The Relative Effects of Artemether-lumefantrine and Non-artemisinin Antimalarials on Gametocyte Carriage and Transmission of *Plasmodium falciparum*: A Systematic Review and Meta-analysis

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Background. Artemisinin-based combination therapies (ACTs) have been widely adopted as first-line agents to treat uncomplicated falciparum malaria due to their activity against multidrug resistant parasites. ACTs may also disrupt transmission through a direct antigametocyte effect, but the extent of this effect is uncertain. We assessed the evidence for and estimated the effects of the most widely-deployed ACT, artemether-lumefantrine (AL), relative to non-ACTs on gametocyte clearance and transmission interruption.

Methods. We searched electronic databases for randomized controlled trials comparing AL to non-ACTs that reported gametocyte counts or results of mosquito-feeding assays. Two authors working independently assessed eligibility, extracted data, and evaluated the risk of bias. We conducted meta-analyses using a random-effects model.

Results. We identified 22 eligible trials. The pooled odds of gametocytemia at 1 week were lower in AL- compared to non-ACT-treated participants (odds ratio [OR] 0.09; 95% confidence interval [CI], 0.06–0.15; $I^2 = 0.60$, $P < .01$; 15 trials). The odds of transmission to mosquitoes were also lower in AL treatment groups (OR 0.06; 95% CI, 0.00–0.47, $P < .01$ at 7 days post-treatment; 1 trial; OR 0.56; 95% CI, 0.36–0.88, $P = .01$ at 14 days post-treatment; 1 trial).

Conclusion. AL is superior to non-ACTs in reducing gametocytemia, and, based on limited evidence, abating transmission to mosquitoes. The transmission-limiting benefit of AL has relevance for policymakers planning optimal utilization of control strategies, including use of ACTs for malaria treatment and chemoprevention.

Keywords. malaria; gametocytes; artemisinin-based combination therapy; artemether-lumefantrine; meta-analysis.

Malaria caused an estimated 212 million infections and 429 000 deaths in 2015, predominantly in children in sub-Saharan Africa [1]. Recently, there has been a renewed call for malaria eradication, building on substantial gains made in the last 15 years [2]. Control and elimination currently center on case management with artemisinin-based combination therapy (ACT) and vector control with insecticide-treated bed nets. Less widely deployed, due to cost and technical constraints, are indoor spraying of insecticides, mass drug administration, and chemopreventive use of drugs. As long as a highly effective

malaria vaccine remains unavailable, drugs that reduce human-to-mosquito transmission offer a vital contribution to control and elimination programs.

Malaria is transmitted by gametocytes in host blood. Following ingestion by mosquito vectors, malaria parasites migrate to the insect midgut and proceed through sporogony, developing from ookinetes to oocysts that contain infectious sporozoites. Few antimalarials possess antigametocyte activity, and individuals may remain infectious for several weeks after treatment [3, 4]. ACTs are more potent than non-ACTs against asexual parasites and have activity against immature gametocytes [5–11]. Some artemisinin derivatives may also possess sporonticidal activity, thereby limiting transmission from mosquitoes to humans [12]. The resultant transmission-limiting benefit of ACTs has relevance for policymakers planning optimal use of control and elimination approaches as stepping stones toward eradication.

Among ACTs, artemether-lumefantrine (AL) is the most widely adopted. Moreover, AL appears to be superior to most

other widely-used ACTs for reducing gametocyte carriage and disrupting transmission [13–16]. The objective of this review is to systematically identify and synthesize the evidence for and quantify the effects of AL relative to non-ACTs on gametocyte carriage and transmission interruption in individuals with uncomplicated falciparum malaria.

METHODS

Eligibility Criteria
We included randomized controlled trials (RCTs) that compared AL (6-dose regimen) to one or more non-ACT regimens for gametocyte clearance or mosquito infectivity. We included studies in endemic regions of participants of any age with a diagnosis of uncomplicated falciparum malaria. We excluded studies of severe malaria and non-falciparum malaria, and trials in migrants, displaced peoples, travelers, and military personnel.

Outcomes
The primary outcomes were the proportion of study participants with circulating gametocytes 7 days after initiation of treatment, measured by microscopy, and the proportion of mosquitoes that developed gut oocysts in feeding studies at any day. Secondary outcomes included the proportion of study participants with circulating gametocytes at post-treatment day 14, mean duration of gametocyte carriage, mean gametocyte density, area under the curve (AUC) of gametocyte density, and proportion of participants in feeding studies who were infectious to mosquitoes.

Search Strategy
We designed an electronic search strategy using terms related to "malaria" and "antimalarial drugs" (Supplementary Table 1). We applied a filter for RCTs to electronic databases for which that feature was available. We searched PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov on February 5, 2016, and manually searched references of relevant papers. The search was not limited by year or language.

Data Extraction
We extracted data pertaining to study design, eligibility criteria, baseline characteristics of the study groups, co-administered interventions, features of the study setting including transmission intensity and locale (rural, urban, peri-urban), duration of follow-up, and attrition. We extracted gametocyte and mosquito-feeding outcomes from text or tables, or estimated them from figures when necessary. At time points for which a denominator was not reported, we estimated it as the sample size at the previous time point if available, otherwise as the initial sample size. Where continuous variables were presented as medians, we assumed a normal distribution and converted medians to means. One trial included a 4-dose AL group, but

only the standard 6-dose AL group was considered in analyses [17]. For the single study that performed polymerase chain reaction (PCR) for gametocytes [18], we only extracted results of microscopy in order to maintain comparability across trials.

Assessment of Risk of Bias
We used the Cochrane Collaboration tool for risk of bias assessments of individual studies [19]. We considered selection, performance, detection, attrition, and reporting biases, graded independently by two authors as low risk, high risk, or unclear risk.

Analysis
We qualitatively assessed the comparability of characteristics and designs of included trials. We assessed statistical heterogeneity among the included trials through visual inspection of forest plots and computation of the I^2 statistic. By convention, I^2 values of 0.3–0.6 were interpreted as evidence of moderate heterogeneity, and values >0.6 as considerable heterogeneity [20]. When no substantial clinical, methodological, or statistical heterogeneity was present, we conducted meta-analyses using a random-effects model in RevMan 5.0 (The Cochrane Collaboration).

We conducted prespecified subgroup analyses by age (≤5 and >5 years of age), comparator drug (amodiaquine plus sulfadoxine/sulfalene-pyrimethamine, AQ-SP; and chloroquine plus sulfadoxine-pyrimethamine, CQ-SP), and geographic region (Africa and South/Southeast Asia). We assessed small-study effects by visual inspection of funnel plots for asymmetry. We performed a sensitivity analysis excluding studies with high or unclear risk of detection bias, based on whether study microscopists were masked.

RESULTS

Study Selection
We identified 7602 unique records from our searches and included 22 RCTs in the systematic review (Figure 1). Fifteen studies reported sufficient data for inclusion in meta-analyses.

Study Characteristics
Of the 22 included RCTs, only 2 were designed explicitly to evaluate malaria transmission [18, 21]. All others reported gametocyte and mosquito infectivity results as secondary outcomes. The trials were predominantly done in children; only 3 included adults [22–24]. Eight recruited children <5 years of age [25–32]. Most trials were conducted in sub-Saharan Africa (17 out of 22), the remainder in South and Southeast Asia.

The trials examined a total of 60 treatment groups, of which 23 groups received AL, 10 groups ACTs other than AL, and 27 groups non-ACTs (Table 1). Non-ACT regimens mainly comprised mono- or combination therapies of AQ (10 trials), CQ (7 trials), and SP (18 trials). Dosing schedules for the non-ACT
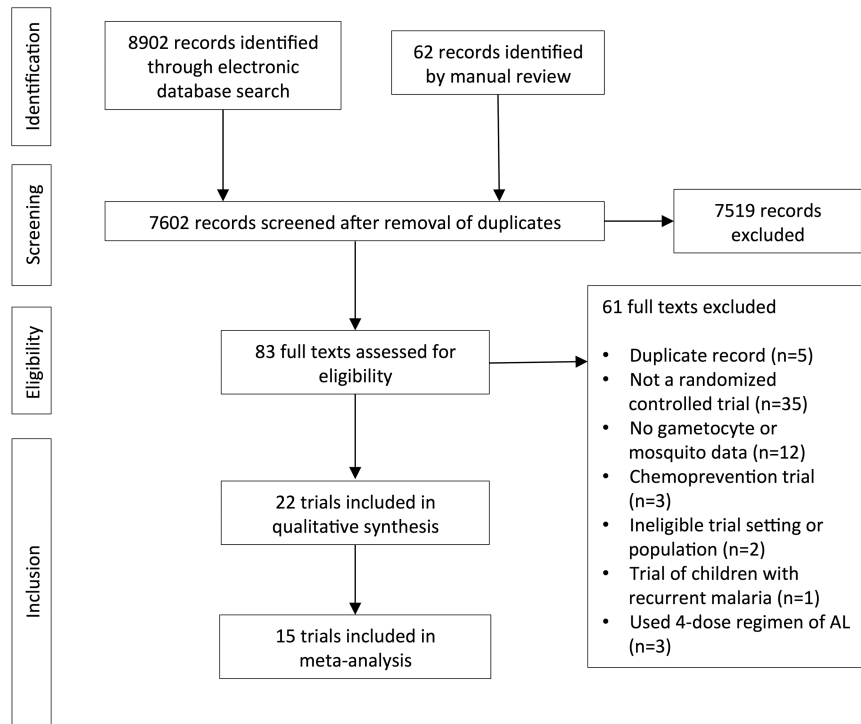
Figure 1. Flowchart of inclusions and exclusions from the systematic review. Abbreviation: AL, artemether-lumefantrine.

groups were standard. Two trials reported co-interventions: 1 administered iron supplementation [33], and 1 administered the gametocytocide primaquine to study participants with gametocytemia at any follow-up visit, which resulted in a greater number of participants in the non-ACT group receiving the drug [22].

Seventeen trials reported the proportion of participants with gametocytemia at post-treatment day 7 and/or 14, and 2 reported results of mosquito feeding assays. Additional gametocyte-related measures included mean or median gametocyte density [21–23, 34–36], cumulative prevalence of gametocytemia [22, 37], mean duration of gametocytemia [21], probability of remaining gametocyte-free [34], gametocyte clearance rate [31], AUC of gametocyte density [34], ratio of means of gametocyte density [21], total person-time with gametocytes [21, 30], and mean gametocyte sex ratio [34]. One trial restricted its follow-up gametocyte measurements only to participants who were gametocytemic at baseline [34]. Every trial included genotyping (e.g., *pfmsp1* and *pfmsp2* alleles) to distinguish reinfection from recrudescence in participants with recurrent parasitemia, but none provided information relating new or recrudescent asexual parasitemia to the presence of gametocytes.

Risk of Bias of Included Trials

There was an overall low risk of bias within trials (Table 2, Supplementary Table 2). Outcome assessments were unmasked in 2 trials [25, 38] and not described in 8 others [17, 21, 24, 27, 33, 35, 37, 39]. Attrition bias was low, with retention rates

>90% in nearly all trials; 3 trials reported losses to follow-up >20% in one or more treatment groups [21, 26, 33]. A funnel plot of effect estimates from studies that reported 7- and 14-day gametocyte prevalence displayed a near-symmetric distribution about the pooled estimate, indicating low evidence of small-study effects (Figure 2).

Relative Effects of Artemether-lumefantrine

We found that AL significantly reduced the odds of gametocyte carriage one week after treatment compared to non-ACTs (OR 0.09; 95% confidence interval [CI], 0.06–0.15, $I^2 = 0.60$, $P < .01$; 15 trials) (Figure 3). The proportion of participants with gametocytemia at one week ranged from 0–19% in the AL groups to 1–83% in the non-ACT groups. High statistical heterogeneity precluded pooled analysis of results at two weeks ($I^2 = 0.75$; 15 trials), but 9 of the 15 trials showed AL to be significantly better than non-ACTs and, among the remainder, all except 2 trended toward AL (Figure 4). Trials that reported other gametocyte outcomes all showed fewer gametocytes or faster clearance of gametocytes among AL treatment groups than non-ACT groups, though not all results attained statistical significance (data not shown). The only trial that examined gametocyte sex ratios was limited by small sample size, and did not detect a statistically significant difference between AL and the non-ACT comparator [33]. We performed a sensitivity analysis including only trials that reported a procedure for masking study microscopists during gametocyte assessments.

Table 1. Characteristics of Included Trials

Study Author and Publication Year	Country (No. sites)	Transmission Intensity	Study Period	Participant Ages	Day(s) of Assessment for Gametocytes (Mosquitoes)	Treatment Groups[a] (No.)	Baseline Parasite Density (Count/µL)	Day 7 Gametocyte Carriage (%)	Day 14 Gametocyte Carriage (%)	Proportion of Infected Mosquitoes (%)
von Seidlein 1998 [32]	Gambia (2)	…	1996–1997	1–5 y	2, 3, 4, 15	AL (144) SP (143)	141 000 168 000	…	0/125 (0.0) 37/128 (28.9)	…
Hatz 1998 [25]	Tanzania (1)	…	…	1–5 y	1, 2, 3, 7	AL (130) CQ (130)	55 017 53 575	2/130 (1.6) 8/130 (6.2)	…	…
Mayxay 2004 [35]	Laos (1)	…	2002–2003	≥ 1 y	Not specified	AL (110) CQ-SP (110)	29 363 26 122	…	…	0/195 (0.0) 14/345 (4.1)
Sutherland 2005 [21]	Gambia (1)	…	2002	1–10 y	7, 14, 28 (7)	AL (406) CQ-SP (91)	56 689 55 203	16/336 (4.8) 27/74 (36.5)	11/356 (3.1) 27/79 (34.2)	…
Mutabingwa 2005 [26]	Tanzania (1)	…	2002–2004	4–59 mo	14	AL (519) AQ (270) AQ-SP (507)	24 100 24 350 24 400	…	20/333 (6.0) 24/128 (18.8) 73/284 (25.7)	…
Koram 2005 [27]	Ghana (2)	…	2003	6–59 mo	1, 2, 3, 5, 7, 14	AL (51) SP (27) CQ (36)	28 175 25 064 28 134	1/51 (2.0) 10/27 (370) 1/36 (2.8)	1/47 (2.1) 6/27 (22.2) 0/36 (0.0)	…
van den Broek 2005 [37]	Bangladesh (2)	High	2003	≥ 1 y	2, 3, 7, 14, 21, 28, 35, 42	AL (121) CQ-SP (122)	11 814 12 016	3/121 (2.5) 22/51 (43.1)	1/121 (0.8) 44/122 (36.1)	…
Bousema 2006 [18]	Kenya (1)	High	2003–2004	6–120 mo	3, 7, 14, 28 (14)	AL (75) SP (152) AQ-SP (127)	11 887 10 122 11 452	12/75 (16.0) 83/135 (61.5) 55/119 (46.2)	5/75 (6.7) 58/152 (38.2) 38/127 (29.9)	27/750 (3.6) 52/750 (6.9) 41/750 (5.5)
Mulenga 2006 [23]	Zambia (4)	Moderate	2003–2005	15–50 y	3, 7, 14, 28	AL (485) SP (486)	8405 8787	2/436 (0.5) 88/405 (21.7)	…	…
Faye 2007 [17]	Senegal (5)	Moderate	2002–2003	…	3, 7, 14, 21, 28	AL (149) AQ-SP (161)	15 398 27 000	9/149 (6.0) 19/161 (11.8)	5/149 (3.4) 0/161 (0.0)	…
Fanello 2007 [28]	Rwanda (2)	…	2004–2005	12–59 mo	2, 3, 7, 14, 21, 28	AL (251) AQ-SP (249)	23 323 22 070	2/246 (0.8) 19/247 (7.7)	2/246 (0.8) 9/247 (3.6)	…
Dorsey 2007 [56]	Uganda (1)	…	2004–2006	1–10 y	2, 3, 4–14	AL (202) AQ-SP (253)	10 939 13 170	…	…	…
Zongo 2007a [33]	Burkina Faso (3)	High	…	≥ 6 mo	Not specified	AL (188) AQ-SP (184)	27 110 22 884	…	…	…
Zongo 2007b [38]	Burkina Faso (3)	High	2005	≥ 6 mo	2, 3, 7, 14, 21, 28	AL (275) AQ-SP (273)	27 689 27 137	0/261 (0.0) 3/260 (1.2)	0/275 (0.0) 0/273 (0.0)	…
Thapa 2007 [22]	Nepal (1)	Low	2005	> 5 y	3, 7, 14, 21, 28	AL (66) SP (33)	6492 2997	9/66 (13.6) 27/33 (81.8)	1/66 (1.5) 14/33 (42.4)	…
Sowunmi 2008 [34]	Nigeria (1)	High	2005–2006	≤ 10 y	1, 7, 14, 21, 28, 35	AL (90) AQ-SP (91)	46 541 50 784	1/90 (1.1) 3/91 (3.3)	3/90 (3.3) 2/91 (2.2)	…
Karunajeewa 2008 [29]	Papua New Guinea (2)	High	2005–2007	6–59 mo	1, 2, 3, 7, 14, 28, 42	AL (127) CQ-SP (110)	48 507 43 869	24/127 (18.9) 91/110 (82.7)	6/127 (4.7) 78/110 (70.9)	…

Table 1. Continued

Study Author and Publication Year	Country (No. sites)	Transmission Intensity	Study Period	Participant Ages	Day(s) of Assessment for Gametocytes (Mosquitoes)	Treatment Groups[a] (No.)	Baseline Parasite Density (Count/µL)	Day 7 Gametocyte Carriage (%)	Day 14 Gametocyte Carriage (%)	Proportion of Infected Mosquitoes (%)
Gürkov 2008 [39]	Ethiopia (1)	…	2006	> 5 y	0, 7, 28	AL (30) QN (35) AP (32)	21 189 15 469 13 028	2/30 (6.7) 10/34 (29.4) 16/32 (50.0)	…	…
Achan 2009 [30]	Uganda (1)	High	2007–2008	6–59 mo	7, 14, 28	AL (89) QN (86)	16 124 14 107	1/89 (1.1) 10/59 (1.7)	1/89 (1.1) 5/62 (8.1)	…
Okafor 2010 [36]	Nigeria (1)	…	2005	6–120 mo	3, 7, 14, 28, 42	AL (70) AQ-SP (70)	11 320 9717	2/69 (2.9) 15/69 (21.7)	1/69 (1.4) 8/69 (11.6)	…
Valecha 2012 [24]	India (3), Thailand (1)	…	…	12–65 y	28	AL (80), OZ-PIP (160)	22 221, 21 497	…	…	…
Chandra 2015 [31]	Africa, multiple (6)	…	2008–2010	6–59 mo	Not specified	AL (126) CQ-AZ (120)	…	…	…	…

Abbreviations: AL, artemether-lumefantrine; AP, Atovaquone-proguanil; AQ, amodiaquine; AZ, azithromycin; CQ, chloroquine; OZ, arterolane; PIP, piperaquine; QN, quinine; SP, sulfadoxine/sulfalene-pyrimethamine; …, not done or not reported.

[a] Omits artemisinin-containing study arms except AL.

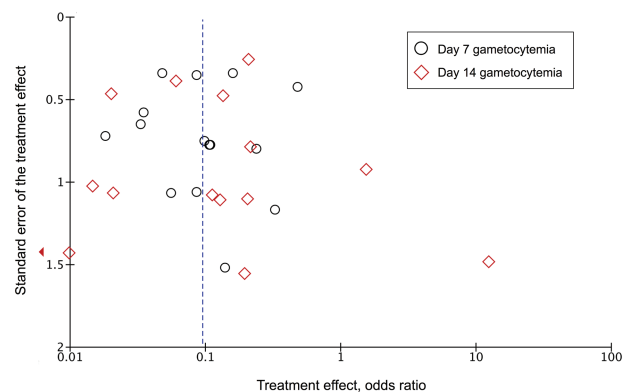**Table 2. Summary of Risk of Bias of Included Trials**

Type of Bias	Risk of Bias, No. of Studies		
	Low	High	Unclear
Random sequence generation (selection bias)	16	3	3
Allocation concealment (selection bias)	10	4	8
Blinding of participants and personnel (performance bias)	2	15	5
Blinding of outcome assessment (detection bias)	12	2	8
Incomplete outcome data (attrition bias)	15	3	4
Selective reporting (reporting bias)	21	0	1
Intention-to-treat analysis (bias due to incomplete reporting)	19	0	3
Group similarity at baseline (selection bias)	17	4	1
Co-interventions (performance bias)	19	1	2
Compliance (performance bias)	16	2	4
Timing of outcome assessment (detection bias)	20	0	2

The sensitivity analysis showed similar results to the primary meta-analysis (OR 0.07; 95% CI, 0.04–0.13; I^2 = 0.52, $P < .01$; 8 trials).

We identified 2 trials that carried out mosquito feeding assays [18, 21]. One trial performed assessments on post-treatment day 7 in participants treated with either AL or CQ-SP [21], the other on day 14 in participants receiving AL, SP, or AQ-SP [18]. Both demonstrated significantly fewer infected mosquitoes among those fed on blood from AL-treated participants compared to non-ACT-treated participants (day 7: OR 0.06; 95% CI, 0.00–0.47; $P < .01$; day 14: OR 0.56; 95% CI, 0.36–0.88; $P = .01$).
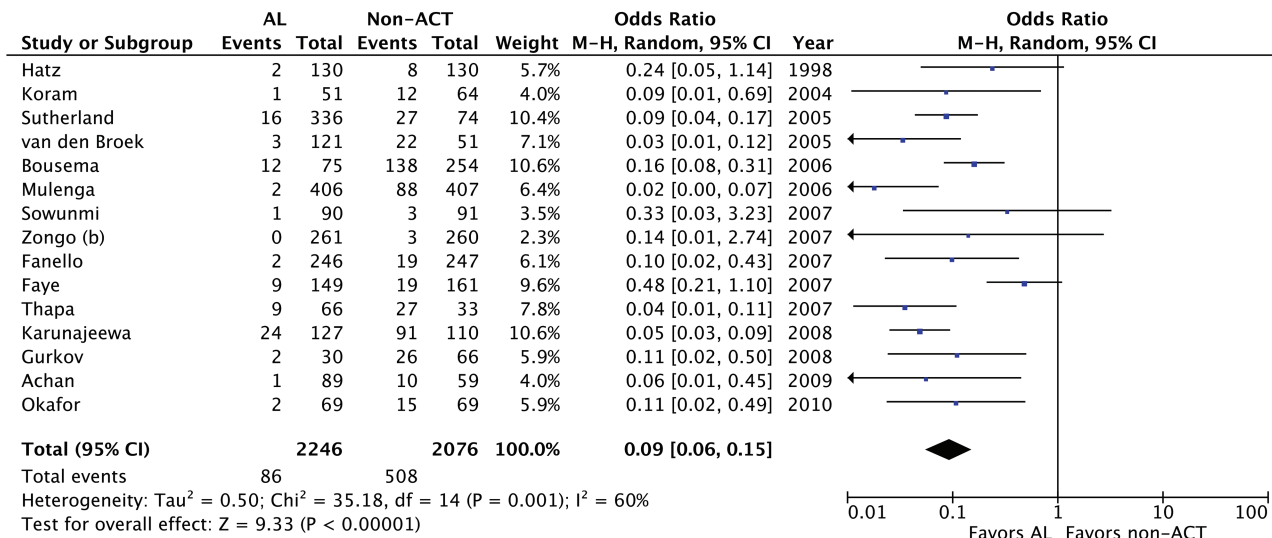
Subgroup Analyses

We performed subgroup analyses by participant age, comparator drug, and geographic region (Table 3). We found no detectable difference in gametocyte clearance between

Figure 2. Funnel plot of gametocyte clearance effect measures.

Study or Subgroup	AL Events	AL Total	Non-ACT Events	Non-ACT Total	Weight	Odds Ratio M-H, Random, 95% CI	Year	Odds Ratio M-H, Random, 95% CI
Hatz	2	130	8	130	5.7%	0.24 [0.05, 1.14]	1998	
Koram	1	51	12	64	4.0%	0.09 [0.01, 0.69]	2004	
Sutherland	16	336	27	74	10.4%	0.09 [0.04, 0.17]	2005	
van den Broek	3	121	22	51	7.1%	0.03 [0.01, 0.12]	2005	
Bousema	12	75	138	254	10.6%	0.16 [0.08, 0.31]	2006	
Mulenga	2	406	88	407	6.4%	0.02 [0.00, 0.07]	2006	
Sowunmi	1	90	3	91	3.5%	0.33 [0.03, 3.23]	2007	
Zongo (b)	0	261	3	260	2.3%	0.14 [0.01, 2.74]	2007	
Fanello	2	246	19	247	6.1%	0.10 [0.02, 0.43]	2007	
Faye	9	149	19	161	9.6%	0.48 [0.21, 1.10]	2007	
Thapa	9	66	27	33	7.8%	0.04 [0.01, 0.11]	2007	
Karunajeewa	24	127	91	110	10.6%	0.05 [0.03, 0.09]	2008	
Gurkov	2	30	26	66	5.9%	0.11 [0.02, 0.50]	2008	
Achan	1	89	10	59	4.0%	0.06 [0.01, 0.45]	2009	
Okafor	2	69	15	69	5.9%	0.11 [0.02, 0.49]	2010	
Total (95% CI)		**2246**		**2076**	**100.0%**	**0.09 [0.06, 0.15]**		
Total events	86		508					

Heterogeneity: Tau^2 = 0.50; Chi^2 = 35.18, df = 14 (P = 0.001); I^2 = 60%
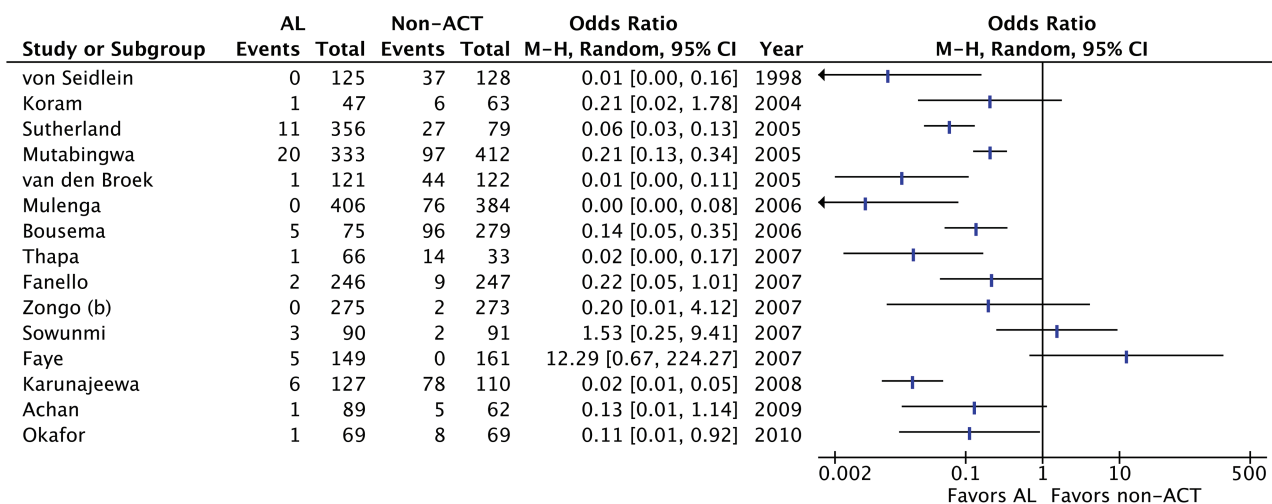Test for overall effect: Z = 9.33 (P < 0.00001)

Figure 3. Meta-analysis of trials comparing AL to non-ACTs for gametocyte clearance at post-treatment day 7. Abbreviations: ACT, artemisinin-based combination therapy; AL, artemether-lumefantrine; CI, confidence interval; M-H, Mantel-Haenszel.

children ≤5 years (OR 0.07; 95% CI, 0.04–0.11; I^2 = 0, P < .01; 5 trials) and children >5 years (OR 0.04; 95% CI, 0.01–0.10; I^2 = 0.36, P < .01; 3 trials). We found a smaller effect size in trials comparing AL to AQ-SP (OR 0.22; 95% CI, 0.12–0.40; I^2 = 0.17, P < .01; 6 studies) than those comparing it to CQ-SP (OR 0.06; 95% CI, 0.04–0.10; I^2 = 0.15, P < .01; 3 trials) with non-overlapping CIs. AL appeared to exhibit greater effect in trials done in South and Southeast Asia (OR 0.04; 95% CI, 0.03–0.07; I^2 = 0, P < .01; 3 trials) compared to sub-Saharan Africa (OR 0.12; 95% CI, 0.07–0.21; I^2 = 0.50, P < .01; 12 trials), but the association with geographic region is likely confounded by the exclusive use CQ-SP comparators in trials in Asia, whereas the African trials included a mix of comparators.

DISCUSSION

We assessed the body of evidence comparing the effects of AL and non-ACTs on *P. falciparum* gametocyte clearance and transmission interruption. We found a consistent, large effect favoring AL. At 1 week following treatment, AL reduced the odds of gametocyte carriage by 91% relative to non-ACTs and disrupted transmission to mosquitoes. The quality of the evidence was judged to be good overall, with low risk of bias. Thus, an important advantage of AL over non-ACT regimens, in addition to better efficacy against clinical illness, is better ability to prevent transmission to mosquitoes.

Study or Subgroup	AL Events	AL Total	Non-ACT Events	Non-ACT Total	Odds Ratio M-H, Random, 95% CI	Year	Odds Ratio M-H, Random, 95% CI
von Seidlein	0	125	37	128	0.01 [0.00, 0.16]	1998	
Koram	1	47	6	63	0.21 [0.02, 1.78]	2004	
Sutherland	11	356	27	79	0.06 [0.03, 0.13]	2005	
Mutabingwa	20	333	97	412	0.21 [0.13, 0.34]	2005	
van den Broek	1	121	44	122	0.01 [0.00, 0.11]	2005	
Mulenga	0	406	76	384	0.00 [0.00, 0.08]	2006	
Bousema	5	75	96	279	0.14 [0.05, 0.35]	2006	
Thapa	1	66	14	33	0.02 [0.00, 0.17]	2007	
Fanello	2	246	9	247	0.22 [0.05, 1.01]	2007	
Zongo (b)	0	275	2	273	0.20 [0.01, 4.12]	2007	
Sowunmi	3	90	2	91	1.53 [0.25, 9.41]	2007	
Faye	5	149	0	161	12.29 [0.67, 224.27]	2007	
Karunajeewa	6	127	78	110	0.02 [0.01, 0.05]	2008	
Achan	1	89	5	62	0.13 [0.01, 1.14]	2009	
Okafor	1	69	8	69	0.11 [0.01, 0.92]	2010	

Figure 4. Summary of results of trials comparing AL to non-ACTs for gametocyte clearance at post-treatment day 14. High statistical heterogeneity (I^2 = 0.75) precluded meta-analysis of these trials. Abbreviations: ACT, artemisinin-based combination therapy; AL, artemether-lumefantrine; CI, confidence interval; M-H, Mantel-Haenszel.

Table 3. Results of Subgroup Meta-analyses of AL vs. Non-ACTs for Gametocyte Clearance at Post-treatment Day 7

Subgroup	Description	No. Studies	OR (95% CI)	I²-Statistic	P Value
All studies		15	0.09 (0.06–0.15)	0.60	<.01
Age	Children ≤ 5 years	5	0.07 (0.04–0.11)	0.00	<.01
	Children > 5 years	3	0.04 (0.01–0.10)	0.36	<.01
Comparator drug	AQ-SP	6	0.22 (0.12–0.40)	0.17	<.01
	CQ-SP	3	0.06 (0.04–0.10)	0.15	<.01
Geographic region	Sub-Saharan Africa	12	0.12 (0.07–0.21)	0.50	<.01
	South and Southeast Asia	3	0.04 (0.03–0.07)	0.00	<.01

Abbreviations: AQ, amodiaquine; CI, confidence interval; CQ, chloroquine; OR, odds ratio; SP, sulfadoxine/sulfalene-pyrimethamine.

The combination of artemether's direct antigametocyte action and faster killing of *P. falciparum* asexual stages likely explains the decreased gametocyte carriage and mosquito infectivity of AL-treated participants compared to non-ACT-treated participants [9–11]. Direct activity against early-stage gametocytes precludes maturation to transmissible late-stage gametocytes, and clearance of asexual stages is hypothesized to deplete the pool from which gametocytes arise [40]. Artemisinins also may interrupt gametocyte progression through sporogony once they are taken up by vector mosquitoes [12]. The non-artemisinin component of AL, lumefantrine, also may have antigametocyte and sporonticidal action [41–43]. Subgroup analyses illustrated a hierarchy of antigametocyte efficacy among specific comparators (AL > AQ-SP > CQ-SP), consistent with results previously reported in the literature [44]. The results of the trial that administered the gametocytocide primaquine to participants with gametocytemia at any follow-up visit were consistent with those observed in other trials despite more in the non-ACT group receiving primaquine, offering a conservative estimate of the relative effect of AL [22].

Gametocytemia is an imperfect marker of infectivity; infected individuals can remain infective after gametocytes fall below microscopically detectable concentrations, and factors in addition to absolute counts, such as gametocyte sex ratios, may modulate transmission [45–47]. Mosquito feeding assays remain the most direct means of assessment of transmissibility, but these are challenging to do. Only 2 trials included feeding assays [18, 21]. They showed that blood from AL-treated participants reduced infectivity to mosquitoes on post-treatment days 7 and 14 compared to blood from those treated with non-ACT regimens. The single trial that correlated treatment regimens to gametocyte sex ratios found no difference between AL and the non-ACT comparator, AQ-SP, but its small number of gametocytemic individuals may have led to insufficient statistical power to detect a difference [34].

Age-related immunity is believed to contribute to gametocyte clearance [3], and we hypothesized it would influence the observed effect sizes in children of different age groups. However, in subgroup meta-analyses comparing trials of children above and below 5 years of age, we found no significant difference in gametocyte clearance. This finding was unexpected, as older children have been shown to display increased immune responses directed against gametocytes compared to younger children [3, 48]. Surprisingly, field trials suggest gametocyte carriage may persist longer in older than younger children [49]. Immune-mediated clearance of gametocytes remains incompletely characterized, and age-related immunity appears to differ in regard to clearance of gametocytes and that of asexual parasites [49–51].

Impressive gains in malaria control and elimination made over the last decade are threatened by political instability, repercussions of climate change, stagnating funding, rising insecticide resistance, and the prospect of artemisinin-resistant parasites spreading to sub-Saharan Africa [2, 52]. These threats can be mitigated by optimizing our use of available tools. To this end, future trials of the relative effects of different ACTs on transmission of parasites to mosquitoes will be helpful. A network meta-analysis that extends the scope of the present study to compare the relative effects of different ACTs to each other and to non-ACTs would be informative.

Beyond malaria case management, the relative transmission impacts of antimalarials may have relevance for other drug deployment strategies. Treated symptomatic cases continue to contribute to the infectious reservoir due to persistent circulation of gametocytes for a duration that varies by therapy. But asymptomatic cases, a heterogeneous group, also contribute to the infectious reservoir [53–55]. Asymptomatic cases are targeted by intermittent preventive therapy, mass drug administration, and screen-and-treat programs. Studies and mathematical models of the comparative effects of these interventions using different antimalarial drugs could further aid in optimizing malaria control strategies.

There were limitations to this review. We only included trials with an AL treatment group, limiting the generalizability of our results to other ACTs. We compared AL to a number of different regimens, limiting our ability to tease out effects of individual drugs. Only 2 trials were designed to assess treatment impact on transmission. Misclassification bias was potentially high, due to reliance mainly on microscopy rather than more sensitive PCR-based methods of gametocyte detection. Although all included

trials used genotyping to distinguish treatment failure from reinfection, none reported the association between gametocyte outcomes and reinfection or recrudescence; it was therefore not possible to distinguish among persistent gametocytemia following initial treatment, recrudescent gametocytemia, or new gametocytemia due to reinfection. Despite these limitations, the large effect size for AL strongly suggests that it offers benefit over non-ACT regimens in abating malaria transmission.

CONCLUSIONS

AL is superior to non-ACT regimens in reducing gametocyte carriage and interrupting transmission in individuals with uncomplicated falciparum malaria. In a meta-analysis of 15 trials, treatment with AL led to a 91% reduction in the odds of gametocytemia at one week compared to non-ACTs. Two trials showed reduction in transmission to mosquitoes at 1 and 2 weeks post-treatment. The benefit of transmission interruption conferred by ACTs has relevance for policy makers planning optimal utilization of currently available control and elimination tools, including the use of ACTs for malaria treatment and chemoprevention.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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