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 piperazine 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 fifteen eligible trials conducted in Kenya was done. Generally combined odds of gametocyteemia at 7 days 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 1 week 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.
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 0–25% were considered as moderate heterogeneity, and values >25% 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 two 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 AL or DP, 2 groups 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 (3 trials).

**Table 1 Characteristics of Included Trials**

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

**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 29-31.

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 (Q- NASBA, qRT-PCR) unlike microscopy, indicating a prolonged gametocytaemia. Previous studies have reported the limit of ACT against the mature gametocytes 32-34 and this may suggest the existence of gametocytes on days 21,28 and 42 following treatment. Gametocytaemia 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 35-37. Mosquito feeding assays remain the most direct measurement of infected mosquitoes and this may suggest the existence of gametocytes in the mosquitoes and that this may have a significant effect on the transmission of malaria. Mosquito feeding assays remain the most direct measurement of infected mosquitoes and this may suggest the existence of gametocytes in the mosquitoes and that this may have a significant effect on the transmission of malaria.

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 RCTs. 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 potential low, due to reliance mainly on more sensitive PCR based methods rather than Microscopy in gametocyte detection.

**CONCLUSION**

AL and DP may reduce gametocytaemia 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.

**REFERENCES**

combination with artesunate. International Journal for Parasitology, 36(4), 403-408.


