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## Recommended Citation

Simba, D., Warsame, M., Kimbute, O., Kakoko, D., Petzold, M., Tomson, G., Premji, Z., Gomes, M. (2009). Factors influencing adherence to referral advice following pre-referral treatment with artesunate suppositories in children in rural Tanzania. *Tropical Medicine & International Health*, 14(7), 775-783.

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## Summary

**OBJECTIVE** WHO recommends artemisinin suppository formulations as pre-referral treatment for children who are unable to take oral medication and cannot rapidly reach a facility for parenteral treatment. We investigated factors influencing caretakers' adherence to referral advice following pre-referral treatment of their children with rectal artesunate suppositories.

**METHODS** The study was nested within an intervention study that involved pre-referral treatment of all children who came to a community dispenser for treatment because they were unable to take oral medications because of repeated vomiting, lethargy, convulsions or altered consciousness. All patients who did not comply with referral advice were stratified by actions taken post-referral: taking their children to a drug shop, a traditional healer, or not seeking further treatment, and added to a random selection of patients who complied with referral advice. Caretakers of the children were interviewed about their socio-economic status (SES), knowledge about malaria, referral advice given and actions they took following pre-referral treatment. Interview data for 587 caretakers were matched with symptoms of the children, the time of treatment, arrival at a health facility or other actions taken post-pre-referral treatment.

**RESULTS** The majority (93.5%) of caretakers reported being given referral advice by the community drug dispenser. The odds of adherence with this advice were three times greater for children with altered consciousness and/or convulsions than for children with other symptoms [odds ratio (OR) 3.47, 95% confidence interval (CI) 2.32–5.17,  $P < 0.001$ ]. When questioned, caretakers who remembered *when* (OR 2.19, 95% CI 1.48–3.23,  $P < 0.001$ ) and *why* (OR 1.77, 95% CI 1.07–2.95,  $P = 0.026$ ) they were advised to proceed to health facility – were more likely to follow referral advice. Cost did not influence adherence except within a catchment area of facilities that charged for services. In these areas, costs deterred adherence by four to five times for those who had previously paid for laboratory services (OR = 0.25, 95% CI: 0.09–0.67,  $P = 0.006$ ) or consultation (OR 0.20, 95% CI: 0.06–0.61,  $P = 0.005$ ) compared with those who had not.

**CONCLUSION** When given referral advice, caretakers of patients with life-threatening symptoms adhere to referral advice more readily than other caretakers. Health service charges deter adherence.

**keywords** malaria, referral, artesunate, community based, rural

## Introduction

In severe malaria, death occurs rapidly. Mortality is avoidable, and reflects delay in effective treatment (Barnes

*et al.* 2004; White 2004; Dondorp *et al.* 2005), especially in African children who are at high risk (Snow & Guerra 2005). Without successful control of uncomplicated malaria, a small proportion of patients will progress to

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severe malaria requiring immediate effective parenteral antimalarial treatment. Risk of mortality is usually highest within the first 48 h after onset of severe symptoms, that is within one cycle of the blood stage infection. Many patients die either before reaching hospital (Bremar 2001) or immediately thereafter (Dondorp *et al.* 2005). These deaths can be avoided by a single inexpensive artesunate suppository at the time of referral (Gomes *et al.* 2008). The artemisinin derivatives act rapidly and kill young parasites, thereby preventing their development to mature pathogenic stages (White 2004), a valuable characteristic in treating severe malaria. Current WHO Guidelines for the Treatment of Malaria recommend use of artemisinin-based suppositories as an emergency treatment prior to referral of the patient to health a facility for comprehensive management (WHO 2006). Adherence to referral advice is critical to the success of this strategy.

There are no data on routine compliance with referral advice or the factors that influence compliance with such advice after pre-referral treatment, although it has been reported that severity of the illness, need for permission to make the journey to clinic and bear associated costs, juggling child care responsibilities, perceived quality of hospital care and health workers' communication skills are important factors influencing adherence advice to proceed to hospitals (De Zoysa *et al.* 1998; Kalter *et al.* 2003). There are concerns as to whether and how many treated patients will follow referral advice if pre-referral treatment becomes routinely available at the community level: failure to adhere to referral advice might delay identification of the real cause of the disease while rapid recovery may lead to caretakers' perception that no further treatment is necessary (Hinton *et al.* 2007). This study was therefore undertaken to better understand the factors influencing parents' decisions to comply with advice to go to a health facility following pre-referral treatment, so that these factors could assist in designing appropriate health education materials to improve compliance.

## Methods and materials

### Study area and population

The study was conducted from June to August 2007 in Mtwara Rural District, southern Tanzania. The district has a total population of 212 000 residing in 112 villages, of which 67 have either no health facility or are situated more than 5 km from a health facility, leading to delays in health care in life-threatening circumstances. The intervention was conducted in these 67 villages without immediate access to health care facilities. Malaria transmission is stable and high with falciparum malaria as the leading

cause of outpatient attendances and hospital admissions, predominantly among children under-five (Warsame *et al.* 2007). The backbone of the district's health services is a network of health facility units at different levels: 30 dispensaries with outpatient services, four health centres with limited in-patient services and a regional hospital. In each village, there are two trained village health workers and several traditional birth attendants who deliver community-based health services.

The study was nested within a community-based intervention deploying artesunate suppositories as pre-referral treatment in children assessed as probably having malaria, and unable to take oral medication because of repeated vomiting, lethargy, altered consciousness or convulsions. Community drug dispensers comprised registered village health workers or about four selected mothers per village, who were trained to treat, refer all treated children to the nearest health facility for comprehensive management, follow-up the child at home post-treatment to establish outcome and document treatment-seeking practices after suppository treatment. Emphasis on the importance of compliance with advice to go to a health facility post-pre-referral treatment was communicated through community educational posters prior to and during the intervention in which community drug dispensers treated patients, stressed immediate referral to health facilities in addition to providing a referral slip to the parents of the sick child.

### Study design and sample size

Parents of children who did not comply with referral advice were identified from 2200 children treated in the intervention study, and grouped by their actions taken following pre-referral treatment: taking their children to drug stores, traditional healers or nowhere. The target was to have a minimum of 200 caretakers sampled by their post-pre-referral treatment actions. However, the target was not reached; if there were fewer than or approximately 200 children in a group, caretakers of *all* children in that stratum were selected; thus, all 52 caretakers who sought care from traditional healers, all 201 who did not seek definitive care for the respective episode and all 202 who went to purchase drugs from a drug shop were identified for interview. A further 286 of the 1810 caretakers who followed referral advice to go to a health facility were randomly selected as a comparison group, as well as 16 caretakers with no information on any action taken following pre-referral treatment. This gave us a sampling frame of 757 caretakers to be visited and interviewed to determine factors influencing adherence to referral advice.

### Study conduct

Four research assistants were trained to administer a questionnaire on SES and actions taken after pre-referral treatment with an artesunate suppository; interviews were supervised by the principal investigator (DO Simba) and two associate researchers (D Kakoko and O Kimbuta) throughout the conduct of the study. The caretakers who were present during the treated episode were interviewed at their homes after obtaining written informed consent. Where a caretaker who had been available at the time of the treated episode was not available for interview, a maximum of two additional visits were attempted.

Through a pre-tested structured questionnaire information on: (i) demographic status (age, sex, level of education and marital status), (ii) SES using 19 assets as proxies adopted from the demographic and health survey and the national census that included household assets (such as possession of radio, bicycle and livestock and other assets and household characteristics such as materials of the floor, walls and roof), (iii) knowledge about malaria (cause, transmission, prevention and appropriate treatment for malaria) and (iv) attitude of caretakers towards the quality of health care provided by health facilities (staff adequacy in number, availability of drugs, promptness of services and perceived adequacy of care) prompting caretakers to describe very poor, inadequate, undecided, adequate or very good services. Caretakers were also asked how much they normally paid for consultation, drugs and laboratory services at health facilities. To encourage neutral and unbiased questioning of caretakers, interviewers were not aware of whether caretakers had adhered with referral advice until data analysis.

Data generated through the interviews were matched with the following information on the index episode obtained at the time of treatment: presenting symptoms (inability to eat, drink or suck, repeated vomiting, lethargy, convulsions or altered consciousness), time of treatment categorized into morning (0500–1200 h), afternoon (1200–1600 h), evening (1600–1800 h) and night (1800–0500 h), and actions taken after the child had been treated. Management of the child at any health facility after treatment defined adherence to referral advice; adherence was established by tracing the referral slips given to the parent at the time of treatment and other documentation at health facilities which confirmed whether the child had arrived at the facility or not; this procedure was successful for almost three-quarters (73.4%: 210/286) of the patients arriving at the facility. We were not able to confirm adherence for the remainder (76/286 cases) because of inadequate record keeping in the referral health facilities. Non-adherence was defined as not going to a health facility

but going to drug shops, to traditional healers or not consulting any health practitioners.

### Data analysis

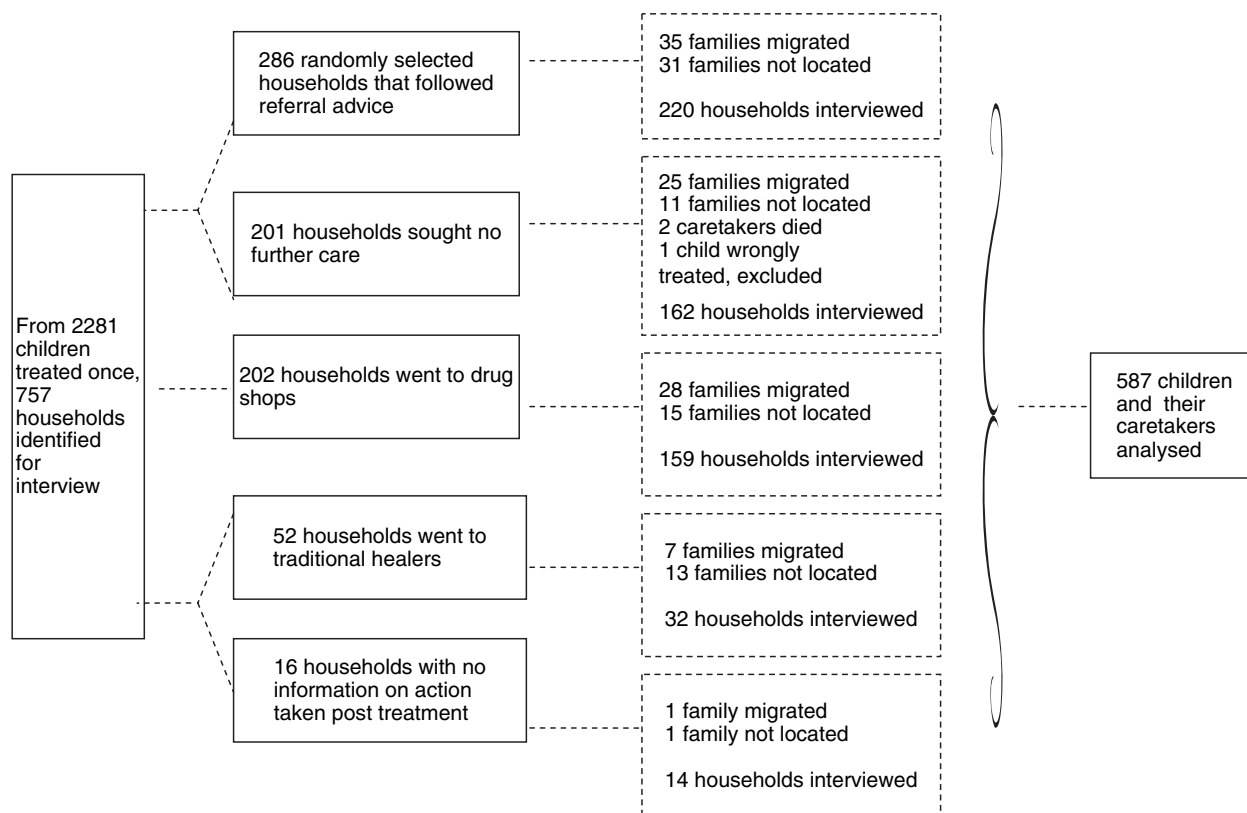
EPI-DATA software (EpiData Association, Odense, Denmark) was used for double data entry and validation. STATA versions 9 and 10 (Stata Corp., College Station, TX, USA) was used for analysis. Factors (independent variables) likely to influence adherence to referral advice (outcome variable) were analyzed using  $2 \times 2$  tables. Strength of association was measured using chi-square tests; for  $P$ -values  $<0.05$ , the significance level is stated. Multiple logistic regression models were used to establish the independent effect on adherence (the dependent variable) of: demographic variables, clinical symptoms, caretakers' knowledge about cause of malaria and caretakers' memory of referral instructions given by drug dispenser. Because the sampling fraction for those who completed referral was different from the other strata, weighted regression analysis was applied in a pooled analysis. The measure of association selected was the odds ratio (OR) with 95% confidence intervals (CI).

### Ethical issues

Ethical approval for the adherence study was obtained from the Muhimbili University College of Health Science and from the National Institute of Medical Research. Ethical review and approval for the intervention study was obtained from the National Institute of Medical Research and the World Health Organization Ethics Review Committee. Permission to conduct the study was obtained from the regional, district and village authorities. Individual informed consent was sought and obtained from the caretakers of the children in both the intervention and the nested adherence study.

### Results

Of the 757 selected caretakers, 588 (77.7%) were successfully located and interviewed but one child was removed from the analysis as the patient did not meet the indication for treatment. Of the remaining 587 caretakers, 96 had migrated to other areas and 71 could not be found at their homes after three visits to the household during the study period (Figure 1). Attrition was not apparently biased except for follow-up of patients who were taken to traditional healers: 77–81% successful follow-up overall with 81.0% (163/201) follow-up among patients who did not go anywhere; 78.7% (159/202) follow-up of patients who went to drug shops; 76.9% (220/286) follow-up of



**Figure 1** Flowchart. The number of children whose caretakers were interviewed and numbers not interviewed.

those who went to health facilities but 61.5% (32/52) follow-up among caretakers who went to traditional healers. There was no child in the sample who died.

Table 1 summarizes the socio-demographic profile of the caretakers, presenting symptoms of their children at the time of pre-referral treatment and adherence by caretakers to referral advice. There was no significant difference in adherence by caretakers' age, level of education and marital status. Almost one-third (30.8%) of the children presented with altered consciousness and/or repeated convulsions and two-thirds (68.5%) had repeated vomiting, lethargy and/or were unable to eat/drink/suck (Table 1). The majority of caretakers of children with altered consciousness and/or convulsions adhered to advice to proceed to health facility compared with parents of patients with other symptoms ( $P < 0.0001$ , Table 1). There was no significant difference in the actions taken by gender of the child.

Table 2 presents actions taken by caretakers following pre-referral treatment and symptoms of their children at presentation. More patients with relatively serious symptoms, such as altered consciousness and/or convulsions, went to a health centre; fewer of these patients went to a drug

shop and there was no indication that these patients were systematically taken to a traditional healer (Table 2).

Table 3 provides the results of multiple logistics regression analysis assessing factors that independently influenced adherence; the pooled analysis gives the weighted results. Variables introduced into the model included demographic and socio-economic background of caretakers, clinical symptoms of the children, time at which pre-referral treatment was sought and caretakers' recollection of instructions regarding referral advice. The odds of adhering to referral advice to go to a health facility was three times greater for patients with altered consciousness and/or convulsions as compared with children with the other symptoms (OR 3.47, 95% CI 2.52–5.17,  $P < 0.0001$ ), confirming the results of the test of proportions and signifying that the results were not diluted by the introduction of other independent variables into the regression model. Factors that were not significant at the 0.05 level were education, age, marital and SES of the caretakers and time of the day at which treatment was sought.

Most caretakers reported that they had been instructed to go to a health facility for further management of their

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Characteristics of parent and child	All patients		Adhered to referral advice		Did not adhere to referral advice		Chi-square	P-value
	No.		<i>n</i>	%	<i>n</i>	%		
Marital status								
Unmarried	112		39	34.8	73	65.2	0.4171	0.518
Married	475		181	38.1	294	61.9		
Total	587		220	37.5	367	62.5		
Caretaker's age								
15–24	87		39	44.8	48	55.2	3.1007	0.376
25–35	231		80	34.6	151	65.4		
35–44	175		68	38.9	107	61.1		
45+	93		33	35.5	60	64.5		
Total	586†		220	37.5	366	62.5		
Caretaker's education								
Below 7 years	282		117	41.5	165	58.5	3.4740	0.062
7 years and above	300		102	34.0	198	66.0		
Total	582‡		219	37.6	363	62.4		
Child's symptoms at treatment								
Altered consciousness/convulsions	181		102	56.4	79	43.6	43.4	0.000
Repeated vomiting, unable to eat, drink or suck, lethargic	402		115	28.6	287	71.4		
Not known	4		3	75.0	1	25.0		
Total	587		220	37.5	367	62.5		

†Age missing for one caretaker.

‡Level of education missing for five caretakers.

**Table 2** Actions taken by caretakers after treatment, by gender and clinical status of the treated child

Action taken after treatment	No.	%	Male no.	%	Female no.	%
Went to hospital/health centre	220	37.5	116	52.7	104	47.3
Went to a drug shop	159	27.0	74	46.5	85	53.5
Went to a traditional healer	32	5.5	16	50.0	16	50.0
Did not take any action	162	27.6	86	53.1	76	46.9
Not known	14	2.4	11	78.6	3	21.4
Total	587	100	303	51.6	284	48.4

Action taken by clinical status of child	No.	%	Altered consciousness or convulsions	%	Lethargy, vomiting, unable to eat, drink or suck	%	Not known	%
Went to hospital/health centre	220	37.5	102	46.4	115	52.3	3	1.3
Went to a drug shop	159	27.1	32	20.8	126	79.2	0	0.0
Went to a traditional healer	32	5.5	13	40.6	19	59.4	0	0.0
Did not take any action	162	27.6	31	19.1	130	80.3	1	0.6
Not known	14	2.3	2	14.3	12	85.7	0	0.0
Total	587	100	181	30.8	402	68.5	4	0.7

children (93.5%; 549/587) and of these 39.0% (214/549) were in the stratum that complied with the referral advice. Caretakers who remembered *when* to go to a health facility

were twice as likely to comply with referral advice (OR 2.19, 95% CI 1.48–3.23,  $P < 0.001$ ). If they remembered *why* they were instructed to go to the health facility they



**Table 3** Factors affecting adherence to referral advice, with adjusted odds ratio (OR) from logistical regression analysis ( $n = 587$ )

	OR	95% CI	P-value
Health facility <i>vs</i> all actions (pooled results)*			
Presenting more severe symptoms†	3.47	2.32–5.17	0.000
Knowledge about cause	0.45	0.30–0.69	0.000
Advice given about when to refer	2.19	1.48–3.23	0.000
Advice given why referring	1.77	1.07–2.95	0.026
Health facility <i>vs</i> traditional healers			
Presenting more severe symptoms†	1.53	0.73–3.19	0.259
Have knowledge about cause	0.99	0.45–2.17	0.983
Advice given about when to refer	1.95	0.91–4.22	0.088
Advice given why referring	0.18	0.02–1.41	0.103
Health facility <i>vs</i> drug shops			
Presenting more severe symptoms†	3.25	2.02–5.25	0.000
Have knowledge about cause	0.44	0.27–0.70	0.001
Advice given about when to refer	1.59	1.02–2.48	0.041
Advice given why referring	2.10	1.21–3.67	0.009
Health facilities <i>vs</i> no action			
Presenting more severe symptoms†	4.00	2.43–6.60	0.000
Have knowledge about cause	0.52	0.32–0.83	0.006
Advice given about when to refer	3.05	1.94–4.79	0.000

\*Pooled analysis done weighting by action taken.

†Symptoms at treatment were inability to eat, drink or suck, repeated vomiting, lethargy, repeated convulsions or altered consciousness. The latter two symptoms were classified as 'more severe' in the regression analysis.

were 1.8 times more likely to adhere (OR 1.77, 95% CI 1.07–2.95,  $P = 0.026$ ) than those who remembered that they had been given referral advice but did not remember the content of the advice given.

Table 3 presents the odds of adherence within each of the actions taken by caretakers following referral advice. Severity of symptoms at the time of treatment and caretakers' memory of the referral advice given (when to go to the clinic and why) continued to be significant predictors of adherence in the *health facility-drug shop* comparison and in the *health facility-no action* comparison. In the *health facility-traditional healer* comparison, there were no variables introduced in the model, whether demographic, socio-economic or clinical symptoms of the child that contributed to an explanation of non-adherence and this is likely to be a result of the small numbers involved in this sub-group (Table 3).

About half of the caretakers, 56.1% (329/587) reported paying for drugs. However, only a minority, 13.6% (80/587) reported paying for laboratory services or for consultation with a health professional: 21.1% (124/587). Payment for services was clustered in 11 villages served by a health facility that required payment. In these villages, many caretakers reported paying for health services. For them, the odds of adhering to referral advice were four times lower (in the *health facility-drug shop* comparison and *health facility-no action*) and five times lower (in the *health facility-no action* comparison) than those who did

not pay. There was no indication that severity of symptoms influenced adherence to referral advice. In villages served by public health facilities, payment for health care was rare for children under the age of 5 and consequently did not deter adherence to referral advice.

There was no apparent association between the perceived quality of care from the health facility, distance to facility, means of transport, SES of the caretaker and adherence to referral advice. However, caretakers who reported that they did not know the cause of malaria transmission had higher odds of adhering to referral advice (Table 3). We were unable to establish why this was the case.

## Discussion

In remote rural communities without immediate access to parenteral medicines, any potential of pre-referral artesunate suppositories to halt disease progression and save life can only be realized if patients are given pre-referral treatment early and caretakers proceed with the patient to a clinic for assessment and management. Our results provide strong evidence that symptoms associated with cerebral malaria, which carries a high risk of death, or residual neurological damage in survivors (Molyneux 1989; Newton & Krishna 1998; Carter *et al.* 2005; Ngougou *et al.* 2006), were the most important factors influencing adherence to referral advice given by



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community drug dispensers. There was no apparent preference to seek traditional care among children with convulsions or altered consciousness.

It has previously been reported from qualitative studies that convulsing children in Tanzania and elsewhere are either taken first or predominantly to traditional healers for the management of convulsions, even when they prefer modern care; when the moment of crisis is over or when their expectations of rapid cure are not met, they proceed to health facilities (Comoro *et al.* 2003; De Savigny *et al.* 2004; Kaona & Tuba 2005; Okeke *et al.* 2006; Warsame *et al.* 2007). However, quantitative data on behaviour in fatal cases show a preference for modern care (De Savigny *et al.* 2004). Although we do not know whether parents chose treatment with rectal artesunate *after* a prior consultation at traditional care, once they sought rectal artesunate treatment, parents of children that were convulsing or had altered consciousness readily followed modern care and remembered referral advice given. Our study contributes to the literature that suggests that central nervous symptoms and referral advice can trigger modern (and in a minority of cases, traditional) care. Adherence was appropriate and decisive once felt to be necessary, since the time of day or night at which the child presented with these symptoms, distance to clinic, cost, gender, perceived quality of care at referral facility, literacy or SES did not interfere with adherence to referral advice for children with these symptoms. Indeed, caretakers who complied with referral advice had a clear memory of the advice that they had been given as to when and why they were advised to go health facility.

The results corroborate other findings that caretakers follow through on referrals to hospital when their child is critically ill and when they have been instructed to do so (De Zoysa *et al.* 1998; Muller *et al.* 2003). This implies that effective communication during provider–client interaction improves adherence (Winch *et al.* 2003; Chinbuah *et al.* 2006). Caretakers who remembered the referral advice given and recalled the reasons why they had been told to go to health facility had a higher chance of going there. This might argue strongly for a policy of training and supporting providers to treat, refer and *effectively communicate to parents the reasons for rapid transfer to a hospital*. There may be a need to reinforce referral advice in children with other danger signs – repeated vomiting, inability to take oral medication and lethargy.

Cost of treatment deterred adherence in the catchment area of a mission facility where payment for drugs, laboratory services or medical consultation was required. Although mission health facilities often charge less than private, for-profit, health facilities, the costs, even if small, were a deterrent for some caretakers in a society where

nearly 40% of the population live below the poverty line (National Bureau of Statistics 2002). Cost did not influence adherence elsewhere in the study area. This is probably because the health system in Tanzania, unlike other countries where cost of treatment has been reported as a major factor influencing the choice of care for severe illness, exempts young children from user fees (De Zoysa *et al.* 1998; White 1998; Kalter *et al.* 2003; Peterson *et al.* 2004).

The lack of association between adherence to referral advice and geographic or socio-economic factors and a very high correlation between adherence, symptoms and the nature of the advice given is unusual. In many other studies, geographic and socio-economic factors were directly associated with adherence to referral advice (De Zoysa *et al.* 1998; Kalter *et al.* 2003; Macintyre *et al.* 2003; Kallander *et al.* 2006). One explanation is a lack of variation in SES in our study area compared with other areas studied. Secondly, the drug dispensers were trained to advise caretakers on the need for immediate transfer to the nearest health facility and although we had no means of establishing whether such advice was given, 98% of the respondents stated that they were referred to the nearest clinic. This high referral rate probably made the group treated more homogeneous. Furthermore, our study involved a narrow group of children, all of whom had danger signs and were treated with artesunate; other studies reported caretaker behaviour in circumstances where children had both urgent and non-urgent conditions (De Zoysa *et al.* 1998; Kallander *et al.* 2006) or caretakers were assessing referral from primary health facilities to hospitals (Kalter *et al.* 2003; Macintyre *et al.* 2003).

Follow-up therapy and management obtained by the treated children was not the subject of this study. Monotherapy with pre-referral artesunate suppositories for children with malaria which is not followed up by a combination curative therapy brings increased risk of drug resistance (McCombie 1996; Ansah *et al.* 2001; Hinton *et al.* 2007), as it is probable that the treated group will be hyperparasitaemic. Although parenteral artemisinins are also monotherapy, they are normally given under controlled conditions at hospitals where consolidation therapy can be initiated before discharge. In a community setting, the risk of using rectal artesunate must be weighed against the risk of death from severe malaria but should be followed by oral artemisinin combination therapy as soon as the child can take oral treatment reliably.

The weakest link in seeking effective care is likely to be in traditional societies in which traditional care for convulsions and altered consciousness may be the first resort or where switching between traditional and modern

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care, or using only the former, will delay effective treatment. It may even be worthwhile exploring whether traditional healers can contribute in the provision of pre-referral artesunate treatment and immediate referral of patients to hospital.

**Methodological considerations**

Symptoms, time of treatment and arrival at a health facility were obtained from a case record form filled out by the treatment provider at the time of treatment at the respective health facility. All other findings are reported by the caretakers, so there could be variations in recall when there was a long time lag between the index episode and the interview. Given the seriousness of the episode and the unusual treatment provided, we believe it is likely that caretakers remembered the circumstances surrounding the provision of treatment in the acute phase. Loss-to-follow-up was highest in the group that went to traditional healers post-treatment. This and the small number of those who went to traditional healers weakens the analysis of this group.

Although we had 19 variables as proxies for SES, we observed during analysis that many variables had a skewed outcome, that is 90% or more of the respondents were found in one category, reflecting a homogeneous SES in the sampled households. Of the variables that had a larger degree of variance, only roofing materials had any statistical relationship to adherence. The lack of variation in SES limited exploration of its influence upon adherence to referral advice.

**Conclusion**

Caretakers of patients with convulsions and/or altered consciousness who are asked to go to the nearest health facility after pre-referral treatment do so readily and remember the reasons why they were asked to go there. This reassuring finding suggests that, with adequate training of providers to give referral advice, caretakers of patients with a high absolute risk of death tend to access a health facility at which appropriate diagnosis and complete treatment can be provided.

**Acknowledgements**

We thank the Muhimbili University College of Health Sciences (MUHAS)/Karolinska Institutet (KI) collaboration for supporting the research and sub-study that led to this paper. The intervention 'deployment' study was supported by the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical

Diseases. We convey special thanks to Annika Janson for her helpful advice and comments in the design of this study and to Mr Jan Singlovic for sampling the households for the sub-study and providing matched data from the deployment study, on symptoms, time of treatment and adherence. Our gratitude also goes to Prof Massele for the coordination of the MUHAS/KI collaboration through which this study was conducted. Finally, we express our gratitude to all participants, research assistants and others involved in support of the logistics arrangements for conducting of this study. The study on which this paper is based was funded by SIDA/SAREC through the MUHAS/KI – Malaria Project.

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