THE MORTALITY CONSEQUENCES OF THE CONTINUED USE OF CHLOROQUINE IN AFRICA: EXPERIENCE IN SIAYA, WESTERN KENYA

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Abstract. In spite of increasing resistance, chloroquine remains the primary drug for treatment of malaria in most sub-Saharan African countries. We evaluated the effect of drug treatment policy on the case-fatality rates of children, adjusting for differing distributions of malaria and severe anemia. In 1991, 63% of children were treated with chloroquine while the remaining 37% were treated with a regimen that would eliminate and clear parasitemia. Case-fatality rates were 13% and 4.1%, respectively; the proportion of deaths attributable to chloroquine treatment was 69%. The trend in case-fatality rates for malaria decreased as an increasing proportion of children received an effective treatment regimen; adjusted malaria case-fatality rates were 5.1%, 3.6%, and 3.3% in 1992, 1993, and 1994, respectively, when 85% of children in 1992 and 97% of children in 1993–1994 received effective therapy. These 4 years of data provide strong evidence that continued use of chloroquine in areas with resistance is contributing to excess Plasmodium falciparum-related deaths.

INTRODUCTION

A cornerstone of policies to reduce malaria-related morbidity and mortality in Africa has been early diagnosis and prompt, effective therapy. The criteria used to define an effective regimen have been evolving and include assessments of parasitologic and clinical cures. Chloroquine is the primary drug used for treatment in most sub-Saharan countries, even though there is increasing resistance. The rationale for its continued use is based on not only cost and availability but also the observation that despite parasite resistance, chloroquine treatment is associated with rapid resolution of clinical symptoms and reduction in parasite density.

However, clinical consequences of Plasmodium falciparum chloroquine resistance also have been recognized: persistent parasitemia, return of clinical symptoms such as fever, and persistent anemia despite drug treatment. In addition, a study among children hospitalized with malaria in a district hospital in western Kenya showed a 3-fold higher risk of dying among those treated with chloroquine compared with patients treated with drugs to which P. falciparum was fully susceptible. Children who received chloroquine treatment had a 33% case-fatality rate within 8 weeks of hospitalization compared with an 11% rate among those who received either pyrimethamine/sulfa, quinine, or 5 days of trimethoprim/sulfamethoxazole. Because of its striking effect on survival, pyrimethamine/sulfa has been provided since February 1992 as first-line therapy for children with malaria admitted to that hospital. The objective of this investigation was to evaluate the effect of changing drug treatment policy on the case-fatality rates of children hospitalized with malaria over a 4-year period.

MATERIALS AND METHODS

The study was conducted at Siaya District Hospital (SDH), a 200-bed Ministry of Health hospital serving a population of 600,000 in western Kenya. Children younger than 5 admitted to SDH’s 40-bed pediatric ward were studied, with informed consent obtained from the parent or guardian at the time of enrollment. The baseline period was from March through September 1991, corresponding to the months of highest malaria transmission. Follow-up study periods were during the same months in 1992 and 1994, and from June through September in 1993. Information collected from all children admitted included age, gender, admission hemoglobin, blood smear for malaria parasites, and outcome of hospitalization.

Children received routine in-hospital evaluation and care by the SDH staff. The admission diagnosis assigned by the hospital staff and all treatments administered during hospitalization were recorded. Treatment decisions were made by the SDH medical staff assigned to care for pediatric patients. During the study period, chloroquine was the first-line drug for the treatment of malaria, according to Kenyan national policy. The treatment that each patient received for malaria was recorded for a systematically sampled subgroup of children who were enrolled in concurrent studies.

This study was approved by the scientific steering and ethical review committees of the Kenya Medical Research Institute and the investigational review board of the U.S. Centers for Disease Control and Prevention.

Laboratory. Hemoglobin was measured from a capillary finger-prick using a Hemocue® (Mission Viejo, CA) machine. Thick and thin blood smears were stained with 3% Giemsa for 30 minutes. The number and species of Plasmodium parasites were read per 300 white blood cells (WBC). Parasite density was calculated based on the number of WBC/mm³ determined by the complete blood count. If the WBC count was not available, parasite density was calculated using the population mean of 8,000 WBC/mm³.

Analysis. Data were analyzed using EpiInfo 5 (Centers for Disease Control and Prevention, Atlanta) and SAS (SAS Institute, Inc., Cary, NC) statistical package software. Categorical variables were analyzed using frequency distributions, and differences among groups were assessed using χ² or Fisher’s exact tests, as appropriate. The Wilcoxon rank sum test or a two-tailed t test was used to compare the distribution of continuous variables. Direct standardization was used to account for differing distributions of malaria and severe anemia (defined as an admission capillary hemoglobin < 5.0 g/dL) among children admitted each year. The 1991 admission data were

*Use of trade names is for identification only and does not imply endorsement by the Public Health Service or the U.S. Department of Health and Human Services.
used as the standard population. The adjusted number of deaths each year among children with malaria was calculated separately for children with hemoglobin < or ≥ 5.0 g/dL, using the observed category-specific case-fatality rates for that year.

**Malaria case definition.** Because of the high prevalence of falciparum parasitemia in this setting, (approximately 80–90% of children in the community and over 60% of hospitalized children have a blood smear positive for asexual parasites of *P. falciparum*), the analysis was restricted to those children who met criteria for malaria illness. The case definition for malaria illness used was: a parasite density of ≥ 5,000 parasites/mm³ and documented axillary temperature of ≥ 37.5°C or a parasite density of ≥ 20,000 parasites/mm³ irrespective of documented temperature.

**RESULTS**

During the 1991 baseline 6-month study period, a total of 1,223 children younger than 5 were admitted to the pediatric ward. Among those admitted, 467 (38%) met the case definition for malaria illness. There were 46 in-hospital deaths, for a case-fatality rate of 9.9% (Table 1). The corresponding numbers of children admitted during the 1992–1994 study years were 1,117, 970, and 1,453, respectively; 62–69% of children had a positive blood smear with asexual parasites of *P. falciparum*, and the proportion of children meeting the malaria case definition varied from 25–38% (Table 1). The unadjusted case-fatality rates for children with malaria illness in 1992, 1993, and 1994 were 5.0%, 3.3%, and 2.8%, respectively.

The proportions used for standardizing the case-fatality rates were 55.7% for those children meeting the malaria case definition (467 in 1991/total number of children with a positive blood smear in 1991) and 30% for the proportion of children with severe anemia. Adjusted malaria case-fatality rates were 5.1%, 3.6%, and 3.3% in 1992, 1993, and 1994, respectively (Table 2). Cerebral malaria and hyperparasitemia were uncommon manifestations of malaria in this setting, accounting for less than 2% of all children with malaria illness.

In 1991, of the 467 children with malaria, 296 (63%) were treated with chloroquine alone, while the remaining 171 were treated with either pyrimethamine/sulfa, quinine, or 5 days of trimethoprim/sulfamethoxazole. Children treated with chloroquine had a 13% case-fatality rate compared with a 4.1% rate among those treated with the other three regimens; relative risk = 3.22 (95% CI:1.47, 7.04). The proportion of malaria-related deaths attributable to chloroquine treatment was 69%. The case-fatality rate for malaria declined from 1991 through 1994 as the percentage of children who received an effective treatment regimen increased (Figure 1).

**DISCUSSION**

These results extend previous observations that chloroquine resistance is associated with increased clinical failures and hospitalizations for malaria, and clearly link drug resistance and malaria treatment with survival among hospitalized children. During 1991, the proportion of deaths attributable to chloroquine treatment was 69%, indicating that two-thirds of deaths could have been prevented, a result supported by the decline in the malaria case-fatality rates observed from 1992–1994 in association with a change in treatment policy. These 4 years of data provide strong evidence that the continued use of chloroquine in areas with resistance is contributing to *P. falciparum*-related deaths.

In this setting, the need to change drug treatment policy is apparent, but the real challenge is to recognize when first-line therapy is no longer effective before resistance is associated with significant malaria-related mortality. The controversy has been over identifying indicators to adequately monitor the consequences of resistance, including both parasitologic and clinical failures. Commonly used measurements to define responses to treatment have included parasitologic clearance at 72 hours, clinical status (recurrent fever) at 14 days, and hematologic recovery.

At present, recommended standardized procedures in children younger than 5 include treatment at day 0, with follow-up parasite density and temperature measurements at days 3, 7, and 14. This approach targets the non-immune population at greatest risk for severe disease and provides information on the proportion of children who fail to eliminate their parasites and those who become ill again within a timeframe consistent with recrudescence infection rather than reinfection. Several sources have suggested that *in vivo* clinical failure rates of 14–25% for a first-line treatment should indicate the need to change drug policy.

Factors in the decision on when to change the first-line treatment will include programmatic considerations, assessment of costs, available second-line agents, and the acceptable proportion of clinical failures. The reluctance to abandon chloroquine is based, in part, on its low cost, wide availability, and acceptance. Chloroquine results in rapid initial

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Total number of children admitted to Siaya District Hospital and the number of children with parasitemia, malaria, severe anemia, and malaria-related deaths from 1991–1994 (unadjusted data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months):</td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>12.6</td>
</tr>
<tr>
<td>median</td>
<td>9</td>
</tr>
<tr>
<td>Number of children with a positive blood smear (%)</td>
<td>838 (69%)</td>
</tr>
<tr>
<td>Number of children with malaria illness (%)</td>
<td>467 (38%)</td>
</tr>
<tr>
<td>Number of children with severe anemia (%)</td>
<td>141 (30%)</td>
</tr>
<tr>
<td>Total number of malaria-related deaths (%)</td>
<td>46 (9.9%)</td>
</tr>
</tbody>
</table>

* Admissions from March through September.
† Admissions from June through September.
improvement of clinical symptoms (e.g., headache and fever), which has contributed to its widespread acceptance and the perception that it remains effective, leading to an unwillingness of both health workers and patients to discontinue using chloroquine.

The higher cost of second-line treatment, such as Fansidar (pyrimethamine/sulfadoxine) or combination therapy with artemisinin derivatives, often is cited as prohibitive for most sub-Saharan countries where the average health-care expenditure per person is low. However, providing efficacious first-line treatment is more cost-effective when compared with the cost of recurrent illness and retreatment where drug resistance levels are high. The higher cost of second-line drugs and combination treatment protocols, as well as concern about the development of drug resistance in the “next-line” drug, although valid considerations, cannot justify withholding life-saving treatment. Of additional concern are observations suggesting that the use of chloroquine to treat chloroquine-resistant *P. falciparum* infections may lead to greater spread of the resistant strains because of enhanced gametocyte infectivity—thus worsening the problem. The ongoing monitoring of drug resistance also will be important to detect the development of resistance in the “next-line” drug used or to detect regained sensitivity to a drug that has not been used recently, as has been described for chloroquine, to develop rational drug treatment policies.

These observations in western Kenya were made in the context of routine care; except for providing anti-malarial medications, there were no changes in the care or availability of supportive therapies during the study period. In this setting, the most prevalent manifestation of severe *P. falciparum* illness is severe anemia. Overall, case-fatality rates were higher for severely anemic children than those whose hemoglobin levels were greater than 5.0 g/dL, but the benefits of effective malaria therapy did not depend on hemoglobin level and also were demonstrated for survival at 8 weeks after hospitalization, suggesting a causal role for recrudescent parasitemia. The malaria case-fatality rates among children hospitalized at SDH were reduced to approximately the 3–4% levels seen in developed countries and locations where cerebral malaria is more common. It is striking that in a different setting on the coast of Kenya, where 28% of children met the WHO criteria for cerebral malaria, the overall malaria case-fatality rate was 3.5%. These observations suggest that a case-fatality rate of 3–4% for malaria among hospitalized children, regardless of the case-mix of severe disease, may

### Table 2

<table>
<thead>
<tr>
<th>Year</th>
<th>1991*</th>
<th>1992*</th>
<th>1993†</th>
<th>1994*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of children with a positive blood smear</td>
<td>838</td>
<td>731</td>
<td>598</td>
<td>1008</td>
</tr>
<tr>
<td>Number of children with malaria illness (%)</td>
<td>467 (56%)</td>
<td>407 (56%)</td>
<td>333 (56%)</td>
<td>561 (56%)</td>
</tr>
<tr>
<td>Number of children with severe anemia (%)</td>
<td>141 (30%)</td>
<td>122 (30%)</td>
<td>100 (30%)</td>
<td>168 (30%)</td>
</tr>
<tr>
<td>Number of deaths among children with severe anemia</td>
<td>17</td>
<td>11</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Number of deaths among children with a hemoglobin level ≥ 5.0 g/dL</td>
<td>29</td>
<td>10</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Total number of malaria-related deaths (%)</td>
<td>46 (9.9%)</td>
<td>21 (5.1%)</td>
<td>12 (3.6%)</td>
<td>19 (3.3%)</td>
</tr>
</tbody>
</table>

* Admissions from March through September.
† Admissions from June through September.

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**Figure 1.** Case-fatality rates and proportion of children receiving effective treatment for malaria, Siaya District Hospital.
represent a useful measurement for monitoring overall quality of treatment.\textsuperscript{19} This observation will require validation from a number of sites to determine its utility.

This study was conducted in a health facility where laboratory testing was available, documentation of the treatment received was possible, and cause-specific mortality was obtained. The applicability of hospital-based observations to mortality patterns in the community may be questioned, as it is well recognized that most malaria-related deaths among children occur outside a health facility.\textsuperscript{20} However, recent evidence from Senegal supports the belief that increasing chloroquine resistance is also causing increased malaria-related child mortality at the community level.\textsuperscript{21} The need to ensure access to and availability of effective malaria treatment will be critical if we are to reduce the death toll caused by this disease.\textsuperscript{22}

Improved child survival in Africa will require more-effective case management of malaria. Persistent parasitemia from treatment with an inefficacious drug is associated with increased malaria-related mortality. While we try to understand the clinical consequences of parasite resistance, we must not lose sight of the most important of all clinical outcomes: death. Efficacious therapy does improve survival, and this strategy is practical for implementation in hospital settings in Africa. Chloroquine resistance has been reported from all countries in sub-Saharan Africa; children are being treated with chloroquine in settings where clinical failures already exceed 25%.\textsuperscript{23–28} The debate about chloroquine drug resistance is no longer about the increased cost of second-line medications—it is about the cost of life. We cannot justify allowing children to die in Africa because they are not receiving effective treatment.

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