Azithromycin plus Artesunate versus Artemether-Lumefantrine for Treatment of Uncomplicated Malaria in Tanzanian Children: A Randomized, Controlled Trial

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Background. Acute febrile illness is the most common cause of outpatient attendance and mortality for children in Africa. Malaria and bacterial disease are difficult to differentiate with limited diagnostic facilities. Combinations of antibiotics and antimalarials are potentially attractive for treatment of the syndrome. Azithromycin plus artemesunate (AT+AS) is an effective antimalarial combination for adults in Asia.

Methods. We performed an individually randomized, open-label trial of AZ+AS versus artemether-lumefantrine (AL) involving children (age, 6–59 months) with uncomplicated malaria in Muheza, Tanzania. The primary outcome was parasitological failure by day 28. Parasitological failure by day 42 and failure corrected for reinfection were major secondary outcomes.

Results. Of 2497 children screened, 261 were eligible; 129 were randomized to the AZ+AS arm, and 132 were randomized to the AL arm; 92% and 91%, respectively, underwent follow-up to 28 days. Planned interim analysis was performed after 200 patients reached day 28 follow-up and led the Data and Safety Monitoring Board to halt further recruitment. All children had a complete initial response to treatment, but 69 (58%) of 119 children in the AZ+AS arm and 24 (20%) of 120 in the AL arm had asexual parasites at or by day 28 (adjusted odds ratio for failure with AZ+AS treatment, 6.1; 95% confidence interval, 3.3–11.4; P < .001). When analysis was restricted to children with recrudescence, the parasitological failure rate was 32% in the AZ+AS arm and 9% in the AL arm. This difference was maintained at day 42.

Conclusions. This trial does not support the use of AZ+AS as treatment for malaria or acute febrile illness in children in areas of Africa with high levels of existing antimalarial drug resistance.

Clinical trials registration. ClinicalTrials.gov NCT00694694.

In Africa, differentiating between malaria and other causes of acute febrile illness in children is often difficult. Clinical algorithms have not been successful [1, 2]. Both malaria and bacterial illness contribute substantially to mortality [3, 4]. The relative contribution of malaria varies across the continent and may be decreasing in some areas, particularly East Africa [5]. Simultaneously, drug resistance has emerged. Artemisinin combination therapy formulations provide excellent anti-malaria treatment, provided that both drugs remain effective. In areas where the companion drug to the artemisinin is failing, the combination begins to fail as well, and the mismatch between half-lives of artemisinins and current companion drugs means development of resistance is inevitable [6–8]. A pipeline of possible alternative combinations must be maintained.

There are 2 possible approaches to improving management of acute febrile illness in peripheral settings. One is to improve targeted use of antimalarials and antibiotics using new diagnostic tests, but early experiences with rapid diagnostic tests have often proven to be disappointing [9]. An alternative is to use syndromic treatment, which, for acute febrile illness, in-
volves combining antimalarials and an antibiotic. The combination of azithromycin plus artesunate (AZ+AS) is potentially attractive. Azithromycin is an effective antibiotic with a course of treatment similar to that of artesunate. It is active against a wide variety of organisms, including the principal causes of bacterial infection—related mortality in children in Africa, Streptococcus pneumoniae and salmonellae [10–13].

Azithromycin has significant antimalarial activity in vitro [14]. AZ+AS has proven to be an effective antimalarial treatment in trials of adults in Asia [15–17]; in pregnant women in Africa, it appears to be promising when administered with sulfadoxine-pyrimethamine [18]; and when given as monotherapy, azithromycin has proven to be an effective prophylactic against malaria in Africa [19]. Artesunate and azithromycin used independently have been found to be safe and well tolerated in children in Africa [20]. AZ+AS is, therefore, a potentially useful for syndromic treatment of febrile children. Until recently, cost has been a significant drawback, but with azithromycin going off-patent, it is likely that costs will decrease.

The AZ+AS combination could be considered either as an alternative treatment of malaria or as potential syndromic treatment for children with acute febrile illness in Africa, where diagnostic facilities are limited. However, to our knowledge, there are no data from Africa on whether it is an effective antimalarial. Therefore, we performed a trial of AZ+AS versus artemether-lumefantrine (AL), the current standard treatment in Muheza, Tanzania, where the rate of antimalarial drug resistance is among the highest reported in Africa [21]. If trials provide evidence of effectiveness of an antimalarial in Muheza, the antimalarial agents have a high chance of being effective elsewhere in Africa.

**METHODS**

A randomized, open-label trial of children with nonsevere falciparum malaria was conducted in the reproductive and child health clinic of Muheza Designated District Hospital (Muheza, Tanzania). The trial was preceded by a 3-month pilot program that included discussion with village communities and testing consent procedures.

The study was explained verbally to mothers or guardians of children while they waited to be seen in the reproductive and child health clinic. All children aged 6 months to 59 months were then screened. If children presented with a fever (axillary temperature, >37.5°C) or history of fever within the previous 48 h, parents or guardians were invited to allow the children to undergo a rapid diagnostic test for malaria (Parahit) [22]. Children whose parents or guardians reported symptoms suggestive of severe febrile disease (based on modified World Health Organization criteria for severe malaria) or who were unable to tolerate drugs orally were triaged for rapid assessment for admission to a pediatric ward and were not included in the study. Those with a negative rapid diagnostic test result were referred to hospital clinic staff and were treated according to hospital protocols. Children with a positive rapid diagnostic test result were seen by study doctors, and parents or guardians were asked to provide written informed consent to be included in the trial; if mothers or guardians were unable to read, witnessed consent was provided. A standardized history and examination were undertaken. Blood samples were obtained for a research malaria slide, determination of hemoglobin concentration, and filter paper for genotyping of malaria.

The inclusion criteria for entering the trial were as follows: axillary temperature, >37.5°C or a history of fever in the previous 48 h; Plasmodium falciparum asexual parasite densities >2000 and <200,000 parasites/µL of blood (50–5000 parasites/200 white blood cells); hemoglobin concentration, >7 g/dL; living in a study catchment area; and willingness to attend study follow-up visits and to provide written informed consent. Exclusion criteria were as follows: symptoms or signs of severe malaria, inability to feed or to take drugs by the oral route, an obvious alternative cause of fever, use of an effective antimalarial drug in the previous 7 days, mixed plasmodial infection, or known hypersensitivity to a study drug. If children met inclusion criteria, they were randomized to receive either AL at a dosage of 1 tablet (for those with a body weight <15 kg) or 2 tablets (for those with a body weight >15 kg) twice daily, which is Tanzanian national policy, or to receive AZ+AS. Azithromycin was prescribed at a dosage of 20 mg/kg body weight once daily, and artesunate was prescribed at dosage of 4 mg/kg body weight once daily. This dosage of azithromycin was chosen because it would have significant bacterial activity against common pathogens found in this age group and matches the activity of artesunate.

Randomization occurred in blocks of random sizes using Stata software, version 8 (Stata Corp). Slips with study allocation were placed in sealed opaque envelopes and were opened in front of parents or guardians. Opening the envelope defined entering the trial, and analysis was performed on the basis of randomized allocation. A random sample of the trial AZ+AS was tested for quality of drug using liquid chromatography/mass spectrometry (LC/MS) and was found to be of expected quality.

Doses of AZ+AS were given once daily for 3 days under direct observation of a study nurse. Children randomized to receive AL had their morning dose administered under direct observation, and their evening dose was given by mothers at home. If children vomited within half an hour after receipt of the dose, they were redosed with the same drug. If they vomited again within half an hour, they were withdrawn from the study and admitted for parenteral treatment with quinine.
Figure 1. Flow chart for the trial. AL, artemether-lumefantrine; AZ+AS, azithromycin plus artesunate; Hb, hemoglobin; Pf, Plasmodium falciparum; RDT, rapid diagnostic test.

After the first 3 days of drug administration, children were seen on days 7, 14, 28, and 42 following enrolment (day 0), and mothers were asked to bring children back if they were concerned on any day. Treatment was free, and transport costs were met. If children did not attend the scheduled follow-up visits, village health workers went to their homes to find them or recorded whether the children had moved out of the study area. At all visits, a blood specimen was obtained for a slide for malaria, filter-paper for genotyping of parasites, and a hemoglobin test. In addition, on days 0 and 14, blood specimens were obtained for a complete blood cell count and liver function tests. Mothers or guardians were asked about possible adverse effects, which were classified according to World Health Organization criteria. In the event of treatment failure, oral quinine (10 mg/kg body weight per day in 3 doses) was given over 7 days as rescue treatment.

Slides for malaria were stained with Giemsa and were analyzed by 2 readers, and those with discordant or uncertain results (ie, discordance between positive vs negative results, a >2-fold difference in parasite density, or parasite load <10 asexual parasites/200 white blood cells) resolved by a third reader. Parasite density was calculated from thick films, assuming a white blood cell count of 8000 cells/µL. Hemoglobin concentration was measured by HemoCue 201 (HemoCue), and complete blood cell counts were determined with an automated counter (SFRI Sari). Liver enzyme levels were determined using Reflotron Plus (Roche). To differentiate recrudescence from reinfection, the polymorphic repetitive regions were amplified.
by nested polymerase chain reaction for block 3 of msp2 [23].
With use of the template of the first polymerase chain reaction,
allele-specific primer pairs were used to test for the presence
of the allelic variants from FC27 and 3D7/IC families of the
msp2.

The primary outcome of the trial was parasitological failure,
which was defined as the presence of asexual malaria parasites
after treatment (after day 3) on or before day 28, irrespective
of symptoms. Secondary outcomes were clinical failure by day
28 (parasitological failure, with symptoms compatible with ma-
laria); parasitological and clinical failure by day 42; parasito-
logical failure by days 28 and 42 corrected for reinfection, as de-
termined by genotyping; mean hemoglobin concentration; ear-
ly treatment failure over time were calculated.

The study sample size was calculated using and
p
b
0.8
to detect a difference between parasitological failure
at day 28 of 97% to 90% (222 in each arm) or of 90% to 80%
(219 in each arm). Allowing for a 10% dropout rate, the target
sample size was 250 children in each arm. A predetermined
mid-point analysis of the primary outcome was undertaken
when 100 patients had been randomized to each arm and ob-
served to day 28, with a decision by the independent Data and
Safety Monitoring Board to continue the trial, suspend recruit-
ment, or stop it. No other interim analyses were planned. Analysis
involved the initial study allocation, irrespective of subsequent
treatment. Data were double-entered into Access (Microsoft) and
were analyzed in Stata software, version 10 (Stata Corp). The
analytical plan was predefined. Odds ratios for the primary out-
come and major secondary outcomes were calculated, both un-
adjusted and with adjustment for predefined potential confound-
ing factors, using logistic regression; the predefined factors were
age, sex, initial parasite count, initial hemoglobin concentration,
and number of years of the mother’s education (as a proxy for
socioeconomic status). Kaplan-Meier curves for parasitological
failure over time were calculated.

The trial was approved by the ethics committees of the Na-
tional Institute for Medical Research (Dar-es-Salaam, Tanza-
nia) and the London School of Hygiene & Tropical Medicine
(United Kingdom). The trial was prospectively registered at
ClinicalTrials.gov NCT00694694.

RESULTS
The study ran from June 2008 through December 2008. Of
2497 children (age, 6–59 months) screened, 261 were eligible
for the trial and were randomized before the study was stopped
by the Data and Safety Monitoring Board (Figure 1). There
were 129 children randomized to the AZ+AS arm and 132 to
the AL arm, with follow-up durations up to 28 days (the pri-
mary end point) for 116 (90%) and 120 (91%), respectively.
Baseline characteristics of the 2 arms are shown in Table 1.

A planned interim analysis was performed after 100 patients
had been randomized to each arm and reached day 28 follow-
up. On the basis of this analysis, the Data and Safety Monitoring
Board decided to halt further recruitment to the trial, pending
all patients already recruited being followed up. AL is the stan-
dard of care, and at the time of the interim analysis, the AZ+AS
combination was less effective than conventional treatment, and
the chances of it returning to a point at which it would have
a realistic chance of being significantly better than AL (statistical
uncertainty) seemed low. Because the trial did not move close
to statistical uncertainty when all enrolled patients reached their
primary end point, it was closed. The data presented are, there-
fore, for the trial at the point that it closed.

All children had a complete initial response to treatment,
with no clinical failures before day 7. Two children in each arm
had parasites without symptoms on day 7 and were treated.
Clinical and parasitological failure rates are shown in Table 2.
For the primary end point of parasitological failure rate, 69
(58%) of 119 children in the AZ+AS arm and 24 (20%) of 120
in the AL arm had asexual parasites at or by day 28. The
unadjusted odds ratio for failure with AZ+AS versus AL was
5.52 (95% confidence interval, 3.1–9.8; P < .001), and the odds
ratio was 6.1 (95% confidence interval, 3.3–11.4; P < .001) with
adjustment for potential confounding factors. When restricted
to those with true recrudescence (excluding cases of reinfec-
tion), the parasitological failure rate was 32% in the AZ+AS

![Table 1. Baseline Characteristics of Study Participants](#)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AZ+AS arm</th>
<th>AL arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median months (IQR)</td>
<td>30 (18–42)</td>
<td>27 (16–42)</td>
</tr>
<tr>
<td>Proportion of female children (%)</td>
<td>66/132 (50)</td>
<td>60/132 (45)</td>
</tr>
<tr>
<td>Temperature, mean °C ± SD</td>
<td>38.0 ± 1.2</td>
<td>38.0 ± 1.3</td>
</tr>
<tr>
<td>Median parasite count per 200 white cells (IQR)</td>
<td>524 (262–1321)</td>
<td>607 (337–1180)</td>
</tr>
<tr>
<td>Hemoglobin concentration, median g/dL (IQR)</td>
<td>9.1 (8.3–10.2)</td>
<td>9.1 (8.2–10.1)</td>
</tr>
<tr>
<td>Granulocyte count, median k/μL (IQR)</td>
<td>3.85 (2.4–5.6)</td>
<td>4 (2.6–6.1)</td>
</tr>
<tr>
<td>Bilirubin level, mean mg/dL ± SD</td>
<td>1.1 ± 0.35</td>
<td>1.1 ± 0.47</td>
</tr>
</tbody>
</table>

**NOTE.** AL, artemether-lumefantrine; AZ+AS, azithromycin plus artesunate; IQR, interquartile range; SD, standard deviation.
Table 2. Clinical and Parasitological Outcomes

<table>
<thead>
<tr>
<th>Period, outcome</th>
<th>AZ+AS arm</th>
<th>AL arm</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>By day 14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical failure</td>
<td>1/120 (0.08)</td>
<td>0/121 (0)</td>
<td>.5a</td>
</tr>
<tr>
<td>Parasitological failureb</td>
<td>9/120 (7.5)</td>
<td>5/121 (4)</td>
<td>.26</td>
</tr>
<tr>
<td>Hemoglobin concentration, mean g/dL</td>
<td>10.4</td>
<td>10.2</td>
<td>.8</td>
</tr>
<tr>
<td>By day 28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical failure</td>
<td>36/116 (31)</td>
<td>8/121 (6.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Parasitological failureb</td>
<td>69/119 (58)</td>
<td>24/120 (20)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Failure including SAEs or admission to hospital for parental treatment</td>
<td>70/120 (58.3)</td>
<td>33/129 (25.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Parasitological failure due to recrudescencec</td>
<td>34/63 (54)</td>
<td>9/21 (43)</td>
<td></td>
</tr>
<tr>
<td>Parasitological failure rate after correction of reinfection, %</td>
<td>32</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>By day 42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical failure</td>
<td>38/115 (33)</td>
<td>15/119 (13)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Parasitological failureb</td>
<td>76/115 (66.1)</td>
<td>41/119 (34.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Parasitological failure due to recrudescencec</td>
<td>37/71 (52)</td>
<td>13/37 (35)</td>
<td></td>
</tr>
<tr>
<td>Parasitological failure rate after correction of reinfection, %</td>
<td>34</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Data are proportion of children (%), unless otherwise indicated. AL, artemether-lumefantrine; AZ+AS, azithromycin plus artesunate; SAE, serious adverse event.

a Determined by the Fisher exact test.
b Parasitological failure includes clinical failure.
c Excluding cases in which polymerase chain reaction results were not available.

arm and 9% in the AL arm (Table 2). The time to presentation with parasitological failure is shown in Figure 2.

Both drug combinations were well tolerated, and no severe adverse events or deaths were recorded. Nonsevere adverse events and hematological and biochemical abnormalities that occurred during the follow-up period are outlined in Table 3. Overall, 39 children in the AZ+AS arm and 33 in the AL arm had clinical adverse events; with the exception of gastrointestinal complaints, none were considered likely to have been due directly to the drugs, and most were probably due to intercurrent infections.

**DISCUSSION**

The combination of AZ+AS is potentially very attractive for the syndromic management of fever in peripheral settings where there are limited facilities for parasitological diagnosis, but only if the combination is an effective antimalarial. In this study, in an area with some of the highest antimalarial drug resistance recorded in Africa, the combination of AZ+AS was not as effective as AL, the current first-line treatment in Tanzania and most of East Africa [24]. The 58% parasitological failure rate by day 28 is sufficiently high that, in this region at least, it clearly would not be an appropriate first-line treatment either for malaria or for syndromic treatment of fever at this dosing regimen.

Data from southeast Asia have demonstrated that this combination can be effective against malaria [15, 16]. Studies of azithromycin from Africa have demonstrated that it is an effective antimalarial prophylactic drug [19, 20]. The relative lack of efficacy compared with AL is therefore disappointing, but in this setting, it is clear-cut. This does not exclude the possibility that AZ+AS might be effective in areas where malaria drug resistance has historically been much lower, such as in West Africa, or in different dosing regimens. This trial cannot test the reasons for this difference from southeast Asia, but they include the fact that local parasites are exposed to macrolide antibiotics (including azithromycin, used as mass treatment in trachoma control) and have developed resistance. An alternative is that the effective dose of azithromycin absorbed in these often malnourished children is not sufficient to achieve the levels found in adults in Asia.

The Kaplan-Meier plot suggests treatment effects seem to separate from day 21. This may well relate to the different pharmacokinetic and pharmacodynamic properties of azithromycin and lumefantrine. The half-life of lumefantrine is longer (4–10 days) than that of azithromycin (~3 days), although this complicated by the prolonged elimination of azithromycin due to its concentration in tissues. Azithromycin is also intrinsically less potent than lumefantrine as an antimalarial, although in Asia, this difference did not seem to lead to reduced efficacy in vivo.

The combination of AZ+AS was well tolerated. It had broadly comparable rates of minor adverse events to AL [25] and led to no serious adverse events. There is good evidence of the safety of azithromycin and artesunate used independently, and this provides useful evidence that the combination does not cause additional problems.

Investigators went through a number of steps to ensure that this lack of efficacy was not due to external factors. Both the
azithromycin and the artesunate were tested and found to be of high quality and to contain the doses expected. Dosing schedules were assessed carefully, and there is no evidence of underdosing either overall or for individual cases. Dose administrations were all observed by study nurses, with administration being repeated when children vomited. Therefore, it seems unlikely that the results were either because the children did not receive any drug, were underdosed, or received a drug of low quality. Therefore, we think that the results demonstrate the true efficacy of the combination at this dose in this setting.

The concept of syndromic treatment remains controversial, with legitimate concerns that, if it were deployed widely, it could lead to the spread of antibiotic resistance [26]. On the other hand, with malaria incidence decreasing, the relative importance of nonmalarial, potentially treatable causes of severe febrile illness is increasing, and this, in practice, means bacterial disease. The prevalence of bacteremia among febrile children in outpatient settings in Africa is lower than that among severely ill children, but it is still significant [27], and once this progresses to severe febrile illness, the mortality rate is higher than for malaria [28]. Bacteremic children present late and moribund, leaving too short a window for effective antibacterial treatment; early treatment is therefore desirable. In the absence of clear evidence that the diagnostic tests for malaria can effectively guide treatment in peripheral settings, syndromic treatment will remain one of the potential solutions to the current problem of the misdiagnosis of acute febrile illness.

In this context, antimalarial and antibiotic combinations are potentially attractive, at least in some settings. This study does not support the use of AZ+AS as a syndromic combination alone. Trials are ongoing (not at this center) of the combination of azithromycin plus chloroquine, which appear to be synergistic in vitro [29]. Other antibiotic-antimalarial combinations need to be investigated.

### Table 3. Adverse Events and Laboratory Abnormalities

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>AZ+AS arm</th>
<th>AL arm</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>9</td>
<td>7</td>
<td>.6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
<td>2</td>
<td>.02</td>
</tr>
<tr>
<td>Dermatological (including itching)</td>
<td>7</td>
<td>4</td>
<td>.35</td>
</tr>
<tr>
<td>Respiratory (including respiratory infection)</td>
<td>15</td>
<td>21</td>
<td>.3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
<td>1</td>
<td>.62&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Convulsions</td>
<td>1</td>
<td>3</td>
<td>.62&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>By day 14, proportion of children (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin concentration, &lt;7 g/dL</td>
<td>0/120</td>
<td>1/121</td>
<td>.99&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Platelet count, &lt;10&lt;sup&gt;10&lt;/sup&gt; platelets/L&lt;sup&gt;b&lt;/sup&gt;</td>
<td>11/111</td>
<td>6/107</td>
<td>.2</td>
</tr>
<tr>
<td>Neutrophil count, &lt;1&lt;sup&gt;10&lt;/sup&gt; cells/L&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7/113</td>
<td>15/109</td>
<td>.06</td>
</tr>
</tbody>
</table>

**NOTE.** AL, artemether-lumefantrine; AZ+AS, azithromycin plus artesunate.

<sup>a</sup> Determined by the Fisher exact test.

<sup>b</sup> The automated counter was not working for some of the study period.
We report a trial of AZ+AS in an area of high drug resistance and demonstrated that, in this setting and in contrast to encouraging reports in adults in Asia, the efficacy against malaria was too low to be appropriate for consideration as a potential antimalarial agent or for potential syndromic treatment of febrile illness in children where malaria is common and where diagnostic facilities are limited.

Acknowledgments

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