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INTRODUCTION

Malaria kills approximately 1 million children every year, most of them in sub-Saharan Africa. The mainstay of malaria control remains early, effective treatment of clinical cases. Yet the effectiveness of this policy is likely to decrease as resistance to many of the available and affordable antimalarial drugs increases. Resistance to chloroquine (CQ), a common first-line treatment for malaria in endemic countries, is widespread and has been associated with an increase in mortality. However, the decision to change antimalarial treatment guidelines is complex; limited alternatives exist, and the decision to change should take into consideration a large number of variables, including the efficacy, cost, and availability of drugs, the public health impact of resistance, treatment-seeking behavior, and the likely durability of the new policy. The latter is largely determined by the rate at which resistance to the first-line drug develops, itself a function of the mechanisms of resistance.

There is considerable interest in the use of multiple drugs, with different mechanisms of action, for the treatment of malaria cases. Such combination treatment (CT) is likely to extend the useful lifetime of the constituent drugs by reducing the rate at which resistance develops. The “protection” of the individual drugs is a function of the likelihood of a resistance-conferring mutation arising at two (or more) relevant gene loci and is very much lower than the rate at which resistance develops, especially in situations in which the drug pressure is high, have been borne out by molecular and in vivo studies and by the short duration of its efficacy in Thailand. If SP is to be a useful component of CT, it needs to be protected until combinations with artesunate are shown to be safe, effective, and available. Even a rational combination of drugs will yield poor results if resistance to one of the component drugs is high.

There has been renewed interest in amodiaquine (AQ) as a malaria treatment in endemic settings. Because it is a congener of chloroquine, cross-resistance may limit its efficacy as a first-line antimalarial treatment. Nevertheless, it is being considered as a second-line treatment in some countries.

Anecdotal reports suggest that CQ and SP have been increasingly coprescribed in areas of high CQ resistance despite a lack of safety and efficacy data. If AQ and SP become widely available, it seems likely that these too will be coadministered. Both agents are associated with adverse reactions affecting the skin and bone marrow and it may be that their combined use will produce an unacceptably high rate of adverse events.

Because of the urgent need to protect SP and generate safety data on AQ+SP, we undertook a three-arm, randomized, open-label safety and efficacy study of AQ, SP, and AQ+SP in the treatment of uncomplicated Plasmodium falciparum malaria in young Tanzanian children.

MATERIALS AND METHODS

Study area, population, and recruitment. The study was conducted in the malaria holoendemic setting of Ifakara, situated in the rice-growing flood plains of the Kilombero River, southern Tanzania, and described in detail elsewhere. Children were recruited from the Mother and Child Health (MCH) Clinic of the 380-bed St. Francis Designated District
Hospital (SFDDH) between May and August 1999. Malaria is the leading cause of pediatric admission and outpatient attendances. A Day-7 parasitological chloroquine failure rate of 65% has been described in children aged 1–5 years. SP has been available at health facilities for many years as a second-line malaria treatment. AQ has not been readily available, and there are no previous local efficacy estimates.

After verbal consent from the parent, permanent residents of Ifakara between the ages of 6 months and 5 years presenting to the MCH Clinic with an axillary temperature \( \geq 37.5^\circ\text{C} \) were screened for \( P. falciparum \) parasitemia. Those with an asexual \( P. falciparum \) parasitemia of \( \geq 2,000/\mu\text{L} \) were eligible for enrollment. The trial objective and procedures were explained in Kiswahili, and a series of questions were asked to assess adequate comprehension. Written informed consent was then requested from the guardians of all children before recruitment to the study. Children were examined by a project clinical officer, and demographic and clinical data were recorded. Children were excluded if they were unable to tolerate oral medication or had any signs indicative of severe or complicated malaria. Known chronic underlying disease and sensitivity to trial medication were additional exclusion criteria.

Randomization, treatment, and follow-up. Children were randomly allocated to receive AQ, SP, or AQ+SP (all from Shelys Pharmaceuticals, P.O. Box 3016, Pugu Rd, Dar es Salaam, Tanzania) according to a computer-generated list of treatments randomly assigned to study numbers in blocks of nine. Envelopes marked with the study number contained a piece of paper with the allocated treatment for that number printed on it. Study numbers were allocated sequentially to children as they presented. Children were issued with an identity card bearing their study number and other identification information.

All antimalarial doses were given by a member of the research team, the first dose at the MCH Clinic and the second and third doses of AQ at the children’s homes. Dosages were administered according to a weight-dosing schedule, which ensured that the minimum dosages received were 25 mg/kg for AQ (aiming to administer 10 mg/kg for Doses 1 and 2 and 5 mg/kg for Dose 3) and 25 mg/kg of sulfadoxine with 1.25 mg/kg of pyrimethamine. A replacement dose was given if vomiting occurred within 30 min of administration, and rescue medication was given if there was vomiting of the replacement dose. All children were given a single dose of paracetamol, 250 mg, 30 min before administration of the trial drug, to control fever. Rescue medication consisted of nine doses of quinine sulphate, 30 mg/kg/day, in line with the Tanzanian National Treatment Guidelines, and was only given to children with symptomatic parasitemia. Children who were parasitemic on Day 28 received one of the alternative treatment regimens, regardless of fever, as recommended by WHO.

Children were visited at home by a trained field worker 1, 2, 3, 14, and 21 days after recruitment. Children were asked to return to the clinic for assessments on Days 7 and 28, and mothers were encouraged to bring their child to the project clinical officer at any time during follow-up if they were concerned about the child’s well-being. At all contacts, including admissions to the pediatric ward, standardized forms were completed to facilitate the detection of any adverse events. A symptom report form, based on the National Institutes of Health common toxicity criteria, was completed at routine follow-up visits when the axillary temperature was measured and a blood slide and filter paper sample were collected for later parasitological and molecular analysis, respectively. In addition, capillary blood collected on Days 0 and 28 in a microtainer was used to measure packed cell volume (PCV), total and differential white cell counts, platelets, alanine transaminase (ALT), \( \gamma \)-glutamyl transferase (\( \gamma \)-GT), and creatinine as part of the safety assessment. The study protocol was reviewed and approved by the Ifakara Health Research and Development Centre’s Scientific and Ethical review committees.

Laboratory techniques. Field’s stain of thick blood films was used to screen children before recruitment when 20 high-power fields were examined. Thick films stained with Giemsa were used for definitive parasite counts. A total of 200 thick film fields were screened for non-falciparum Plasmidia, and the number of asexual forms per 200 leukocytes were recorded and converted into parasite density per microliter by assuming an average white cell count of 8,000/\( \mu \text{L} \). Gametocytes were counted against 500 leukocytes. Hence, the limit of detection of asexual forms was 40/\( \mu\text{L} \) and for gametocytes 16/\( \mu\text{L} \). Each slide was read at least twice; a third reading was performed for major discrepancies between the results of the first two readings (either positive/negative discrepancies or a ratio of the readings < 0.66 or > 1.33). The majority reading for positive/negative discordances or the geometric mean of three positive readings was taken as the definitive result. PCVs were measured using a microhematocrit tube and microcentrifuge (Hawksley, Lancing, UK). Total and differential white cell counts were estimated using a semiautomated Coulter-counter type (Sysmex 800, TOA Medical Electronics Ltd, Kobe, Japan). Alanine transaminase (ALT), \( \gamma \)-GT, and creatinine concentrations were measured using a multilayer analyzer (Vitros 250, Ortho-Clinical Diagnostics, Johnson & Johnson). Electronic thermometers were used to measure axillary temperature and were calibrated weekly using a water bath and mercury thermometer.

Outcome measures, data management, and statistical methods. The safety profile was evaluated by documenting the numbers and timing of deaths, admissions, and outpatient attendances in study children. Particular attention was paid to skin reactions and evidence of bone marrow suppression. The proportions of children reporting symptoms absent at baseline but developing during the course of follow-up were compared to assess adverse drug effects. The proportion of children with hematological and biochemical parameters falling outside the normal range at Day 28 was also documented. The efficacy of the different regimens in terms of resolution of symptoms present at baseline was assessed by comparing the total duration of symptoms in the different groups. All comparisons were made relative to SP because this is a standard treatment.

Proportions of children with different levels of parasitological resistance are presented at different times during follow-up. Standard WHO clinical end points were used: early treatment failure (ETF), defined as the development of danger signs in the presence of parasitemia or severe malaria during follow-up on Days 0, 1, 2, or 3, an axillary temperature \( \geq 37.5^\circ\text{C} \) on Day 2 with parasitemia greater than Day 0, axillary temperature \( \geq 37.5^\circ\text{C} \) on Day 3 with any parasitemia or Day 3 parasitemia \( \geq 25\% \) of Day 0 parasitemia; late treatment failure (LTF), defined as the development of danger
signs in the presence of parasitemia or severe malaria during follow-up on Days 4 to Day 28, without previous ETF or a temperature \(\geq 37.5^\circ C\) in the presence of parasitemia during follow-up on Days 4 to Day 28 without previous ETF; and adequate treatment response (ATR), defined as the absence of parasitemia, irrespective of temperature, without previous ETF or LTF, defined at each time point (i.e., 3, 7, 14, 21, and 28 days).

Data were double entered into FoxPro (version 2.6) databases, and discordances were resolved before range and consistency checks were performed. Analysis was performed using Stata (version 5.0). Dichotomous outcomes were compared using Pearson’s chi-square or Fisher’s exact test, as appropriate. Mean values of normally distributed variables were compared using Student’s \(t\) test. This sample size was calculated to estimate failure rates to within 4.3% of a true failure rate of 5% and to within 10% of a true failure rate of 50%.

RESULTS

A total of 361 children were randomized to receive AQ, SP, or AQ+SP (Figure 1). Three children were subsequently found to be younger than 6 months, and four had definitive parasite counts less than 2000/\(\mu L\). Data from these children were not included in the analyses. Baseline characteristics (Table 1) and completeness of follow-up (see Figure 1) were similar in all groups, although children receiving AQ alone tended to be older than those receiving other treatments. Overall, 35 (9.9%) children moved to the family farms during follow-up, 56 (15.8%) failed to attend one or more follow-up visits, and 15 (4.2%) were withdrawn for other reasons, including two children who failed to receive a dose of AQ. There were no significant differences in these reasons between the different groups.

Safety (Table 2). A 1-year old girl who received SP became drowsy 6 h after recruitment and was admitted with an axillary temperature of 38.5°C, Blantyre coma score of 4/5, and mild dehydration. Convulsions shortly after admission were controlled with diazepam, and she received intravenous quinine. Her condition continued to deteriorate, and she died.

![Figure 1](image-url)  
**Figure 1.** Trial profile. Completeness of follow-up: AQ (n = 91) versus SP (n = 79) versus AQ+SP (n = 78); \(\chi^2(2) = 4.3, P = 0.12\). Violate: missed a scheduled contact for reason other than requiring rescue treatment.

<table>
<thead>
<tr>
<th>Variable</th>
<th>AQ (n = 118)</th>
<th>SP (n = 117)</th>
<th>AQ + SP (n = 119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. males (%)</td>
<td>47 (39.8%)</td>
<td>58 (49.6%)</td>
<td>59 (49.6%)</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>2.51 (2.28–2.73)</td>
<td>2.22 (2.01–2.43)</td>
<td>2.11 (1.89–2.33)</td>
</tr>
<tr>
<td>Mean PCV</td>
<td>29.2 (28.1–30.3)</td>
<td>28.6 (27.5–29.7)</td>
<td>29.4 (28.3–30.5)</td>
</tr>
<tr>
<td>No. with PCV &lt; 25% (%)</td>
<td>23 (20.0%)</td>
<td>27 (23.4%)</td>
<td>22 (18.6%)</td>
</tr>
<tr>
<td>Mean temperature (°C)</td>
<td>38.5 (38.3–38.7)</td>
<td>38.7 (38.5–38.9)</td>
<td>38.7 (38.5–38.9)</td>
</tr>
<tr>
<td>Mean weight (kg)</td>
<td>11.1 (10.7–11.6)</td>
<td>10.6 (10.1–11.1)</td>
<td>10.8 (10.1–11.4)</td>
</tr>
<tr>
<td>Parasite density (μL) Geometric mean range</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>43,026</td>
<td>53,955</td>
<td>45,570</td>
</tr>
<tr>
<td>Range</td>
<td>2,542–399,960</td>
<td>2,236–399,960</td>
<td>2,908–399,960</td>
</tr>
<tr>
<td>Reported symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of fever (%)</td>
<td>116/117 (99.2)</td>
<td>115/115 (100)</td>
<td>118/119 (99.2)</td>
</tr>
<tr>
<td>Anorexia (%)</td>
<td>24/117 (20.5)</td>
<td>21/114 (18.4)</td>
<td>19/119 (16.0)</td>
</tr>
<tr>
<td>Vomiting (%)</td>
<td>34/117 (29.1)</td>
<td>32/115 (27.8)</td>
<td>25/119 (21.0)</td>
</tr>
<tr>
<td>Diarrhea (%)</td>
<td>5/117 (4.3)</td>
<td>3/116 (2.6)</td>
<td>3/119 (2.5)</td>
</tr>
<tr>
<td>Difficulty in breathing (%)</td>
<td>17/117 (14.5)</td>
<td>16/115 (13.9)</td>
<td>15/119 (12.6)</td>
</tr>
<tr>
<td>Lethargy (%)</td>
<td>9/117 (7.7)</td>
<td>7/115 (6.1)</td>
<td>9/119 (7.6)</td>
</tr>
<tr>
<td>Rash (%)</td>
<td>4/117 (3.4)</td>
<td>6/115 (5.2)</td>
<td>6/118 (5.1)</td>
</tr>
<tr>
<td>Unable to sit/stand as normal (%)</td>
<td>2/113 (1.8)</td>
<td>4/112 (3.6)</td>
<td>5/116 (4.5)</td>
</tr>
</tbody>
</table>

Figures in brackets are 95% confidence intervals unless otherwise specified. AQ, amodiaquine; SP, sulfadoxine-pyrimethamine; PCV, packed cell volume.
later the same day. The clinical assessment was a progression of her clinical malaria rather than an adverse reaction to SP.

More children were admitted after treatment with AQ alone than children treated with SP or AQ+SP. These admissions tended to be later during the course of follow-up and were mostly (14/16, or 87.5%) due to malaria. Hence, these admissions reflect low efficacy of AQ rather than adverse responses to the treatment. The total number of outpatient attendances was similar in all groups, as was the frequency of any skin rash. The 14 non-scabetic rashes were all asymptomatic macular-papular eruptions noticed incidentally at presentation.

More children receiving SP reported vomiting during the course of follow-up than children receiving AQ alone (see Table 2). There was also a suggestion that children receiving SP alone were more likely to give a history of breathing difficulties during the course of follow-up than children receiving AQ or AQ+SP. There were no significant differences in the proportion of children with abnormal hematological or biochemical test results on Day 28 (see Table 2).

**Clinical efficacy (Table 3).** Clinical outcomes in the three groups were similar in the first 7 days of follow-up. There were no late treatment failures in either the SP or AQ+SP groups. However, there were a considerable number of late treatment failures among children treated with AQ alone, particularly after Day 14 and reaching 27% by the end of follow-up. By Day 21 children treated with AQ+SP were significantly less likely to require rescue medication than those treated with AQ alone, and by Day 28 children treated with SP alone were also significantly less likely to require rescue medication than those in the AQ group. There were no differences in the prevalence of severe anemia (PCV < 25%) at the end of follow-up (AQ 3/80, SP 4/89, AQ+SP 3/94: $\chi^2 = 0.2, P = 0.9$).

Children who received SP alone were significantly more likely to be febrile (axillary temperature $\geq 37.5^\circ$C) at each contact up to and including Day 7 ($P < 0.01$ at each contact; Figure 2). By Day 21 children treated with AQ alone were more likely to be febrile (5/77) than those treated with AQ+SP (0/80; Fisher’s exact test $P = 0.027$). Analysis of the time taken for the other symptoms reported at recruitment (see Table 1) to resolve suggested no other differences between the treatment regimens.

**Parasitological efficacy (Table 4).** None of the 13 ETFs fulfilled criteria for R1–3 resistance and were excluded from the analysis of parasitological efficacy. In the remainder, the rate of parasite clearance was similar in the three groups over the first 3 days (see Figure 3), although children who received SP were significantly more likely to have clearance of parasites ($\chi^2 = 6.85, P = 0.009$) compared to those treated with AQ alone ($\chi^2 = 13.01, P = 0.0003$).
alone were significantly less likely to be parasitemic on Day 2 than children in the other groups ($P < 0.01$). Overall levels of R-I resistance were considerably higher in children treated with AQ than in those receiving the other treatments, although the level of R-I resistance to SP is notable.

Only three children were gametocytemic at recruitment (AQ/H11505 1, AQ+SP/H11505 2). Of the 77 children with a PCV < 25% at recruitment, 24 (31.2%) became gametocytemic compared with 12 (11.1%) of the 108 children with a PCV ≥ 33% at this time ($\chi^2 = 11.4, P = 0.003$). In comparison with children receiving AQ+SP, those treated with SP alone were more likely to be gametocytemic during follow-up, and these gametocytes tended to arise later during the course of follow-up (see Figure 4).

**DISCUSSION**

We have documented the safety and efficacy of AQ, SP, and AQ+SP in the treatment of uncomplicated *P. falciparum* malaria in young children in southern Tanzania. The study was based on the standard WHO in vivo test protocol with follow-up to 28 days. The number of children lost to follow-up and the reason-specific rates were comparable between the groups. Treatment with AQ alone produced good parasitological (78%) and clinical (94%) responses in the first 7 days and was associated with a shorter fever clearance time than SP alone. However, by the end of follow-up, AQ-only recipients were subject to a markedly higher level of R-I type resistance than children in the other treatment groups and were at least five times more likely to require rescue medication. These findings are striking in an area where AQ has not previously been readily available but where a 7-day parasitological cure rate of only 35% was documented for CQ.20 Concerns over cross-resistance between CQ and AQ seem to be legitimate, although the results of molecular studies will be needed to distinguish recrudescences from reinfections. Interestingly, anecdotal reports during the trial suggested that the faster symptom resolution associated with AQ gave an impression of it being a “stronger” drug, and mothers specifically requested retreatment with AQ. Such perceptions could be an important factor in the successful implementation of treatment policies.23

The only death in the study cohort was a child who received SP alone and was due to progression of the malarial disease. It is not possible to say whether treatment with a faster-acting antimalarial would have altered the outcome for this child. Although the overall clinical cure rate for SP was good (94%), it was associated with more vomiting than AQ alone and its slower onset of action was reflected by a prolonged

![Figure 2](image2.png)

**Figure 2.** Fever clearance time.

![Figure 3](image3.png)

**Figure 3.** Resolution of parasitemia over Days 1–3. Day 2: SP 29.9% (32/107) versus AQ 51.4% (56/109) $\chi^2 = 10.3, P = 0.001$.

![Figure 4](image4.png)

**Figure 4.** Gametocyte prevalence during follow-up. AQ versus SP: $\chi^2 = 2.9, P = 0.09$. SP versus SP+AQ: $\chi^2 = 10.6, P = 0.001$.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sensitive</th>
<th>R-I</th>
<th>R-II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AQ (n = 103)</td>
<td>80 (77.7%)</td>
<td>6 (5.8%)</td>
<td>17 (16.5%)</td>
</tr>
<tr>
<td>SP (n = 99)</td>
<td>74 (74.8%)</td>
<td>13 (13.1%)</td>
<td>12 (12.1%)</td>
</tr>
<tr>
<td>AQ + SP (n = 102)</td>
<td>84 (82.4%)</td>
<td>9 (8.8%)</td>
<td>9 (8.8%)</td>
</tr>
<tr>
<td>Day 14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AQ (n = 97)</td>
<td>66 (68.0%)</td>
<td>14 (14.4%)</td>
<td>17 (17.5%)</td>
</tr>
<tr>
<td>SP (n = 90)</td>
<td>62 (68.9%)</td>
<td>16 (17.8%)</td>
<td>12 (13.3%)</td>
</tr>
<tr>
<td>AQ + SP (n = 89)</td>
<td>68 (76.4%)</td>
<td>12 (13.5%)</td>
<td>9 (10.1%)</td>
</tr>
<tr>
<td>Day 21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AQ (n = 95)</td>
<td>46 (48.4%)</td>
<td>32 (33.7%)</td>
<td>17 (17.9%)</td>
</tr>
<tr>
<td>SP (n = 84)</td>
<td>54 (64.3%)</td>
<td>18 (21.4%)</td>
<td>12 (14.3%)</td>
</tr>
<tr>
<td>AQ + SP (n = 84)</td>
<td>60 (71.4%)</td>
<td>15 (17.9%)</td>
<td>9 (10.7%)</td>
</tr>
<tr>
<td>Day 28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AQ (n = 97)</td>
<td>36 (37.1%)</td>
<td>44 (45.4%)</td>
<td>17 (17.5%)</td>
</tr>
<tr>
<td>SP (n = 82)</td>
<td>49 (59.8%)</td>
<td>21 (25.6%)</td>
<td>12 (14.6%)</td>
</tr>
<tr>
<td>AQ + SP (n = 81)</td>
<td>52 (64.2%)</td>
<td>20 (24.7%)</td>
<td>9 (11.1%)</td>
</tr>
</tbody>
</table>

AQ, amodiaquine; SP, sulfadoxine-pyrimethamine.

* $P = 0.012$.
† $P = 0.038$. 

* $P = 0.002$. 
† $P = 0.038$. 

**Table 4**

Proportion of parasitological failures at days 7, 14, 21, and 28
fever clearance time. The parasitological profile after treat-
ment with SP is also cause for concern. An R-I resistance level
of 26% and an R-II level of 15% are bad news at a time when
SP drug pressure is likely to increase dramatically as a result of
the change in the national malaria treatment policy. Based
on experience from elsewhere,10–12 it is likely that clinical
resistance to SP will develop rapidly. This is of particular
concern because several studies of CT include SP as a con-
stituent drug; consequently, it may be that by the time SP-
containing CT regimens are available, their effectiveness will
have been undermined by increased levels of SP resistance.
More importantly, approaches to malaria control that require
long half-life drugs, such as intermittent treatment in in-
fants,24 may also be compromised.

The coadministration of AQ+SP appeared to combine the
rapid symptomatic relief associated with AQ with the greater
longer-term efficacy of SP. However, it is not clear whether
regular use of antipyretics during the first 2–3 days after pre-
sentation would be as effective in resolving symptoms as
treatment with amodiaquine. The clinical and parasitological
profiles after treatment with AQ+SP were similar to those
after treatment with SP alone.

Assessment of safety depended on data from outpatient
attendances, admissions to hospital, systematically collected
data on reported symptoms, and the results of hematological
and biochemical testing. More weight should be given to the
admission and outpatient department visit data than the re-
ported symptom data because the latter was more often un-
available for children who were admitted than for children
who were not, and these children were clearly more likely to
be symptomatic. The data presented are thus likely to under-
estimate the prevalence of symptoms in children receiving
only AQ. The higher rate of admission in the AQ-only group
reflected its antimalarial efficacy rather than adverse reac-
tions to the drug per se. Similarly, the increased tendency to
give a history of breathing difficulties in children who re-
ceived SP is likely to be a reflection of its slower onset of
action compared with AQ. Hence, no drug-related severe ad-
verse reactions were documented in any treatment group. It
was particularly reassuring that there was no suggestion of
increased frequencies of rash or bone marrow suppression in
children receiving AQ+SP.

Children who were anemic at baseline were more likely to
develop gametocytemia, in keeping with the findings from
another setting25 and presumably reflecting either a survival
strategy of *P. falciparum* or a longer period of *P. falciparum*
infection. Assuming the infectivity of gametocytes appearing
after treatment with SP is 40% and after AQ it is 60%,26 the
data suggest that treatment of 100 individuals with SP would
result in 12 infectious individuals compared with 13 with AQ
and 5 with AQ/SP. This extrapolation merits further investiga-
tion through mosquito-feeding assays, although its rel-
ance to the intensity of transmission in an area would de-
pend on the malaria treatment rates in the group of individu-
als constituting the main reservoir of infection.

The evolution and dynamics of resistance to antimalarials
require new strategic thinking. Monotherapy with SP may not
be an optimal choice for first-line treatment of malaria in
endemic settings: the long half-life will tend to lead to the
development of resistance more rapidly than shorter half-life
drugs, reducing the effective life span of treatment policies
depending on it. However, as resistance to chloroquine in-
creases, National Malaria Control Programs are required to im-
plement policies with cheap, available, and effective anti-
malarial drugs; SP is one of a very few alternatives. We have
shown that significant levels of resistance to AQ exist in an
area historically devoid of AQ but with high levels of CQ
resistance, and that there are considerable levels of parasito-
logical resistance to SP. The combination of AQ+SP ap-
ppeared to be safe and combined the benefits of rapid symp-
tom relief with an improved parasitological response. An in-
terim policy in which AQ+SP was recommended would
combine the treatment benefits of the combination and might
reduce the rate at which SP resistance develops. Both AQ and
SP are readily available and thus not subject to the likely time
constraints of implementing a policy where SP is coadminis-
tered with artemether. Furthermore, these drugs are cheap; a
treatment course of AQ costs TSh 23 (U.S. $0.01) and a
course of SP about TSh 11.27,28 Finally, by reducing the rate
at which resistance develops to SP, coadministration of
AQ+SP may protect SP for use as intermittent treatment and
buy time while alternative, preferably short half-life, antima-
larial treatments are evaluated for inclusion alongside arte-
mother in malaria CT regimens.

Acknowledgments: We thank the mothers and the MCH clinic staff
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