



## COCHRANE COLUMN

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Highlighting Cochrane Reviews applicable to health care in low- and middle-income countries



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## Dihydroartemisinin-piperaquine for treating uncomplicated falciparum malaria

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The World Health Organization (WHO) estimates that there were almost 200 million malaria cases and half a million malaria-related deaths in 2013, mostly occurring in sub-Saharan Africa.<sup>1</sup> Of the four species of malaria parasite, *Plasmodium falciparum* causes most cases and nearly all malaria-related deaths worldwide.<sup>1</sup> WHO recommends treatment of uncomplicated falciparum malaria with artemisinin-based combination therapies (ACTs), which consist of an artemisinin component and a longer-acting partner drug with a different mode of action. WHO currently recommends five

different ACTs, including dihydroartemisinin-piperaquine (DHAP) which was added to WHO's list in 2010.

In this Cochrane Column, we summarize and comment on the relevance to low- and middle-income countries of a Cochrane Review which evaluated the effects of DHAP for the treatment of uncomplicated falciparum malaria.<sup>2</sup> This systematic review was among the evidence syntheses that informed the new WHO guidelines for malaria treatment, with a particularly thorough analysis of safety.<sup>3</sup>

## Summary of Cochrane Review on DHAP for malaria

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### Background

This review evaluates the effectiveness and safety of DHAP compared with other WHO-recommended artemisinin-based combination therapies (ACTs) for treating uncomplicated *falciparum* malaria in adults and children.<sup>2</sup>

### Methods

We searched the Cochrane Infectious Diseases Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, LILACS and the metaRegister of Controlled Trials (mRCT) up to July 2013.

## Results

We included 27 randomized controlled trials (RCTs) which enrolled 16 382 adults and children with uncomplicated malaria. Most RCTs excluded infants aged less than 6 months and pregnant women.

In Africa, DHAP is superior to artemether-lumefantrine in treating uncomplicated malaria and in preventing further parasitaemia at day 28 (high-quality evidence) (Table 1).

DHAP has a longer prophylactic effect on new infections, which may last for up to 63 days (high-quality evidence). In Asia and Oceania, little or no differences were seen at day 28 (moderate-quality evidence) or day 63 (low-quality evidence) between DHAP and artemether-lumefantrine. In addition, few or no differences were seen between the two drug combinations in prolonged QTc interval (low-quality evidence) and no cardiac arrhythmias were reported. The frequency of other adverse events was similar between the two combinations (moderate-quality evidence).

In Asia, DHAP is more effective in treating the infection, and is as effective as artesunate plus mefloquine at

preventing further parasitaemia at day 28 (high-quality evidence). Both combinations contain partner drugs with very long half-lives, and no consistent difference in preventing new infections has been seen at day 63 (moderate-quality evidence). In the only RCT from South America, there were fewer episodes of recurrent parasitaemia at 63 days with artesunate-mefloquine (low-quality evidence), but no differences were seen when the analysis controlled for new infections (low-quality evidence). In addition, DHAP is associated with less nausea, vomiting, dizziness, sleeplessness and palpitations compared with artesunate-mefloquine (moderate-quality evidence). Finally, DHAP was associated with more frequent prolongation of the QTc interval (low-quality evidence), but no cardiac arrhythmias were reported.

## Conclusion

In Africa, DHAP reduces overall treatment failure compared with artemether-lumefantrine, although both drugs have polymerase chain reaction (PCR)-adjusted failure rates of less than 5%. In Asia, DHAP is as effective as artesunate-mefloquine, and is better tolerated.

**Table 1.** Grading of Recommendations, Assessment, Development and Evaluation (GRADE) summary of findings table for the comparative effects of DHAP and artemether-lumefantrine in uncomplicated *falciparum* malaria in Africa

Population: Patients with uncomplicated *Plasmodium falciparum* malaria

Settings: Malaria-endemic settings in Africa

Intervention: Dihydroartemisinin-piperazine (DHAP)

Outcomes	Illustrative comparative risks <sup>a</sup> (95% CI)		Relative effect (95% CI)	No. of participants (trials)	Quality of the evidence (GRADE) <sup>b</sup>
	Assumed risk AL6	Corresponding risk DHA-P			
Treatment failure Day 28	PCR-unadjusted		RR 0.34 (0.30–0.39)	6200 (9 trials)	⊕⊕⊕⊕ high
	23 per 100	8 per 100 (7–9)			
	PCR-adjusted		RR 0.42 (0.29–0.62)	5417 (9 trials)	⊕⊕⊕⊕ high
	3 per 100	1 per 100 (1–2)			
Treatment failure Day 63	PCR-unadjusted		RR 0.71 (0.65–0.78)	3200 (2 trials)	⊕⊕⊕⊕ high
	45 per 100	32 per 100 (29–35)			
	PCR-adjusted		RR 0.72 (0.50–1.04)	2097 (2 trials)	⊕⊕⊕⊕ high
	6 per 100	4 per 100 (3–6)			

CI, confidence interval; RR, risk ratio; PCR, polymerase chain reaction.

<sup>a</sup>The basis for the assumed risk is the median risk in the artemether-lumefantrine (AL6) arm across included studies. The corresponding risk (and its 95% CI) is based on the assumed risk in the dihydroartemisinin-piperazine (DHAP) group and the relative effect of DHAP (and its 95% CI).

<sup>b</sup>GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

## Commentary on DHAP for malaria: more studies are needed on safety

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DHAP is one of the five ACTs recommended by WHO for treating uncomplicated malaria.<sup>3</sup> The Cochrane review by Zani *et al.* reviewed the effectiveness and safety of DHAP.<sup>2</sup> Increasingly countries have used DHAP alongside other ACTs in comparison with the comparator, artemether-lumefantrine, in settings where these are most likely to be used.<sup>4,5</sup> These studies demonstrate that the cure rates are above 95% for DHAP, artemether-lumefantrine, artesunate-amodiaquine or artesunate-mefloquine,<sup>2,4,5</sup> with little or no differences in parasite or fever clearance times between treatments or in the occurrence of adverse events among treatment groups.<sup>5</sup> However, to conclude that DHAP is associated with less nausea, vomiting, dizziness, sleeplessness and palpitations than artesunate-mefloquine may require studies with

better blinding than currently described.<sup>2</sup> These studies provide evidence to inform policy for prescription alternatives, especially as DHAP holds the advantage of fewer numbers of tablets and does not require a meal for its administration. In the effort not to waste ACTs, it is advisable to use rapid diagnostic tests to cut down on the prescription to febrile non-malarious patients,<sup>6</sup> especially in areas of seasonal malaria transmission or the elimination of malaria. In Africa, adherence to treatment is a major concern for physicians who worry that patients may stop treatment when given too many rules to follow. DHAP is simple to administer, but needs more pharmacokinetic data, dose adjustment and safety information in children. In addition, more safety data are needed on DHAP in pregnant women.

## Commentary on DHAP for malaria: highly efficacious, but more data are needed to guide dosing regimens

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Since 2010, DHAP has been one of the five ACTs recommended by WHO for the treatment of uncomplicated falciparum malaria. DHAP has been introduced as first- or second-line treatment in several Asian countries and is considered by a growing number.

Antimalarial drug efficacy trials are highly standardized studies<sup>7</sup> in terms of their procedures and outcome measures, which make them ideal for a Cochrane meta-analysis approach. The DHAP Cochrane review included 27 RCTs comparing DHAP with other recommended ACTs, providing high statistical power and high-quality evidence on comparative efficacy levels.<sup>2</sup> The review established that in Africa, DHAP reduced overall treatment failure compared with artemether-lumefantrine, although both drugs had polymerase chain reaction (PCR)-adjusted failure rates of

less than 5%. In Asia, DHAP proved as effective as and better tolerated than artesunate-mefloquine. This provides strong evidence of the efficacy of the drug to both policy makers and programme managers.

However, the programmatic success of a drug is determined by its effectiveness and safety in real-life settings. Dose-dependent drug effects cannot be accurately captured by the Cochrane approach. The WorldWide Antimalarial Resistance Network (WWARN) recently conducted a large pooled individual-level analysis including 7072 patient records from DHAP efficacy studies.<sup>8</sup> This pooled analysis concluded that the DHAP dose regimen currently recommended by the manufacturer is suboptimal for children weighing < 25 kg, attributing 3-fold higher risk of treatment failure.<sup>8</sup> These findings were further supported by a

population pharmacokinetic study.<sup>9</sup> Based on these dosing concerns, WHO recently updated their DHAP dose recommendation for children <25 kg.<sup>3</sup> However, the recommended therapeutic dose range for piperazine is very narrow, both in children <25 kg (20–32 mg/kg/day for 3 days) and older children (16–27 mg/kg/day), the narrowest range among our current arsenal of antimalarials.

A narrow dose range does not affect the findings of efficacy trials, as these carefully select participants and tend to assess a specific company-recommended weight-based regimen or a bespoke regimen designed to achieve a dose as close as possible to the target dose by using tablet fractions. In practice, there are programmatic challenges for implementing the new dosing recommendations in low-resource settings. In these settings, antimalarials are widely dosed by age, leading to a much wider range of drug exposure than typically used in RCTs. In addition, antimalarials are used across the population, with concomitant presence of factors that may alter drug exposure levels such as comorbidities, concomitant drug use and others. It is therefore difficult to extrapolate findings from RCTs to programmatic conditions in low-income settings.

The main pending concern with DHAP is its cardiac safety as it is associated with dose-dependent prolongation of the QT interval.<sup>10</sup> Dose-optimization studies, pharmacokinetic studies or observational studies focusing on effectiveness and safety (such as the INDEPTH Effectiveness and Safety Study<sup>11</sup>) are usually not performed as RCTs. The standardized Cochrane methodology thus misses out on key evidence. The Cochrane Review authors concluded that the quality for the evidence on adverse events was moderate-to-low and stressed the need for further research to investigate safety especially in children and pregnant women, but little attention is drawn to the fact that this conclusion represents the difficulty of capturing standardized safety data within RCTs, or that RCTs are not the study design of choice to explore dose-dependent safety issues, with the inherent limitation to capturing dose-dependent safety signals through trials.

The malaria community is in a good position with both Cochrane and WWARN reviews of DHAP efficacy and pharmacokinetic profiles, but we urgently need more information on dose-dependent safety to guide and support successful programmatic implementation. This is even more pertinent as WHO has just launched its global

ambitious malaria control plan,<sup>12</sup> and DHAP is increasingly considered for use in mass treatment efforts.

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