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A REVIEW ON THE EFFECT OF ACTS ON *PLASMODIUM FALCIPARUM* GAMETOCYTE CARRIAGE IN KENYA.

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ABSTRACT

Artemisinin-based combination therapy (ACT) is currently adopted drug regimen the management of both uncomplicated and severe falciparum malaria, targeting asexual blood-stage *Plasmodium falciparum* parasites. However, the effect of ACT on sexual-stage parasites remains debatable. We evaluated the evidence for and estimated the effects of the most widely-deployed ACTs, artemether-lumefantrine (AL) and Dihydroartemisinin piperaquine phosphate (DP) on gametocyte clearance and transmission interruption in Kenya.Electronic databases for randomized controlled trials evaluating the effect of AL and DP that reported gametocyte prevalence and densities or results of mosquito-feeding assays were searched. Two authors working independently assessed suitability, extracted data, and assessed the risk of bias. Identification of 15 eligible trials conducted in Kenya was done. Generally combined odds of gametocytemia at 7days were lower in both AL and DP treated groups (odds ratio [OR] 0.08; 95% confidence interval [CI], 0.05–0.10; I2 = 0.60, P < .01; 15 trials). The odds of transmission to mosquitoes were also lower but not significant in AL and DP treatment groups (OR 0.16; 95% CI, 0.01–0.4, P < .05 after 1week post-treatment; 1).AL and DP may reduce gametocytemia however presence of submicroscopic gametocytes shortly after treatment with AL and DP in children highlights the limitation of interventions that aim to reduce malaria transmission by use of antimalarial drugs therefore a gametocidal drug in combination to ACTs will be useful in blocking malaria transmission more efficiently.

KEYWORDS

Plasmodium Falciparum, Gametocyte clearance rate, uncomplicated malaria, Artemisinin Combination Therapy, Kenya.

INTRODUCTION

Malaria, the most significant public health problem in sub-Saharan Africa, is a mosquito-borne disease caused by a protozoan parasite of genus *Plasmodium* Female *Anopheles* mosquitoes mediate the spread of malaria parasites to human hosts when taking a blood meal by inoculating infective *Plasmodium* sporozoites to initiate infection[1]. Six species of *Plasmodium* typically cause malaria in human namely: *P. falciparum, P. vivax, P. ovale curtisi, P. ovale wallikeri, P. malariae* and *P. knowlesi*[1,2]. While *P. falciparum* and *P. vivax* pose the greatest threat to the human population, the former is the most lethal[2], accounting for over 90% of malaria-related deaths in the world[1,2].

Antimalarial drug treatments against *Plasmodium falciparum* malaria target asexual blood-stage parasites, which are responsible for clinical diseases and death. Gametocytes, the sexual stages of the malaria parasite, do not cause clinical disease; they are produced in the human host but remain in a state of arrested cell development until ingested by a feeding mosquito[3]. The subsequent development of mosquito-specific stages results in infection of the mosquito salivary glands with sporozoites and malaria transmission to humans. With each subsequent blood meal, parasites are transmitted to a new person, resulting in the spread of malaria among the human population. Gametocytes are thus vital to the maintenance of the malaria transmission cycle[2,3].

Artemisinin derivatives are highly effective against asexual parasites and young gametocytes but not mature gametocytes[4]. In Kenya, Artemether-Lumefantrine (AL) and Dihydroartemisinin-piperaquine phosphate (DP) were officially implemented in 2006 as the first-line and second line drugs respectively for management of uncomplicated *P. falciparum* malaria[5]. Adoption of this regimen for management of uncomplicated malaria has been beneficial because of their gametocytocidal activity and consequently transmission of malaria[5,6]. The efficacy of AL in clearance of gametocytes in Kenya has recently been described in a cohort study conducted in Western Kenya. The findings indicated that a larger proportion of both asymptomatic and symptomatic infections are characterized with submicroscopic gametocyte densities[6]. It was also shown that management of uncomplicated *P. falciparum* malaria with AL may reduce the proportion of individual with gametocytes after 12 weeks of follow-up[6,7]. However, other studies indicate that submicroscopic gametocytes persist following treatment with ACTs mostly thus associated with a longer duration of gametocyte carriage and high transmission intensity[7]. Comparative studies on the risk of residual submicroscopic gametocytes after treatment with AL versus DP have also reported controversial results with some showing increased risk of gametocyte carriage after treatment with AL, while other studies reported that AL had a more pronounced effect on malaria transmission following treatment compared to DP[7].

We evaluated the evidence for and estimated the effects of the most widely-deployed ACT, artemether-lumefantrine (AL) and Dihydroartemisinin piperaquine phosphate (DP) on gametocyte clearance and transmission interruption in Kenya.

METHODS

Inclusion Criteria

We included randomized controlled trials (RCTs) that compared AL (6-dose regimen) to DP for gametocyte clearance or mosquito infectivity[8]. We included studies in endemic regions of participants of any age with a diagnosis of uncomplicated falciparum malaria in Kenya. We included studies of severe malaria and uncomplicated *P. falciparum* malaria.

Outcomes

The initial findings were the proportion of study subjects with circulating gametocytes 7 days following treatment, measured by RNA-based methods (qRT-PCR, and QT-NASBA) and the proportion of mosquitoes that developed gut oocysts in feeding studies at any day. Then the proportion of individuals with circulating gametocytes at day 14 following treatment, 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 criteria

We developed an electronic search strategy using terms related to "malaria" and "antimalarial drugs" (Table 1). RCTs filters were applied to electronic databases for which that feature was available[8]. Cochrane Central Register of Controlled Trials (CENTRAL) was utilized as well as Pubmed and manually we searched references of relevant papers in google scholar. The search was not limited by language or year

Data Extraction

We obtained data by identifying the study design, inclusion criteria, baseline characteristics of the study groups, treatment regime used, study setting features including intensity of transmission and follow-up duration, and attrition. We obtained gametocyte and mosquito-feeding results from tables, or figures when necessary. At the different time points where denominator was not reported, we estimated it as the sample size at the previous time point if available, otherwise as the initial sample size[9]. We assumed the data was normally distributed where continuous variables were presented as medians, and converted medians to means.

Risk of Bias

We adapted Cochrane Collaboration tool for risk of bias assessments of individual studies. Selection, performance, detection, and reporting

biases were considered and 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 I2 statistic. By convention, I2 values of 0.2–0.4 were reported as evidence of moderate heterogeneity, and values >0.4 as considerable heterogeneity. We conducted prespecified subgroup analyses by age (≤5 and >5 years of age). We assessed small-study effects by visual inspection of funnel plots for asymmetry.

RESULTS

Study Selection We identified 802 unique records from our searches and included 22 RCTs in the systematic review (Figure 1). Fifteen studies reported sufficient data for inclusion in the analyses.

Characteristics of the study

Of the 20 included RCTs, only 2 were designed explicitly to evaluate malaria transmission. All others reported gametocyte and mosquito infectivity results as secondary outcomes. The trials were predominantly done in children below the age of 14 years. Most trials were conducted in Western Kenya (9 out of 15), the remainder in Coastal regions of Kenya. The trials examined a total of 20 treatment groups, of which 15 groups received either AL or DP, 2groups ACTs other than AL and DP, and 3 groups non-ACTs (Table 1). Non-ACT regimens mainly comprised mono- or combination therapies of AQ (1 trials) and SP (3trials).

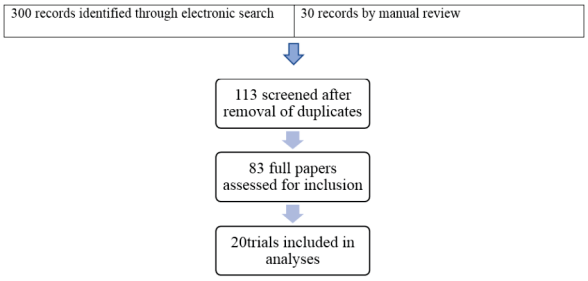


Figure 1 Flowchart of inclusions and exclusions from the systematic review.

Table 1 Characteristics of Included Trials

Study author and publication yr	Site	Transmission intensity	Period of study	Ages	Baseline parasite density	Days of assessment	Treatment group	Day7 Carriage	Day14 carriage	Proportion of infected mosquitoes
Bousema 2006	Western Kenya	High	2003-2004	6m-10yrs	10,122	7,14	AL, SP			14%
Oesterholt 2009	Western Kenya	High	2004-2005	6m-12yrs	12,080	7,14,28	AS, SP			24.4%
Okell 2008	Western Kenya	High	2005-2006	6m-12yrs	21,178	7, 14	AL			20%
Mens 2009	Western Kenya	High	2006-2007	6m-10yrs	12,145	7,21,28	AL, DP	11	12	
Schneider 2006	Western Kenya	High	2006	6m-12yrs			AS, SP			

DISCUSSION

We assessed a number of evidences evaluating the effects of ACTS on P. falciparum gametocyte clearance and transmission interruption. We found a consistent, large effect favoring AL. At day 7 following treatment, both AL, DP and other ACTs used in Kenya reduced the odds of gametocyte carriage by 90% 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 ACTs in addition to better efficacy against clinical illness, is better ability to prevent transmission to mosquitoes[8-10].

The two widely used drugs in Kenya AL and DP have shown no significant difference in reduction of gametocyte carriage according to the previous findings. However, substantial number of submicroscopic gametocytes still persist as shown by RNA based methods (QT-NASBA, qRT-PCR) unlike microscopy, indicating a prolonged gametocytaemia. Previous studies have reported the limitation of ACT against the mature gametocytes[10,11-17] and this may suggest the existence of gametocytes on days 21,28 and 42 following treatment. 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[18,20-26]. Mosquito feeding assays remain the most direct means of assessment of transmissibility, but these has been challenging to do in most of the trials we assessed.

There were limitations to this review. We only included trials in Kenya with either DP or AL treatment groups, 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. Not all trials were designed to assess treatment impact on transmission. However, bias was potentially low, due to reliance mainly more sensitive PCR based methods rather than Microscopy in gametocyte detection.

CONCLUSION

AL and DP may reduce gametocytemia however presence of submicroscopic gametocytes shortly after treatment with AL and DP in children highlights the limitation of interventions that aim to reduce malaria transmission by use of antimalarial drugs therefore a gametocidal drug in combination to ACTs will be useful in blocking malaria transmission more efficiently.

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