ANTI-MALARIAL DRUG USE AMONG PRESCHOOL CHILDREN IN AN AREA OF SEASONAL MALARIA TRANSMISSION IN KENYA

HANS VERHOEF, ELSA HODGINS, TEUNIS A. EGGELTE, JANE Y. CARTER, ORGENES LEMA, CLIVE E. WEST, AND FRANS J. KOK

Division of Human Nutrition and Epidemiology, Wageningen Agricultural University, Wageningen, The Netherlands; African Medical and Research Foundation (AMREF), Nairobi, Kenya; Medical Anthropology Unit, and Department of Clinical Pharmacology and Pharmacotherapy, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

Abstract. The aims of this study were to estimate the proportion of asymptomatic Kenyan preschool children using anti-malarial drugs, to identify factors associated with chloroquine use, and to assess the validity of frequency of febrile episodes and drug use reported by mothers or carers. Of 318 children studied, 38% (95% confidence interval [CI] = 30–47%) tested positive for chloroquine or sulfadoxine. Of chloroquine-positive children, 15% had concentrations exceeding the estimated minimum therapeutically effective values. Among those testing negative for sulfadoxine, chloroquine-positive children were more frequently parasitemic (odds ratio = 2.6, 95% CI = 1.3–5.2), and had lower mean hemoglobin concentrations (6.1 g/L, 95% CI = 2.1–10.1) than chloroquine-negative children. Mothers over-reported the frequency of malaria or fever episodes as usually defined in medical studies, and underreported anti-malarial drug use. We conclude that anti-malarials are frequently given for treatment of malaria or malaria-associated illness, rather than prophylactically or for symptoms unrelated to malaria. Questionnaire surveys cannot replace biochemical markers to obtain information on anti-malarial drug use.

In developing countries, drugs are often used without prescription. They may be purchased from local shops, markets, or street vendors, obtained by sharing with other users, or used when left over from previous treatments. Home treatment or prophylaxis of illnesses with anti-malarials is more often the rule than the exception in many countries endemic for malaria.1–3 Little is known about the administration of anti-malarial drugs to children by their parents. While early diagnosis and prompt treatment is one of the elements of the global strategy for malaria control,4 overuse may lead unnecessarily to the intensification and spread of drug-resistance and to increased risk of adverse effects associated with these drugs.

Studies in eastern Africa up to now exclusively used interviews to obtain information on anti-malarial use. In one such study in western Kenya, where malaria is holoendemic, Ruebush and others5 estimated that anti-malarial drugs, mostly chloroquine, were used for 67% of incident febrile episodes self-diagnosed as malaria, and for 28% of those diagnosed otherwise. On the Kenyan coast, where malaria endemicity is much lower, Snow and others6 conducted a community survey to study treatment and prevention of childhood malaria by mothers. When asked what they would do in a hypothetical situation in which their child had fever, 72% of the mothers reported that they would purchase anti-malarials at shops for self-treatment, while 67% claimed they would buy chloroquine-based drugs. In the same area, Mwenesi and others7 found that of 118 mothers who had diagnosed their child as having malaria currently or in the 2 weeks prior to questioning, 26% had given anti-malarials, 27% had given antipyretics or other medications, 23% said they had taken the child to a health facility, 6% had given a home remedy, and 18% had not given any treatment or done anything about treatment.

Little is known about the validity of questionnaire surveys in studying reported self-medication with anti-malarial drugs. We studied anti-malarial drug use by blood test and by questionnaire among asymptomatic preschool children living in an area of seasonal transmission in Kenya. The aims of the study were to estimate the proportion of children testing positive for anti-malarial drugs in their blood, to identify factors associated with chloroquine use, and to assess the validity of the frequency of febrile episodes and drug use reported by mothers or carers. The study was conducted as part of a larger cross-sectional study on the prevalence and risk factors for anemia.

SUBJECTS AND METHODS

Study area. Data were collected in the first annual rainy season (April to June) of 1997 in three administrative areas (Kathekani, Muthingiini, and Mangelete) in Mtito Andei Division, Makuenei District, Kenya. The area is located halfway along the road between Nairobi and Mombasa. The study area comprises approximately 720 km² with more than 40,000 inhabitants living in scattered homesteads. No entomologic or epidemiologic data on malaria had been collected previously in the area. The study was conducted before the harvest, and after a wet season (November–December 1996) that failed to produce rain. As a result, many people were probably short of cash.

Muthingiini and Mangelete each have a dispensary staffed with a nurse, and there are a government clinic and a pharmacy in Mtito Andei town, located within 30 km of each homestead in the study population. The nearest health center with microscopic facilities for malaria diagnosis is in Kibwezi town, located about 40 km west of Mtito Andei. Malarial infections reported at this facility are exclusively due to Plasmodium falciparum. Through a project implemented in the study area by the African Medical and Research Foundation over the last few decades, hundreds of community health workers and traditional birth attendants have been trained in basic health issues. Most villages have one or more of these auxiliary health workers, but they have not been trained in malaria diagnosis and treatment, and they are not usually involved in dispensing anti-malarial drugs. Many communities in the study area have shops or kiosks selling drugs, including chloroquine and analgesics. Amodiaquine
and and combination drugs containing a sulfa compound and pyrimethamine are only available in a few larger communities. No mosquito net distribution program is in place, but nets were randomly drawn with replacement from each of the communities. A total of 302 children selected for the study (n of detection for chloroquine and sulfadoxine were 10\(^{-7}\), in-

Sampling procedures. A cluster sampling procedure\(^9\), incorporating modifications proposed by Bennett and others\(^9\) and Brogan and others,\(^10\) was used to draw a sample representative of all asymptomatic children living in the study area and born between April 15, 1994 and February 15, 1997. The sample was drawn in two successive stages (Figure 1). At the first stage, a systematic sample of 45 communities was drawn from a north- to south-ordered list of all 79 communities (clusters) in the study area, with probability proportional to size, and excluding urban centers (Mtito Andei town). At the second sampling stage, 12 households were randomly drawn with replacement from each of the selected communities. For each of these households, the resident children were listed and their dates of birth were recorded from the child health card. All resident children thus identified who were asymptomatic (without illness reported by the mother) and within the desired age range were selected for the study (n = 302). Some children migrated with only part of their household between the time of the census and the time of examination. These households were considered not to have eligible children. Where possible, children who migrated with all of their household, were still missing after repeated visits, or had parents who refused consent, were replaced by children from randomly selected households within the same community.

Field procedures. An inventory of over-the-counter anti-

and malarial drugs and analgesics in the area was made by visiting the only pharmacy in Kibwezi town plus five shops that were well-stocked with these drugs. Visits to other shops did not yield additional brands or types of drugs. All brands and types of anti-malarial drugs and analgesics in stock were purchased and made into a visual display of drug packaging and contents for use during interviews. Mothers or their primary carers were interviewed separately by lay native speakers in their own language. They were questioned using structured interviews with closed-ended questions without additional prompts. When asked to identify drugs, mothers were presented with the visual display. The distance between the child’s residence and the nearest health facility was estimated by asking respondents for the time that would be needed to take the child to the nearest health care facility, using means of transport that would normally be used if the child was sick. Responses were recorded on precoded questionnaire forms, which were designed in English, translated into local language, translated back into English by a different person and compared with the original. All questions contained a precoded category do not know, or no answer. Questionnaires were field-tested by 4 interviewers on a limited number of mothers attending Kibwezi Rural Health Center outpatient department, and modified to ensure that respondents understood the questions. Blood samples were taken from children by finger or heel puncture and collected on filter paper, dried out of direct sunlight, and kept at ambient temperature until laboratory analysis. Additional blood samples were taken for microscopic examination for malaria parasites and for immediate determination in the field of hemoglobin concentration using a meter (HemoCue, Inc., Mission Viejo, CA). Prior consent for the study was obtained from the communities and the parents involved. Children were treated as deemed necessary upon completion of the survey: because such treatment was carried out after all observations were made, this had no influence on the data collected. The study was approved by the African Medical and Research Foundation and the Kenya Medical Research Institute whose ethical standards were followed.

Laboratory procedures. An ELISA to detect whole blood levels of chloroquine has been described by Eggelte.\(^11\) The monoclonal antibody used (F149) show no (\(< 0.1\%)\), or hardly any cross-reactivity with amodiaquine. The limits of detection for chloroquine and sulfadoxine were 10 \(\mu g/L\) and 10 \(\mu g/ml\), respectively.

Blood slides were stained using Field’s stain, and thick films were examined by experienced microscopists and cross-checked independently. At least 100 high-power fields were examined before the slide was considered negative.

Response and missing values. A total of 302 children were selected for study, of whom 16 were double-selected at the second sampling stage (Figure 1). Observations for these 16 children were weighted twice. Thus, 318 cases were included in the study, of whom 35 did not participate or fully participate for the following reasons: refused consent (26), not home or temporarily absent (7), or hospitalized for burns (2). Of these 35 children, 14 were replaced by random selection, which brought the total number included in the analysis to 297. In the case of non-participating children who were not replaced, weighting was used to maintain the validity of assuming of an equal probability sample. Thus, ob-

**Figure 1. Framework for selection and analysis.**
servations on those who participated within the same cluster were inflated by weighting with a multiplication factor calculated as the number of selected children in that cluster divided by the number of participating children. This brought the number back to 318 children; sample sizes reported below this value are due to missing values.

**Statistical analysis.** Data were entered, cleaned, and managed on a personal computer using SPSS (version 7.5 for Windows; SPSS Inc., Chicago IL). Computations were performed in SUDAAN, stand-alone version 7.5.2a for Windows (Research Triangle Institute, Research Triangle Park NC) assuming 2-staged cluster sampling with replacement at the first sampling stage. Because the variance estimates under this assumption do not take account that clusters were sampled from a finite population, the standard error values under this assumption do not take account that clusters were sampled from a finite population, the standard error values and confidence intervals reported here are overestimates, and the statistical tests are less sensitive in detecting an existing effect.

**RESULTS**

**Interviews.** Of the various brands and types of anti-malarial drugs available in the stores in Kibwezi, 7 contained chloroquine, 3 contained amodiaquine, and 5 contained combinations of sulfa compounds with pyrimethamine. The brands with sulfa drugs all contained sulfadoxine, except for 2 brands that contained sulfamethoxypyridazine and sulfalene. Sulfadoxine was exclusively available in combination with pyrimethamine. Of 317 respondents, 58 (18%) reported that the child had received anti-malarials in the two weeks prior to the interview. No child was reported having received a sulfa compound-pyrimethamine drug, and only 2 were reported having received amodiaquine. When asked to indicate what they considered to be the best medicine for malaria, 186 (59%) of 314 respondents named an analgesic, 97 (31%) a drug containing chloroquine, 2 (1%) a sulfa compound-pyrimethamine drug and 29 (9%) did not know or named other drugs.

**Table 1**

Frequency distribution of anti-malarial or analgesic drugs use as reported in the previous 14 days and anti-malarial drug use detected by ELISA

<table>
<thead>
<tr>
<th>Antimalarials reportedly taken</th>
<th>Drug use tests by ELISA</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Indoor</td>
<td>Chloroquine</td>
<td>Chloroquine</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>respondents</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Amodiaquine</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>None</td>
<td>3</td>
<td>7</td>
<td>71</td>
<td>178</td>
</tr>
</tbody>
</table>
| Total                          | 3                       | 10        | 108       | 196       | 317

* S + P = combined sulfa drug plus pyrimethamine; no child was reported to have taken S + P in the previous 14 days.

In the local language (Kikamba), there are words or expressions to distinguish malaria or malaria-like illnesses (ndetema) from the physical phenomenon of an elevated body temperature. When asked if the child had ndetema in the 2 weeks prior to the interview, 190 (60%) of 317 respondents answered positively (Table 2). Of the same respondents, 226 (71%) reported positively when asked if the child had an elevated body temperature, and 178 (56%) reported that the child had both ndetema and an elevated body temperature.

When asked if the respondent had discussed the child’s health with anyone, and if so, with whom, 213 of 316 respondents reported not to have discussed it with anyone. Of 103 respondents who had consulted someone, 10 had seen a relative, 10 a community health worker, 16 a traditional birth attendant, 40 a government health facility, 7 a non-government health facility, 30 a private health facility, and 2 had used other sources (respondents could name more than 1 source).

**Anti-malarial blood tests and parasitemia.** The results of the blood tests for chloroquine and sulfadoxine are summarized in Table 3. Of 318 children, 37% tested positive for the presence in blood of chloroquine (95% confidence interval [CI] = 29–46%), 4% tested positive for sulfadoxine (95% CI = 2–7%), and 38% tested positive for either chloroquine or sulfadoxine (95% CI = 30–47%). Sulfadoxine was reported to have been taken by 11% children whose blood tested positive for anti-malarial drugs, and most (10 of 13) had taken sulfadoxine in combination with chloroquine. Figure 2 shows the relative distribution of children in relation to estimated chloroquine concentrations. The median blood concentration of children testing positive was 56 µg/L for chloroquine and 9.9 µg/L for sulfadoxine. To examine the relationships of a positive chloroquine test result with malaria or hemoglobin concentration, we excluded children testing positive for sulfadoxine. In the remaining children (Table 4), the odds ratio of malaria for testing positive to testing negative for chloroquine was 2.6 (95% CI = 1.3–5.2). In the same group, children testing positive for chloroquine...
roquine had lower mean \( \pm SE \) hemoglobin concentrations than children testing negative for chloroquine (98.3 \( \pm \) 2.1 g/L compared with 104.4 \( \pm \) 1.0 g/L; difference = 6.1 g/L, 95% CI = 2.1–10.1). Whether or not children tested positive for chloroquine was not statistically significantly influenced by sex, the presence or absence of the mother, father, or grandmother in the household, or whether or not the mother had activities to support her income. Children with a positive blood test result for chloroquine did not live at a greater distance from the nearest health facility than children with a negative blood test result \( (\chi^2 = 7.01, \text{ degrees of freedom} = 5, P = 0.24; \text{ Figure 3}) \).

**DISCUSSION**

To our knowledge, this is the first report to assess anti-malarial drug use in eastern Africa by blood tests. We found 37% of the children to be positive for chloroquine, 4% for sulfadoxine, and 38% for either of these drugs. When those testing positive for sulfadoxine were excluded from analysis, children who tested positive for chloroquine had malaria more frequently and lower mean hemoglobin concentrations than children testing negative for chloroquine. Although chloroquine resistance is most likely to occur in the area, as in other parts of eastern Africa, this drug remains the most widely used anti-malarial as assessed by blood test and as reported by mothers or carers.

The study concerned a representative sample of asymptomatic children born between April 15, 1994 and February 15, 1997 (corresponding to an age range of 2–37 months) and resident in the study area. Non-response was 11%, and decreased after replacement by random selection of 14 children to 7%. Blood test results were missing for 4 children (1%). We therefore judge the conclusions to be valid for the study population.

Our estimated prevalence of chloroquine use corresponds to a value of 35% for positive chloroquine test results by ELISA in Gambian children between 6 months and 5 years of age (Alonso and others;\textsuperscript{13} non-intervention group). Surveys in rural Zimbabwe\textsuperscript{13} showed that 8% of the urine samples tested positive for 4-aminoquinolines (a group of anti-malarial compounds including chloroquine and amodia-}

**TABLE 4**

<table>
<thead>
<tr>
<th>Malaria parasitemia</th>
<th>Chloroquine in blood</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
</tr>
<tr>
<td>Positive</td>
<td>28</td>
</tr>
<tr>
<td>Negative</td>
<td>80</td>
</tr>
<tr>
<td>Total</td>
<td>108</td>
</tr>
</tbody>
</table>

**FIGURE 2.** Relative frequency distribution of blood samples in relation to chloroquine concentrations.

**FIGURE 3.** Relative frequency distribution of children in relation to the traveling time between their residence and the nearest health facility, as reported by their mothers or caretakers.
A similarly high 14-day cumulative malaria incidence (73%) require drug treatment. Anti-malarial drug use, which was reported in 18% of the children in the past 2 weeks, may have been further underestimated by the long recall period used in our study. For inconspicuous events, such as the use of drugs, Kroeger\textsuperscript{23} recommended to reduce the length of the recall time to several days. Schulpen and Swinkels,\textsuperscript{28} in a study area close to ours, found 60% underreporting of self-medication when a recall period of 2 weeks was used instead of 1 day.

To obtain valid information on anti-malarial drug use, we recommend that questionnaires should be used in addition to biochemical markers, but not to replace them. Blood tests measure the prevalence of drug use, whereas interviews measure a cumulative incidence. Asking for history of anti-malarial drug use as part of the medical examination has limited value. Biochemical markers, however, have the disadvantage of not being able to quantify the incidence or quantity of drug use, or to describe the social or cultural context in which people use drugs.

The relationship between fever and the level of parasitemia is at the core of recent attempts to find suitable case definitions of malaria attacks for use in epidemiologic studies.\textsuperscript{29±34} Both anti-malarials and anti-pyretics may influence this relationship. The finding that a large proportion of children may have anti-malarials in their blood requires further research to assess if and how the presence of these drugs can be taken into account in case definitions.

We conclude that anti-malarials are frequently given for treatment of malaria or malaria-associated illness, rather than prophylactically or for symptoms unrelated to malaria. Questionnaire surveys overestimate the occurrence of febrile episodes. They should be used in addition to biochemical markers, but not to replace them.

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Authors’ addresses: Hans Verhoef, Clive E. West, and Frans J. Kok, Division of Human Nutrition and Epidemiology, Wageningen Agricultural University, PO Box 8129, 6700 EV Wageningen, The Netherlands. Elsa Hodgins, Medical Anthropology Unit, University of Amsterdam, Amsterdam, The Netherlands. Teunis A. Eggelte, Department of Clinical Pharmacology and Pharmacotherapy, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands. Jane Y. Carter and Orgenes Lema, African Medical and Research Foundation, Nairobi, Kenya.

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The whole blood chloroquine concentrations in our study ranged between 0 and 466 μg/ L, with a median value of 56 μg/L. Only 15% of the children who tested positive for chloroquine had concentrations exceeding 150 μg/L. These findings do not take into account when chloroquine was taken. They should not be interpreted as providing evidence to support the common supposition by field workers that self-treatment using anti-malarial drugs often occurs at subtherapeutic dosages. Children whose blood tested positive for chloroquine were not found to be living at a greater distance from the nearest health facility than children who tested negative. Physical access to health care facilities did not appear to be an important constraint for chloroquine use, although it may act as a contributory factor for self-treatment and as a barrier for seeking health care.

Additional motivation for self-medication with anti-malarial drugs and their implications for public health and clinical practice has been discussed by many workers and are well-summarized by Foster.\textsuperscript{1,3} The remainder of this paper will focus on the usefulness of proxy reporting for detecting malaria episodes in children in our study and the implications of our findings for future research studies.

Most studies on anti-malarial drug use have relied on questionnaire surveys.\textsuperscript{3,7,13,18±22} One concern about the use of interview surveys to estimate morbidity and drug use is their amenability to bias.\textsuperscript{23,24} How well does the occurrence of illness episodes and drug use reported in questionnaire surveys correspond to the occurrence of such episodes measured using biomedical criteria? In our study, 60% and 71% children were said to have ntedema and elevated body temperature, respectively, in the 2 weeks prior to the interview. A similarly high 14-day cumulative malaria incidence (73%) was noted in children < 4 years of age in a questionnaire survey in western Kenya.\textsuperscript{20} Over-reporting of fever is inevitable if body temperature is assessed without a thermometer, particularly at community level.\textsuperscript{25} In children < 5 years of age attending an outpatient service in Cameroon, mothers or carers correctly reported fever in 46% of the cases, and the absence of fever in 92% of the cases (fever defined as an axillary body temperature ≥ 37.5°C).\textsuperscript{26} When these predictive values are applied to our study, the 2-week cumulative incidence of fever decreases from 72% to 35%.

This adjusted value is still higher than would be expected on the basis of previously conducted prospective studies. In Mali, the 9-day cumulative incidence of fever (oral temperature > 38°C) in children 1–3 years of age who were examined daily was 14.2% in the wet season,\textsuperscript{27} which extrapolated to a 14-day period, would have been 22.1%. This estimate is lower than ours, despite being measured during the wet season in an area where malaria was more endemic. Our reported values therefore appear to be overestimates of the cumulative incidence of fever measured by thermometer.

One explanation for this bias is a desire for drugs by the respondents participating in the study. This may have caused them to exaggerate the frequency of illness and downplay prior use of drugs. The desire for drugs was obvious on various occasions during the survey and became even more apparent in mothers who did not receive drugs upon completion of the survey. Many remained dissatisfied even when it was explained to them that their child’s condition did not


