

## SHORT REPORT: HIGH EFFICACY OF TWO ARTEMISININ-BASED COMBINATIONS (ARTESUNATE + AMODIAQUINE AND ARTEMETHER + LUMEFANTRINE) IN CAALA, CENTRAL ANGOLA

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**Abstract.** In April 2004, 137 children 6–59 months of age with uncomplicated *Plasmodium falciparum* (*Pf*) malaria (Caala, Central Angola) were randomized to receive either artemether-lumefantrine (Coartem) or artesunate + amodiaquine (ASAQ). After 28 days of follow-up, there were 2/61 (3.2%) recurrent parasitemias in the Coartem group and 4/64 (6.2%) in the ASAQ group ( $P = 0.72$ ), all classified as re-infections after PCR genotyping (cure rate = 100% [95% CI: 94–100] in both groups). Only one patient (ASAQ group) had gametocytes on day 28 versus five (Coartem) and three (ASAQ) at baseline. Compared with baseline, anemia was significantly improved after 28 days of follow-up in both groups (Coartem: from 54.1% to 13.4%; ASAQ: from 53.1% to 15.9%). Our findings are in favor of a high efficacy of both combinations in Caala. Now that Coartem has been chosen as the new first-line anti-malarial, the challenge is to insure that this drug is available and adequately used.

Angola reports 1.5 million clinical cases of malaria each year.<sup>1</sup> After studies conducted in 2002 in several sites documented high failure rates of first- (chloroquine [CQ]) and second-line (sulfadoxine-pyrimethamine [SP]) drugs,<sup>2</sup> the country decided to shift to artemisinin-based combination (ACT), namely artemether-lumefantrine (Coartem; Novartis Pharma, Basel, Switzerland).<sup>3</sup> We report the results of an ACT *in vivo* efficacy study conducted 2 years later in Caala where high (CQ, 83.5%), rather high (SP, 25.3%), and relatively low (amodiaquine [AQ], 17.3%) failure rates of monotherapies had been recorded in 2002.<sup>2</sup> We measured the efficacy of artemether + lumefantrine (Coartem), the newly introduced first-line drug, and that of an alternative, namely amodiaquine + artesunate (ASAQ). The study was approved by the Ministry of Health of Angola.

The study was conducted in Caala town located in a meso-endemic area of Huambo province (central Angola) previously described.<sup>2</sup> The design was the classic World Health Organization (WHO) protocol for assessing the *in vivo* efficacy of antimalarials in areas of high transmission.<sup>4</sup> It followed the latest recommendations and outcome definitions.<sup>4</sup> In brief, children 6–59 months of age with confirmed clinical *pf* malaria and responding to well-defined inclusion and exclusion criteria<sup>4</sup> were recruited at the Caala health center, after written, informed consent was obtained from caregivers. Patients were randomized to receive either ASAQ (4 mg/kg/day; Arsumax; Sanofi, Paris, France and 10 mg base/kg/day; Camoquine; Park Davis, Dakar, Senegal) or artemether + lumefantrine (Coartem, 20 mg arthemeter + 120 mg lumefantrine; Novartis Pharma, Dhaka, Bangladesh) for 3 days. The dosage of Coartem (twice daily for 3 days) depended on body weight and followed manufacturer's instructions. All doses were directly observed at the health center except for the evening doses of Coartem, which were given at home under the supervision of a health worker.

On day 0, hemoglobin (Lovibond; Assistant Co., Sondheim Rhon, Germany) and presence of gametocytes were re-

corded, and a capillary blood sample was collected (Whatman no. 3) for possible genotypic analysis to distinguish recrudescence from re-infections. After treatment (days 0, 1, and 2), children were re-assessed clinically and parasitologically on days 3, 7, 14, 21, and 28. Hemoglobin and presence of gametocytes were re-measured on day 28, and a second blood sample was collected for genotypic analysis in case of recurrence. Rescue therapy with quinine was administered on treatment failure. Children were withdrawn from the study during follow-up in case of 1) vomiting any study dose twice, 2) serious allergic reaction to study drug, 3) onset of a serious febrile illness, 4) intake of any anti-malarial, 5) mixed parasitemia, and 6) withdraw of consent. Children who skipped any dose or did not finish the 28-day follow-up were considered lost to follow-up.

Examination for malarial parasites followed WHO recommendations,<sup>5</sup> with slides being checked at the laboratory by a senior supervisor who made the final decision concerning patient classification. In addition, as a quality control procedure, 100 slides (50 positive and 50 negative) were checked in an independent laboratory (Mbarara, Uganda) by a trained laboratory technician masked to the original results (results showed that 4% were discordant, i.e., there was a difference in parasite density > 50% between the two readings, but none of these differences changed the classification of the patient). Anemia was defined as hemoglobin < 11 g/dL. The genotypic analysis was performed at the Epicentre laboratory at Mbarara University (Uganda) according to a published method considering the three *P. falciparum* gene loci merozoite surface protein-1 (*m*sp-1), merozoite surface protein-2 (*m*sp-2), and glutamate rich protein (GLURP).<sup>6</sup> Cases in which pre- and post-treatment genotypes were identical were considered as recrudescence, i.e., failures; cases in which pre- and post-treatment genotypes were different were considered as re-infections; mixed genotypes were classified as failures. Data were entered in EpiData (The EpiData Association, Odense, Denmark) and analyzed in Stata 8.2 (Stata, College Station, TX).

Between April and July 2004, 742 children were screened; 137 were included and randomized in the Coartem (68) and

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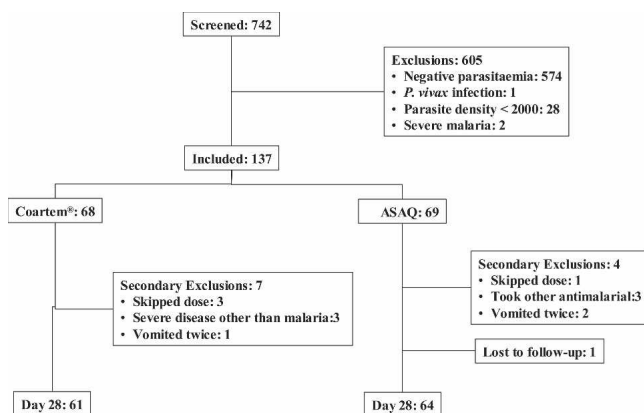


FIGURE 1. Details on study inclusions and follow-up.

ASAQ (69) groups (Figure 1). Baseline characteristics were similar across treatment groups (Table 1). Eleven patients (8.0%) were excluded during follow-up, and 1 (0.7%) was lost to follow-up, leaving 61 (Coartem) and 64 (ASAQ) patients for analysis (Figure 1). After 28 days, there were 2/61 (3.2%) recurrent parasitemias in the Coartem group and 4/64 (6.2%) in the ASAQ group ( $P = 0.72$ ). These recurrences were all classed as re-infections after polymerase chain reaction (PCR) analysis (cure rate = 100%; 95% CI, 94–100 in both groups). Only one (1.5%) patient (in the ASAQ group) had gametocytes on day 28 versus five (7.3%, Coartem) and three (4.3%, ASAQ) at baseline. Compared with baseline, anemia was significantly improved after 28 days of follow-up in both groups (Coartem: from 54.1% [33/61] to 13.4% [8/60]; ASAQ: from 53.1% [34/64] to 15.9% [10/63]); the patient missing in each denominator on day 28 corresponds to recurrent parasitemias before day 28 (i.e., patients not attending day 28).

This *in vivo* study provides new data on the efficacy of two artemisinin-based combinations in an area of Angola where no information on ACT efficacy was available. It provides new information on the performance of ASAQ and Coartem (Angola's new first-line anti-malarial regimen) based on a PCR-adjusted 28-day follow-up.

The main limitation of this study was its rather small sample size, and we acknowledge that this was a weakness in this trial. Indeed, because the efficacy of both drugs was high, a study enrolling few patients in each arm was highly unlikely to find any difference, even if one existed. However, our main objective was not to compare one regimen against the other,

but rather to measure the individual efficacy of each treatment. In this sense, we are confident that the design allowed us to draw reliable conclusions regarding the efficacy of both regimens. A second limitation is that the follow-up was rather short, and therefore could have missed late recrudescence infections appearing after day 28. However, extending the follow-up to 42 days, which was recommended recently for the assessment of Coartem,<sup>7</sup> was difficult in the context of a humanitarian mission such as the one in Caala. Our estimates are therefore likely to over-estimate, to some extent, the efficacy of each ACT. A final, although minor, point concerns the examination of gametocytes, which was done through the standard method recommended by the WHO to examine asexual stages of the plasmodium. Reliable examining for gametocytes requires at least 500 fields to be counted; therefore, we may have under-estimated the presence of gametocytes.

Both combinations were highly efficacious, confirming recent findings in Zanzibar.<sup>8</sup> In addition, both treatments reduced gametocyte carriage, which reflects transmissibility and is an important consideration for malaria control programs. Finally, the proportion of anemic children was significantly reduced in both groups, when comparing baseline levels of anemia to that at the end of follow-up. Anemia is aggravated by parasite resistance,<sup>9</sup> which highlights the added benefit of treating patients with a highly efficacious drug. For all these reasons, Coartem and ASAQ are both valid alternatives for treatment of *P. falciparum* malaria in this setting.

This is the first evaluation of the new malaria treatment policy implemented in the country. Our results provide important baseline information on the efficacy of this new first-line drug. Now that the decision to use Coartem has been taken and funds have been made available to finance this change,<sup>10</sup> the challenge is now to make the drug available and to deploy the drug at the peripheral level to maximize its effectiveness.<sup>11</sup> A recent study in Zambia showed that, even where ACTs were freely available and clinic staff knew they were being observed, only a low proportion of patients actually received them.<sup>12</sup> If we want the efficacy of this drug to remain high in Angola, we need to ensure that it is adequately used.

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TABLE 1  
Baseline (day 0) characteristics of included patients

Characteristic on inclusion		Coartem (n = 68)	ASAQ (n = 69)	P value
Age (months)	Median (IQR)	25 (18–37)	26 (16–42)	0.60
Sex ratio	(M/F)	1.06 (35/33)	1.22 (38/31)	0.67
Malnutrition (MUAC < 125 mm)	n (%)	10 (14.7)	4 (5.8)	0.08
Axillary temperature (°C)	Median (IQR)	39 (38.3–39.8)	39 (38–40)	0.99
Hemoglobin (g/dL)	Median (IQR)	10.7 (10.7–11.7)	10.7 (9.7–11.7)	0.39
Anemia (g/dL)				0.20
Moderate (5–7.9)	n (%)	4 (5.9%)	10 (14.5%)	
Mild (8–10.9)	n (%)	34 (50%)	28 (40.6%)	
Absence (≥ 11)	n (%)	30 (44.1%)	31 (44.9%)	
Presence of gametocytes	n (%)	5 (7.3%)	3 (4.3%)	0.69
Parasitaemia (μL)	Geometric mean (95% CI)	30,522 (25,354–36,742)	27,914 (22,584–34,503)	0.71

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