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Treatment History and Treatment Dose Are Important Determinants of Sulfadoxine-Pyrimethamine Efficacy in Children with Uncomplicated Malaria in Western Kenya

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This study retrospectively studied amendable determinants of sulfadoxine-pyrimethamine (SP) efficacy involving 2869 treatments among 1072 Kenyan children <5 years old who had uncomplicated malaria. The dose was based on age: one-quarter tablet was given to infants <1 year old, one-half tablet was given to 1–3-year-old children, and a full tablet was given to 4-year-old children. Only 23.5% received the internationally recommended target dose of 25/1.25 mg of SP per kg of body weight. SP intake in the previous 15–35 days (adjusted relative risk, 1.67; 95% confidence interval, 1.35–2.07) and low SP dose (<27.5/1.375 mg/kg) (adjusted relative risk, 1.58; 95% confidence interval, 1.17–2.13) explained 38% of parasitological treatment failures by day 7. Patients with recent SP intake are likely to have recrudescent infections and may need close follow-up if treated with SP or alternative treatment. Applying our weight-for-age data to 31 existing age-based SP dose recommendations predicted that 22 of them would result in underdosing of >25% of children <5 years. Many age-based dose recommendations need urgent revision, because SP is increasingly used as first-line treatment in sub-Saharan Africa.

Over the last decade, 11 countries in sub-Saharan Africa have replaced, or are in the process of replacing, chloroquine (CQ) with sulfadoxine-pyrimethamine (SP) or a combination of CQ plus SP for first-line treatment of uncomplicated Plasmodium falciparum malaria. The long half-lives of sulfadoxine and pyrimethamine (180 and 95 h, respectively) [1] favor the selection of resistant parasites [2, 3], and there is a general concern that

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This study was approved by the institutional review boards of the Kenya Medical Research Institute and the Centers for Disease Control and Prevention. Informed consent was obtained from all caregivers after explanation of the study procedures in the local language.

This is Asembo Bay Cohort Project manuscript number XVIII.

The opinions or assertions contained in this manuscript are those of the authors and are not to be construed as official or reflecting the views of the US Public Health Service or Department of Health and Human Services. Use of trade names is for identification only and does not imply endorsement by US Public Health Service or Department of Health and Human Services.
the effective life of SP monotherapy may be limited in Africa [2, 3]. In Thailand, SP replaced CQ in the early 1970s, but, within 5 years, radical cure rates by day 28 had dropped from 83% in 1975 to 22% in 1979 [4]. Increasing treatment failure rates with SP have also been observed recently in northeastern Tanzania and Kenya [5–7]. In most of the remaining part of sub-Saharan Africa, however, it remains very effective [8, 9], which suggests that there is considerable geographical variation in the development and distribution of SP resistance. Close monitoring of SP efficacy will be necessary to assess its durability in specific areas.

In vivo antimalarial treatment failures may be caused by insufficient drug concentrations, host factors, parasite factors (including drug resistance), or a combination of them [10]. Although all these factors can cause treatment failure in the individual, they may also contribute to the development and intensification of parasite drug resistance in the population by increasing the likelihood of exposure of parasites to suboptimal drug levels [10, 11]. Knowledge of the determinants of SP treatment outcome will help to identify individual patients who are at risk of treatment failure and will assist in the adequate interpretation of treatment outcome in comparative antimalarial treatment studies or longitudinal surveillance of SP efficacy. They also help to identify modifiable factors that may contribute to the development of resistance. We studied these putative, modifiable determinants of SP treatment outcome among children <5 years old with symptomatic uncomplicated falciparum malaria in western Kenya.

PATIENTS, MATERIALS, AND METHODS

Study area and population. This study was conducted between April 1993 and April 1997 in 15 villages in Rarieda Division on the shores of Lake Victoria in western Kenya, as part of a larger ongoing community based study of the acquisition of natural immunity in children <5 years old (Asembo Bay Cohort Project [ABCP]). The study site and methodology have been described in detail elsewhere [12, 13]. In brief, the population was ethnically homogeneous, with >95% belonging to the Luo tribe. Of the children enrolled in the ABCP, 17.4% had sickle cell trait [14]. This area has intense perennial malaria transmission, with a mean range of 60–300 infected bites/person/year [15]. Of the children <5 years old, 60%–90% have detectable P. falciparum parasitemia at any time [16]. More than 95% of these infections are due to P. falciparum, and almost all of the remainder are due to P. malariae. Infections with P. ovale are rare [13]. High-grade resistance to CQ is widespread [17].

Mothers were enrolled during pregnancy, together with their newborns and other children <5 years old. Each child enrolled in the ABCP was visited every 2 weeks by a village monitor, who was a resident in the same village. At each visit, a morbidity questionnaire was completed, which included questions on the history of antimalarial use in the previous 2 weeks, and the axillary temperature was taken. At every other visit (approximately monthly), the child’s weight and height were measured, and a blood sample (250–500 µL) was taken by finger or heel prick for the determination of hemoglobin concentrations and the presence of malaria parasites. Mothers were asked to bring their children to the village monitor in between scheduled visits whenever they thought their child was ill. In case of a documented fever (temperature, ≥37.5°C), an additional malaria smear was taken. During the study period, SP was not widely available in the area outside of the Centers for Disease Control and Prevention (CDC)/Kenya Medical Research Institute research setting, but it was introduced as part of the new national malaria treatment policy in late 1998 through early 1999.

Study design and procedures. The current treatment study was nested within the larger ABCP, as described elsewhere [18]. Children were enrolled in the treatment study if they fulfilled the following criteria: age 0–59 months, axillary temperature ≥37.5°C, no signs of severe malaria (hemoglobin ≥5g/dL, parasitemia ≤100,000/µL, and normal mental status) [19], no history of SP treatment in the previous 14 days [20], and P. falciparum infection (pure or mixed species).

The dose of SP in this study was, as in many parts of Africa, based on age, as opposed to body weight, and was designed to obtain an average of 25/1.25 mg/kg SP, the internationally recommended target dose. Infants were given one-quarter tablets, 1–3-year-old children were given one-half tablets, and 4-year-old children were given full tablets [21]. Each tablet contained 25 mg of pyrimethamine and 500 mg of sulfadoxine. The brands of SP used during the 4-year study period were Fansidar (Hoffman–La Roche), Falcidin (Cosmos), and Orodar (Elys Chemical Industries). The quality of the local brands was confirmed by high-performance liquid chromatography in the CDC laboratories in Atlanta. The tablets were crushed and given with water under supervision of the study staff. Every child was observed for 30 min to see if vomiting occurred, and, if so, the full dose was repeated. Hemoglobin concentrations were measured using the Haemocue method (Haemocue). Each child was visited at home on days 2 and 7, at which time a morbidity questionnaire was completed, and the axillary temperature and a malaria blood smear were taken. If the study participants could not be found on the scheduled days, the village monitor revisited the homes on day 3 or 4 and day 8, 9, or 10.

Definitions. Treatment failures and successes were defined using a modified version of the World Health Organization (WHO) classification system [22]. Early clinical failure (ECF) was defined as either clinical deterioration requiring alternative treatment or persistence of fever with pure or mixed falciparum
parasitemia on day 2 that was greater than the pretreatment density or persistence of any *P. falciparum* parasites with fever by day 3 or 4 [22]. Parasitological treatment failure (PTF) was defined as the presence of *P. falciparum* parasites on days 7–10, regardless of the presence of symptoms. The presence of other plasmodium species in the absence of *P. falciparum* was not considered to be a treatment failure in this analysis. Cumulative treatment failure (CTF) by day 7 was defined as having either an ECF by days 2–4 or a PTF by days 7–10. Clinical treatment failures were retreated according to WHO guidelines [22] with halofantrine (Halfan 3 × 8 mg/kg; SmithKlineBeecham), which is effective in the retreatment of mulidrug-resistant *P. falciparum* malaria [23]. The use of halofantrine as retreatment antimalarial was discontinued in 1996 after the discovery of its potential adverse cardiac effects [24]; it was replaced by amodiaquine [20].

**Determinants studied.** We retrospectively studied the following putative determinants of treatment failure: age, sex, year of treatment, season, history of recent SP or CQ treatment, pretreatment parasite density, axillary temperature, infection with mixed or pure plasmodium species, gametocytemia, hemoglobin level, SP dose in milligrams per kilogram of body weight, nutritional status (weight-for-age, weight-for-height, and height-for-age z scores ≤2), number of days of symptoms prior to treatment, and sickle cell hemoglobin (HbS) phenotype [18, 25–30]. Three of these determinants were considered to be amendable: SP dose, history of recent CQ treatment, and history of recent SP treatment.

**Estimates of over- and underdosing.** The potential risk of over- and underdosing were calculated for different age-based dose recommendations for SP. This was done using a weight-for-age data set containing weight relative to age from a random sample of 3575 children enrolled in cross-sectional surveys as part of a larger study of the impact of insecticide-treated bed nets on childhood morbidity and mortality conducted between 1996 and 1999 [31]. This analysis was done weighted for “malaria risk,” with young children contributing relatively more to the analysis than older children. This weight factor was based on the age distribution of >20,000 children treated for malaria in peripheral health clinics in the same study area over a 4-year period between 1995 and 1999. To compare the different dose regimens an index score for over- and underdosing was calculated as \((1 \times \text{proportion underdosed}) + (5 \times \text{proportion overdosed})\), where underdosing was defined as <25/1.25 mg/kg SP, and overdosing as >70/3.5 mg/kg SP. The definition of overdosing was based on the increased risk of severe bone marrow depression resulting in potentially fatal megaloblastic anemia described for pyrimethamine doses above this threshold [32]. Overdosing was given, arbitrarily, 5 times more weight than underdosing, because the risk of potentially fatal adverse events due to overdosing was considered to be more serious than treatment failure due to underdosing.

**Data management and statistical analysis.** Data forms were checked, coded, and entered using Clarion software (Top-speed/Soft Velocity). Data were cleaned using range and internal consistency checks. Confidence intervals (CIs) and *P* values were corrected for multiple observations per child in both univariate and multivariate analysis. Variables associated with treatment outcome in the univariate analysis (*P* < .10) were included in the full multivariate model. All models were created using Proc Genmod, a procedure within the SAS software package (version 8.0; SAS Institute), by use of a log-link function and a binomial distribution [33]. Age and study year were always forced into the model. All other factors included in the full model were considered to be candidates for removal. The population attributable fraction (PAF) was calculated as follows: \([\text{prevalence} \times (\text{RR} - 1)]/(1 + \text{prevalence} \times (\text{RR} - 1))\), where “RR” denotes “relative risk.” The overall PAF for a combination of determinants (which is not additive) was calculated as follows: \(1 - \left(\left[1 - \text{PAF}_1\right] \times \left[1 - \text{PAF}_2\right] \times \ldots \times \left[1 - \text{PAF}_n\right]\right)\) [34]. For all statistical tests, a 2-sided *P* < .05 was considered to be significant.

**RESULTS**

**Patient characteristics.** Between April 1993 and April 1997, 3620 treatments were given to 1195 children. The median number of treatments per child was 2 (interquartile range [IQR], 1–5 treatments). Of all treatments, 42.6% (1543) were given to infants, and the proportion of treatments given to older children declined with age (1 year, 29.0%; 2 years, 14.8%; 3 years, 9.0%; and 4 years, 4.7%). Overall, 82.9% (3001/3620) of treatments could be followed up successfully on either day 2 (64.2%), day 3 (13.7%), or day 4 (5.0%), and 78.0% (2823/3620) were followed up on “day 7” (54.3% on day 7 and 23.7% on days 8–10). This resulted in an overall success rate of follow-up by day 7 of 79.3% (2869 treatments). The baseline characteristics of these 2869 treatments are summarized in table 1. There were no differences between the characteristics of the treatments followed-up successfully and those lost to follow-up by day 7, except for the year of study, with lower follow-up rates at the very beginning and at the very end of the study (data not shown). Overall, 2.2% (66/3001) of the treatments resulted in an ECF, and 16.6% (465/2803) resulted in a PTF. The CTF risk by day 7 was 18.5% (531/2869).

**Determinants of treatment failure.** The only independent determinant of ECF was age. ECF was most prevalent during the first 2 years of life (age <24 months vs. ≥24 months: RR, 3.4; 95% CI, 1.4–8.2) (figure 1). Age was also a determinant of PTF, although, unlike ECF, the risk of PTF increased with age until age 3 years. By contrast, 4-year-old children were at Amendable Determinants of SP Efficacy • JID 2003:187 (1 February) • 469
Table 1. Univariate analysis of factors associated with cumulative treatment failure by day 7.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>All patients</th>
<th>Patients with treatment success (n = 2338)</th>
<th>Patients with treatment failure (n = 531)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>2869</td>
<td>1388 (48.4)</td>
<td>1119 (47.9)</td>
<td>269 (50.7)</td>
<td>.29</td>
</tr>
<tr>
<td>Age, median months (IQR)</td>
<td>2869</td>
<td>14.4 (8.0–26.9)</td>
<td>14.1 (7.9–27.3)</td>
<td>15.4 (8.4–26.0)</td>
<td>.52</td>
</tr>
<tr>
<td>Year of study</td>
<td>2869</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>April 1993– March 1995</td>
<td>1553</td>
<td>54.1</td>
<td>1286 (55.0)</td>
<td>267 (50.3)</td>
<td></td>
</tr>
<tr>
<td>April 1995– March 1997</td>
<td>1316</td>
<td>45.9</td>
<td>1052 (45.0)</td>
<td>264 (49.7)</td>
<td>.06</td>
</tr>
<tr>
<td>Axillary temperature, mean °C (SE)</td>
<td>2599</td>
<td>38.3 (0.02)</td>
<td>38.3 (0.02)</td>
<td>38.3 (0.04)</td>
<td>.45</td>
</tr>
<tr>
<td>Parasite density, geometric mean (95% CI)</td>
<td>2869</td>
<td></td>
<td></td>
<td></td>
<td>.54</td>
</tr>
<tr>
<td>1–4999 parasites/µL</td>
<td>975</td>
<td>34.0</td>
<td>820 (35.1)</td>
<td>155 (29.2)</td>
<td></td>
</tr>
<tr>
<td>5000–14,999 parasites/µL</td>
<td>826</td>
<td>28.8</td>
<td>636 (27.2)</td>
<td>190 (35.8)</td>
<td></td>
</tr>
<tr>
<td>≥15,000 parasites/µL</td>
<td>1068</td>
<td>37.2</td>
<td>892 (37.7)</td>
<td>186 (35.0)</td>
<td>.0008</td>
</tr>
<tr>
<td>Mixed vs. pure species</td>
<td>2869</td>
<td>6.7</td>
<td>159 (6.8)</td>
<td>33 (6.2)</td>
<td>.61</td>
</tr>
<tr>
<td>Gametocytes</td>
<td>2850</td>
<td>6.0</td>
<td>140 (6.0)</td>
<td>30 (5.7)</td>
<td>.76</td>
</tr>
<tr>
<td>Hemoglobin, mean g/dL (SE)</td>
<td>2263</td>
<td>9.3 (0.06)</td>
<td>9.4 (0.06)</td>
<td>9.1 (0.12)</td>
<td>.06</td>
</tr>
<tr>
<td>Hemoglobin &lt;8.0 g/dL</td>
<td>642</td>
<td>28.4</td>
<td>505 (27.5)</td>
<td>137 (32.4)</td>
<td>.05</td>
</tr>
<tr>
<td>HbS phenotype</td>
<td>2274</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>1867</td>
<td>82.1</td>
<td>1472 (80.4)</td>
<td>395 (89.0)</td>
<td></td>
</tr>
<tr>
<td>AS</td>
<td>344</td>
<td>15.1</td>
<td>305 (16.7)</td>
<td>39 (8.8)</td>
<td></td>
</tr>
<tr>
<td>SS</td>
<td>63</td>
<td>2.8</td>
<td>53 (2.9)</td>
<td>10 (2.3)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Wasted, WHZ &lt;2</td>
<td>2702</td>
<td>2.4</td>
<td>54 (2.5)</td>
<td>11 (2.2)</td>
<td>.69</td>
</tr>
<tr>
<td>Stunted, HAZ &lt;2</td>
<td>2775</td>
<td>35.3</td>
<td>801 (35.4)</td>
<td>179 (34.9)</td>
<td>.83</td>
</tr>
<tr>
<td>Underweight, WAZ &lt;2</td>
<td>2763</td>
<td>14.3</td>
<td>328 (14.6)</td>
<td>66 (12.7)</td>
<td>.23</td>
</tr>
<tr>
<td>Severity symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of fever, median days (IQR)</td>
<td>2869</td>
<td>2 (2–4)</td>
<td>2 (2–4)</td>
<td>2 (2–4)</td>
<td>.32</td>
</tr>
<tr>
<td>Temperature &gt;39°C plus vomiting</td>
<td>1659</td>
<td>10.8</td>
<td>152 (11.3)</td>
<td>27 (8.5)</td>
<td>.13</td>
</tr>
<tr>
<td>SP dose, mean mg/kg (SE)</td>
<td>2726</td>
<td>1.06 (0.007)</td>
<td>1.06 (0.007)</td>
<td>1.03 (0.01)</td>
<td>.01</td>
</tr>
<tr>
<td>Pyrimethamine &lt;1.375 mg/kg</td>
<td>2726</td>
<td>85.1</td>
<td>1866 (84.1)</td>
<td>455 (89.6)</td>
<td>.0015</td>
</tr>
<tr>
<td>SP Rx in previous 15–35 days</td>
<td>2869</td>
<td>11.9</td>
<td>240 (10.3)</td>
<td>100 (18.8)</td>
<td>.0001</td>
</tr>
<tr>
<td>CQ Rx in previous 2 weeks</td>
<td>2869</td>
<td>18.2</td>
<td>427 (18.3)</td>
<td>94 (17.7)</td>
<td>.76</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of patients, except where noted. There were 2869 treatments among 1072 children <5 years old. CI, confidence interval; CQ, chloroquine; HAZ, height-for-age z score; HbS, sickle cell hemoglobin; IQR, interquartile range; Rx, treatment; SP, sulfadoxine-pyrimethamine; WAZ, weight-for-age z score; WHZ, weight-for-height z score.

a markedly lower risk of PTF (7.1%) (figure 1). Apart from age, the following factors were associated with treatment failure (PTF and CTF) in univariate analysis (P < .10) and were considered for evaluation in a multivariate model: study year, HbS phenotype, pretreatment parasite density, and pretreatment hemoglobin level (all nonamendable factors), and history of recent SP intake and SP dose in mg/kg based on body weight (both amendable factors) (table 1). At the time of the study, SP was not widely available in this area outside of the ABCP infrastructure. During the whole study period, caretakers reported 35 SP treatments that could not be accounted for in our study records and that, presumably, were obtained outside the study setting. The history of recent SP intake could, therefore, be reliably assessed using the SP treatment records from the study.

In subsequent multivariate analysis (after adjusting for the nonamendable risk factors that were retained in the model [i.e., age, study year, parasite density, and HbS phenotype]), recent SP intake and SP dose were found to be strong predictors of PTF and CTF by day 7 (table 2). This effect of recent SP intake was evident for a period up to 35 days (figure 2). Among the 3620 treatments, 428 (11.8%) were associated with a history of SP intake in the previous 15–35 days (10.4% among children <1 year old and 12.9% among older children). The median dose obtained with this regimen was 20.2/1.01 mg/kg SP (IQR, 0.83–1.25 mg/kg SP), and more than three-fourths of the doses received (76.2%) were <25/1.25 mg/kg, the internationally recommended target dose. Comparison of sensitivity, specificity, and Youden’s index scores showed that a dose of 27.5/1.375 mg/kg SP was the most discriminative threshold concentration.
below which an increased risk of treatment failure was observed (figure 3 and table 2). Overall, 85.2% of the treatments received were at a dose below 27.5/1.375 mg/kg. The rates of PTF and CTF in the group who had both risk factors were 28.0% (82/293) and 29.9% (90/301), respectively, compared with 10.3% (38/369) and 12.4% (47/378), respectively, in the group with no recent SP intake and who received ≥27.5/1.375 mg/kg.

**PAF.** The PAFs for PTF and CTF were calculated for these 2 preventable determinants of treatment failure. For CTF, this was 24.0% for SP doses <27.5/1.375 mg/kg and 7.1% for recent SP intake in the previous 15–35 days (table 2). The overall preventable PAF, which is not additive, was 29.6%, which suggests that, with this given level of drug resistance and age distribution, more than one-fourth of all instances of CTF can potentially be prevented when sufficient dosing and alternative retreatment guidelines are used. The corresponding overall PAF for PTF was 38.0%.

**Comparison of recent and current SP treatment guidelines.** We were surprised that, with our age-based dose regimen, such a large proportion of children in our study had received less than the target dose of 25/1.25 mg/kg SP recommended by the WHO when calculated against the body weight of the child. We, therefore, reviewed recent and current international dose recommendations for SP for children <5 years old from WHO, UNICEF, and key pediatric, infectious diseases, and tropical medicine textbooks (English language) (figure 4). This indicated that important variation exists in current treatment recommendations for SP in young children. Almost all recommendations that specifically mention a target dose in mg/kg use 25/1.25 mg/kg SP, and a minority recommend 20/1.00 mg/kg [65–68]. One recent guideline from UNICEF recommends doses lower than this [69]. Overall, 31 age-based dose recommendation for children <5 years old could be identified, representing 11 different variations. Overdosing was rare for all regimens. However, underdosing was predicted to occur in ≥25% of the children at 22 of the 31 dose recommendations. The dose used in the current study was recommended by most of the American textbooks [36–49], either as monotherapy or in combination or subsequent to oral quinine. The dose recommended by the Oxford Textbook of Medicine [35] resulted in the lowest overall dose, with 79.2% of children predicted to receive <1.25 mg/kg. The different dose recommendations by the WHO resulted in the highest proportion of adequate dosing [59, 60, 62, 64]. The groups at particular risk for underdosing in the most commonly used age based regimens were the 6–12-month-old infants (if one-fourth tablet instead of one-half tablet is used) and the 3 and 4 year-old children (if one-half tablet is used instead of three-fourths or a full tablet) (figure 5).

**DISCUSSION**

We retrospectively identified 2 preventable, independent determinants of treatment outcome with SP in children <5 years old with uncomplicated falciparum malaria. A low SP dose based on body weight (milligrams/kilograms) and a history of SP intake in the previous 5 weeks explained approximately one-third of all treatment failures and may contribute to the development or intensification of SP resistance.

In contrast to several previous studies of predictors of treatment efficacy [25–29], we observed a trend towards increasing failure risk by day 7 with increasing age in the age group <3 years old (figure 1). This result was unexpected, because natural immunity is acquired rapidly in this area of intense malaria transmission and, as a result, older children typically show better treatment responses [25–29]. The lower failure risk in the <6-month-old versus 6–12-month-old infants can be explained

Table 2. Modifiable determinants of treatment failure: multivariate analysis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>PTF</th>
<th></th>
<th></th>
<th>CTF</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (95% CI)</td>
<td>P</td>
<td>PAF, %</td>
<td>RR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>SP intake in previous 15–35 days</td>
<td>1.67 (1.35–2.07)</td>
<td>&lt;.0001</td>
<td>7.3</td>
<td>1.65 (1.36–2.01)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>SP dose &lt;27.5/1.375 mg/kg</td>
<td>1.58 (1.17–2.13)</td>
<td>.003</td>
<td>33.1</td>
<td>1.37 (1.05–1.81)</td>
<td>.02</td>
</tr>
</tbody>
</table>

**NOTE.** Data were adjusted for sickle cell hemoglobin phenotype, parasite density, age, and year of study. CI, confidence interval; CTF, cumulative treatment failure (i.e., early clinical failure on day 2–4 or any parasitemia on day 7–10); PAF, population attributable fraction; PTF, parasitological treatment failure (i.e., any parasitemia on day 7–10); RR, relative risk.
by the presence of protective factors in the very young infants, such as fetal hemoglobin and maternal antibodies against malaria. A likely explanation for the increasing proportion of failures with age is the impact of underdosing. The dose of SP in this study was, as in many parts of Africa, determined by age, as opposed to weight. As children grow older, and become heavier, they receive relatively less drug per kilogram of body weight within a given dose/age category. This was particularly evident in the 2- and 3-year-old children who had received one-half tablet; 93.7% of them had received less than the recommended target dose of 25/1.25 mg/kg SP, as opposed to 1.4% of the 4-year-old children, who all had received a full tablet. The CTF rate was only 7.1% in the 4-year-old children, compared with 20.5% in the 2- and 3-year-old children. Although better acquired immunity in the 4-year-olds is likely to have contributed to this difference, the association between treatment failure and low dose in milligrams per kilogram of body weight was found to be independent of age (i.e., treatment was more likely to fail in heavier children regardless of age; table 2). One other study has also documented an association in vivo between antimalarial treatment dose and treatment failure in adults [70].

The review of the literature indicated that weight-based dose recommendations usually indicate a “target” dose of 1.25 mg/kg pyrimethamine and 25 mg/kg sulfadoxine. However, there appears considerable variation in age-based dose recommendations (figure 4). Although the original dose recommendation by WHO includes a one-half tablet for infants and a full tablet for 1–5-year-old children [64], aiming at 25/1.25 mg/kg as a minimum dose, most other recommendations result in lower doses. Age-based dose regimens such as those previously recommended by the Kenyan Ministry of Health [71] or by Hoffmann–La Roche, the manufacturer of Fansidar [53, 72], as well as those used in our study [36–7] are widely deployed in sub-Saharan Africa and result in a large proportion of children <5 years old receiving <25/1.25 mg/kg SP (figure 4). Suboptimal dosing is believed to be a major determinant of the rate at which antimalarial drug resistance develops [11, 70, 73, 74]. Selection and persistence of resistant strains will increase the risk of transmission and, hence, the biomass of resistant genotypes in the population [10]. Patients whose infections respond slowly to treatment or recrudesce subsequently are more likely to carry gametocytes than those whose respond rapidly or are cured [75–77]. SP is known to stimulate infective gametocytemia more than any other antimalarial [78, 79].

To address these concerns, WHO recently updated their dose recommendations for SP using a large weight-for-age reference population of >100,000 preschool children from countries where malaria is endemic [62]. This indicated that adequate age-based dosing can be achieved with minimal risk to overdosing [62]. Toxicity due to pyrimethamine results in reversible (by folate supplementation) dose-dependent hematological effects associated with bone marrow depression, including life threatening megaloblastic anemia, leukopenia, and thrombocytopenia. The

Figure 2. Relationship between the history of recent sulfadoxine-
pyrimethamine (SP) intake (X-axis) and the probability of cumulative treat-
ment failure following (re)treatment with SP (Y-axis). The second Y-axis
represents the relative risk (RR) of cumulative treatment failure, with the
group who had no history of SP treatment in the previous 56 days as
the reference group. The error bars represent the 95% confidence intervals
for values on the left

Figure 3. Relationship between treatment dose (in milligrams) of pyri-
methamine (lower X-axis) and sulfadoxine (upper X-axis) received per
kilogram of body weight and the probability of a treatment failure by day
7 (cumulative treatment failure). Error bars represent the 95% confidence
intervals for values on the left Y-axis, corrected for multiple observations
per child. Each point represents the failure rate at the mean value for
each of the 6 dose categories (0–0.84, 0.85–1.04, 1.05–1.24, 1.25–1.44,
1.45–1.64, and >1.65 mg/kg). The right

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threshold dose associated with severe bone marrow depression is not well known, particularly in children, but doses <3.5mg/kg are usually considered to be acceptable [31]. Although severe, potentially fatal, skin reactions to sulfonamide have been reported, this has been reported mainly associated with prophylactic use [80]. When used as a single treatment dose, the risk appears to be low (estimated 1:50,000 to 1:200,000 for single dose treatment with SP at doses between 25/1.25 and 42/2.0 mg/kg) [81–83].

We also found that children who received SP within the previous 15–35 days had a 1.7 times higher failure risk by day 7 than those who had no history of recent SP intake, probably reflecting an increased likelihood that these are retreatments of recrudescent infections with a selected parasite population of resistant genotypes (figure 2). In the absence of molecular genotyping, we cannot distinguish between treatment failure (recrudescence) and new infections (reinfection). However, these results are consistent with a study in Tanzanian children <5 years old where parasite DNA was studied for point mutations in the genes encoding dihydrofolate reductase and dihydropteroate synthetase [6, 7]. This result suggests that, in settings where treatment is based on microscopy results, patients should be provided with alternative antimalarial therapy if they have a history of SP use in the previous month, instead of the currently recommended 14-day period [20]. This is particularly relevant in young children.
with high-density parasitemias and insufficient host-immunity to clear surviving resistant parasites [10]. However, in rural settings, treatment is often based on fever instead of microscopy and, thus, is less specific for malaria, and alternative treatment may not be widely available. In those settings, a febrile patient with a history of SP in the previous month requires malaria diagnostics where available and may benefit from closer follow-up of this SP “retreatment.”

These results also have implications for surveillance of SP efficacy. When excluding children who had a history of SP in the previous 35 days and those who had received a treatment dose of <27.5/1.37 mg/kg SP, the CTF rate was 12.4%, versus 29.9% among those with both risk factors and 18.5% in the overall study population. When not taking these factors into account, the “true” SP resistance by day 7 will thus be overestimated. Furthermore, with increasing resistance, a higher percentage of the study population is likely to have been exposed to the study drug within the previous month. Thus, the history of SP in the previous month should either be added as an exclusion criterion or should be adjusted for in subsequent analyses. These results also suggest that the failure rates assessed on day 7 or 14 underestimate resistance in the population. With slowly eliminated drugs such as SP, most recrudescences in areas with predominantly low grade resistance occur >14 days after treatment, because this is the time required to reach patent parasitemia from low parasite numbers with multiplication rates being suppressed by host defenses and residual inhibitory concentrations of the drug [10, 84].

We used a modified version of the WHO criteria to define early treatment outcome in this study. We excluded the 75% decline in parasitemia by day 2 or 3 as criterion for early treatment or parasitological failure, because low pretreatment parasite density was not an exclusion criterion in this study, and we aimed to represent ECF, as opposed to early treatment failure. Use of the old WHO definition for parasitological failure by day 7 [31], commonly used at the time this study was conducted, or the current WHO classification [22], which combines clinical and parasitological criteria, did not change the conclusion (data not shown).

The relatively low success rate of follow-up in this study deserves further mention. This treatment study was nested in a larger ongoing cohort study of children <5 years old, which included routine monthly finger pricking. Although most caregivers consented to treatment follow-up, a relatively high proportion subsequently refused to have their child pricked for the additional day 2 and day 7 treatment follow-up visits. Although treatments without follow-up on day 2 or 7 did not differ in age, severity of illness, or any other characteristics at the time of treatment from those with a complete follow-up, refusal is more likely to occur for children who are clinically improved and this may have resulted in an overestimation of the clinical failure risk in particular.

There is an urgent need to reevaluate the dosing guidelines for SP, because most existing dose recommendations result in considerable underdosing. This is particularly timely, because it is expected that several more African countries will replace CQ with SP, or combination therapy including SP, within the near future. We recommend that, when feasible, antimalarial dosing should be based on body weight. However, this is not an option in most settings in sub-Saharan Africa. If antimalarial treatment guidelines for SP are based on age, they should aim to obtain a minimum, rather than average, target dose of 25/1.25 mg/kg SP. For most sub-Saharan African populations of preschool children, the new WHO age-based dose recommendation [62] will result in adequate dosing for >95% of them, with minimal risk of overdosing.

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