

Dosing accuracy of artesunate and amodiaquine as treatment for falciparum malaria in Casamance, Senegal

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Summary

OBJECTIVES Several products of artesunate plus amodiaquine (AS + AQ) are being deployed in malaria-endemic countries for treating uncomplicated falciparum malaria but dosing accuracy and consequential effects on efficacy and tolerability have not been examined.

METHODS Patients with parasitologically confirmed, uncomplicated falciparum malaria were treated and followed by research teams or local health centre staff in Casamance, Senegal. AS + AQ was given as: (i) loose combination (AS 50 mg, AQ 200 mg), dosed on body weight, or (ii) co-blistered product (AS 50 mg, AQ 153 mg) dosed by weight or age. Target doses were: (i) AS 4 (2–10) mg/kg/day and (ii) AQ 10 (7.5–15) mg/kg/day. Patients receiving therapeutic doses defined dosing accuracy. Treatment-emergent signs and symptoms (TESS) were recorded.

RESULTS A total of 3277 patients were treated with loose ($n = 1972$, weight-dosed) or co-blistered ($n = 1305$, 962 age-dosed, 343 weight-dosed) AS + AQ by the research team ($n = 966$) or clinic staff ($n = 2311$). AS was dosed correctly in >99% with all regimens. Loose AQ by weight was 98% correct. The co-blistered AQ overdosed 18% of patients when dosed by age and underdosed 13% by weight. Low weight was an independent risk factor for overdosing. The co-blistered had significantly more TESS than the loose product [117/1305 (9%) vs. 41/1972 (2%), relative risk = 4.3 (95% CI: 3.0–6.1, $P < 0.0001$)]. Age-based dosing accounted for the difference. TESS occurred mostly within one day (72%) and were mild or moderate (75%).

CONCLUSION Artesunate is easier to dose than AQ. Currently available age-dosed, co-blistered AS + AQ tends to overdose AQ and is less well tolerated than loose tablets. It is not the optimal presentation of AS + AQ.

keywords falciparum malaria, artesunate, amodiaquine, dosing, presentation, Senegal

Introduction

Artemisinin-containing combinations (ACTs) are being actively implemented in 42 countries for the treatment of acute, uncomplicated *Plasmodium falciparum* malaria based on 28-day, ACT efficacy trials in Africa (Adjuik *et al.* 2004).

Experience with large-scale, long-term deployments of ACTs is limited to the low transmission areas of the on the Thailand–Myanmar border (Brockman *et al.* 2000; Nosten *et al.* 2000) and the South Africa–Mozambique border, where artesunate–mefloquine and artemether–lumefantrine,

respectively (Barnes *et al.* 2005), have resulted in large reductions of the malaria burden (Price *et al.* 1996). By contrast, no such data exist from areas of moderate or high transmission.

Artesunate–amodiaquine (AS + AQ) is one ACT that is being used in several African countries and is national policy in Senegal since 2006. Although its efficacy varies across regions, in chloroquine-resistant Casamance, southern Senegal, both AQ alone and AS + AQ have consistently resulted in high cure rates (>90%) in recent years (Brasseur *et al.* 1999; Sokhna *et al.* 2001; Adjuik *et al.* 2002; Agnamey *et al.* 2005, 2006). The combination

P. Brasseur *et al.* **Dosing artesunate + amodiaquine**

is available as either loose tablets dosed by weight, necessitating the use of multiple tablet fractions, or the same drugs distributed in a blister pack and dosed by age, with tablet fractions only used for children <1 year.

Little attention has been paid to the dose of drugs actually taken by patients and how this might affect tolerability, efficacy and parasite sensitivity. These are important questions because ACTs are being used on a wide scale. Using a limited number of age-based dosing categories is easier than weight-based dosing but may result in systematic dosing errors because some patients will receive doses below or above the recommended therapeutic dose ranges. As part of the development of a new fixed-dose combination (FDC) of AS + AQ of different tablet strengths, new therapeutic ranges for AS (2–10 mg/kg/day) and AQ (7.5–15 mg/kg/day) were defined based on published and unpublished safety and efficacy data. Computer modelling of a large African anthropometric database predicted that 99.9% of patients would receive correct doses of AS and 83.4% of AQ (Taylor *et al.* 2006). There are no data examining the dosing accuracies of loose AS and AQ using the conventional doses (4 and 10 mg/kg/day respectively) or the newly defined recommended doses.

Herein, we report the accuracy of the age and weight-based dosing regimens of the currently available loose and blister-packed AS + AQ in malaria patients and the ways this affected efficacy and tolerability.

Methods

Study methodology

From 2000 to 2006 in Oussouye District, Casamance (southern Senegal), patients seen at health posts with parasitologically confirmed (Giemsa-stained thick blood smear) *P. falciparum* malaria were enrolled into one of two studies:

- Dispensary study. Dispensary staff, supervised by district medical officers MC and MB, used a simplified 3-day protocol. Supervised treatment was given on days 0, 1 and 2 and patients reviewed on day 3 (thick blood smear). Efficacy was defined as parasite clearance on day 3. Age, sex, weight, doses given, days 0 and 3 parasitaemia, clinical status and adverse events were recorded on a case record form.
- Efficacy and safety 28-day study conducted by PB and PA. Study methodology is detailed elsewhere (Brasseur *et al.* 2007). Patients were seen on days 0–3, 7, 14, 21 and 28 for clinical and parasitological (thick blood smear) assessments. Efficacy was defined as sustained parasite clearance to day 28.

In both studies, patients were treated with either the loose or blister-packed AS + AQ once daily for 3 days (dosed 4 mg/kg/day for AS and 10 mg/kg/day for AQ) with the following drugs:

- Loose weight-based regimen: Arsumax® 50 mg artesunate tablets (sanofi-aventis, France) 4 mg/kg/day, and Camoquin® 200 mg AQ base tablets (Parke-Davis, France), 10 mg/kg. Tablet fractions were used as appropriate.
- Age- and weight-based blister regimen Arsucam®: Arsumax® (as above) and Flavoquine® 153 mg amodiaquine base tablets (sanofi-aventis). Treatment by age was given according to the manufacturer's instructions: (i) for children <1 year (weight <10 kg) = ½ tablet of each drug; (ii) 1 to <6 years (10–20 kg) = one tablet of each drug; (iii) ≥6 to <13 years (21–40 kg) = two tablets of each drug and (iv) ≥13 years (>40 kg) = four tablets of each drug.

Ethical approval

The study was approved by the Senegalese National Ethical Committee.

Statistical methods

Data analyses

Data were double-entered into Microsoft Excel, checked and analysed with SAS version 9.3.1 (SAS Institute, Cary, NC, USA). All tests were two-tailed. $P < 0.05$ was considered significant. Non-normally distributed data, assessed by the Kolmogorov–Smirnov test, were analysed by the Mann–Witney U -test or the geometric least square mean ratio (parasite counts). Dichotomous variables were analysed using the chi-squared test.

Dosing assessment

Dosing accuracy was assessed by determining the proportions of patients who received AS and AQ doses within the therapeutic dosing ranges (Taylor *et al.* 2006) of 2–10 mg/kg/day (AS) and 7.5–15 mg/kg/day (AQ) supplemented by box plots [median, mean, interquartile ranges (IQ), fence (within $1.5 \times IQ$), outliers (outside $1.5 \times IQ$)] of the actual dose in mg/day *vs.* target dose range for each patient by age. The magnitude of under- and overdosing for all patients combined was determined by calculating the difference between the mean doses received (mg/day) outside the therapeutic range and the mean doses of the therapeutic range. A logistic model explored possible risk factors for dosing below and above the therapeutic ranges. A saturated model was adjusted by age and weight

categories, type of study, product and year of study and method of dosing (by age or weight). A descending stepwise modelling based on the likelihood ratio test between subsequent models was carried out.

Tolerability

Treatment-emergent signs and symptoms (TESS) were defined as events which were not present pre-treatment or worsened with treatment. Information from the patient was solicited from a pre-defined symptoms list and any other symptoms reported. Symptom intensities were graded as 0–4 (none, mild, moderate, severe and very severe). The incidence of the different symptoms pre-treatment (day 0) was tabulated by year. TESS were analysed by age category, intensity, type of study and day of occurrence. The TESS frequency and the number of patients with ≥ 1 TESS were tabulated.

Drug doses received and outcomes

The relationships between an under- and overdose were explored with: (i) the occurrence of TESS between the dispensary and research team studies, (ii) the proportions of aparasitaemic patients on day 3 and (iii) the day 28 cure rate.

Results

Study overview

From 2000 to 2006, 20 696 blood smears were done; 7736 (37%) patients were positive for *P. falciparum* and 3385 were treated with AS + AQ. Other patients were treated mostly with quinine or chloroquine (Agnomey *et al.* 2005). Records were unavailable for 108 (3%), leaving 3277 patients who could be assessed: 966 (30%) and 2311 (70%) were treated and followed up by the research and local teams respectively (Figure 1). All 966 patients contributed to the day 28 efficacy analysis but safety was assessed in 752 (78%) patients (Brasseur *et al.* 2007). Safety data are available for the 2311 recruited patients and 2245 (97%) had a smear on day 3.

Treatments administered

Of the 3277 patients assessed, 1972 (60%) received loose AS and AQ and were dosed by weight and 1305 (40%) were treated with the co-blistered product, 962 dosed by age and 343 by weight (Figure 2).

Baseline characteristics

Nearly half (49%) of patients were aged 6–15 years; patients <11 years constituted 42% of the total. The age

structure of the population was consistent throughout the period of the study. Few patients (4%) weighed ≤ 10 kg; 45% weighed 11–30 kg. When comparing the baseline characteristics of patients treated with the loose or the co-blistered product, or enrolled by the research or local team (Table 1), statistically significant but clinically irrelevant differences were seen for age, weight, sex and pre-treatment parasitaemia. The mean doses administered by research and local teams were very similar for AQ (10.7 ± 1.8 vs. 10.4 ± 1.5 mg/kg/day) and AS (4.0 ± 0.5 vs. 4.0 ± 0.6 mg/kg/day).

Dosing accuracy

Body weight was available for 1962 (99%), 337 (98%) and 359 (37%) of the patients treated with the loose, co-blister weight-based and co-blister age-based respectively. Based on the newly defined therapeutic dose range, the weight-based loose drugs were the most accurate for AQ resulting in 98% of patients dosed correctly; other proportions were 85.2% (blister-packed by weight), 79.9% (blister-packed by age), and 87.6% if the new FDC had been used (Table 2). All regimens dosed AS correctly between 99.2% and 100%. The co-blister pack under-dosed AQ in 12.8% of patients when given by weight and overdosed 17.8% when dosed by age.

The overall mean AQ under-doses were 67.9 ± 44.3 mg/day ($n = 8$), 33.5 ± 32.7 mg/day ($n = 43$), and 55.5 ± 38.9 mg/day ($n = 18$) for co-blister age-based, co-blister weight-based and loose combinations respectively. The corresponding mean figures for overdosing were 54.7 ± 63.8 mg/day ($n = 64$), 33.1 ± 58.8 mg/day ($n = 7$) and 46.7 ± 59.7 mg/day ($n = 22$).

The age-dosed, co-blistered AQ under-dosed seven patients, four in age group ≥ 7 –13 years, and three in age group ≥ 14 years. Of the 64 overdosed, 13 patients (3.6%) were overdosed by a mean 43 mg (1–6 years group), 30 (8.4%) by 40 mg (≥ 7 –13 years) and 21 (5.8%) by 83 mg (≥ 14 years group). When dosed by weight, the AQ co-blister underdosed seven patients (2.1%) by a mean 25 mg (1–6 years), 11 (3.3%) by 25 mg (≥ 7 –13 years) and 25 (7.4%) by 40 mg (≥ 14 years) (Figure 3).

The logistic model identified weight, type and year of study as risk factors for incorrect dosing. Weighing <9 kg carried a higher risk of receiving an inadequate dose relative to patients weighing 18–35.9 kg [OR 6.7 (95% CI = 1.6; 27.5)] and 9–18 kg [OR 1.6 (95% CI = 1.0; 2.5)] but not compared to patients with weights >36 kg. Patients enrolled in the dispensary study had a lower risk of being inaccurately dosed [OR 0.6 (95% CI = 0.4; 0.9)]. From 2002 onwards (year of the introduction of the co-blister), each year except 2003 (borderline) carried a supplementary risk with respect to 2000.

P. Brasseur *et al.* Dosing artesunate + amodiaquine

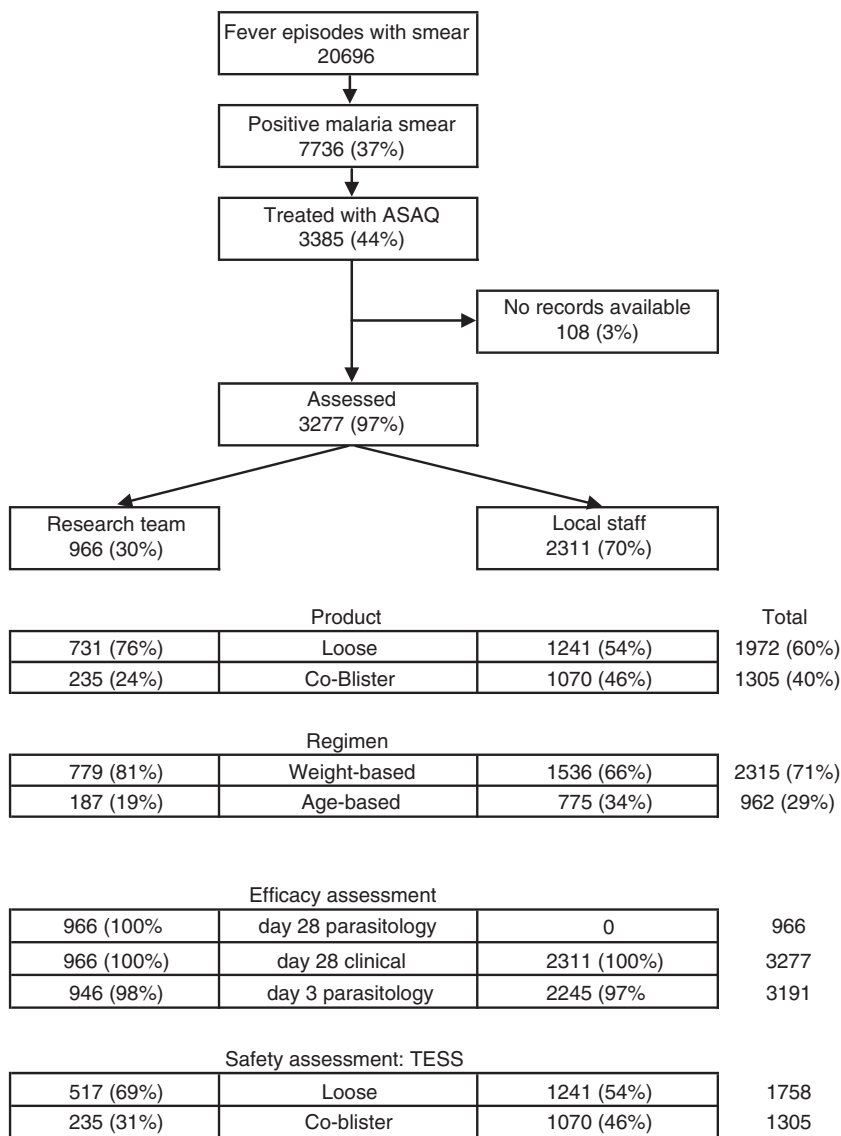


Figure 1 Trial structure.

Treatments administered by the research team resulted in a dose outside the therapeutic range for AQ in 62/941 (6.6%) patients as compared to 77/1536 (5.0%, $P = 0.098$) for the dispensary staff [NB: the actual dose could not be calculated for 603/962 (63%) of patients given the co-blister by age because weights were not recorded].

Tolerability

One hundred and fifty-eight (4.8%) of the 3277 patients experienced 207 TESS: 165 (blister) *vs.* 42 (loose, $P = 0.09$); 117/1305 (9%) of the blister-treated patients

had ≥ 1 TESS compared with 41/1972 (2%) in the loose group ($P < 0.0001$) for a relative risk of 4.3 [95% CI: 3.0–6.1]. This difference is accounted for by the age-dosing of the co-blistered product with 147 TESS (71% of the 207 total events) in 109 patients (3.3% of the total 3277 patients and 11.3% of those on this regimen, compared with 2.3% and 2.1% in the other two groups, $P < 0.0001$).

The dispensary team (who saw 70% of patients) detected 121 TESS (58% of all TESS) and the research team 85 (42%). The dispensary team reported relatively more cases of headache (19.8% of the TESS reported by this group, 31.6% of whom had AQ overdosed), pruritus

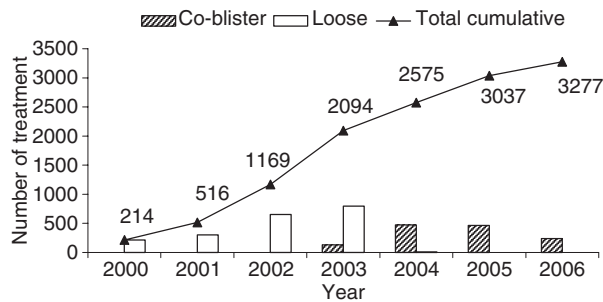
P. Brasseur *et al.* Dosing artesunate + amodiaquine

Figure 2 Yearly and cumulative number of treatments with the loose and co-blistered AS + AQ combination, 2000–2006.

(15.7%) and diarrhoea (9.9%), while the research team detected relatively more vomiting (42.4%, 61.1% of whom had AQ overdosed) and asthenia (12.9%).

Overall, 2/158 (1.3%) of the patients with ≥ 1 TESS had AQ under-dosed, 48/158 (30.4%) had AQ overdosed, and 108/158 (68.3%) had a therapeutic dose. TESS frequencies and gradings are detailed in Table 3; most (75%) were mild or moderate in severity and 149/207 (72%) occurred on the first day of treatment; 53 events were recorded on day 2, three events on day 3, and two events on day 4. In particular, of the 64 cases of vomiting, 52 (81.25%) occurred on day 1 and 11 on day 2. Nine blister-treated patients discontinued treatment owing to an adverse event; all were dosed by age and seven had AQ within the therapeutic range (Table 4).

Efficacy

The crude, PCR-unadjusted efficacy rates are 94.6% (95% CI: 92.9–95.9) and remained stable over the period under study, ranging from 88.5% to 96.7% (Brasseur *et al.* 2007). Cure rates were independent of dose received (Table 4). There were no failures in AQ-overdosed patients but seven (10.6%) were lost to follow up. Of the 16 AQ under-dosed patients, one failed and none were lost to follow-up. Of the 3191 patients who had a slide taken on day 3, 10 (0.3%) were positive for *P. falciparum*: 0.62% (blister pack dose by weight), 0.44% (blister pack dose by age) and 0.2% (loose dose by weight, $P = 0.18$).

Discussion

We have shown that dosing accuracy varies markedly with different AS + AQ presentations when using a newly defined and expanded therapeutic dosing range for each drug. Co-blistered AS + AQ dosed less accurately and was associated with more side effects; however, this did not lead to more drug withdrawals.

Table 1 Baseline characteristics

	n (% total)	All patients	Loose combination	Co-blister	Recruited by		P-value
					research team	local staff	
Age (years)*	3215 (98%)	15.1 \pm 12.1	15.0 \pm 12.3	15.2 \pm 11.9	13.8 \pm 11.2	15.6 \pm 12.5	<0.001†
Sex F:M	3276 (100%)	45.5%:54.5%	46.7%:53.3%	43.7%:56.3%	43.4%:56.6%	46.4%:53.6%	0.11‡
Weight (kg)*	2659 (81%)	35.7 \pm 18.7	35.8 \pm 19.1	35.6 \pm 17.5	33.3 \pm 17.2	37.1 \pm 19.3	<0.001†
Parasitaemia day 0§	3219 (98%)	23 763 (11 346–60 281)	24 538 (11 601–66 421)	22 586 (10 910–52 414)	31 854 (12 001–93 801)	20 965 (10 801–54 841)	<0.001¶
Temperature day 0*	3223 (93%)	38.5 \pm 6	38.4 \pm 1.1	38.5 \pm 9.4	38.4 \pm 1.0	38.5 \pm 7.1	0.62‡
Signs and symptoms day 0	3277	1619	1060 (65.5%)	559 (34.5%)	1003 (61.9%)	606 (38.1%)	<0.001‡
Patients with at least 1 signs and symptoms day 0	3277	609 (18.6%)	368 (18.7%)	241 (18.5)	311 (32.2%)	298 (12.9%)	<0.001‡

*Mean \pm SD. †Mann–Whitney. ‡Chi-square. §Geomean (Q25–Q75). ¶Geometric least square mean ratio.

P. Brasseur *et al.* Dosing artesunate + amodiaquine**Table 2** Frequency of patients who received doses within, under and over the therapeutic ranges for amodiaquine and artesunate for the loose and co-blistered drugs

	Dose, mg/kg/day						Total
	Amodiaquine ≥ 7.5 to ≤ 15			Artesunate ≥ 2 to ≤ 10			
	Under	Adequate	Over	Under	Adequate	Over	
Loose weight based	18	1922	22	1	1961	0	1962
%	0.9%	98.0%	1.1%	0.1%	99.9%	0.0%	
Co-blister weight based	43	287	7	0	337	0	337
%	12.8%	85.2%	2.1%	0.0%	100.0%	0.0%	
Co-blister age based*	8	287	64	2	356	1	359
%	2.2%	79.9%	17.8%	0.6%	99.2%	0.3%	
FDC age based†	137	2170	169	4	2472	0	2476
%	5.5%	87.6%	6.8%	0.2%	99.8%	0.0%	

A simulation for the new FDC combination when dosed by age was also done.

*Age groups by manufacturer: 1–6; >6–13; >13 years.

†Simulation with ASAQ FDC and age groups as per Taylor *et al.* (2006): 0 to <1; 1–6; >6–13; >13 years.

AQ, amodiaquine; AS, artesunate; FDC, fixed dose combination.

This is, to our knowledge, the largest dataset prospectively documenting the use of different dosing programmes and presentations of the AS + AQ combination, their dosing accuracies, and consequential effects on efficacy and tolerability from an area of moderate malaria transmission. The patient and malariometric characteristics during this study were similar to those before the introduction of AS + AQ (Agnamey *et al.* 2005). *P. falciparum* was detected in 37% of the patients with suspected malaria and the age distribution of patients has not changed; about half of the malaria patients were 6–15 years old, consistent with moderate malaria transmission and an entomological inoculation rate of 25 bites per person-year (Sokhna *et al.* 2001).

Dosing accuracy

When deploying a new drug, combination or dosing method of established drugs, it is important to document dosing accuracy and to determine if patients are systematically under-dosed (potentially resulting in treatment failure and the setting of conditions for the selection of drug-resistant parasites), or overdosed (potentially producing drug toxicity). This is not unusual for antimalarials since they are not normally developed on pharmacokinetic/dynamic evidence; 76% of Kenyan children <5 years were found to be systematically under-dosed when sulfadoxine/pyrimethamine was given following the internationally recommended age-based dosing schedule (Terlouw *et al.* 2003) and this may have contributed to the emergence of parasite resistance to the drug.

The recommended target doses for AS and AQ are 4 and 10 mg/kg/day respectively. Their respective therapeutic

windows have been extended to 2–10 and 7.5–15 mg/kg/day based on a review of available clinical data and computer modelling of an anthropometric database numbering ~88 000 individuals (Taylor *et al.* 2006).

During the course of the staggered deployment of AS + AQ in Casamance, patients received first a loose combination of individually packaged AS (50 mg tablets) and AQ (200 mg base) dosed by weight, using tablet fractions if necessary, followed by co-blistered AS (50 mg) and AQ (153 mg base) dosed either by age or weight, according to the manufacturer's instructions. These drug doses and dosing instructions differ from those of the newly developed FDC (Taylor *et al.* 2006). The therapeutic index is wide for AS, so dosing accuracy was high, but narrower for AQ and dosing accuracy varied markedly between ~80% for the age-dosed blister and 98% for the weight-dosed, loose AQ. The former overdosed ~18% of patients by a mean of 55 mg/day. The FDC would be dosed accurately in 87.6% of these patients, performing slightly better than the 83.4% predicted by the database used by Taylor *et al.* (2006). The AQ tablet strength of 153 mg in the co-blister was clearly less flexible than the 200 mg loose tablets and the 67.5/135 mg tablet strengths of the FDC.

Based on these results, particular care should be taken when treating patients with a low body weight (weighing <9 kg was a risk factor for overdosing) because these presentations are not adapted to small children.

The health posts in Oussouye have weighing scales and health workers dosed AS + AQ remarkably well, but dosing by age is more expedient. Offering age- and weight-based dosing would seem to be a reasonable strategy in Senegal and similar settings, but in many tropical areas dosing by age is the only option. With the current co-blister

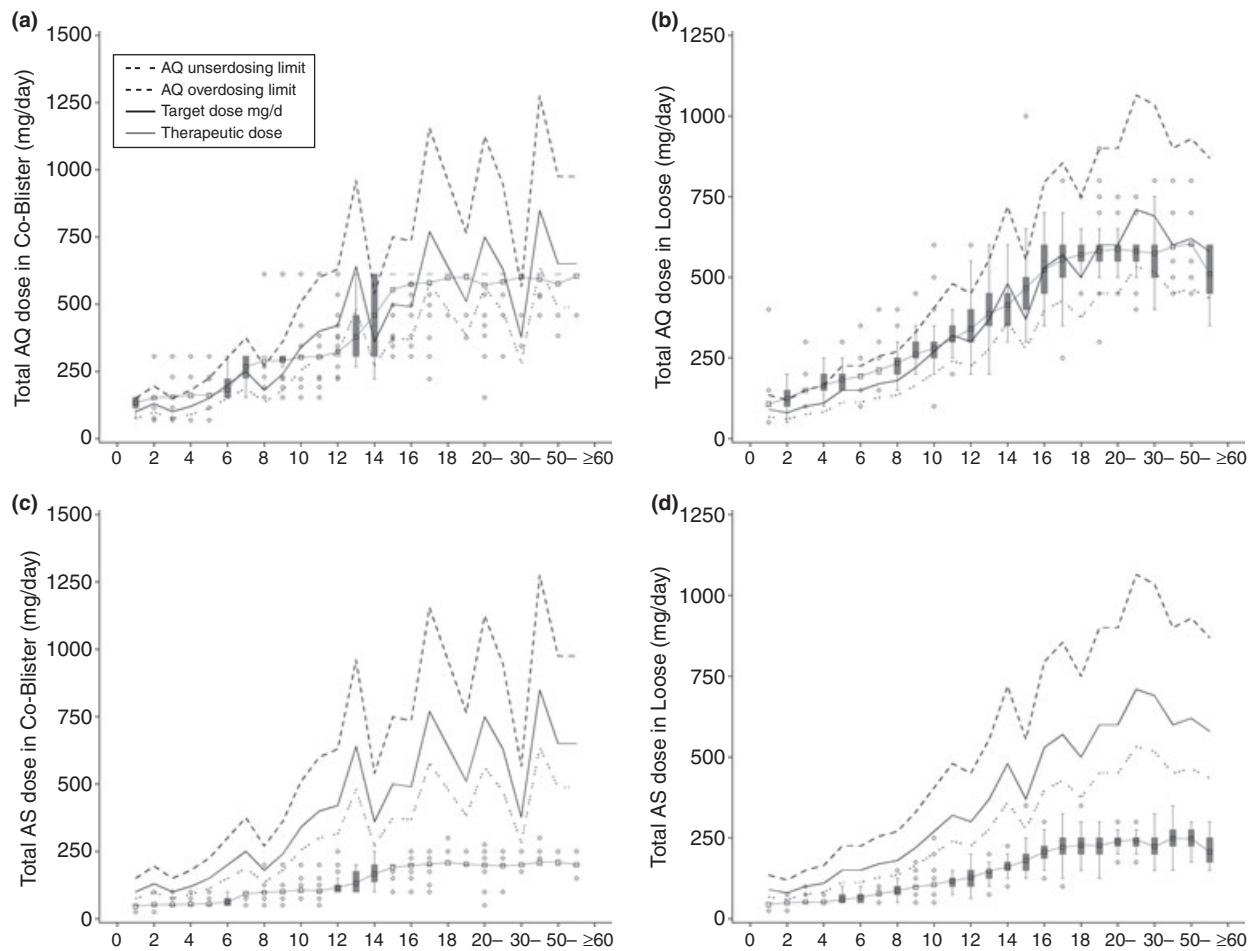


Figure 3 Boxplots of dose (mg/day) by age of AQ administered as (a) loose and (b) co-blistered product and AS as (c) loose and (d) co-blistered product. The orange lines represent the dosing limits using the new therapeutic dosing ranges for each drug (2–10 mg/kg/day AS, 7.5–15 mg/kg/day AQ). The green line represents the drug dose that would be given if using strictly the target doses for each drug (4 mg/kg/day AS, 10 mg/kg/day AQ). The blue line is the average actual dose.

this carries the highest risk of inaccurate dosing because it uses approximated age/weight correlations, whereas the FDC has specifically designed age- and weight-based regimens; the latter ensures that patients receive AQ within the 7.5–15 mg/kg/day therapeutic window, a distinct advantage.

Monitoring treatment effects

Artesunate + AQ was generally well tolerated: <5% patients complained of side effects, which were generally of mild or moderate intensity. The co-blister pack was less well tolerated than the loose combination and was about four times more likely to cause toxicity. This essentially happens when the co-blister is dosed on age rather than

weight. Over and under-dosing were not significantly associated with either drug toxicity, failure or parasite positivity on day 3 but the sample sizes were small and these events were rare. A small number of patients had unremarkable haematology and biochemistry results (Brasseur *et al.* 2007) insufficient to detect possible neutropaenia or drug-induced hepatitis; both tend to be asymptomatic. Future studies must monitor the total and differential white cell counts and liver enzymes.

Implications for research and practice

There are limitations to these analyses. Patients were not randomized to either study, one of which had more intensive monitoring compared to the more pragmatic,

P. Brasseur *et al.* Dosing artesunate + amodiaquine

Symptoms	Intensity				Total	%
	Mild grade 1	Moderate grade 2	Severe grade 3	Very severe grade 4		
Abdominal pain	5	5	0	0	10	4.9
Anorexia	2	2	9	0	13	6.3
Diarrhoea	5	7	2	1	15	7.3
Headache	18	2	5	1	26	12.6
Nausea	1	1	3	1	6	2.9
Pruritus	7	9	10	1	27	13.1
Rash	0	0	1	1	2	1.0
Vertigo	15	23	4	1	43	20.9
Vomiting	17	37	8	2	64	31.1
Total	70	86	42	8	206	
%	34.0%	41.7%	20.4%	3.9%		

Table 3 Treatment emergent signs and symptoms by intensity (206/207 TESS with intensity recorded)

TESS, treatment emergent signs and symptoms.

Table 4 Frequencies of patients who received adequate or inadequate doses based on the new therapeutic dose ranges of 7.5–15 mg/kg/day of AQ and 2–10 mg/kg/day AS daily and their outcomes during 28 days of follow up

	AQ dose			Total	AS dose			Total
	Under	Adequate	Over		Under	Adequate	Over	
LTF	1 6.25	35 3.96	0 0	36	0 0	36 3.81	0 0	36
Success	14 87.5	817 92.42	58 87.9	889	1 100	870 92.06	18 90	889
Lost to follow up	0 0	25 2.83	7 10.6	32	0 0	30 3.17	2 10	32
Withdrawn due to AE	1 6.25	7 0.79	1 1.52	9	0 0	9 0.95	0 0	9
Total	16	884	66	966	1	945	20	966

AQ, amodiaquine; AS, artesunate; LTF, late treatment failures; AE, adverse events.

dispensary study. The blister pack currently distributed in Senegal by the National Malaria Control Programme is not the same brand of the one used in this study but has the same presentation, tablet strength and dosing instructions. Loose products should not be available, as advocated by the World Health Organization (WHO 2006).

It will be important to document clinically manifested toxicity, but also to monitor neutropaenia and hepatitis, and explore the effects of repeated treatment over time. Senegal is fortunate to have a good health infrastructure and is able to supervise ACT treatment. However, dosing accuracy, drug effectiveness and patient adherence should also be assessed with unsupervised AS + AQ dosed by age, as this would be common practice. Essential information (e.g. age, weight, dose and treatment effects) should be systematically collected to enable data pooling and analysis

(Price *et al.* 2007; Sibley *et al.* 2007). Drug levels should also be measured in order to define the relationships between dose and treatment outcomes.

Some of these activities can be conducted as part of a dispensary daily routine. Here, local staff proved to be as good as a dedicated team in dosing drug and detecting clinical toxicity.

To conclude, dosing the currently available co-blister by age was the least accurate, exceeding the upper dose limit in ~18% of patients and causing more side effects. If the new, age-based AS + AQ FDC were deployed in the same population, AQ would be correctly dosed in ~88% with under- and overdosing in equal proportions (~6% and ~7% respectively). The long-term, population-wide implications of the under- and overdosing of antimalarials demonstrate the need for more research.

Acknowledgements

We are grateful to the personnel of the health posts and the patients of the district of Oussouye. We wish to thank Dr P. Olumese for critically reviewing the manuscript. This study was funded by the UNICEF/UNDP/WB/WHO Special Programme for Research & Training in Tropical Diseases (TDR), the French Ministry of Foreign Affairs (FAC 2000) and Ministry of Research (PAL+). The Drugs for Neglected Diseases initiative (DNDi) contributed to the conduct of laboratory tests, data management and analyses. The drugs were donated by sanofi-aventis. Neither DNDi nor sanofi-aventis had any role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

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