

Combination Therapy for Uncomplicated Falciparum Malaria in Ugandan Children A Randomized Trial

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JAMA. 2007;297(20):2210-2219.

Context Combination therapy is now widely advocated as first-line treatment for uncomplicated malaria in Africa. However, it is not clear which treatment regimens are optimal or how to best assess comparative efficacies in highly endemic areas.

Objective To compare the efficacy and safety of 3 leading combination therapies for the treatment of uncomplicated malaria.

Design, Setting, and Participants Single-blind randomized clinical trial, conducted between November 2004 and June 2006, of treatment for all episodes of uncomplicated malaria in children in an urban community in Kampala, Uganda. A total of 601 healthy children (aged 1-10 years) were randomly selected and were followed up for 13 to 19 months, receiving all medical care at the study clinic.

Interventions Study participants were randomized to receive 1 of 3 combination therapies (amodiaquine plus sulfadoxine-pyrimethamine, amodiaquine plus artesunate, or artemether-lumefantrine) when diagnosed with their first episode of uncomplicated malaria. The same assigned treatment was given for all subsequent episodes.

Main Outcome Measure 28-Day risk of parasitological failure (unadjusted and adjusted by genotyping to distinguish recrudescence from new infection) for each episode of uncomplicated malaria treated with study drugs.

Results Of enrolled children, 329 of 601 were diagnosed with at least 1 episode of uncomplicated malaria, and 687 episodes of *Plasmodium falciparum* malaria were treated with study drugs. The 28-day risk of treatment failure (unadjusted by genotyping) for individual episodes of malaria were 26.1% (95% CI, 21.1%-32.1%) for amodiaquine plus sulfadoxine-pyrimethamine, 17.4% (95% CI, 13.1%-23.1%) for amodiaquine plus artesunate, and 6.7% (95% CI, 3.9%-11.2%) for artemether-lumefantrine ($P < .05$ for all pairwise comparisons). When only recrudescence treatment failures were considered, the risks of failure were 14.1% (95% CI, 10.3%-19.2%), 4.6% (95% CI, 2.5%-8.3%), and 1.0% (95% CI, 0.3%-4.0%) for the same order of study drugs, respectively ($P \leq .008$ for all pairwise comparisons, except amodiaquine plus artesunate vs artemether-lumefantrine, $P = .05$). There were no deaths or cases of severe malaria. Significant reductions in anemia (9.3% [95% CI, 7.0%-12.0%] at enrollment vs 0.6% [95% CI, 0.1%-

2.2%] during the last 2 months of follow-up; $P < .001$) and asymptomatic parasitemia (18.6% [95% CI, 15.5%-22.1%] at enrollment vs 2.3% [95% CI, 1.5%-3.5%] during the last 2 months of follow-up; $P < .001$) were observed according to routine testing.

Conclusions Artemether-lumefantrine was the most efficacious treatment for uncomplicated malaria in the study population. With all study regimens, the provision of prompt and reasonably effective facility-based treatment was associated with good outcomes in long-term health measures.

Trial Registration isrctn.org Identifier: [ISRCTN37517549](https://www.isrctn.com/ISRCTN37517549)

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