



The effect of dose on the antimalarial efficacy of artemether-lumefantrine: a systematic review and pooled analysis of individual patient data

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Summary

Background Artemether–lumefantrine is the most widely used artemisinin-based combination therapy for malaria, although treatment failures occur in some regions. We investigated the effect of dosing strategy on efficacy in a pooled analysis from trials done in a wide range of malaria-endemic settings.

Methods We searched PubMed for clinical trials that enrolled and treated patients with artemether–lumefantrine and were published from 1960 to December, 2012. We merged individual patient data from these trials by use of standardised methods. The primary endpoint was the PCR-adjusted risk of *Plasmodium falciparum* recrudescence by day 28. Secondary endpoints consisted of the PCR-adjusted risk of *P falciparum* recurrence by day 42, PCR-unadjusted risk of *P falciparum* recurrence by day 42, early parasite clearance, and gametocyte carriage. Risk factors for PCR-adjusted recrudescence were identified using Cox's regression model with frailty shared across the study sites.

Findings We included 61 studies done between January, 1998, and December, 2012, and included 14 327 patients in our analyses. The PCR-adjusted therapeutic efficacy was 97·6% (95% CI 97·4–97·9) at day 28 and 96·0% (95·6–96·5) at day 42. After controlling for age and parasitaemia, patients prescribed a higher dose of artemether had a lower risk of having parasitaemia on day 1 (adjusted odds ratio [OR] 0·92, 95% CI 0·86–0·99 for every 1 mg/kg increase in daily artemether dose; $p=0\cdot024$), but not on day 2 ($p=0\cdot69$) or day 3 (0·087). In Asia, children weighing 10–15 kg who received a total lumefantrine dose less than 60 mg/kg had the lowest PCR-adjusted efficacy (91·7%, 95% CI 86·5–96·9). In Africa, the risk of treatment failure was greatest in malnourished children aged 1–3 years (PCR-adjusted efficacy 94·3%, 95% CI 92·3–96·3). A higher artemether dose was associated with a lower gametocyte presence within 14 days of treatment (adjusted OR 0·92, 95% CI 0·85–0·99; $p=0\cdot037$ for every 1 mg/kg increase in total artemether dose).

Interpretation The recommended dose of artemether–lumefantrine provides reliable efficacy in most patients with uncomplicated malaria. However, therapeutic efficacy was lowest in young children from Asia and young underweight children from Africa; a higher dose regimen should be assessed in these groups.

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Introduction

Artemisinin-based combination therapies are the first-line treatment for uncomplicated *Plasmodium falciparum* malaria in most malaria-endemic countries,¹ and they have been advocated to counter the threat of antimalarial drug resistance by delaying its emergence and spread.² As such, artemisinin-based combination therapies are a key component of malaria elimination efforts.³

The combination of artemether and lumefantrine was originally introduced as a four-dose regimen that proved to be efficacious in studies done in China,⁴ Africa,⁵ and India;⁶ however, after detailed pharmacokinetic–pharmacodynamic assessment,⁷ the regimen was revised to comprise six doses, which was safe and effective even against multidrug-resistant parasites.^{8–10} In 2011, the six-dose regimen of artemether–lumefantrine (Coartem, Novartis, Basel, Switzerland) was the first artemisinin-based combination therapy to be prequalified by WHO.¹¹ It is now registered in 86 countries and accounts for

three-quarters of all artemisinin-based combination therapies used in clinical practice.¹ In 2009, artemether–lumefantrine dispersible tablets (Coartem Dispersible) were approved for use in young children,¹¹ with more than 200 million treatments of this formulation dispensed since then.¹²

Although the six-dose artemether–lumefantrine regimen has high efficacy in most endemic areas, the usefulness of this combination is under threat from the emergence of parasites with reduced susceptibility to the artemisinins.¹³ Optimum dosing of antimalarial drug regimens is vital for containment of the spread of drug resistance; however, in clinical practice, pragmatic drug distribution results in dosing being based on weight or age banding, with patients at the margins of the bands having either lower or higher weight-adjusted doses than those in the middle of the bands.¹⁴ Young children are particularly vulnerable to suboptimum dosing because drugs are often given as

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tablets or fractions of tablets rather than paediatric formulations or suspensions.¹⁵ In this pooled analysis, we investigated the key determinants of the therapeutic efficacy of artemether–lumefantrine, with particular attention to the range of artemether and lumefantrine doses and the effect of these factors on clinical outcome.

Methods

Search strategy and selection criteria

We did a systematic literature review in PubMed to identify all clinical trials published from 1960 to December, 2012, selecting those that enrolled and treated patients with artemether–lumefantrine (appendix). We selected studies for the meta-analysis if patients were treated with the six-dose artemether–lumefantrine regimen and were prospectively assessed for clinical efficacy against *P. falciparum* (either alone or in mixed infections) for a minimum of 28 days. Investigators were contacted by email and asked to share individual patient data and any unpublished study they might have. We included studies in the analysis if information was available on the dose given and on the age and weight of the patient, and if PCR genotyping was done to distinguish between recrudescence and new infections. Individual patient data were uploaded into the Worldwide Antimalarial Resistance Network (WWARN) secure repository, anonymised, and processed using standard methods described in the data management and statistical analysis plan.¹⁶

All data included in this analysis were obtained in accordance with ethical approvals from the country of origin. Ethical approval to undertake individual participant data meta-analyses was granted by the Oxford Tropical Research Ethics Committee.

Procedures

We calculated the doses of artemether and lumefantrine administered from the individual number of daily tablets given to each patient. For studies in which the daily tablet count was not available, we did back calculations on the basis of the dosing plan presented in the study protocol, assuming correct adherence. Only patients who completed the six-dose treatment regimen over 3 days were included in the final analysis. Study sites were categorised as low, moderate, or high transmission settings on the basis of the transmission estimates obtained from the Malaria Atlas Project (appendix).¹⁷ In children younger than 5 years, we assessed nutritional status using the weight-for-age Z score, with standardised age-specific and sex-specific growth references according to WHO 2006 recommendations.¹⁸ Patients were classified as being underweight for age if the weight-for-age Z score was less than -2 . Scores outside the range -6 to 6 were treated as outliers.

Outcomes

The primary endpoint was the PCR-adjusted risk of *P. falciparum* recrudescence by day 28. Secondary endpoints consisted of the PCR-adjusted risk of

P. falciparum recurrence by day 42, PCR-unadjusted risk of *P. falciparum* recurrence by day 42, early parasite clearance, and gametocyte carriage

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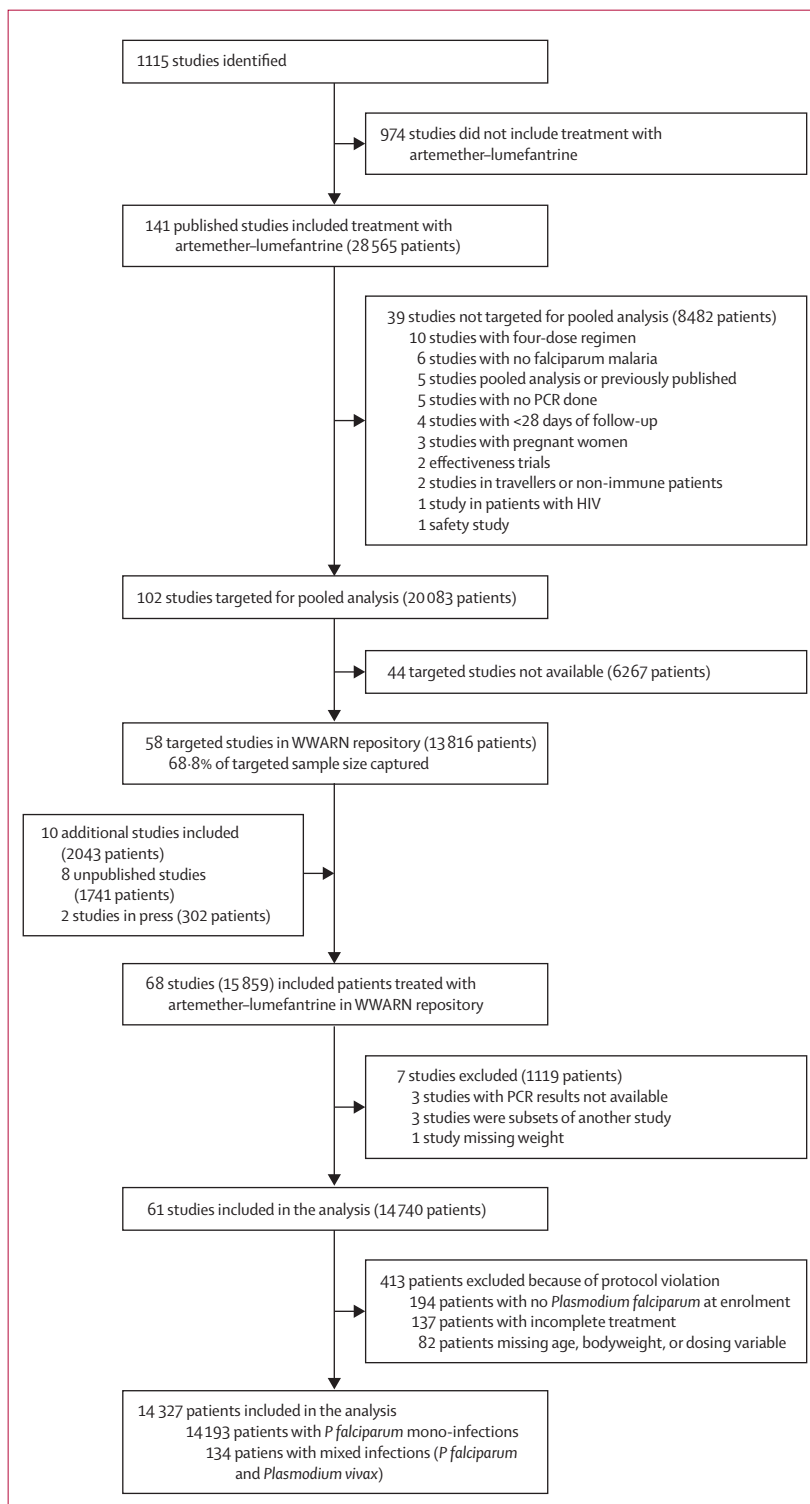


Figure 1: Study flowchart

WWARN=Worldwide Antimalarial Resistance Network.

Statistical analysis

We did all statistical analyses using R (version 2.14.0), on the basis of an a-priori statistical plan.¹⁹ We computed the incidence risks for the primary endpoint by survival analysis and compared Kaplan-Meier curves by the log-rank test after stratifying by study site. Definitions of

outcome status and censoring are detailed in the WWARN clinical module data management and statistical analysis plan.¹⁶ The dose of lumefantrine was regarded primarily as a risk factor for recrudescence because of its long half-life, whereas the dose of artemether was regarded as the primary determinant of the early parasitological response.

	Asia (n=2359)	Africa (n=11 809)	South America (n=159)*	Overall (n=14 327)
Study period	1998–2010	2002–12	2007–08	1998–2012
Sex†				
Female	929 (39%)	5538 (47%)	63 (40%)	6530 (46%)
Male	1430 (61%)	5973 (51%)	96 (60%)	7499 (52%)
Age, years				
Median (range)	16.0 (0.5–80.0)	3.5 (0.0–77.0)	23.0 (12.0–56.0)	4.0 (0.0–80.0)
<1	6 (<1%)	809 (7%)	0	815 (6%)
1 to <5	373 (16%)	6960 (59%)	0	7333 (51%)
5 to <12	503 (21%)	2477 (21%)	0	2980 (21%)
≥12	1477 (63%)	1563 (13%)	159 (100%)	3199 (22%)
Weight, kg				
Median (range)	41.0 (6.0–88.0)	13.7 (5.0–102.0)	64.0 (30.0–110.0)	15.0 (5.0–110.0)
5 to <10	61 (3%)	2013 (17%)	0	2074 (14%)
10 to <15	334 (14%)	4623 (39%)	0	4957 (35%)
15 to <25	404 (17%)	2992 (25%)	0	3396 (24%)
25 to <35	206 (9%)	753 (6%)	4 (3%)	963 (7%)
35 to <70	1341 (57%)	1278 (11%)	105 (66%)	2724 (19%)
≥70	13 (1%)	150 (1%)	50 (31%)	213 (1%)
Treatment supervision‡				
Full	1824 (77%)	9086 (77%)	159 (100%)	11 069 (77%)
Partial	373 (16%)	1563 (13%)	0	1936 (14%)
Unsupervised	162 (7%)	1160 (10%)	0	1322 (9%)
Treatment coadministration				
With fatty meal	656 (28%)	5635 (48%)	159 (100%)	6450 (45%)
Without fatty meal	0	1191 (10%)	0	1191 (8%)
Advised to consume with fat	820 (35%)	1326 (11%)	0	2146 (15%)
Not stated	883 (37%)	3657 (31%)	0	4540 (32%)
Drug tradename				
Coartem (Novartis)	2359 (100%)	11 126 (94%)	159 (100%)	13 644 (95%)
Coartem dispersible (Novartis)	0	431 (4%)	0	431 (3%)
Co-artesiane (Dafra, Turnhout, Belgium)	0	134 (1%)	0	134 (1%)
Atrin (LIC Pharmaceuticals, Abidjan, Côte d'Ivoire)	0	118 (1%)	0	118 (1%)
Enrolment clinical variables				
Parasitaemia, parasites per µL	9559 (13–450 440)	21 360 (16–420 360)	4241 (1008–44 744)	19 921 (13–450 440)
Parasitaemia >100 000/µL	226 (10%)	1131 (10%)	0	1357 (9%)
Mixed infection with <i>Plasmodium vivax</i>	134 (6%)	0	0	134 (1%)
Haemoglobin, g/L	114 (25.8)	101 (21.2)	NR	104 (22.9)
Anaemic, haemoglobin <100 g/L	600/2179 (28%)	4030/8287 (49%)	NR	4630/10 466 (44%)
Gametocytes present	128/1118 (11%)	541/7850 (7%)	10 (6%)	679/9127 (7%)
Fever, temperature >37.5°C	1199/2195 (55%)	6973/10 854 (64%)	103 (65%)	8275/13 208 (63%)
Children underweight for age§	173/471 (37%)	1352/7825 (17%)	NR	1525/8296 (18%)

Data are number (%), median (IQR), or mean (SD), unless otherwise specified. Some percentages do not add up to 100 because of rounding. NR=not reported. *Data from one study done in Colombia. †Data were not available for 298 patients from Africa. ‡Patients with only morning daily doses supervised and evening doses taken at home with no supervision were classified as partly supervised. Patients were classified as unsupervised if all six doses were unobserved or if the first dose was observed at the clinic with remaining five doses unobserved. §Defined using a weight-for-age score <-2 in children <5 years of age. Scores outside the range -6 to 6 were treated as outliers.

Table 1: Demographics and baseline characteristics

We assessed risk factors associated with recrudescence with Cox's proportional hazards model with shared frailty fitted on the combination of study and study sites to account for within-study clustering and any unreported heterogeneity.²⁰ In the multivariable analysis, we forced known confounders (ie, age and parasitaemia) and dose (in mg/kg) into the model irrespective of their statistical significance. We categorised the origin of the studies into three groups: Africa, Asia, and South America. Other covariates significant at the 10% level in univariable analyses were added to the multivariable analyses and their inclusion was on the basis of a likelihood ratio test.²¹ We calculated the population-attributable risks associated with the risk factors on the basis of the prevalence and adjusted hazard ratio (HR).²² The proportions of patients with patent (microscopy-detected) parasitaemia were computed on days 1, 2, and 3 (parasite positivity rates), and gametocyte carriage was assessed as the proportion of patients with microscopy-detected *P. falciparum* gametocytes (gametocyte positivity rates) on any given day during the follow-up period. Risk factors for parasite positivity rates and gametocyte positivity rates were analysed with mixed-effects logistic regression with sites (combination of study and study site) fitted as a random effect.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 151 clinical trials of artemether–lumefantrine done between January, 1998, and December, 2012 (141 published, two in press, and eight unpublished), of which 115 (76%) were randomised trials (figure 1; appendix). Individual patient data were available from 58 published studies (n=13 816 [69% of the targeted sample of 20 083]), two studies in press (n=302), and eight unpublished studies (n=1741). Seven studies (n=1119) did not meet the inclusion criteria and an additional 413 patients were excluded for protocol violations. Patients were followed up for 28 days in 34 studies (n=7460), for 42 days in 23 studies (n=6004), for 56 days in one study (n=359), and for 63 days or longer in three studies (n=504). Parasite genotyping was done in all of the studies, with at least three markers used in 34 (56%) studies.

Table 1 details the baseline characteristics of patients included in the analysis. The median age of patients was 4 years (range 1 month to 80 years), with 815 (6%) younger than 1 year and 7333 (51%) aged 1 year to younger than 5 years. Patients from Africa were significantly younger than those from either Asia or South America ($p<0.0001$) and had higher baseline parasitaemia ($p=0.03$; table 1). All the patients from Asia and South America were from low or moderate

transmission settings, whereas only 6415 (54%) of 11 809 patients in Africa were from low or moderate transmission settings.

Overall, the median total dose of lumefantrine given was 68.6 mg/kg (IQR 57.6–80.0, range 26.2–144.0) and that of artemether was 11.4 mg/kg (IQR 9.6–13.3, range 4.4–24.0). The total dose of both components varied significantly between the different weight categories ($p<0.0001$; table 2). The proportion of patients who did not receive the therapeutic dose of lumefantrine varied across weight categories and regions (appendix). The lowest median lumefantrine doses were given to children aged 3–5 years (62.6 mg/kg, IQR 55.4–84.7) and to patients weighing more than 70 kg (38.4 mg/kg, IQR 36.0–40.6). Treatment administration was fully supervised in 11 069 (77%) of 14 327 patients, partly supervised in 1936 (14%), and unsupervised in 1322 (9%).

Information regarding acute vomiting of drugs was available for 14 studies (n=5024), with 221 (4%) of 5024 patients vomiting at least one dose of drug within 1 h of administration during the treatment course; this proportion was greatest (18 [11%] of 171) in infants younger than 1 year (appendix). After adjusting for age, fever at presentation, and baseline parasitaemia, the risk of acute vomiting was associated with increasing dose of lumefantrine, with every 5 mg/kg increase in lumefantrine dose associated with an 8.7% (95% CI 3.4–14.2; $p=0.001$) increased risk of vomiting. There was no relation between the dose of lumefantrine and either late vomiting or diarrhoea in the first week.

	Number	Lumefantrine dose, mg/kg		Artemether dose, mg/kg		
		Median (IQR)	Range	Median (IQR)	Range	
Overall	14 327	68.6 (57.6–80.0)	26.2–144.0	11.4 (9.6–13.3)	4.4–24.0	
Age category, years						
<1	815	90.0 (81.8–102.9)	40–144	15.0 (13.6–17.1)	6.7–24	
1 to <5	7333	68.6 (60.0–80.0)	37.9–144	11.4 (10–13.3)	6.3–24	
5 to <12	2980	73.8 (65.5–83.1)	32–120	12.3 (10.9–13.8)	5.3–20	
≥12	3199	57.6 (49.7–65.5)	26.2–91.9	9.6 (8.3–10.9)	4.4–15.3	
Weight category, kg						
5 to <10	2074	85.7 (80.0–94.7)	37.9–144.0	14.3 (13.3–15.8)	6.3–24.0	
10 to <15	4957	60.0 (55.4–67.3)	42.9–100.7	10.0 (9.2–11.2)	7.1–16.8	
15 to <25	3396	80.0 (72.0–90.0)	39.6–105.0	13.3 (12.0–15.0)	6.6–17.5	
25 to <35	963	74.5 (68.4–83.1)	42.4–96.9	12.4 (11.4–13.8)	7.1–16.2	
35 to <70	2724	57.0 (50.5–64.0)	30.9–82.3	9.5 (8.4–10.7)	5.1–13.7	
≥70	213	38.4 (36.0–40.6)	26.2–41.1	6.4 (6.0–6.8)	4.4–6.9	
Region						
Asia	2359	61.3 (55.4–72.0)	30.9–120.0	10.2 (9.2–12.0)	5.1–20.0	
Africa	11 809	71.3 (60.0–80.9)	28.2–144.0	11.9 (10.0–13.5)	4.7–24.0	
South America	159	45.0 (40.6–53.3)	26.2–82.3	7.5 (6.8–8.9)	4.4–13.7	
Drug tradename						
Artrin	118	74.8 (60–90.0)	51.4–120.0	12.5 (10–15.0)	8.6–20.0	
Co-artesiane	134	71.1 (69.4–74.8)	60.7–79.2	11.8 (11.6–12.5)	10.1–13.2	
Coartem	14 075	68.4 (57.6–80.0)	26.2–144.0	11.4 (9.6–13.3)	4.4–24.0	

Table 2: Total lumefantrine and artemether doses

The early therapeutic response was rapid. At 24 h after starting treatment, 5534 (60%) of 9208 patients were parasite positive, falling to 910 (8%) of 12 055 by day 2 and 96 (1%) of 12 829 by day 3; the age-stratified proportion of individuals who were parasite positive on these days are presented in the appendix. In multivariable analysis, baseline parasitaemia was the only independent predictor of parasite positivity on all days (table 3). Patients from Asia were at increased risk of parasite positivity on days 1 and 2, and those from South America were at increased risk on day 2 compared with patients from Africa (table 3). After controlling for baseline parasitaemia, region, and age category, a higher total daily dose of artemether was associated with a lower risk of parasite positivity on day 1 ($p=0.024$). There was no significant association between artemether dose and parasite positivity on days 2 or 3 (table 3).

2310 (16%) of 14 327 patients had a recurrent parasitaemia detected during follow-up, and in 386 (17%) cases these could be confirmed as recrudescence infections by PCR. In patients who were followed up for 42 days, 139 (70%) of 200 recrudescences occurred before day 28. The overall PCR-adjusted Kaplan-Meier therapeutic efficacy was 97.6% (95% CI 97.4–97.9) at day 28 and 96.0% (95.6–96.5) at day 42. The overall risk of recrudescence was similar between patients from Asia and Africa (table 4). The PCR unadjusted and adjusted risk of recurrence for individual studies are presented in the appendix.

In univariable analyses, three risk factors on presentation were associated with a greater risk of recrudescence by day 28: age ($p=0.001$), bodyweight ($p=0.001$), and baseline parasitaemia ($p=0.0002$; table 4). The risk of recrudescence was similar between patients who were fully supervised and those who were partly or not supervised, and in patients who took the drug with or without a fatty meal (table 4). In multivariable analyses,

baseline parasitaemia ($p=0.0012$) and young age (1–5 years; $p=0.005$) were the only independent risk factors associated with recrudescence by day 28 (table 4). We further investigated the relation between age and weight for children younger than 5 years. 679 (18%) of 3752 children aged 1–3 years were underweight for their age. Children aged between 1 and 3 years who were underweight for age had an increased risk of recrudescence compared with those who were not (HR 1.56, 95% CI 1.04–2.43; $p=0.033$; figure 2), but there was no difference between groups for those aged 3–5 years (0.59, 0.31–1.14; $p=0.12$).

There was a significant interaction between regions and both lumefantrine dose ($p_{\text{interaction}}=0.005$) and baseline parasitaemia ($p_{\text{interaction}}=0.012$). Therefore, we generated separate models for Asia and Africa. We could not fit a model for patients from South America because of the small sample size. In Africa, the greatest risk of recrudescence was in underweight for age children between 1 and 3 years, among whom the PCR-adjusted efficacy was 94.3% (95% CI 92.3–96.3) compared with 96.9% (96.2–97.5) in those of similar age who were not underweight (adjusted HR 1.66, 95% CI 1.05–2.63; $p=0.028$; table 5). For Asia, the corresponding adjusted HR was 1.07 (95% CI 0.17–6.78; $p=0.94$). The dose of lumefantrine was not associated with the risk of recrudescence in Africa, either overall (adjusted HR for every 5 mg/kg increase in dose 0.98, 95% CI 0.94–1.03; $p=0.42$) or in the subgroup of children who were underweight for their age (0.95, 0.81–1.10; $p=0.47$). By contrast, in Asia, the dose of lumefantrine was associated with the risk of recrudescence (adjusted HR 0.77, 95% CI 0.67–0.90; figure 3); efficacy was lowest in children weighing 10–15 kg who received a total lumefantrine dose of less than 60 mg/kg (91.7%, 95% CI 86.5–96.9). Patients who received less than 60 mg/kg (the WHO

	Risk for positivity on day 1			Risk for positivity on day 2			Risk for positivity on day 3		
	Total N (n)*	Adjusted OR (95% CI)	p value	Total N (n)*	Adjusted OR (95%CI)	p value	Total N (n)*	Adjusted OR (95%CI)	p value
Baseline parasitaemia, parasites per μL every ten-times increase	9208 (5534)	3.39 (3.09–3.73)	<0.0001	12 055 (910)	2.28 (1.97–2.64)	<0.0001	12 829 (96)	1.85 (1.23–2.78)	0.003
Artemether daily dose, mg/kg†	9208 (5534)	0.92 (0.86–0.99)	0.024	12 055 (910)	0.96 (0.87–1.07)	0.69	12 829 (96)	0.76 (0.56–1.04)	0.087
Age category, years									
≥12	2205 (1155)	Reference	..	2541 (206)	Reference	..	2860 (14)	Reference	..
<1	474 (286)	1.70 (1.21–2.39)	0.002	734 (57)	1.43 (0.89–2.3)	0.14	751 (7)	4.18 (1.16–15.09)	0.029
1 to <5	4641 (2993)	1.82 (1.47–2.26)	<0.0001	6256 (493)	1.38 (1.1–1.89)	0.050	6500 (50)	2.17 (0.88–5.35)	0.094
5 to <12	1888 (1100)	1.38 (1.14–1.67)	0.001	2524 (154)	1.11 (0.83–1.49)	0.483	2718 (25)	3.08 (1.33–7.15)	0.009
Region									
Africa	7194 (4335)	Reference	..	9976 (677)	Reference	..	10766 (64)	Reference	..
Asia	2014 (1199)	7.16 (1.49–34.4)	0.014	1923 (183)	4.40 (1.19–16.27)	0.026	1904 (29)	4.35 (0.98–19.35)	0.054
South America	NT	NT	NT	156 (50)	40.36 (1.22–1336.69)	0.038	159 (3)	19.41 (0.52–727.38)	0.108

OR=odds ratio. NT=measurements not taken. *Number of patients (number with positive parasitaemia). †For every mg/kg increase in total daily artemether dose.

Table 3: Risk factors for patent parasitaemia on days 1, 2, and 3

	Total N (n)*	Univariable analyses		Multivariable analyses†		PAR calculations‡	
		Crude HR (95% CI)	p value	Adjusted HR (95% CI)	p value	Frequency§	PAR
Age, every 1-year increase	14 139 (304)	0.96 (0.94–0.99)	0.001
Bodyweight, every 1 kg increase	14 139 (304)	0.98 (0.97–0.99)	0.001
Lumefantrine dose, every 5 mg/kg increase	14 139 (304)	0.98 (0.95–1.02)	0.380	0.98 (0.94–1.02)	0.380	27.46%	6.30%
Enrolment clinical variables							
Parasitaemia, parasites per μ L every ten-times increase	14 139 (304)	1.47 (1.2–1.81)	0.0002	1.41 (1.15–1.74)	0.0012	9.51%	4.01%
Fever, temperature >37.5°C	13 024 (290)	1.09 (0.85–1.41)	0.500
Haemoglobin, every 10 g/L increase	10 303 (221)	0.95 (0.88–1.01)	0.100
Anaemia, haemoglobin <100 g/L	10 303 (221)	1.24 (0.93–1.65)	0.150
Gametocytes present	9008 (198)	1.01 (0.62–1.65)	0.970
Sex							
Female	6448 (143)	Reference
Male	7393 (156)	0.95 (0.76–1.20)	0.690
Age category, years							
≥ 12	3160 (34)	Reference
<1	809 (21)	1.73 (0.92–3.29)	0.091	1.78 (0.89–3.55)	0.100	5.72%	4.76%
1 to <5	7231 (204)	2.17 (1.35–3.47)	0.001	2.00 (1.23–3.23)	0.005	51.14%	37.92%
5 to <12	2939 (45)	1.33 (0.81–2.18)	0.260	1.27 (0.76–2.12)	0.360	20.79%	7.96%
Transmission setting							
Low	3432 (60)	Reference
High	5336 (160)	1.75 (0.92–3.33)	0.086
Moderate	5371 (84)	1.13 (0.58–2.23)	0.720
Region							
Africa	11 674 (260)	Reference
Asia	2306 (43)	0.81 (0.34–1.90)	0.630
South America	159 (1)	0.25 (0.02–4.16)	0.330
Treatment supervision							
Full	10 929 (232)	Reference
Partial	1909 (51)	1.40 (0.76–2.59)	0.280
Unsupervised	1301 (21)	1.31 (0.52–3.28)	0.570
Coadministration with fat							
With fatty meal	6346 (142)	Reference
Without fatty meal	1181 (23)	0.95 (0.34–2.67)	0.920
Advised with fatty meal	2120 (39)	0.98 (0.40–2.41)	0.960
Dose calculation method							
Per protocol	9473 (231)	Reference
Tablet counts	4666 (73)	0.73 (0.43–1.24)	0.250
Drug tradename							
Coartem	13 891 (296)	Reference
Generic artemether-lumefantrine	248 (8)	1.12 (0.42–2.99)	0.820

HR=hazard ratio. PAR=population-attributable risk. *Number of patients (number with recrudescence by day 28). †The assumption of proportional hazard held for the model ($p=0.47$ for global test) and for all the individual covariates in the multivariable model ($p>0.05$). The variance of random effect was 0.95. The likelihood ratio test was not significant for bodyweight ($p=0.19$), haemoglobin ($p=0.29$), and transmission ($p=0.53$) in the presence of mg/kg dose, parasitaemia, and age category; thus, these were dropped from the multivariable analysis. ‡Overall PAR for model: 51.1%. Cumulative PAR for parasitaemia >100 000 parasites per μ L and age 1 to <5 years: 40.4%. §The proportion of patients with the risk factor. Continuous covariates were categorised as follows: baseline parasitaemia at 100 000 parasites per μ L and mg/kg lumefantrine dose at 60 mg/kg (lower bound of WHO therapeutic range). The adjusted HR used for estimating the PARs (obtained from the categorised model) were 1.44 for baseline parasitaemia, 1.24 for lumefantrine dose <60 mg/kg, 1.87 for age <1 year, 2.19 for age 1–5 years, and 1.42 for age 5–12 years.

Table 4: Risk factors for PCR-confirmed recrudescence at day 28

recommended lower bound) were at greater risk of recrudescence (adjusted HR 2.73, 95% CI 1.40–5.32; $p=0.003$), accounting for 41% of all treatment failures. Using the same model, we predicted that if patients from

Asia with parasitaemia less than 267 000 parasites per μ L received a minimum total lumefantrine dose of 60 mg/kg, then adequate cure would be achieved in at least 95% of cases (figure 3).

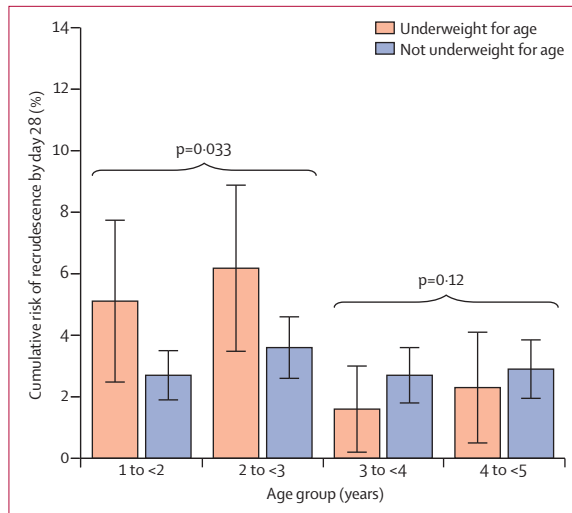


Figure 2: Cumulative risk of PCR-confirmed recrudescence by day 28 in children aged 1–5 years
Error bars are 95% CIs.

272 patients had patent gametocytaemia during follow-up. In 198 (73%) of these cases, gametocytes were present on or before day 14 of follow-up. In a multivariable model, after controlling for baseline gametocyte carriage, asexual parasite density, and age category, a higher artemether dose was associated with a lower gametocyte presence within 14 days of treatment (adjusted odds ratio 0.92, 95% CI 0.85–0.99; $p=0.037$ for every 1 mg/kg increase in total artemether dose).

Discussion

This pooled analysis of individual patient data comprises more than half of all clinical trials that have been published on the six-dose artemether–lumefantrine treatment regimen. Our findings confirm that artemether–lumefantrine treatment is an efficacious antimalarial regimen, resulting in a rapid therapeutic response. In more than

90% of patients, fever was resolved and peripheral parasitaemia was cleared within 48 h. Overall, the therapeutic efficacy of artemether–lumefantrine was 97.6% on day 28 and 96.0% on day 42, with only a slight effect of the total dose on these parameters. Patients who received a lower daily dose of artemether had an increased risk of parasitaemia on day 1 (8% for each 1 mg/kg decrease in daily artemether dose) and an increased risk of gametocyte carriage within 14 days (8% for each 1 mg/kg decrease in total artemether dose). Although high treatment efficacy was achieved in all age and weight categories, there were important regional differences. Patients from Asia had a slower initial therapeutic response compared with patients from Africa and a greater risk of recrudescence. The dose of artemether–lumefantrine was an independent predictor of recrudescence in Asia but not Africa. These regional differences could represent either lower host immunity, in what are mostly low-transmission settings, or reduced parasite susceptibility to lumefantrine and artemether in the *P. falciparum* parasites circulating in the Greater Mekong region.^{23,24} Our analysis shows that patients receiving less than 60 mg/kg of lumefantrine accounted for almost 42% of treatment failures in Asia, the effect being most noticeable in young children. Ensuring a lumefantrine dose above 60 mg/kg would achieve greater than 95% cure in all patients, provided they presented with a parasitaemia less than 267000 parasites per μ L.

Since there was a significant interaction between regions and both lumefantrine dose and baseline parasitaemia, we generated separate models for Asia and Africa. In Africa, the risk of recrudescence was greatest in young children, especially those who were underweight for their age. The higher efficacy in older children and adults in Africa is probably a result of previous and repeated exposure to malaria, associated with the development of premunition.^{25,26} By contrast, infections in younger patients with lower host immunity are associated with higher baseline parasitaemia,

	Africa*					Asia*				
	Total N (n)†	Adjusted HR (95% CI)	p value	Frequency	PAR	Total N (n)†	Adjusted HR (95% CI)	p value	Frequency	PAR
Lumefantrine dose <60 mg/kg	11547 (255)	1.20 (0.85–1.68)	0.30	24.1%	4.5%	2300 (43)	2.73 (1.40–5.32)	0.003	41.0%	41.5%
Baseline parasitaemia, >100000 parasites per μ L‡	11547 (255)	1.44 (0.99–2.1)	0.054	9.6%	4.1%	2300 (43)	1.76 (0.78–3.97)	0.18	9.8%	6.9%
Age category, kg										
≥12, reference	1551 (10)	1	1450 (23)	1
<1§	803 (21)	2.20 (0.94–5.17)	0.071	7.0%	7.7%
1 to <3 UWA	641 (31)	4.05 (1.78–9.18)	0.001	5.6%	14.5%	38 (2)	3.97 (0.87–18.16)	0.075	1.7%	4.7%
1 to <3 not UWA	2986 (84)	2.52 (1.19–5.34)	0.016	25.9%	28.2%	87 (3)	3.38 (0.92–12.43)	0.067	3.8%	8.2%
3 to <5	3113 (73)	2.18 (1.04–4.56)	0.038	27.0%	24.2%	239 (6)	1.73 (0.66–4.51)	0.27	10.4%	7.0%
5 to <12	2453 (36)	1.67 (0.77–3.59)	0.19	21.2%	12.4%	486 (9)	1.50 (0.65–3.46)	0.34	21.1%	9.6%

HR=hazard ratio. PAR=population-attributable risk. UWA=underweight for age. *The assumption of proportional hazards was met for each model ($p=0.54$ for Africa and $p=0.18$ for Asia by the Schoenfeld’s test). The overall PAR was 66.5% for Africa and 59.9% for Asia. †Number of patients (number with recrudescence by day 28). ‡Adjusted HRs were 1.31 (95% CI 1.03–1.66) and 2.2 (1.37–3.54) for every increase of ten times. §Only six patients aged <1 year in Asia had no PCR-confirmed failure. HR could not be estimated for this group.

Table 5: Multivariable models for risk for recrudescence in patients from Africa and Asia by day 28

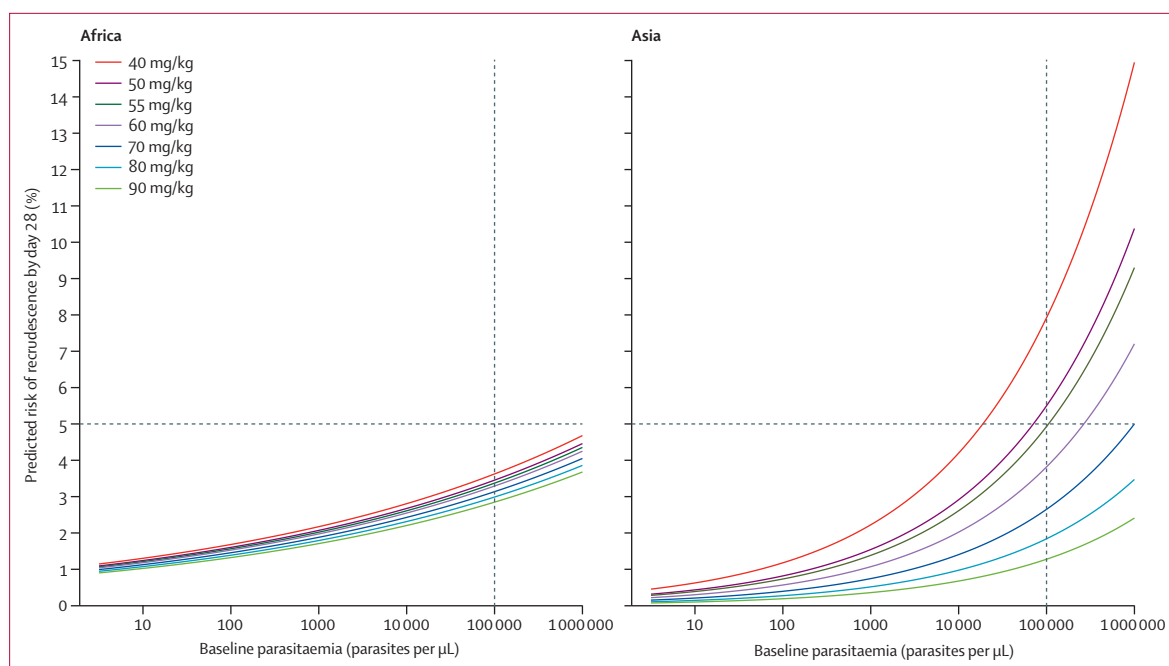


Figure 3: Risk of recrudescence by day 28 in Africa and Asia

The predicted risk of recrudescence by day 28 for a given enrolment parasitaemia and total lumefantrine dose in Africa and Asia. The risks were estimated using the coefficients for parasitaemia and lumefantrine dose from a Cox's model containing age, dose, and baseline parasitaemia for Africa. For Asia, the model contained dose and baseline parasitaemia. We assumed zero study effects. The horizontal line represents the 5% treatment failure rate threshold from WHO that should be used to assess if a new drug can be introduced for treatment of uncomplicated malaria. The vertical line is the parasitaemia of 100 000 per μL , a threshold used in the multivariable models for calculating the population-attributable risk estimates.

increasing the risk of treatment failure,²⁷ especially in underweight children.²⁸

The main determinant of artemether–lumefantrine clinical efficacy is the area under the curve of lumefantrine.²⁹ The highly lipophilic lumefantrine is erratically absorbed, its bioavailability being affected by coadministration of food and the acute phase of the infection.²⁹ The area under the curve for lumefantrine varies markedly with age and the nutritional status of the patient, with young children having a more rapid dose-normalised drug clearance compared with adults.³⁰ To accommodate these differences, the dosing schedule of artemether–lumefantrine was modified in the early stages of drug development to ensure a higher mg/kg dose in young children.⁷ Our study shows the importance of this factor in this vulnerable group. Those who were underweight for their age were at increased risk of treatment failure. This effect could be due to either reduced drug absorption or an increased volume of distribution in malnourished children, both of which result in lower plasma drug concentrations.³¹

An increase in dose, particularly in children weighing 13–15 kg, might not necessarily result in higher blood concentrations since the absorption of lumefantrine saturates at recommended doses.³² Furthermore, an increase to the next dose band would result in these children receiving over 100 mg/kg of lumefantrine—a level that is associated with an increased risk of

acute vomiting. A dispersible formulation of artemether–lumefantrine for administration in young children is now available, but this might not necessarily allow greater precision in achieving therapeutic blood concentrations, and its absorption kinetics and gastrointestinal tolerability at higher than recommended doses have yet to be well characterised. Administration of a 5-day (augmented dose) regimen might circumvent the dose-limited absorption and tolerability issues⁸ and increase the efficacy in high-risk patients, but effectiveness in clinical practice needs to be assessed.

Our study has several limitations. First, although the clinical data used in the analysis constitute almost 60% of the relevant published work on this treatment regimen, 44 studies ($n=6267$) were not available, most of which (27 [61%]) were from Africa. However, there was no obvious selection bias between studies that were excluded from the analysis. Second, in only 4718 (33%) of 14 327 patients could drug doses be calculated from the actual number of tablets given; in the remainder of patients the total dose was extrapolated from the number of tablets to have been given per protocol, assuming complete adherence. However, when the method of dose calculation was included in the multivariable analysis the results remained unchanged. Third, ideally the weight-for-age Z scores to define nutritional status of the children should be calibrated to take regional variation into account. We controlled for these differences by

stratifying the analysis on the basis of region (Asia and Africa), and the relation between nutritional status and treatment outcome remained. However, we were not able to differentiate between acute and chronic malnutrition, because data on patients' height were not available.

In summary, the efficacy of artemether–lumefantrine remains excellent in most endemic areas. However, young children in the 10–15 kg weight band received a lower mg/kg total dose of artemether–lumefantrine, and this was associated with reduced efficacy, particularly in patients from Asia who presented with high parasitaemia and in malnourished patients from Africa. Further studies are warranted to optimise treatment strategies in these vulnerable populations. Although we found no evidence of temporal patterns in treatment failure, continued surveillance of artemether–lumefantrine efficacy is crucial to assure that appropriate responses to any decline can be implemented to prolong the clinical efficacy of this antimalarial drug in the long term.

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Declaration of interests

PA is an employee of Novartis Pharma, Basel, Switzerland. SD is an employee of Medicines for Malaria Venture, Geneva, Switzerland. KH is an employee of Novartis Pharmaceuticals, East Hanover, NJ, USA. KIB, ET, and NJW are members of the WHO Technical Expert Group on Malaria Chemotherapy. QB and UD'A have received speaker fees and travel grants from Novartis. All other members of the study group declare no competing interests.

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