

## PREDICTORS OF CHLOROQUINE TREATMENT FAILURE IN CHILDREN AND ADULTS WITH FALCIPARUM MALARIA IN KAMPALA, UGANDA

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**Abstract.** Chloroquine-resistant falciparum malaria is a serious problem in much of sub-Saharan Africa. However, it is desirable to continue to use chloroquine as first-line therapy for uncomplicated malaria where it remains clinically effective. To identify predictors of chloroquine treatment failure, a 14-day clinical study of chloroquine resistance in patients with uncomplicated falciparum malaria was performed in Kampala, Uganda. Among the 258 patients (88% follow-up), 47% were clinical failures (early or late treatment failure) and 70% had parasitological resistance (RI–RIII). Using multivariate analysis, an age less than five (odds ratio [OR] = 3.4, 95% CI = 1.8–6.3) and a presenting temperature over 38.0°C (OR = 2.0, 95% CI = 1.1–3.7) were independent predictors of treatment failure. In addition, patients who last took chloroquine 3 to 14 days prior to study entry were significantly more likely to be treatment failures compared to patients with very recent (less than 3 days) or no recent chloroquine use. In areas with significant chloroquine resistance, easily identifiable predictors of chloroquine treatment failure might be used to stratify patients into those for whom chloroquine use is acceptable and those for whom alternative treatment should be used.

### INTRODUCTION

The spread of chloroquine-resistant *Plasmodium falciparum* through sub-Saharan Africa has become a major obstacle for malaria control efforts. Resistance levels have risen alarmingly over the last 20 years, and in recent studies chloroquine has failed to clear parasites in up to 80% of East-African patients.<sup>1–7</sup> Chloroquine resistance has also been linked to increased malaria-specific mortality.<sup>8</sup> Despite the spread of resistance, most African countries continue to designate chloroquine as the first-line drug for uncomplicated malaria.<sup>9</sup> Arguing against the abandonment of chloroquine as a first-line agent are observations that many patients experience symptomatic relief with chloroquine despite failure to clear parasites from the blood,<sup>3,10,11</sup> the appreciation that chloroquine resistance rates may vary considerably within a country,<sup>12</sup> a lack of ideal alternatives to chloroquine,<sup>12</sup> and the realization that increased use of other agents will lead to increased resistance to these drugs.<sup>13</sup> Sulfadoxine-pyrimethamine (S/P, Fansidar) is generally considered the most appropriate replacement for chloroquine in Africa, and is recommended as first-line therapy for uncomplicated malaria in Malawi and Kenya.<sup>14</sup> However, S/P resistance has already begun to emerge in areas with increased drug pressure.<sup>7,15</sup> Indeed, all available chloroquine replacements are currently limited by resistance, high cost, and/or toxicity.

Considering the concerns noted above, it may be appropriate to continue to use chloroquine in many areas despite the presence of some resistance to this drug. One strategy for extending the period in which chloroquine is useful is to consider host-related characteristics predictive of clinical response when making therapeutic decisions. Using this strategy, patients who are predicted to have a low risk of chloroquine failure can continue to receive this drug, while high-risk patients can be given alternative therapies.

Few studies have considered host-related factors as predictors of antimalarial drug resistance. In a study of largely asymptomatic children in the Solomon Islands, young age, high parasite density, normal spleen size, malnutrition, and

the presence of gametocytes were found to be independent risk factors for chloroquine resistance.<sup>16</sup> In a study of symptomatic children and adults in Thailand, young age, high parasite density, low hemoglobin level associated with recent treatment failure, history of several recent malarial attacks, and diarrhea following treatment were independent risk factors for mefloquine treatment failure.<sup>17</sup> Interpretation of results from the few available studies that report predictors for chloroquine resistance in Africa is limited by small numbers, differing methodologies, and in some cases, failure to control for confounding effects.<sup>3,18–22</sup>

In this report, we analyze the predictive value of host-related factors for chloroquine treatment failure in an urban East-African setting. A small set of easily recognized host-related features offered strong predictive value in identifying patients at increased risk for clinical failure after treatment with chloroquine for uncomplicated falciparum malaria.

### MATERIALS AND METHODS

**Study site.** The study was conducted from August 1998 to March 1999 at Old Mulago Hill Dispensary in Kampala, Uganda. Kampala is an urban center with a population of approximately 800,000 situated at 1,230 meters above sea level. Malaria is meso-endemic in Kampala, occurring perennially with peaks during the two rainy seasons (Ugandan Ministry of Health, unpublished data). Old Mulago Hill Dispensary is an outpatient clinic that provides primary care for patients from Kampala. The Ugandan Ministry of Health currently recommends chloroquine as the first-line agent for uncomplicated malaria in patients of all ages.

**Study subjects.** Consecutive patients presenting with symptoms suggestive of malaria and a positive screening thick blood smear (stained with 10% Leishman's stain for 10 min) were referred for study enrollment. Patients were screened by a study physician for the following inclusion criteria: 1) age of 6 months or greater, 2) either a documented elevated temperature (38.0°C tympanic or 37.5°C axillary) or a patient history of fever in the previous 48 hours,

TABLE 1  
Patient data collected on enrollment

Age, sex, and residence
History of antimalarial use over the prior two weeks
Number of treatments for malaria in the prior 1 year
Pregnancy status (subjective)
Onset of fever and any other symptoms consistent with malaria
Temperature
Spleen size (Hackett's classification system)

3) absence of other causes of fever (based on the impression of the study physician at the time of screening), 4) absence of severe malaria<sup>23</sup> or presence of danger signs (inability to stand or drink, recent convulsions, lethargy, or persistent vomiting in children less than five years of age), 5) willingness to provide informed consent and comply with follow-up, 6) residence within the city of Kampala, and 7) no prior enrollment in the study. Informed consent was obtained from all adult participants and from parents or legal guardians of minors in accordance with the institutional review boards at Makerere University, Kampala and the University of California, San Francisco. For patients who met the screening criteria, a standardized data collection form was completed (Table 1), approximately 2 ml of blood were collected by venipuncture, and urine was also collected. Thin and thick smears were stained with 2% Giemsa for 30 min, and parasite density was determined by counting the number of parasites per 200 white blood cells (WBCs), assuming a WBC count of 8,000/ $\mu$ L of blood.<sup>24</sup> Patients found to have mono-infections with *P. falciparum* and with greater than or equal to 2,000 asexual parasites/ $\mu$ L were enrolled into the study. Urine was tested qualitatively for the presence of chloroquine and its metabolites using the Saker-Solomons test.<sup>25</sup> Hematocrit testing was done using the Hawksley micro-hematocrit calibration system.

**Treatment and follow-up.** All patients were treated with 25 mg/kg of chloroquine (Avlovor, Zeneca; 10 mg/kg on Days 0 and 1; 5 mg/kg on Day 2). All doses of chloroquine were administered directly by the study team. Patients were observed for 30 min after dosing, and if vomiting occurred, the dose was readministered. Patients were seen for follow-up on Days 1, 2, 3, 7, and 14. A standardized history was obtained and on all follow-up days a physical examination was performed including measurement of core temperature using an electronic tympanic thermometer. Finger-prick thick smears were obtained on Days 3, 7, and 14 to determine parasite density using the method described above. If the parasite count dropped below 10 asexual parasites/200 WBCs, the count was made against 500 WBCs. A smear was considered negative if no parasites were seen after viewing 100 high-powered fields. Patients who did not return for follow-up on Days 1, 2, or 3 were visited at home the same day or considered lost to follow-up. Patients not returning on Days 7 or 14 were visited at home within 24 hr or considered lost to follow-up. Patients visited at home underwent the same evaluation procedures as those done in clinic, except the temperature was taken using an axillary thermometer, and all axillary temperatures were converted to core temperatures by adding 0.5°C. This conversion was based on the manufacturer's recommendations (Thermoscan, Braun®)

TABLE 2  
Definitions of clinical and parasitological outcome

<b>Clinical endpoints</b>
Early treatment failure (ETF) = any of the following occurring on Days 1–3
1. Severe malaria/danger signs with parasitemia
2. Temperature on Day 2 $\geq$ 38.0 with parasite density > Day 0 parasite density
3. Temperature on Day 3 $\geq$ 38.0 with parasitemia
4. Day 3 parasite density > 25% Day 0 parasite density
Late treatment failure (LTF) = any of the following occurring on Days 4–14
1. Severe malaria/danger signs with parasitemia
2. Temperature $\geq$ 38.0 with parasitemia
3. History of fever in previous 48 hours with rising parasitemia
Adequate Clinical Response (ACR) = completion of 14 day follow-up without meeting the criteria for ETF or LTF
<b>Parasitological endpoints*</b>
RIII = any of the following
1. Day 3 parasite density > 25% Day 0 parasite density
2. ETF with Day 2 parasite density > Day 0 parasite density <sup>†</sup>
RII = any of the following
1. Day 3 parasite density < 25% Day 0 parasite density and a positive smear Days 4–7
2. ETF with Day 2 or Day 3 parasite density < 25% Day 0 parasite density <sup>†</sup>
RI = Day 3 parasite density < 25% Day 0 parasite density; negative smear on Day 7, and a positive smear Days 8–14
S = Day 3 parasitemia < 25% Day 0 count and negative smears on Days 7 + 14

\* Patients who developed severe malaria/danger signs on Day 1 were not classified.

<sup>†</sup> Modifications of the WHO parasitological classification system.

RI–III = resistant; S = sensitive.

and our own unpublished data. Patients were encouraged to come to clinic on any unscheduled day if they felt ill, and thick blood smears were performed if they presented with a fever or history of recent fever. Patients were excluded from the study for the following reasons: 1) administration of any additional antimalarial drugs during the study period, 2) emergence of any non-malarial febrile illness, 3) relocation away from the study area, or 4) withdrawal of informed consent.

**Outcome classification.** The primary outcome was based on a slightly modified version of the new World Health Organization (WHO) 14-day *in vivo* clinical classification system<sup>26</sup> outlined in Table 2. Patients were also classified according to the WHO parasitological classification system (RI–RIII),<sup>27</sup> with minor modifications made so that the maximum number of patients could be classified in both systems (Table 2). Patients who were identified as clinical treatment failures were treated with 1.25 mg/kg pyrimethamine and 25 mg/kg sulfadoxine (Fansidar, Roche). Patients who developed severe malaria or danger signs were referred to the hospital for therapy with quinine.

**Statistical methods.** Statistical analyses were carried out using the SAS System (SAS Institute Inc., Cary, NC). In all analyses, an adequate clinical response (ACR) was considered a clinical success and an early or late treatment failure (ETF or LTF) was considered a clinical failure. All odds ratios (OR) were calculated from the logistic regression parameter estimates, and Wald confidence intervals were com-

TABLE 3  
Baseline characteristics of patients enrolled in the study

Characteristic	Patients who completed study	Patients who did not complete study
Number	258	36
Gender (% female)	51%	56%
Median age in years	4	3.5
Age range in years	0.5–60	0.5–40
Age < 5 years (%)	55%	56%
Antimalarial use prior 2 weeks (%)*	59%	54%
Chloroquine use prior 2 weeks (%)*	48%	47%
Mean number of treatments for malaria prior 1 year*	3.4	2.8
Palpable spleen (%)	37%	47%
Mean duration of presenting symptoms (days)	4.5	4.0
Mean duration of presenting fever (days)	3.2	3.7
Mean initial temperature (°C)	38.1	38.2
Initial temperature $\geq$ 38.0 (%)	50%	47%
Initial temperature $\geq$ 39.5 (%)	20%	22%
Positive urine chloroquine test (%)*	69%	78%
Mean hematocrit	29.5	28.8
Hematocrit < 30 (%)	53%	61%
Geometric mean parasite density (per $\mu$ L)	91,200	91,400
Parasite density range (per $\mu$ L)	2,000–851,200	2,160–689,280
Parasite density > 100,000/ $\mu$ L (%)	28%	33%

\* Includes only patients in whom data were obtained.

puted. In multivariate analysis, logistic regression was used to fit an initial model that included gender, age, temperature, parasite density, hematocrit, duration of symptoms, duration of fever, spleen size, and two indicator variables representing three categories of pre-study chloroquine use (no chloroquine use within 14 days of enrollment, chloroquine use within 3 to 14 days of enrollment, and chloroquine use within 2 days of enrollment). A final model was selected using the SAS backward selection procedure set at the  $P < 0.05$  level of significance. The same initial model was refitted by substituting urine chloroquine test results for self-reported chloroquine use, and the backward selection procedure was reapplied. Finally, the potential for interaction among the covariates remaining in each of the final multivariate models was assessed by adding all possible two-way, cross-product terms to each model.

## RESULTS

**Enrollment and patient characteristics.** Of the 632 patients referred for screening, 338 were excluded from enrollment. Reasons for exclusion included insufficient parasitemia ( $n = 138$ ), residence outside of Kampala ( $n = 52$ ), concomitant febrile illness ( $n = 44$ ), lack of informed consent ( $n = 41$ ), no documented fever or history of recent fever ( $n = 33$ ), severe malaria or danger signs on presentation ( $n = 15$ ), lack of *P. falciparum* mono-infection ( $n = 13$ , mixed infections with *Plasmodium malariae*), and unsuccessful phlebotomy ( $n = 2$ ). Of the 294 patients who were enrolled in the study, 258 (88%) completed follow-up. Reasons for failure to complete the study included use of additional antimalarial drugs during follow-up ( $n = 18$ ), loss to follow-up ( $n = 11$ ), development of concomitant febrile illness during follow-up ( $n = 3$ ), withdrawal of consent ( $n = 2$ ), and relocation from the study area ( $n = 2$ ). Baseline characteristics of patients enrolled in the study are shown in Table 3. There were no significant differences in baseline character-

istics between patients who did and did not complete the study. Among those who completed the study, 55% were under five years of age. Almost 60% of patients reported antimalarial drug use in the two weeks prior to study entry, and in 86% of these cases chloroquine was used. Among patients who could provide urine (78% of total), 69% had a positive urine chloroquine test. In a comparison of recent chloroquine use based on history with the results of the urine chloroquine test (among patients from whom urine was collected), 93% of those with a positive history of recent chloroquine use had a positive urine chloroquine test, while only 56% of those with a negative history had a negative urine chloroquine test. One half of the patients were febrile at presentation ( $> 38.0^{\circ}\text{C}$  tympanic) and 20% had hyperpyrexia ( $> 39.5^{\circ}\text{C}$  tympanic). Anemia was common; the mean hematocrit was less than 30%. Parasite densities varied greatly, and the geometric mean-parasite density was over 91,000 asexual parasites/ $\mu$ L. Hyperparasitemia (density  $> 100,000/\mu$ L) was present in 28% of patients at presentation.

**Clinical and parasitological outcomes.** Patient outcomes are summarized in Table 4. A total of 258 patients completed the study and were categorized according to clinical response. Of these 258 patients, 255 were also classified according to parasitological outcomes (3 patients who were early treatment failures on Day 1 were not included). The overall incidence of clinical failure was 47%; just under half of these were early treatment failures. Using a parasitological definition of resistance, 70% of patients had an RI, RII, or RIII response after 14 days of follow-up. Only 7 patients, all under the age of 5, developed severe malaria or danger signs, all on Days 1 or 2 (3 with convulsions, 1 with cerebral malaria, 1 unable to sit up, 1 not drinking or breast feeding, and 1 with persistent vomiting and in respiratory distress).

**Predictors of clinical treatment failure.** In a univariate analysis of predictors of clinical outcome, the following factors were significantly associated with an increased risk of chloroquine treatment failure: younger age, higher temper-

TABLE 4  
Patient outcomes

Outcome group	No.	Percent (95% CI)
Clinical Outcomes (n = 258)		
ACR	138	53 (47–60)
ETF	58	23 (18–28)
LTF	62	24 (19–39)
Treatment success	138	53 (47–60)
Treatment failure	120	47 (40–53)
Parasitological Outcomes (n = 255)		
S	76	30 (24–36)
RI	51	20 (15–25)
RII	84	33 (27–39)
RIII	44	17 (13–23)
Sensitive	76	30 (24–36)
Resistant	179	70 (64–76)

ACR (adequate clinical response) = treatment success; ETF (early treatment failure) or LTF (late treatment failure) = treatment failure. RI–III = resistant; S = sensitive.

ature, higher parasite density, lower hematocrit, and a negative urine chloroquine test (Table 5). Although recent chloroquine use was not predictive as a dichotomous variable (OR = 1.3, 95% C.I. 0.8–2.2), consideration of the timing of prior treatment revealed significant results. Compared to patients who reported taking no chloroquine, those with very recent use (within 2 days) were less likely to be treatment failures, while those who last received chloroquine 3 to 14 days prior to study onset were more likely to be treatment failures (Table 5). The following factors were not found to be significantly associated with clinical outcome in univariate analysis: gender, duration of symptoms, duration of fever, number of treatments for malaria in the previous year, or spleen size.

In a multivariate analysis, backward selection logistic re-

TABLE 6  
Multivariate analysis of independent predictors of chloroquine treatment failure

Variable	Odds ratio	95% CI
Model 1 Recent chloroquine use by history (n = 229)		
Age per year increase	0.91	0.87–0.96
Temperature per °C increase	1.75	1.35–2.28
Recent chloroquine use		
No recent chloroquine use	1.00	–
Last dose of chloroquine <3 days prior	0.45	0.23–0.88
Last dose of chloroquine 3–14 days prior	2.91	1.13–7.52
Model 2 Recent chloroquine use by urine test (n = 199)		
Age per year increase	0.92	0.88–0.97
Temperature per °C increase	1.51	1.17–1.95
Urine chloroquine test		
Positive	1.00	–
Negative	2.39	1.21–4.74
Age		
≥5 years	1.00	–
<5 years	3.40	1.84–6.28
Temperature		
<38.0°C	1.00	–
≥38.0°C	2.01	1.09–3.71
Urine chloroquine test		
Positive	1.00	–
Negative	2.07	1.08–3.98

gression was used to build predictive models of clinical outcome. The following variables were significant independent predictors of clinical outcome: age, temperature at presentation, and recent chloroquine use (by history or by results of the urine chloroquine test) (Table 6). Age was a strong predictor of clinical outcome, with decreasing age associated

TABLE 5  
Univariate analysis of potential pre-treatment predictors of chloroquine resistance

Variable (no.)	Number of treatment failures	Odds ratio	95% CI
Age per 1 year increase (258)			
≥5 years (117)	33	1.00	–
<5 years (141)	87	4.10	2.42–6.95
Temperature per °C increase (258)			
<38.0°C (129)	44	1.00	–
≥38.0°C (129)	76	2.77	1.67–4.59
Parasite density per 100,000/μL increase (258)			
<100,000/μL (184)	75	1.00	–
≥100,000/μL (74)	45	2.26	1.30–3.92
Hematocrit per 1 unit decrease (258)			
≥35 (53)	14	1.00	–
<35 (205)	106	2.98	1.53–5.83
Recent chloroquine use (232)*			
No recent chloroquine use (121)	60	1.00	–
Last dose of chloroquine <3 days prior (78)	28	0.57	0.32–1.02
Last dose of chloroquine 3–14 days prior (33)	23	2.34	1.03–5.33
Urine chloroquine test (202)†			
Positive (140)	53	1.00	–
Negative (62)	34	1.99	1.09–3.65

\* Excludes 13 patients who could not recall if they had recently taken chloroquine, 9 patients who could not recall the last day of chloroquine, and 4 patients who took other antimalarials in addition to chloroquine.

† Excludes 56 patients who were unable to provide urine.

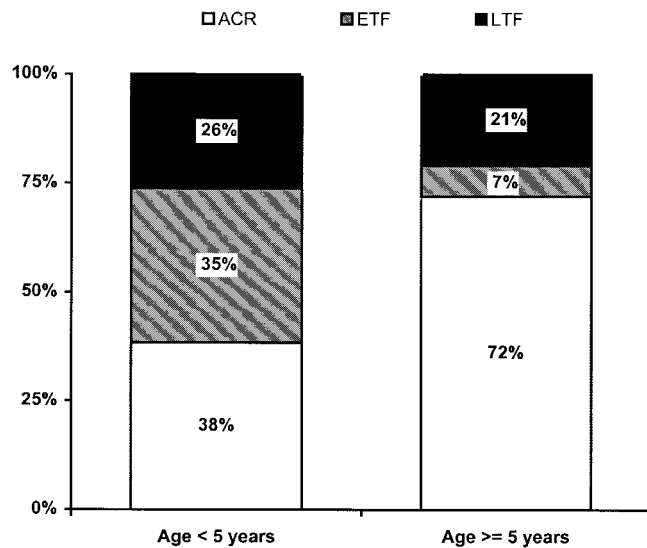


FIGURE 1. Clinical outcomes stratified by age group. ACR = adequate clinical response; ETF = early treatment failure; LTF = late treatment failure.

with an increasing risk of treatment failure. Using 5 years of age as a cut-off, younger patients had more than three times the odds of treatment failure as older patients (OR = 3.4, 95% CI = 1.8–6.3). In addition, among treatment failures, patients in this younger age group were significantly more likely to be early rather than late treatment failures (57% versus 24%,  $P < 0.001$ ) (Figure 1).

Temperature measured at the time of presentation was also a strong predictor of outcome. Increasing temperature was associated with an increased risk of treatment failure. Patients who were febrile at presentation ( $> 38.0^{\circ}\text{C}$ , tympanic) had twice the odds of treatment failure compared to those who were afebrile (OR = 2.0, 95% CI = 1.1–3.7).

A history of chloroquine use during the two weeks prior to study entry was associated with clinical outcome if the data were analyzed according to the timing of prior treatment. Compared to patients who denied recent chloroquine use, those who received their last dose less than 3 days prior to enrollment had half the odds of treatment failure (OR = 0.5, 95% CI 0.2–0.9), while patients who had last taken chloroquine 3 to 14 days prior to enrollment, had almost three times the odds of treatment failure (OR = 2.9, 95% CI 1.1–7.5) (Table 6). Using the Saker-Solomons urine test as an alternative measure of recent chloroquine use, patients with a negative test had over twice the odds of treatment failure (OR = 2.4, 95% CI 1.2–4.7) compared to patients with a positive test (Table 6).

Increasing parasite density and decreasing hematocrit did not retain statistical significance in the multivariate analysis, as parasite density was strongly correlated with temperature ( $\rho = 0.25$ ,  $P < 0.0001$ ) and hematocrit was strongly correlated with age ( $\rho = 0.54$ ,  $P < 0.0001$ ). In the multivariate models there were no significant interactions between any of the covariates.

#### DISCUSSION

Our study revealed a high prevalence of chloroquine-resistant falciparum malaria in Kampala, Uganda. Following

standard therapy with chloroquine, 47% of patients with uncomplicated falciparum malaria were clinical treatment failures and 70% demonstrated parasitological resistance within 14 days. These resistance levels are considerably higher than earlier reports from Uganda,<sup>28,29</sup> but consistent with the 58% risk of parasitological resistance more recently reported from an urban Ugandan setting<sup>30</sup> and reports of resistance from countries neighboring Uganda.<sup>1–7</sup>

Our study identified simple host-related characteristics that were independent predictors of chloroquine treatment failure. Young age was a strong predictor of treatment failure. Compared to older patients, those under the age of five were much more likely to fail therapy and fail early in the course of treatment. These findings are not surprising, as antimalarial immunity increases with age, and as the effectiveness of antimalarial drugs is affected by the immune status of the host.<sup>31,32</sup> Previous studies of mefloquine treatment in Thailand<sup>17,33</sup> and chloroquine treatment in the Solomon Islands<sup>16</sup> and Tanzania<sup>19</sup> have also reported younger age as an independent predictor of treatment failure. Our results and others suggest that age-dependent guidelines for antimalarial drug use may be appropriate in parts of Africa. In areas with a high prevalence of chloroquine resistance, chloroquine may still be appropriate to treat older patients with uncomplicated malaria, while other agents will be necessary for young children. An age-dependent treatment policy should decrease the use of alternative antimalarials, and thus slow the emergence of resistance to these agents. Although our study was not designed to determine the age distribution of chloroquine users in the general population, it is notable that 45% of patients in the study were 5 years of age or older. Treating this large segment of patients with alternative agents would offer relatively little benefit, but increase both cost and pressure on parasites to develop multidrug resistance.

Our study revealed a complex association between recent chloroquine use, which was very common, and clinical outcome. When considered as a dichotomous variable, chloroquine use in the two weeks prior to our study was not significantly associated with clinical outcome, in agreement with other studies.<sup>12</sup> However, we found significant associations between recent chloroquine use and clinical outcome when the time between the last dose of chloroquine and study onset was considered. Patients who reported taking their last dose of chloroquine within 2 days of enrollment did significantly better than those who reported no recent chloroquine use. In addition, patients with a positive urine chloroquine test did significantly better than those with a negative test. A similar result was reported from the United Arab Emirates, where patients with recent chloroquine use (documented by serum drug levels) had significantly less parasitological resistance to chloroquine than patients without recent chloroquine treatment.<sup>34</sup> The opposite effect was seen in patients who had last taken chloroquine 3–14 days prior to presentation. In this situation, clinical treatment failure was significantly more frequent than in patients with no recent chloroquine use. A similar result was seen in Ethiopia and Eritrea, where only 4% of patients returned within two weeks due to chloroquine treatment failure, but 87% of these patients had a subsequent RII or RIII response when chloroquine was readministered.<sup>19</sup> A potential explanation of our

findings is that patients with very recent chloroquine use may benefit from persistent drug levels, while slightly less recent chloroquine use may predict patients with early recrudescence due to selection of a more resistant population of parasites. The impact of recent chloroquine use on clinical outcome is clearly complex.<sup>35</sup> A history of recent treatment (often self-medication) is common in African patients,<sup>36</sup> potentially complicating the therapeutic decision-making process. In areas where chloroquine continues to be the recommended first-line agent, it may be appropriate to treat uncomplicated malaria with chloroquine despite a history of very recent chloroquine use, but to use alternative agents in patients who develop recurrent symptoms 3 days to 2 weeks after initial effective therapy with chloroquine.

Higher temperature at presentation was an independent predictor of chloroquine failure. The underlying mechanism for this association is unclear. A practical implication of this finding is that temperature-based inclusion criteria, which have varied in recent studies,<sup>12,18</sup> could be a source of selection bias. Caution should therefore be taken when comparing studies with different inclusion criteria.

In summary, three easily identifiable host-related factors—age, temperature and recent chloroquine use—were independent predictors of chloroquine treatment failure in Kampala, Uganda. Similar studies of predictors of chloroquine resistance from other areas would be helpful. Ideally, these predictors should be validated prospectively. In areas with significant levels of chloroquine resistance, simple predictors may provide a rational method of stratifying patients into those for whom chloroquine remains an appropriate treatment for uncomplicated malaria and those for whom alternative therapy should be used.

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