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The use of artemether-lumefantrine by febrile children following national implementation of a revised drug policy in Kenya

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Abstract

Objectives—To examine access to, timing and use of artemisinin-based combination therapy among rural Kenyan febrile children before and following the introduction of artemether-lumefantrine (AL) as first-line antimalarial drug policy

Methods—In August 2006 a cohort was established within 72 rural clusters in four sentinel districts to monitor the period prevalence of fever and treatment in children aged 0-4 years though four repeat cross-sectional surveys (1 prior to introduction of AL and 3 post-AL introduction: January-June 2007). Mothers/guardians of children were asked about fever in the last 14 days and related treatment actions including the timing, drugs used, dosing and adherence supported by visual aids of commonly available drug products.

Results—A total of 2,526 child-observations were recorded during the four survey rounds. The period prevalence of fever was between 20% and 26% with little variation between survey rounds. The overall proportion of children with fever receiving antimalarial drugs for their fever was 31 % (95% 26% to 36%) and the proportion of febrile children receiving antimalarial drugs within 48 hours was 23.3% (95% CI 18.6% to 28.0%). The proportion of febrile children who received first-line recommended AL within 48 hours was 10.2% (95% 7.0% to 13.4%), compared to only 4.6% (95% CI 3.8% to 5.4%) of children receiving sulphadoxine-pyrimethamine first line therapy in 2001.

Conclusions—Even though Kenya is less than a year into the new policy implementation and AL is restricted to the public formal sector, access to antimalarial drugs among children within 48 hours and to the first-line therapy has improved, but remains well below national and international

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targets. The continued use of mono-therapies such as amodiaquine and the artemisinin monotherapies remain constraints to the effective implementation of ACT policy in Kenya.

Keywords

Kenya; fever; children under five; access; artemether-lumefantrine; policy change

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Introduction

Clinical infections with *Plasmodium falciparum* pose a serious threat to the survival of young, semi-immune children in Africa (Snow *et al* 1999). The rapid progression to severe complications and death following the onset of fever in paediatric malaria has been well described (Greenwood *et al* 1987; de Savigny *et al* 2004). For these reasons the prompt and presumptive treatment of fevers in young children living in falciparum endemic areas of Africa with effective antimalarials is a cornerstone of current Roll Back Malaria control efforts (RBM, 2005).

Until recently this strategic approach was failing across most of sub-Saharan Africa (SSA) because inexpensive, albeit widely available, mono-therapies used to treat clinical malaria were ineffective. The continued use of failing drugs was one of the proposed drivers for rising malaria mortality in SSA during the 1990's (Snow *et al* 2001). 2004 marked a watershed moment for international recommendations for malaria treatment in SSA (Attaran *et al* 2004) and several countries adopted a change from failing mono-therapy to artemisinin-based combination therapy (ACT). Approximately 40 SSA countries have since adopted ACT as their recommended first line therapy for uncomplicated malaria (Olumese, 2007).

Kenya announced in April 2004 it would abandon sulphadoxine/sulfalene-pyrimethamine (SP) in favour of artemether-lumefantrine (AL) as first line recommended therapy for uncomplicated malaria. After a protracted period of preparation, the new policy finally became operational during the third quarter of 2006 (Amin *et al* 2007a). Kenya, like many other countries adopting ACT, has been cautious in its introduction of this new medicine. At present AL is available as a registered prescription-only medicine at government and mission-sector hospitals, clinics and dispensaries free-of-charge. AL is not officially available as an over-the-counter medicine to enable its use in the wider community such as in the commercial retail sector as was the case for SP. Consequently there is a fear that replacing sub-optimal treatments widely available from multiple providers with effective medicines restricted to a few providers distal to rural households might paradoxically reduce the overall community effectiveness of ACT treatment strategies (Amin *et al* 2004).

In this paper we examine the access, timing and use of ACT among rural Kenyan febrile children immediately before the introduction of the new AL treatment policy and every three months over a nine month period after implementation.

Methods

Study population

Four repeat cross-sectional surveys were undertaken among rural homesteads recruited as part of longitudinal surveys of insecticide-treated net use in 72 community clusters across four sentinel districts (Noor *et al* 2003; 2007). The districts were Greater Kisii a low, seasonal transmission area in the western highlands; Kwale, a seasonal moderate malaria transmission area along the Kenya Indian Ocean coast; Bondo, close to Lake Victoria experiencing high perennial malaria transmission; and Makueni, a semi-arid area with very acute, over-dispersed malaria transmission. These districts were used to describe paediatric

treatment seeking behaviours and antimalarial drug use among 6,287 children in December 2001 (Amin *et al* 2003). In 2001 the 14 day period prevalence of reported fever among children was 42.2%; 28.1% of these children had no action taken to treat the fever, 29.5% sought treatment from government and mission clinics compared to 26.1% using retail sector purchased medicines. Only 4.6% of children received SP, the recommended first line therapy in 2001, within 48 hours and 76.0% of these treatments were obtained from formal clinics compared to 22.3% obtained from the retail sector (Amin *et al* 2003).

Homesteads were geo-located using a Global Positioning System (Garmin *etrex*, Garmin Ltd., Kansas, USA) and enumerated annually between 2001 and 2006 (Noor *et al* 2003; 2007). In August 2006, 20% of homesteads were re-sampled from a universe of 2,600 homesteads, and all children aged less than five years were recruited, following informed consent from their mothers/guardians, to form a longitudinal cohort to examine the period prevalence and treatment of fevers immediately before and after the introduction of the new AL drug policy into clinics in each district. Children exited the cohort during subsequent survey rounds if they out-migrated, homesteads heads or children's guardians refused participation, children reached their fifth birthday or the child died. New children were included into the cohort if they were identified as having been born during the interval through detailed birth histories of all resident women aged 15-49 years. New births that did not survive the interval between census rounds and recent in-migrants were not included in the cohort.

Fever and treatment prevalence surveys

Separate teams of field interviewers were used in each district and trained in the use of local language-specific, pre-tested questionnaires. Mothers or guardians of resident children were asked whether the child had had a fever during the two weeks prior to the survey day and whether the fever had resolved by the day of the interview. We have focused on fever descriptions rather than biologically defined malaria events as national and international recommendations are that more than 80% of all peadiatric fevers, irrespective of cause, are treated with an effective antimalarial (RBM 2005; MoH 2006). Consequently we are unable to define the proportion of fevers directly attributable to malaria. All fevers were further investigated regarding treatment sources, types, timing and completion of all drug and non-drug actions taken in response to the fever by the parents or guardians. These were recorded systematically from first to final treatment actions. Photo-illustrated charts of commonly available antimalarial drugs in the formal and retail sectors were used to assist respondent recall. Clinic records available within the homestead were reviewed and mothers or guardians asked to show medicine packaging if these were still available. Following the first survey in August 2006, before AL was rolled out extensively in each of the sentinel districts, further surveys were undertaken within the same cohort in January 2007, April 2007 and June 2007.

Data analysis

Data were analysed using Stata version 9 (College Station, Texas, USA). Categorical variables are presented as proportions with the 95% confidence interval, where appropriate. Data are presented for all districts and clusters combined. Because the data were obtained from community clusters, Stata's *PSU* command was used to account for clustering when calculating confidence intervals (Williams, 2000).

Ethical approval

Ethical approval was provided by the KEMRI Ethical Review Committee IRB (KEMRI SSC number 1107).

Results

A total of 695 children were identified in 328 homesteads across 72 rural communities in the four study districts in August 2006. Between the January and June 2007 surveys an additional 120 new born children were recruited, 76 children out-migrated, the parents of 10 children subsequently refused participation, 97 children reached their fifth birthdays and weren't interviewed and seven children died. A total of 87 (3.3%) possible interviews were not completed because the child was visiting at the time of one of the four survey rounds between August 2006 and June 2007. A total of 2,526 (96.7%) child-observations were successfully recorded across the four survey rounds.

The period prevalence of fever was between 20% (124/618) and 26% (174/677) with little variation between survey rounds (Table 1) and *any* treatment action taken in response to the fever was high across all surveys (>90%) including treatment actions taken within 48 hours following the onset of the fever (>80%) but lower for reported treatment actions within 24 hours (average 60%, 322/535). The use of a 24 hour time window is often difficult to define during interviews when fevers may start at night and first actions are taken the following morning. Among the 585 identified fevers, 203 children were still febrile at the time of the interview and their treatment actions were possibly incomplete. We therefore focus all subsequent analysis on 14 day and 48 hour treatment windows for the 382 resolved fevers documented during the four survey rounds between August 2006 and June 2007.

Among the 382 resolved fevers, 361 (94.5%) sought some form of treatment and 312 (81.7%) of the fever-treatment actions were within 48 hours following the onset of symptoms. Of these prompt treatment actions (fevers treated within 48 hours) 110 (35.3%, 95% CI 30.1% to 40.4%) involved the use of government or mission hospitals, clinics or dispensaries; 147 (47.1%, 95% CI 40.9% to 53.4%) involved the use of the commercial retail sector (including 41 from private pharmacists); and 46 (14.7%, 95% CI 11.0% to 18.5%) involved the use of medicines available in the household (41) or provided by a community pharmacist visiting the home (5). There were few reported instances of non-drug based interventions such as prayers or traditional medicines (23). Of the 382 resolved fevers, 118 (30.9%, 95% CI 26.0% to 35.8%) were treated with an antimalarial drug at any time during the illness and 89 (23.3%, 95% CI 18.6% to 28.0%) were treated with an antimalarial within 48 hours. Of the 89 fevers treated with an antimalarial within 48 hours, 55 (61.8%, 95% CI 50.8% to 72.8%) were obtained from the formal health services provided by the government or mission health dispensaries, health centres or hospitals, 25 (28.1%, 95% CI 16.9% to 39.3%) were obtained from the retail sector and 9 (10.1%, 95% CI 3.8% to 16.5%) were provided by community pharmacists or self medication using drugs already available in the household.

Across the four surveys, AL was used to treat 39 (10%, 95% CI 7% to 13%) of the 382 resolved fevers, almost all (95%) of these treatments were obtained from the formal health sector (Tables 2 & 3). Three children were prescribed AL pack sizes above their age-weight group and could be considered as errant prescriptions, two of these children completed taking only 6 tablets in accordance with national recommendations for their age. However, one child (2.6%) was prescribed an 18 tablet pack and took all 18 tablets and is a genuine example of over-dose. It was reported that four other children did not complete their full 6-tablet regimens, two children had not completed their scheduled dosing however the remaining two children had suspended their treatment and considered as non-adherent (2/37, 5.4%).

Other artemisinin monotherapies (dihydroartemisinin, artesunate and artemether) were available and used to manage 4 fevers; all were obtained from private pharmacies. The most

commonly used antimalarial from all sectors was amodiaquine (AQ) and obtained from the retail sector to treat 12 fevers and provided at government and mission clinics to treat a further 28 fevers between August 2006 and June 2007. Monotherapies with significantly reduced clinical efficacy such as chloroquine (CQ) and SP (EANMAT, 2003) were used to treat 2 and 25 fevers respectively. Other drug treatment combinations included 2 treatments with AQ and quinine and 1 treatment using a combination of AQ and SP were also used and prescribed at health facilities within the formal health sector (Table 2). Whereas the denominators in Tables 2 and 3 are fevers treated with a given medicine, at times the same fever is treated with more than one medicine and therefore the number of fevers and treatment actions will differ. For instance a fever treated with a combination of AQ and SP will be counted once when looking at the proportion of fevers where *any* antimalarial was used, but counted twice when looking separately at the proportion of fevers where AQ was used and the proportion of fevers where SP was used.

Fevers treated with AL within 48 hours rose from 0.8% (1/118, 95% CI <1% to 2.6%) at the time when the national policy was about to be implemented in August 2006 to 5.6% (5/90, 95% CI 1.0% to 10.1%) immediately after the implementation in January 2007, increasing to 9.4% (8/85, 95% CI 2.6% to 16.2%) in April 2007 and 11.2% (10/89, 95% CI 4.1% to 18.4%) by June 2007 (Table 2). Prior to the wide-scale implementation of the AL drug policy at district levels SP accounted for 50% (13/26) of all antimalarials used to treat fevers in the last 14 days (Table 2). Combining the period January-June 2007, after AL had been introduced, SP accounted for only 12.5% (12/96) of all antimalarial treatment actions. Conversely AL rose from 7.7% (2/26) of all antimalarial treatment actions within 14 days to 38.5% (37/96) over the period following AL implementation at government and mission clinics (Table 2). AQ remained a major contributor to antimalarial treatment actions before (34.6%, 9/26) and after AL was rolled out to clinics (36.5%, 35/96) (Table 2).

Discussion

Compared with results from the same locations in 2001, antimalarial drug use within 48 hours had increased from 15.8% (95% CI 14.0% to 17.7%) (Amin *et al* 2003) to 23.3% (95% CI 18.6% to 28.0%) in 2006/7 (Table 2). The proportion of antimalarials used to treat the fevers sourced from government and mission clinics in 2006/7 was 69% (Table 3) compared to 53% in 2001 (Amin *et al* 2001). Little is known regarding the current clinical efficacy of AQ in Kenya; however this drug was widely used to manage fevers across all four surveys between August 2006 and 2007, including its apparent regular prescription at government and mission clinics. This compares well with health facility based observations on prescription practices of health workers between October and December 2006 where it was reported that 39% of pediatric febrile presentations were prescribed AQ compared to only 26% being prescribed AL (Zurovac *et al* 2007). After the introduction of AL into the formal health sector in the four districts after August 2006 the use of AL by febrile children averaged 14.0% (95% CI 9.3% to 18.7%) and 8.7% (95% CI 5.2% to 12.2%) used AL within 48 hours of the onset of their fever (January-June 2007). Under current health service use patterns and timing, if all AQ prescriptions were converted to AL prescriptions within the formal health sector one might anticipate that over 17.5% of all pediatric fevers would be treated with the first-line, efficacious recommended therapy and 11.2% would be treated with AL within 48 hours. This should be relatively easy to achieve with the simple removal of AQ from current drug stocks at the clinic levels.

Even with inappropriate formal health sector prescriptions, prompt access to effective treatment has improved considerably since 2001 when access to SP within 48 hours from all service providers was only 4.6% (95% CI 3.8% to 5.4%) (Amin *et al* 2003). The current estimate after the implementation of the AL policy is over twice as high when access to AL

is restricted to only the formal health sector and not widely available over-the-counter. This is an important observation because it suggests that increasing access to effective medicines can be improved even when its availability is restricted under prescription.

There are two methodological caveats that deserve some comment. First, the repeated enquiries of fever and their treatment among a fixed cohort of caretakers of young children may have influenced subsequent treatment actions. This Hawthorne effect is almost impossible to control for in longitudinal studies and the slight increases in AL use with survey rounds should be considered with this in mind. Second, mother's and caretaker's rarely reported the use of traditional healers in our survey. This may well have been a result of reluctance to describe these treatment actions to biomedical interviewers (Deming *et al* 1989; Nwanyanwu *et al* 1996).

There have been several important changes in national health policy and services since 2002 which may have resulted in nationwide changes to service use behaviour. In 2003 the Ministry of Health significantly increased funding for essential drugs (MoH, 2003). In 2004 there was a major change in user fee policy abolishing fees for paeditric patients (MoH, 2005). Since 2005 insecticide-treated bed nets (ITN) have been provided at clinics at heavily subsidized prices, 50 KShs (0.75 USD). Finally the announcement of the AL drug policy in 2006 stated that these new medicines would be provided to all patients free-of-charge (Daily Nation, 2006). These combined health system effects may have served to increase the use of formal health services for the management of febrile children between 2001 and 2006/7. Formal health service provision of effective malaria therapy alone will not be able to achieve optimistic targets of 80% of fevers treated within 48 hours. Other approaches to improving access must augment existing clinical services such as making these medicines available closer to home, over-the-counter (WHO, 2003). However we see the results presented here as one argument for using new effective drug policies to bring more people into strengthened existing clinical services.

The regulation of drugs available in the private and retail sector continues to pose problems for Kenya. Recent press releases of fake Duo-cotexcin ® and Cotexcin® have increased concerns about managing drug availability over-the-counter (BBC, 2007). There are currently at least 12 artemisinin monotherapies available on the market in Kenya (Amin *et al* 2007b). During the present study we identified four separate events where artemisinin monotherapies had been used to treat febrile children. These may not seem many but signal a continuing concern that these treatments if they become established will pose a threat to the AL treatment policy. These preparations have dosage regimens of at least five days and compliance to multi-dose medicines used over such a long period is usually poor (Yeung & White, 2005) and increase the likelihood of emerging resistance to these important compounds (Hastings 2001; MoH 2004).

Finally and interestingly fever period prevalence had almost halved between the survey undertaken in December 2001 and the four surveys reported in this paper. This is consistent with observations of an overall decline in malaria admissions (Okiro *et al* submitted) and mortality (Fegan *et al* 2007) reported as effects of a rapidly expanding coverage ITN coverage in Kenya (Noor *et al* 2007). Among the cohort reported here ITN use was above 76% between January and June 2007 compared to less than 7% in 2001. It was not possible to attribute ITN use to reported fever prevalence among the cohort described in this paper but the reduction in reported fevers over time may well contribute to a reduced need for treatment from all sectors.

Overall, treatment with AL from the formal health sector in Kenya represents an important first step to introducing these new medicines nationwide. However, only 8.7% of febrile

children used AL within 48 hours of onset of their illness, well below the recently announced 80% target proposed by RBM (RBM, 2005). Poly-pharmacy of paediatric fevers is a well described treatment pattern in Africa (Hetzel *et al* 2007; Kachur *et al* 2006; Njau *et al* 2006; Deressa *et al* 2003; Diallo *et al* 2001), how these patterns of treatment seeking behaviour change with the introduction of new ACT drugs is important to prospectively document to judge where improved service delivery should be targeted to increase access to effective medicines within 48 hours of fever onset.

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Table 1

Cohort description

	Aug-06	Jan-07	Apr-07	Jun-07	Total
Initial cohort	695	695	651	642	2683
Refused		5	1	4	10
Died		3	3	1	7
Moved		32	29	15	76
Visit	18	30	24	15	87
Old		52	16	29	97
Newborns		48	40	32	120
Total seen	677	621	618	610	2526
Fevers within 14 days (n, %)	174 (25.7%)	140(22.5%)	124(20.1%)	147(24.1%)	585 (23.2%)
Fevers treated within 14 days (n, %)	158 (90.8%)	131(93.6%)	114(91.9%)	132(89.8%)	535 (91.5%)
Fevers treated within 48hrs	132 (83.5%	114(87.0%)	99(86.8%)	116(87.9%)	461 (86.2%)
Fevers treated within 24hrs	87 (55.1%)	92(70.2%)	65(57.0%)	78(59.1%)	322 (60.2%)

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Table 2

Antimalarial treatment actions among resolved fevers within 14 day and 48 hour time windows

	Aug-06	Jan-07	Apr-07	Jun-07
Resolved fevers	118	90	85	89
AM treatment for resolved fevers within 14 days	26	32	29	35
AL	2 (1.7%)	7 (7.8%)	12 (14.1%)	18 (20.2%)
ARM/DHA/ATS	0	2 (2.2%)	0	2 (2.2%)
QN	1 (0.8%)	2 (2.2%)	0	2 (2.2%)
AQ	9 (7.6%)	14 (15.6%)	15 (17.6%)	6 (6.7%)
Monotherapy combinations	0	3 δ π (3.3%)	0	0
SP	13 (11.0%)	4 (4.4%)	1 (1.2%)	7 (7.9%)
CQ	1 (0.8%)	0	1 (1.2%)	0
AM treatment for resolved fevers within 48hrs	19	24	22	25
AL	1 (0.8%)	5 (5.6%)	8 (9.4%)	10 (11.2%)
ARM/DHA/ATS	0	2 (2.2%)	0	1 (1.1%)
QN	0	1 (1.1%)	0	2 (2.2%)
AQ	7 (5.9%)	10 (11.1%)	13 (15.3%)	5 (5.6%)
Monotherapy combinations	0	2 δ (2.2%)	0	0
SP	10 (8.5%)	4 (4.4%)	0	7 (7.9%)
CQ	1 (0.8%)	0	1 (1.2%)	0

δ Drug combinations of AQ+QN

π Drug combination of AQ+SP

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Table 3

Resolved fevers treated with antimalarials (AM) within 48hrs by source and type

	Aug-06	Jan-07	Apr-07	Jun-07
Resolved fevers	118	90	85	89
Total AM treatment for resolved fevers in formal health sector within 48hrs	12	13	16	15
AL	1 (0.8%)	4 (4.4%)	7 (8.2%)	10 (11.2%)
ARM/DHA/ATS	0	0	0	0
QN	0	1 (1.1%)	0	1 (1.1%)
AQ	4 (3.4%)	4 (4.4%)	9 (10.6%)	3 (3.4%)
Monotherapy combinations (AQ and QN)	0	2 (2.2%)	0	0
SP	7 (5.9%)	2 (2.2%)	0	1 (1.1%)
CQ	0	0	0	0
Total AM treatment for resolved fevers in retail sector within 48hrs	7	8	3	7
AL	0	1 (1.1%)	0	0
ARM/DHA/ATS	0	1 (1.1%)	0	1 (1.1%)
QN	0	0	0	0
AQ	3 (2.5%)	4 (4.4%)	2 (2.4%)	2 (2.2%)
Monotherapy combinations (SP and CQ)	0	0	0	0
SP	3 (2.5%)	2 (2.2%)	0	4 (4.5%)
CQ	1 (0.8%)	0	1 (1.2%)	0
Total AM treatment for resolved fevers through self medication and community pharmacist within 48 hours	0	3	3	3
AL	0	0	1 (1.2%)	0
ARM/DHA/ATS	0	1 (1.1%)	0	0
QN	0	0	0	1 (1.1%)
AQ	0	2 (2.2%)	2 (2.4%)	0
Monotherapy combinations	0	0	0	0
SP	0	0	0	2 (2.2%)
CQ	0	0	0	0

AL: Artemether Lumefantrine; ARM: Artemether; **DHA**: Dihydroartemisinin; **ATS**: Artesunate; **QN**: Quinine; **SP**: Sulphadoxine pyrimethamine; **CQ**: Chloroquine; **AQ**: Amodiaquine