Amodiaquine alone, amodiaquine+sulfadoxine-pyrimethamine, amodiaquine+artesunate, and artemether-lumefantrine for outpatient treatment of malaria in Tanzanian children: a four-arm randomised effectiveness trial

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Summary

Background Many countries in Africa are considering a change to combination treatment for falciparum malaria because of the increase in drug resistance. However, there are few effectiveness data for these combinations. Our aim was to study the effectiveness of three drug combinations that have proven efficacious in east Africa compared with amodiaquine monotherapy.

Methods We undertook a randomised trial of antimalarial drug combinations for children (aged 4–59 months) with uncomplicated malaria in Muheza, Tanzania, an area with a high prevalence of resistance to sulfadoxine-pyrimethamine and chloroquine. Children were randomly allocated 3 days of amodiaquine (n=270), amodiaquine +sulfadoxine-pyrimethamine (n=507), or amodiaquine+artesunate (n=515), or a 3-day six-dose regimen of artemether-lumefantrine (n=519). Drugs were taken orally, at home, unobserved by medical staff. The primary endpoint was parasitological failure by day 14 assessed blind to treatment allocation. Secondary endpoints included day 28 follow-up and gametocyte carriage. Analysis was by intention to treat.

Findings Of 3158 children screened, 1811 were randomly assigned treatment and 1717 (95%) reached the 14-day follow-up. The amodiaquine group was stopped early by the data and safety monitoring board. By day 14, the parasitological failure rates were 103 of 248 (42%) for amodiaquine, 97 of 476 (20%) for amodiaquine+sulfadoxine-pyrimethamine, 54 of 491 (11%) for amodiaquine+artesunate, and seven of 502 (1%) for artemether-lumefantrine. By day 28, the parasitological failure rates were 182 of 239 (76%), 282 of 476 (61%), 193 of 472 (40%), and 103 of 485 (21%), respectively. The difference between individual treatment groups and the next best treatment combination was significant ($p<0·001$) in every case. Recrudescence rates by day 28, after correction by genotyping, were 48·4%, 34·5%, 11·2%, and 2·8%, respectively.

Interpretation The study shows how few the options are for treating malaria where there is already a high level of resistance to sulfadoxine-pyrimethamine and amodiaquine. The WHO-packaged six-dose regimen of artemether-lumefantrine is effective taken unsupervised, although cost is a major limitation.

Introduction

Resistance of *Plasmodium falciparum* to chloroquine in nearly all malaria endemic areas and the rapid spread of resistance to sulfadoxine-pyrimethamine has led to strong calls for the introduction of combination treatments.[1,2] In 2001, a WHO expert panel recommended use of artemisinin-based combinations as first-line treatment for uncomplicated falciparum malaria;[3] once governments had to switch from sulfadoxine-pyrimethamine or chloroquine monotherapy they were advised to use one of three artemisinin-based combinations (sulfadoxine-pyrimethamine+artesunate, amodiaquine+artesunate, artemether-lumefantrine) or a substantially cheaper non-artemisinin-based combination (amodiaquine+sulfadoxine-pyrimethamine).

Subsequent trials in various parts of Africa have shown the safety and efficacy of amodiaquine+artesunate[4] and of amodiaquine+sulfadoxine-pyrimethamine,[5] even in areas of moderate resistance to amodiaquine and sulfadoxine-pyrimethamine. Although artemether-lumefantrine is recommended as first-line treatment for uncomplicated malaria in several countries, there is little information about the efficacy of the six-dose artemether-lumefantrine regimen in African children and the four-dose regimen has not proven efficacious.[6] Sulfadoxine-pyrimethamine+artesunate, chloroquine+artesunate, and chloroquine+sulfadoxine-pyrimethamine were not efficacious in areas with substantial levels of resistance to sulfadoxine-pyrimethamine and chloroquine.[5,7,8] In addition to safety and efficacy data, information about effectiveness is essential for the formulation of antimalarial drug policy. Efficacious drugs taken under observation in experimental conditions can be much less effective under real-life conditions, especially when complex dosing schedules are needed.[9] Therefore, we studied the

effectiveness of three drug combinations that have proven efficacy in east Africa, in a clinic setting in which drugs are dispensed and taken at home unobserved by medical staff. The trial was undertaken in Muheza district, north-eastern Tanzania, which has among the highest recorded levels of resistance to sulfadoxine-pyrimethamine and chloroquine in Africa.[10,11] Data from areas with high drug resistance will provide information that will be helpful in guiding treatment policy for areas that have rising drug resistance that has not yet reached a very high level.

Methods

Patients

We recruited patients with non-severe falciparum malaria, proven by blood film, from the Maternal and Child Health Clinic of Teule Hospital, Muheza, Tanzania. Nurses interviewed the parents or guardians of all febrile children who attended the clinic, and those with a recent (previous 12 h) history of fever were referred to the study team. All referred patients were interviewed again and clinically examined to exclude concomitant infections. Duplicate thick and thin blood smears were obtained and examined for the presence of malaria parasites. Children were eligible for inclusion in the trial if they were aged 4–59 months, had symptoms suggestive of clinical malaria and *P falciparum* parasitaemia of at least 2000 parasites per μL of blood, were able to take study drugs by the oral route, were able to attend clinic on stipulated days for follow-up, and if a parent or guardian provided written informed consent for the child to participate in the study. Exclusion criteria consisted of: presence of severe and complicated malaria as defined by WHO;[12] a mixed plasmodial infection, or concomitant disease masking assessment of the response to antimalarial treatment; intake of antimalarials other than chloroquine within the past 7 days; and known hypersensitivity to any of the study drugs.

Once consent had been obtained children were photographed with their parents or guardians and randomly assigned to one of the four study regimens. Randomisation was done by computer (Stata version 6), in London, with blocks of variable sizes. Treatment allocations were put into opaque, sealed and countersigned, sequentially numbered envelopes. In accordance with local practice, parents or guardians were allowed to pick one envelope from within a block. Opening the envelope defined entry to the trial; subsequent intention-to-treat analysis was undertaken on the basis of treatment allocation. Treatment was then dispensed in accordance with the treatment allocation in the envelope. Clinical staff gave basic verbal instructions on dose and frequency, similar to those that would be given at a good outpatients department. Drugs were given to the children by parents or guardians at home unsupervised by medical staff.

Procedures

We undertook an initial pilot study between July, 2002, and September, 2002, to establish the best monotherapy for inclusion in the main trial. From the start of the trial to now, sulfadoxine-pyrimethamine is the recommended first-line treatment and amodiaquine the second-line treatment for uncomplicated malaria in Tanzania. Children were therefore randomised to receive sulfadoxine-pyrimethamine (1·25 mg/kg pyrimethamine and 25 mg/kg sulfadoxine), given as a single dose according to a WHO dispensing chart adopted by the national Government (WHO/MAL/96/1077), or amodiaquine (25 mg/kg) given over 3 days (10 mg/kg on each of the first 2 days and 5 mg/kg on the third day). We chose amodiaquine as the monotherapy group for the main trial on the basis of the results from the pilot study.

The main trial was undertaken between September, 2002, and October, 2004. Patients in the main trial were randomised to receive amodiaquine (Sanofi), amodiaquine+sulfadoxine-pyrimethamine (Roche), artemether-lumefantrine (co-artemether, Novartis), or amodiaquine+artesunate (Sanofi; 4 mg/kg artesunate given for 3 days). A 3-day six-dose regimen of artemether-lumefantrine was used. Children who weighed 10–15 kg received one tablet (20 mg artemether and 120 mg lumefantrine) per dose, those 15–25 kg received two tablets per dose, those 25–35 kg received three tablets per dose, and those weighing more than 35 kg received four tablets per dose. Amodiaquine+artesunate is not coformulated and current blister packs do not have dosing appropriate for children younger than 5 years, so pills had to be taken out of the blisters and given individually.

Parents or guardians were asked to bring their children back to clinic on days 14 and 28 after the start of treatment or on any other day if the child was unwell. During follow-up, the identity of the child was confirmed by checking against the photographs, then two duplicate blood smears were taken and examined and a filter-paper blood spot was taken and stored for future parasite genotyping. Children with other complaints were examined and treated appropriately. Parents or guardians were asked to report any side-effects of the drug, the child's tolerability to the treatment, and their impressions of the usefulness of the treatment. Children with early and late treatment failures were given quinine 10 mg/kg three times a day for 7 days. Patients with any sign of severe malaria were admitted to hospital and treated with intravenous quinine. Children who did not attend on clinic days were visited at their homes by village health workers to establish and document reasons for failure to attend and to obtain blood smears. Unless parents withdrew consent these children were encouraged to attend on the next day. If a child could not be found, the village leader was approached to identify whether they had migrated from the study area.

Thick blood smears were read twice and parasitaemia quantified against 200 white blood cells in two different

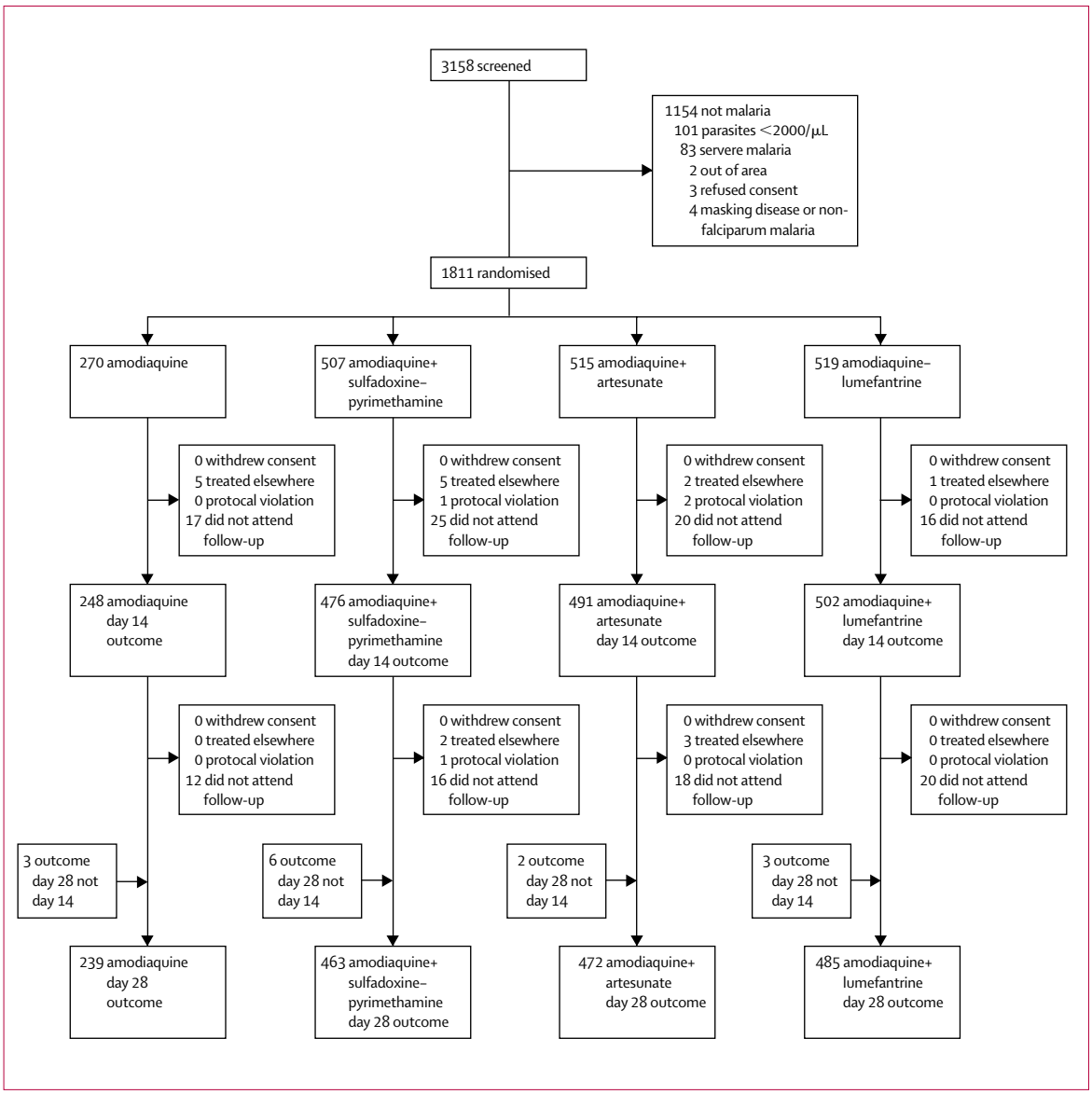

Figure 1: **Trial profile**

	Amodiaquine*	Amodiaquine+ sulfadoxine-pyrimethamine	Amodiaquine+ artesunate	Artemether-lumefantrine
Total	270	507	515	519
Girls	132 (49%)	249 (49%)	256 (49%)	266 (52%)
Median age in months (IQR)	19 (12–29)	23 (12–35)	22 (14–32)	23 (14–35)
Median parasites per 200 white blood cells (IQR)	487 (246–889)	488 (243–801)	473 (231–806)	482 (260–796)
Mean haemoglobin g/L (SD)	90 (18)	90 (17)	90 (17)	90 (16)
Mean temperature °C	37·7	37·7	37·8	37·8
Mean distance of residence from hospital (km)	8·0	7·4	7·8	7·9

*Recruitment to this group terminated early by the data and safety monitoring board.

Table 1: **Baseline characteristics of children, by treatment group**

laboratories unaware of treatment allocation. Discrepant slides were read again by a third slide reader blind to treatment allocation, and the majority opinion was taken. Randomly chosen slides were read by assessors unaware of treatment allocation to quantify gametocytes with 100 high-powered fields. Clinical and parasitological outcomes were graded according to WHO 2002 guidelines.[13] Parasitological failure was defined as parasites recorded at any follow-up visit after day 2 of treatment without the presence of clinical symptoms, and clinical failure was defined as the combination of parasitaemia and clinical symptoms.

To compare the rate of parasite recrudescence in children treated with amodiaquine monotherapy to the rate in those treated with other combinations, samples

from children who failed treatment in the first year were differentiated into recrudescent or new infections by PCR genotyping. The highly polymorphic block 3 region of *Plasmodium falciparum msp2* gene, which has shown sufficient discrimination in African parasite populations,[5,14,15] was amplified with allele-specific primers, and size polymorphisms were detected by gel electrophoresis.[16] All available pairs of DNA samples obtained before and after treatment from year 1 of the study were tested, apart from in the amodiaquine group for which a randomly selected sample of 80% of available pairs were included.

Since incidence of malaria in the study area is very high, the predetermined primary endpoint was parasitological failure by day 14 after start of treatment (this included a day either side to allow inclusion of children who could not be seen on day 14). Predetermined secondary endpoints were parasitological failure by day 28, and clinical failure by days 14 and 28. Change in haemoglobin concentration, drug side-effects, and deaths were also reported. Analysis was by intention to treat, defined as opening the treatment envelope.

Data were double-entered into an Access database (Microsoft XP) and analysed with Stata (version 8.0). Odds ratios were calculated uncorrected and adjusted for potential confounding factors (age, sex, initial parasitaemia, maternal educational level as a proxy for socioeconomic status, and distance of residence from the hospital). The study was designed to have the power to detect a difference between 95% and 90% cure (α 0·05, β 0·8). For the primary analysis, every group was compared with the next best group. To allow for comparison of three groups, $p<0·01$ was deemed statistically significant. A stopping rule was predefined that when 1000 patients had been randomised an interim blinded analysis would be done and if the parasitological failure rate in any group was 40% or more that treatment would be stopped.

The ethics committees of the National Institute for Medical Research, Tanzania, and the London School of Hygiene and Tropical Medicine approved the study. The study was discussed with and approved by community leaders before its start. A data and safety monitoring board, established by the sponsors to monitor the trial, approved the final analytical plan before the data were analysed.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The principal investigators had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

In the pilot study, 200 children, 74 boys and 126 girls, were randomly assigned sulfadoxine-pyrimethamine or amodiaquine. By day 14, 35 of 85 (41%) of those given sulfadoxine-pyrimethamine and 24 of 87 (28%) of those given amodiaquine had parasitaemia (p=0·06). Thus we decided to use amodiaquine as the reference treatment for the main study.

We screened 3158 children for inclusion in the main study; those who met the entry criteria were randomly assigned to one of four treatment groups (figure 1). Table 1 shows baseline characteristics for participants by treatment group. An interim analysis was undertaken by the data and safety monitoring board after 1000 children had been randomised. The amodiaquine group met the pre-defined stopping rules (>40% parasitological failure by day 14) and recruitment to this group was stopped. Enrolment into the other treatment groups continued. Parasitological and clinical outcomes were available for 1717 (95%) children at day 14 and for 1659 (92%) at day 28 (figure 1). 13 children had to be withdrawn before day 14 because they were treated outside the study with drugs active against malaria, and 78 were lost to follow-up. A further 6 children were withdrawn after day 14. Most of those lost to follow-up were reported by village heads to have moved out of the study area.

In the primary analysis, parasitaemia by day 14 ranged from 40% of those given amodiaquine, to about 1% of

	Amodiaquine	Amodiaquine+ sulfadoxine-pyrimethamine	Amodiaquine+ artesunate	Artemether-lumefantrine
Number with outcome by day 14	248	476	491	502
Parasitological failure at day 14	103 (42%)	97 (20%)	54 (11%)	7 (1%)
Clinical failure at day 14	32 (13%)	31 (7%)	10 (2%)	0
Gametocytes at day 14	24/128	73/284	38/318	20/333
Gametocytes at day 14 (95% CI)	19% (12–27)	26% (21–31)	12% (9–16)	6% (4–9)
Mean change haemoglobin g/L (SD) at day 14	5·3 (17)	5·4 (14)	5·8 (14)	6·1 (13)
Number with outcome by day 28	239	463	472	485
Parasitological failure at day 28	182 (76%)	282 (61%)	193 (40%)	103 (21%)
Clinical failure at day 28	54 (23%)	87 (19%)	52 (11%)	38 (8%)

Data are number and percentage unless otherwise stated.

Table 2: **Parasitological and clinical outcomes in children younger than 5 years at days 14 and 28 after treatment**

	Amodiaquine compared with amodiaquine+ sulfadoxine-pyrimethamine	p	Amodiaquine +sulfadoxine-pyrimethamine compared with amodiaquine +artesunate	p	Amodiaquine+ artesunate compared with artemether-lumefantrine	p
Parasitological failure by day 14	2·8 (2·0–3·9)	<0·0001	2·1 (1·4–3·0)	0·0001	8·7 (3·9–19·4)	<0·0001
Parasitological failure by day 14*	2·9 (2·0–4·1)	<0·0001	1·7 (1·2–2·5)	0·005	9·4 (4·2–21)	<0·0001
Clinical failure by day 14	2·1 (1·3–3·6)	0·005	3·4 (1·6–6·9)	0·001	0 failures for artemether-lumefantrine	N/A
Parasitological failure by day 28	2·0 (1·4–2·9)	0·0001	2·3 (1·7–·9)	<0·0001	2·6 (1·9–3·4)	<0·0001
Clinical failure by day 28	1·3 (0·9–1·8)	0·2	1·8 (1·3–2·7)	0·0008	1·5 (0·9–2·3)	0·09

NA=not applicable. Data are odds ratio (95% CI). *Adjusted for age, sex, initial parasitaemia and haemoglobin, mothers educational level, and distance from hospital.

Table 3: **Difference in clinical and parasitological outcomes between each group and the next best group**

	Amodiaquine	Amodiaquine+sulphadoxine-pyrimethamine	Amodiaquine+artesunate	Artemether-lumefantrine
Number of parasitological failures/number followed up to day 14	101/252 (40%)	52/269 (19%)	24/251 (10%)	4/275 (2%)
Number of recrudescences/ number of PCR-positive pairs by day 14	53/70 (76%)	23/35 (66%)	3/20 (15%)	1/2 (50%)
Estimated recrudescence rate by day 14	30·3%	12·7%	1·4%	0·7%
Number of parasitological failures/number followed up to day 28	182/239 (76%)	156/254 (61%)	102/235 (43%)	52/256 (20%)
Number of recrudescences/ number of PCR-positive pairs by day 28	77/121 (64%)	55/97 (57%)	20/72 (28%)	5/37 (14%)
Estimated reinfection rate by day 28	28%	27%	31%	18%
Estimated recrudescence rate by day 28	48·5%	34·8%	12·1%	2·7%

Table 4: **Parasitological failure rates in year 1, corrected for reinfection assessed by *msp2* PCR genotyping**

those given artemether-lumefantrine (table 2). We compared every treatment group to the next best group, with each arm being significantly different from the next best arm (table 3). Adjustment for potential confounding factors did not change this finding. The parasitological failure rates by day 28 are shown in table 2. There was a significant difference in parasitological, although not clinical, failure between groups at day 28 (table 3). There were substantially fewer gametocytes at day 14 in the two artemisinin-containing combination groups than in the amodiaquine+sulfadoxine-pyrimethamine combination group (table 2). Additionally, gametocyte prevalence at day 14 in the artemisinin groups was significantly reduced from that recorded at patient presentation (117 of 556 [21%, 95% CI 18–25]), which is indicative of the broad spectrum of activity of this drug class. The samples taken from patients with parasitological failures over a full year were differentiated into true recrudescence or reinfection. Table 4 shows the corrected recrudescence rate after genotyping and figure 2 summarises the overall parasitological results of the study.

Three patients died during the study. One child in the amodiaquine and sulfadoxine-pyrimethamine group died on the day of randomisation and one in the amodiaquine group died 2 days after randomisation. In both cases, the severity of disease at randomisation was deemed the probable cause of death by the clinical monitor. One child in the artemether-lumefantrine group died on day 20 at home, having been well and parasite free on day 14. One other possible serious adverse event was recorded, a child who needed hospitalisation for a rash on day 20, although it was thought to be unrelated to the study drug.

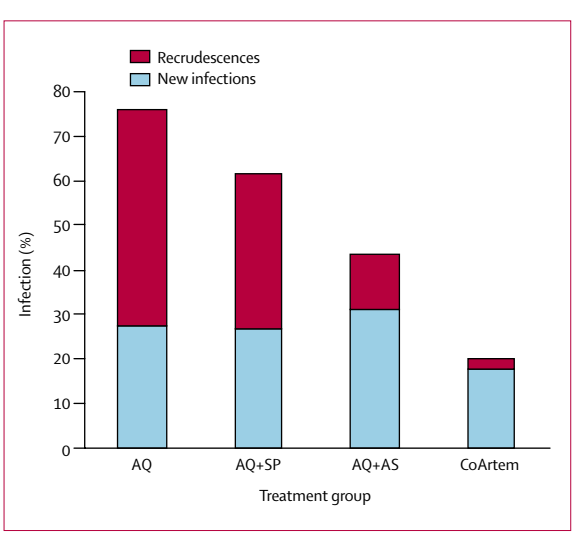

Figure 2: **Parasitological failure rate by day 28**
AQ=amodiaquine; AQ+SP=amodiaquine+sulfadoxine-pyrimethamine; AQ+AS=amodiaquine+artesunate; CoArtem=artemether-lumetantrine

Discussion

Cheap and effective treatment for malaria with one drug is no longer an option for most countries in Africa because of the rapid emergence of drug resistance. This trial provides evidence from a head-to-head effectiveness comparison of three drug combinations that are available in Africa, have reasonable efficacy and safety data to lend support to their use in children, and stand a realistic chance of being deployed. We have shown that the artemether-lumefantrine six-dose regimen works well in an outpatient setting in areas where the level of resistance to sulfadoxine-pyrimethamine and amodiaquine is high. In this setting, amodiaquine+artesunate worked less well, and amodiaquine+sulfadoxine-pyrimethamine, although significantly better than monotherapy, was not a good treatment option, especially when assessed at the day 28 point.

The results of our trial draw attention to the impending malaria treatment crisis in the subregion of east Africa where resistance to chloroquine, amodiaquine, and sulfadoxine-pyrimethamine is established.[17] Combinations of available drugs, such as chloroquine+sulfadoxine-pyrimethamine and chloroquine+artesunate, have not proven effective, even in closely observed efficacy trials in areas where chloroquine resistance is common. Furthermore, sulfadoxine-pyrimethamine+artesunate has been shown to be disappointing in areas where the level of sulfadoxine-pyrimethamine resistance is high.[5,7,8] Addition of an artemisinin to a failing drug has not proven effective in Africa before and did not seem effective in this trial. The very high rates of reinfection in this part of Tanzania led to day 14 being taken as the primary endpoint, but the day 28 results show a widening difference between the groups and this difference in recrudescence rates probably would have continued even beyond this time.

There is considerable, and justified, concern that efficacy data, which are the output from most clinical

trials, are not a realistic measure of the effectiveness of a drug in operational practice, especially when dosing regimens are long or complex.[9] Efficacy trials will always give a best-case outcome and there is clear evidence that this is so for antimalarials.[18] We are encouraged that when these drugs were taken at home, the six-dose artemether-lumefantrine treatment in WHO packaging was highly effective. A study from Uganda lends support to the results from our trial in showing that adherence to the WHO-packaged drug is reasonable.[19]

Our trial is much closer to normal outpatient practice than an efficacy trial; however, no effectiveness trial can be an ideal reflection of reality since to obtain data and mimic entirely normal practice is not possible and our results are probably indicative of the most optimistic end of the scale of the effectiveness of the drugs. Additionally, the drugs in our trial were free, and because they are not yet widely known in this area they are not perceived to have a high market value. Pills were therefore unlikely to have been saved and sold on. If the cost or street value of drugs is high, the likelihood of parents completing the course could be adversely affected, which in turn would reduce the effectiveness of this drug combination.

The effectiveness of the combination of amodiaquine +artesunate could have been affected by the fact that there is no packaging of this combination for young children and infants. A coformulated version is being developed and might improve adherence, especially if it is well packaged. Appropriate packaging of antimalarials improves adherence[20] and hence probably clinical outcome, although this hypothesis has not been investigated directly. The results obtained with amodiaquine+artesunate in this study are, however, in keeping with some efficacy data from areas of east Africa where amodiaquine resistance rates are high;[4] thus this combination should not be used in areas where resistance to amodiaquine is already high. However, the combination has been shown to be efficacious in areas where resistance to amodiaquine is moderate or low,[4] which is the case in much of west Africa at the moment. Our study suggests the need to test any combination in effectiveness trials with the packaging that will be used in practice before any drug is adopted as national policy.

In accordance with results of efficacy studies, artemisinin-containing combinations led to lower gametocyte carriage, suggesting lower infectiousness with these treatments than with other combinations.[14] The amodiaquine+sulfadoxine-pyrimethamine combination, which has been recommended as a short-term or interim strategy before the introduction of an artemisinin-containing combination, has proven efficacious in areas of low to moderate resistance to both drugs even where resistance to chloroquine is high, especially when assessed over long follow-up.[5,21] This combination has the major advantage of being cheap, and with better packaging it might be more effective. The rate of failure in this trial suggests, however, that this combination would probably not be useful as treatment for children in areas where parasite resistance to both drugs is high. This failure rate might not be due entirely to the efficacy of the drugs. Parents of children with malaria are likely to be aware that sulfadoxine-pyrimethamine and amodiaquine are failing in this area, and this factor could reduce adherence.

We have shown how limited the options are for antimalarial treatment in children in the parts of east Africa where levels of resistance are high. The artemether-lumefantrine combination works at present, although the long half-life of lumefantrine might make this combination vulnerable to selection pressure. The cost of the drug means that it is likely to reach only a fraction of those who need it, unless the price is substantially reduced either through market mechanisms or (more realistically) through subsidy.[22] Supply is currently a major problem. This situation is likely to be exacerbated by the fact that malaria is over diagnosed and therefore a substantial proportion of malaria treatment given is for individuals who do not in fact have the disease.[23,24] Drug combinations that can help to fill the gap in the medium term are being developed, of which piperaquine-dihydroartemisinin[25] and chlorproguanil-dapsone-artesunate are among the most promising. Chlorproguanil-dapsone can be effective where sulfadoxine-pyrimethamine has failed.[10] None of the artemisinin combinations is cheap, and this is a serious limitation; addressing this issue in a sustainable way will not be easy.[26] Current efforts by the Global Fund and others will provide cheap artemisinin-containing combinations for several countries, but it is too early to assess the sustainability and scope of these efforts. Our study shows that in areas where chloroquine, amodiaquine, and sulfadoxine-pyrimethamine have failed badly, use of any of these drugs in combination is unlikely to work.

Contributors

T K Mutabingwa and C J M Whitty were the principal investigators and designed, set up, and oversaw the trial and interpreted the data. T K Mutabingwa was the trial leader and C J M Whitty analysed the data. B M Greenwood was involved in trial design and oversight. A Heller and D Anthony were involved in all stages of the running of the trial. R Hallett and J Ahmed designed and undertook the genotyping and C Drakeley did the investigation of gametocytes. All authors contributed to the paper. T K Mutabingwa is the guarantor of the paper.

Conflict of interest statement

We declare that we have no conflict of interest.

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