serious imprecision [5]	
Parasite clearance: parasitaemia on day 2	Relative risk 6.29 (CI 95% 0.33 — 119.69) Based on data from 144 patients in 1 studies. (Randomized controlled)	0 per 1000	40 per 1000 CI 95%	Very low Due to serious indirectness and very serious imprecision [6]	
Gametocytaemia: on day 7	Relative risk 1.38 (CI 95% 0.52 — 3.7) Based on data from 144 patients 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 [7]	

1. **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.
2. **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.
3. **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.
4. **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.
5. **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.