Univariable and multivariable risk factors for PCR-adjusted recrudescence at day 42 (n = 14,679 and 371 recrudescences) for patients treated with artemether-lumefantrine*

Variable	No.	Univariate analysis		Multivariate analysis		Population attributable risk†	
		Crude HR (95% CI)	P	Adjusted HR (95% CI)	P	Frequency	PAR
Age (years)	14,679	0.96 (0.94–0.98)	< 0.001	–	–	–	–
Weight (kg)	14,769	0.98 (0.97–0.99)	< 0.001	–	–	–	–
Lumefantrine dose (mg/kg)	14,769	1 (0.99–1)	0.550	1 (0.99–1.01)	0.860	28.13%	2.26%
Clinical variables							
Baseline parasitemia (log scale)	14,769	**1.15 (1.07–1.25)**	**< 0.001**	**1.13 (1.05–1.23)**	**0.002**	**9.12%**	**4.15%‡**
Baseline parasitemia > 100,000/μL	14,769	1.55 (1.15–2.09)	0.004	–	–	–	–
Baseline gametocytemia	7,659	1.55 (1.04–2.32)	0.031	–	–	–	–
Age category	14,679						
≥ 12 years (reference)							
< 1		1.74 (1.01–3)	0.045	1.55 (0.86–2.78)	0.150	9.01%	5.68%
1 to < 5		**2.69 (1.73–4.17)**	**< 0.001**	**2.38 (1.51–3.75)**	**< 0.001**	**45.72%**	**41.24%‡**
5 to <12		1.51 (0.95–2.38)	0.079	1.39 (0.86–2.23)	0.160	20.63%	9.21%
Weight category	14,769						
≥ 35 kg (reference)							
5 to < 15		2.47 (1.58–3.88)	< 0.001	–	–	–	–
15 to < 25		1.92 (1.21–3.04)	0.005	–	–	–	–
25 to < 35		1.39 (0.75–2.56)	0.300	–	–	–	–
Supervision	14,396						
Full (reference)				–	–	–	–
Partial		0.92 (0.51–1.67)	0.790	–	–	–	–
Unsupervised		1.66 (0.56–4.93)	0.370	–	–	–	–
Co-administration with fat	7,180			–	–	–	–
With fatty meal (reference)							
Without fatty meal		0.91 (0.32–2.61)	0.860	–	–	–	–

* Values in bold are statistically significant. PCR = polymerase chain reaction; HR = hazards ratio; CI = confidence interval; PAR population attributable risk.
† Overall PAR for model: 52.9% calculated as calculated as $1 - \Pi_{r=1}^{R}(1 - PAR_r)$
‡ Cumulative PAR for hyper-parasitemia and age 1 to < 5 years: 43.7%.

Univariable and multivariable risk factors for PCR-adjusted recrudescence at day 42 (n = 7,652 and 220 recrudescences for final model) for patients treated with artesunate-amodiaquine*

Variable	No. (no.)†	Univariable analysis		Multivariable analysis		Population attributable risk‡	
		Crude HR (95% CI)	P	Adjusted HR (95% CI)	P	Frequency	PAR
Amodiaquine dose (mg/kg) (5 units)	7,652 (220)	0.90 (0.8–1.01)	**0.081**	0.92 (0.82–1.04)	0.180	–	–
Clinical variables							
Parasitemia (log scale)	8,224 (223)	**1.53 (1.19–1.97)**	**< 0.001**	**1.5 (1.16–1.93)**	**0.002**	10.7%	5.5%
Proportion of baseline parasitemia > 100,000/μL	8,224 (223)	**1.54 (1.03–2.30)**	**0.034**	–	–	–	–
Baseline fever (temperature > 37.5°C)	7,847 (212)	0.87 (0.64–1.20)	0.400	–	–	–	–
Baseline hemoglobin level	5,708 (193)	**0.93 (0.86–1.00)**	**0.054**	–	–	–	–
Baseline anemia (hemoglobin level < 10)	5,708 (193)	**1.37 (1.00–1.89)**	**0.050**	–	–	–	–
Baseline gametocyte level	4,258 (91)	1.41 (0.76–2.59)	0.270	–	–	–	–
Species at enrollment							
Pure *P. falciparum* infection (reference)	8,189 (220)						
Mixed infections	35 (3)	1.28 (0.37–4.41)	0.700	–	–	–	–
Sex							
F (reference)	3,755 (106)						
M	4,308 (102)	0.87 (0.66–1.15)	0.340	–	–	–	–
Age category							
≥ 12 yrs (reference)	1,289 (14)						
< 1	693 (32)	**3.52 (1.65–7.5)**	**0.001**	**2.2 [1.01–4.78]**	**0.047**	8.4%	11.1%
1 to < 5	4,816 (158)	**3.48 (1.78–6.82)**	**< 0.001**	**2.27 [1.13–4.55]**	**0.021**	58.5%	46.9%
5 to < 12	1,426 (19)	1.72 (0.84–3.54)	0.140	1.51 [0.72–3.17]	0.280	–	–
Drug formulation							
FDC (reference)	4,212 (78)						
nFDC co-blistered	900 (11)	1.19 (0.51–2.78)	0.700	0.98 [0.41–2.32]	0.960	–	–
nFDC loose	3,112 (134)	**3.00 (1.64–5.50)**	**< 0.001**	**2.94 [1.58–5.48]**	**0.001**	36.3%	41.9%
Treatment supervision	8,334						
Fully (reference)	6,287 (74)						
Partial	1,937 (149)	2.08 (0.79–5.46)	0.140	–	–	–	–

* Values in bold are statistically significant. PCR = polymerase chain reaction; HR = hazards ratio; CI = confidence interval; FDC = fixed-dose combination.
† No. = number of patients (No.); no. = number of PCR-confirmed treatment failures.
‡ Overall PAR for the model accounted by significant variables: 74.0% calculated as $1 - \Pi_{r=1}^{R}(1 - PAR_r)$. For PAR calculation, parasitemia was categorized at 100,000/μL. Variance of the random effect = 0.914. Anemia was not kept for multivariable analysis because of missing values. The coefficients for other covariates remain unaffected with or without anemia in the model. The assumption of proportional hazard held true for overall final multivariable model globally (P = 0.584) and individually for each of the covariates (P > 0.05).

SUPPLEMENTAL TABLE 3
Summary of studies included in the analysis*

Region, country	Reference	Study year(s)	Treatment (no.)		Transmission zone (no.)		
			AL	ASAQ	High	Moderate	Low
East Africa							
Ethiopia	67	2006	34				34
Ethiopia	68	2008–2009	348				348
Kenya	Unpublished	2007-2008		54			54
Kenya	69	2005	241		241		
Kenya	15	2007		103		103	
Madagascar	70	2006–2007		17	1	15	1
Sudan	31	2006	91				91
Sudan	16	2003		80			80
Tanzania	71	2007–2008	359		359		
Tanzania	11	2007	244		244		
Tanzania	72	2010	108			108	
Tanzania (Zanzibar)	47	2002–2003		208		208	
Tanzania (Zanzibar)	27	2002–2003	200			200	
Tanzania (Zanzibar)	25	2002–2003	†			†	
Tanzania	73	2004	50		50		
Uganda	74	2004–2007	149	149		298	
Uganda	26	2005	204		204		
Uganda	46	2005		204	204		
Uganda	Unpublished	2007–2008	112		112		
West Africa							
Benin	Unpublished	2007	96	95		191	
Burkina Faso	30	2006	188			188	
Burkina Faso	Unpublished	2004–2006		890	890		
Burkina Faso	75	2005	261			261	
Guinea-Bissau	76	2006–2008	191			191	
Liberia	77	2009	150	149	299		
Mali		2009	337		188	77	72
Mali	49	2002–2004		252	252		
Nigeria	78	2007–2008	47	45	92		
Oceania							
Papua New Guinea	79	2005–2007	176			176	
Asia							
Thailand	34	1995–2002	1,417				1,417
Thailand	29	1995–2002	†				†
Total			**5,003**	**2,246**	**3,136**	**2,016**	**2,097**

*AL = artemether-lumefantrine; ASAQ = artesunate-amodiaquine.
†Samples overlap with previous study.

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Treatment, variable	Asia/Oceania	East Africa	West Africa	Overall
AL				
No. (%)	1,593 (31.9)	2,140 (42.8)	1,270 (25.3)	5,003
Study period	1995–2007	2002–2010	2003–2009	1995–2010
Follow-up (days)				
28	19.5%	32.6%	50.8%	33.0%
42	56.2%	39.3%	49.2%	47.2%
43–63	24.4%	28.0%		19.7%
Median age (IQR, range) (years)	18 (10–30, 0.8–70)	3 (2–5, 0.3–81)	4 (3–7, 0.3–61)	5 (3–14, 0.3–81)
< 1	0.1%	7.7%	3.4%	4.2%
1 to < 5	12.1%	59.9%	47.7%	41.6%
5–11	17.4%	18.6%	38.3%	23.2%
≥ 12	70.5%	13.6%	9.7%	30.7%
Missing	0.0%	0.3%	0.9%	0.4%
Baseline parasites/μL geometric mean (95% CI)	5,371 (4,833–5,969)	14,094 (13,015–15,262)	25,066 (23,411–26,838)	12,086 (11,459–12,748)
Supervision				
Full	64.6%	35.8%	62.2%	51.7%
Partial	11.0%	44.4%	34.1%	31.2%
Unsupervised	0.0%	19.8%	0.0%	8.5%
Not stated/unknown	24.4%	0.0%	3.7%	8.7%
Co-administration				
With food	11.0%	20.7%	26.9%	19.2%
Advised to consume fatty food	0.0%	46.0%	0.0%	19.7%
None	0.0%	9.5%	0.0%	4.1%
Not stated	89.0%	23.7%	73.1%	57.0%
ASAQ				
No. (%)		815 (36.3%)	1,431 (63.7%)	2,246
Study period		2002–2008	2002–2009	2002–2009
Follow-up, days				
28		74.5%	82.9%	79.9%
42		25.5%	17.1%	20.1%
Median age (IQR, range) (years)		3 (2–5, 0.4–60)	3 (2–4, 0.4–38)	3 (2–4, 0.4–60)
< 1		8.3%	7.7%	7.9%
1 to < 5		65.3%	78.6%	73.8%
5–11		19.1%	12.6%	15.0%
≥ 12		7.0%	1.0%	3.2%
Missing		0.2%	0.0%	0.1%
Baseline parasites/μL geometric mean (95% CI)		18,412 (16,480–20,569)	15,661 (14,593–16,806)	16,608 (15,635–17,642)
Formulation				
Fixed dose		3.2%	48.1%	31.8%
Non-fixed dose		94.7%	51.9%	67.4%
Supervision				
Full		63.8%	62.2%	62.8%
Partial			17.1%	10.9%
Not stated/unknown		36.2%	20.8%	26.4%

*AL = artemether-lumefantrine; IQR = interquartile range; CI, confidence interval; ASAQ = artesunate-amodiaquine.