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EFFICACY OF TRIMETHOPRIM-SULFAMETHOXAZOLE COMPARED WITH SULFADOXINE-PYRIMETHAMINE PLUS ERYTHROMYCIN FOR THE TREATMENT OF UNCOMPLICATED MALARIA IN CHILDREN WITH INTEGRATED MANAGEMENT OF CHILDHOOD ILLNESS DUAL CLASSIFICATIONS OF MALARIA AND PNEUMONIA

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Abstract. In Malawi, trimethoprim-sulfamethoxazole (TS) is the recommended first-line treatment for children with Integrated Management of Childhood Illness dual classifications of malaria and pneumonia, and sulfadoxine-pyrimethyamine (SP) plus five days of treatment with erythromycin (SP plus E) is the recommended second-line treatment. Using a 14-day, modified World Health Organization protocol, children with dual IMCI classifications of malaria and pneumonia with *Plasmodium falciparum* parasitemia were randomized to receive TS or SP plus E. Clinical and parasitologic responses and gametocytemia prevalence were obtained. A total of 87.2% of children receiving TS and 80.0% receiving SP plus E reached adequate clinical and parasitologic responses (ACPRs) ($P = 0.19$). Severely malnourished children were less likely to achieve ACPRs than those better nourished (relative risk = 3.34, $P = 0.03$). Day 7 gametocyte prevalence was 55% and 64% among children receiving TS and SP plus E, respectively ($P = 0.19$). Thus, TS and SP plus E remain efficacious treatment of *P. falciparum* malaria in this setting. However, patient adherence and effectiveness of five days of treatment with TS is unknown.

BACKGROUND

The World Health Organization/United Nations Children's Fund guidelines for the Integrated Management of Childhood Illnesses (IMCI) are being implemented in many countries as a means to improve the health and reduce the morbidity and mortality of children. The guidelines assist health workers with limited resources identify and treat children with illnesses that are most likely to result in death. According to IMCI guidelines, a child who lives in an area with high malaria transmission who comes to a health facility with fever should be classified as having malaria, and should be treated with an effective antimalarial drug. Any child who meets the guideline's criteria as having a dual classification of pneumonia and malaria should be treated for both illnesses. Treatment options for dual classifications of pneumonia and malaria include a five-day course of trimethoprim-sulfamethoxazole (TS) to treat both the presumed malaria and pneumonia. This treatment strategy is based on studies that showed a five-day course of TS to be efficacious in clearing malaria parasitemia.[1,2]

In March 1993, the Malawi Ministry of Health and Population was the first sub-Saharan country to adopt sulfadoxine-pyrimethamine (SP) as national first-line treatment of uncomplicated malaria. Since 1997, increasing *Plasmodium falciparum* resistance to SP has been documented, with efficacy studies demonstrating 14-day parasitologic failure rates as high as 35%.[3] Since SP and TS provide their antimicrobial action through inhibition of the same enzymes in the folic acid biosynthetic pathway (pyrimethamine and trimethoprim inhibit dihydrofolate reductase, whereas sulfadoxine and sulfamethoxazole inhibit dihydropteroate synthetase), cross-resistance could develop, and a decrease in the antimalarial efficacy of TS may occur in parallel with SP resistance development. At least two studies have demonstrated that cross-resistance between the two drugs may occur.[4,5]

The Malawi Ministry of Health and Population plans to implement IMCI guidelines in all outpatient health facilities. The adapted Malawian guidelines recommend TS as the first-line treatment option for dual classifications of pneumonia and malaria; SP plus erythromycin (SP plus E) is recommended as second-line treatment. Thus, it is essential that policy makers know the antimalarial efficacy of a five-day course of TS. We conducted a study to measure the efficacy of TS compared with SP plus E for treatment of *P. falciparum* malaria among children with dual IMCI classifications of malaria and pneumonia. We did not design this study to measure the efficacy of TS or E in treating IMCI-classified pneumonia.

MATERIALS AND METHODS

Study site. The study was begun in April 2001, the peak malaria transmission season, and continued until July 2001. The study was conducted at Chilomoni Health Center, a busy peri-urban health facility with inpatient facilities located on the outskirts of Blantyre in the Blantyre District. The Blantyre District is an area of high *P. falciparum* malaria transmission. Malaria transmission occurs year round with seasonal variation and is most intense from January to June. Greater than 90% of malaria infections are caused by *P. falciparum*; the remaining infections are from *P. malariae* and *P. ovale*.[6]

Study design. We conducted a non-blinded, randomized, controlled trial based on a 14-day World Health Organization *in vivo* protocol for assessing the efficacy of antimalarial drugs in areas of intense transmission.[7]

Patients. Inclusion criteria for the study were 1) child between the ages of six months and five years; 2) presentation to

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the outpatient clinic at the Chilomoni health facility with an IMCI classification of malaria (history of or current fever) and pneumonia (cough or difficult breathing and elevated respiratory rate for age) without signs of severe disease; 3) thick and thin blood films with a non-mixed *P. falciparum* infection with at least 2,000 asexual parasites/μL; and 4) informed consent from a guardian with agreement to admit the child to the inpatient facility for five days of observation where study drugs were administered.

Children with signs or symptoms of severe illness, with a hemoglobin level < 5 g/dL, or those with a sulfa or quinine allergy were excluded from the study. Prior antimicrobial drug use was not a reason for exclusion.

The study was reviewed and approved by the United States Centers for Disease Control and Prevention Institutional Review Board and the Malawi National Health Sciences Research Committee.

Enrollment and treatment. Enrolled children provided a thorough history and underwent a physical examination by study clinicians trained in IMCI. Temperatures were taken using an aural thermometer. Children who were found to be febrile, with a temperature ≥ 38.0°C, or who had a history of fever during this illness, and who had an IMCI classification of pneumonia were sent to the laboratory for a thick blood film and a hemoglobin measurement using HemoCue® cuvettes (HemoCue, Ångelholm, Sweden). Those children who were parasitemic, with a screening parasite density of at least 2,000 asexual parasites/μL of blood, were randomized to receive either a five-day course of TS (80 mg of trimethoprim and 400 mg of sulfamethoxazole per tablet [1 tablet for children weighing 10–19 kg; half a tablet for children weighing < 10 kg]) or SP (500 mg of sulfadoxine and 25 mg of pyrimethamine per tablet [1.25 mg of pyrimethamine/kg of body weight]) plus a five-day course of erythromycin (125 mg four times a day if they weighed < 10 kg; 250 mg four times a day if they weighed ≥ 10 kg) to treat the respiratory infection.

Enrolled children were given the study medication orally and admitted to the study ward (considered day 0) where they were observed throughout the period that study medications were administered (days 0–4). The study ward was staffed by study nurses who remained on the ward at all times and who assessed every child's vital signs and health status every six hours. A senior clinician or medical officer was available to the nursing staff at all times, and lead daily study ward rounds.

Children were observed for 30 minutes after the study drug was administered. Those who vomited the study drug(s) within 30 minutes of administration were provided a second full dose of the medication(s). Those with hemoglobin levels ≥ 5.0 g/dL and ≤ 8 g/dL received a 30-day course of daily iron without folate, beginning on day 0, according to Malawi guidelines for treatment of malaria–associated anemia. Children > 2 years old who had not received albendazole within the past six months were given this drug, in accordance with Ministry of Health guidelines. All children received paracetamol every eight hours for fever.

Malaria microscopy. After randomization, a second fingerprick was done for malaria thick and thin films. The second film, and all follow-up films, were dried and stained with Giemsa in the clinic. Parasite density was determined by counting the number of asexual parasites against 200 leukocytes, and by assuming a white blood cell count of 8,000/μL of blood. Slides were considered negative if no parasites were found after examining 100 high-powered fields.

Each blood smear was examined by two study technicians, who independently recorded parasite densities. Parasite density readings for each slide were compared and those that differed by greater than three-fold were read by a third technician. The geometric mean of the two nearest estimates of parasite density was used in the analysis.

Study drug. Brand name TS and SP were obtained from reputable multinational pharmaceutical companies. Samples from single pharmaceutical lots of TS and SP were tested to evaluate quality of the study drugs. The levels of active ingredients for both TS and SP were tested using high-performance liquid chromatography at the Centers for Disease Control and Prevention (Atlanta, GA). Both TS and SP were found to have acceptable levels of active ingredients.

Follow-up. Children were evaluated daily on the study ward until the five-day course of antimicrobials was completed. After discharge, they were followed on days 7 and 14, or earlier if they returned to the health facility due to illness. Each day on the study ward and at every follow-up visit, the child was checked for, or parents were asked about, eating patterns, vomiting, convulsions, and the use of other medications. Each child was examined, and temperature was measured. A blood sample was taken for a thick malaria smear on days 1–4, 7, 14, or any sick visit, and hemoglobin was measured on day 14. The presence or absence of gametocytemia was recorded. For all day 7 blood smears, gametocyte density was determined. Children classified as treatment failures were treated with oral quinine.

Outcome measures. Clinical and parasitologic outcomes were defined using a modified version of the World Health

TABLE 1

Modified World Health Organization definitions for clinical and parasitologic responses for areas of intense *Plasmodium falciparum* transmission, 2002

Early treatment failure (ETF)	Development of danger signs or severe malaria on days 1, 2, or 3, in the presence of parasitemia; Parasitemia on day 3 with an aural temperature ≥ 38.0°C; Parasitemia on day 2 higher than on day 0; Parasitemia on day 3 ≥ 25% of day 0
Late clinical failure (LCF)	Development of danger signs or severe malaria after day 3 in the presence of parasitemia; Presence of parasitemia and aural temperature ≥ 38.0°C on any day from day 4 to day 14 or reported fever from day 5 to day 14, without previously meeting any of the criteria of ETF
Late parasitologic failure (LPF)	Presence of parasitemia on day 14, and aural temperature ≤ 38.0°C, without previously meeting any of the criteria of ETF or LCF
Adequate clinical and parasitologic response	Absence of parasitemia on day 14, irrespective of axillary temperature, without previously meeting any of the criteria for ETF, LCF, or LPF

TABLE 2
Parasitologic outcomes

RIII	A day 2 parasite density that is ≥ 25% of the day 0 parasite density
RII	A positive day 2 blood smear with a parasitic density that is < 25% of the day 0 density and a positive day 7 blood smear
Early RI	**Either** a negative day 2 blood smear with a positive blood smear on any day between day 3 and day 14, inclusive **or** a positive day 2 blood smear with a parasitic density that is < 25% of day 0, a negative day 7 blood smear, and a positive blood smear on any day between day 8 and day 14, inclusive
Sensitive/late RI	A day 2 parasite density that is < 25% of the day 0 density and negative blood smears on every follow-up examination between day 7 and day 14, inclusive. Because follow-up lasts only 14 days, it is not possible to distinguish sensitive responses from late recrudescence; therefore, these responses are combined

Organization classification system for clinical and parasitologic response. Outcomes were classified as an early treatment failure (ETF), late clinical failure (LCF), late parasitologic failure (LPF), or adequate clinical and parasitologic response (ACPR).[8] We included children with reported fever during the 24 hours prior to enrollment, regardless of their temperature on presentation. At follow-up visits, a reported fever during the previous 24 hours or an aural temperature ≥ 38.0°C were considered true fever when determining clinical response (Table 1).

To compare time until last fever, we used only measured temperatures. Temperatures were measured every six hours during the first five days, then daily on days 7 and 14, and at any unscheduled sick visit. The last febrile episode was defined as the last measured temperature ≥ 38.0 during the follow-up period. Children who had persistent fever at day 14 were censored in the analysis.

To compare results presented in this report with results from prior efficacy studies, we also present outcome data using the World Health Organization definitions for adequate clinical response (ACR) and for parasitologic outcome that were standard prior to the year 2003.[7] An ACR can be calculated by combining the percentage of children with ACPR and LPF. In reporting parasitologic response, we combined late RI with sensitive responses because late RI (days 15–28) could not be assessed in this 14-day trial (Table 2).

Statistical analysis. Data were analyzed using SAS version 8.01 (SAS Institute Inc., Cary, NC). Continuous variables were compared using the Student's *t*-test or Wilcoxon rank sum test for nonparametric variables. Proportions were analyzed using chi-square test or two-tailed Fisher's exact test. Time to drug failure and time to fever resolution were analyzed using the log rank test of Kaplan-Meier survival curves.

RESULTS

Study population. A total of 794 children came to the health facility with a history of fever and cough, and were found to have mixed IMCI classifications of malaria and pneumonia. Among them, 207 had parasitemia ≥ 2,000 parasites/μL of blood, fever within the previous 24 hours, and no exclusion criteria. Parents of 205 children consented to enrollment in the study.

Of the 205 enrolled children, 104 children were randomized to the TS arm and 101 children were randomized to the SP plus E arm. The clinical and parasitologic characteristics of the children and their illnesses are summarized in Table 3, and did not differ by treatment arm. Two children (one randomized to each of the treatment arms) were withdrawn from the study after enrollment because their mothers were needed at home. No children were lost to follow-up.

Three children developed danger signs after enrollment. One child died on day 0, approximately 10 hours after enrollment. The child had been moderately ill for two days prior to presentation, and had received no prior treatment. At enrollment, she had a temperature of 41°C, a heavy parasitemia (recorded as 4+), a hemoglobin level of 7.4 g/dL, and was alert without clinical signs of severe disease. Initially, the child responded to treatment, with a decrease in temperature to 37.5°C and a reduced respiratory rate, but decompensated and developed respiratory distress. Arrangements were made to transfer the child by ambulance to a referral hospital. Unfortunately, the child died *en route.* She was classified as an ETF. A second child, randomized to receive TS, who came to the health facility on day 0 with a hemoglobin level of 8.8 g/dL, and who responded to therapy with reduced fever, respiratory rate, and resolution of parasitemia, developed severe anemia on day 4 (hemoglobin level = 4.2 g/dL), and was

TABLE 3
Characteristics of 205 children at enrollment

	Trimethoprim-sulfamethoxazole	Sulfadoxine-pyrimethamine plus erythromycin	*P*
Number of children enrolled	104	101	0.83*
Median/mean age in months (range)	19.0/22.4 (6–59)	17.0/20.1 (6–52)	0.28†
Females (%)	44 (42)	39 (39)	0.67*
Median/mean weight (range)	10.0/10.3 (6.6–16.8)	9.5/10.0 (5.8–16.2)	0.35†
Median/mean temperature (range)	39.1/38.9 (35.2–41.1)	38.8/38.9 (36.0–41.5)	0.71†
Median/mean respiratory rate (range)	56/57 (40–96)	58/57 (40–88)	0.62†
Median/geometric mean parasite density/μL of blood	28,089/51,139	30,368/65,885	0.23†
Median/mean hemoglobin, g/dL (range)	8.8/8.6 (5.0–14.9)	8.1/8.3 (5.1–12.2)	0.17†
Number (%) with reported prior sulfasoxine-pyrimethamine use	4 (3.9)	3 (3.0)	1.00‡
Number (%) with reported prior trimethoprim-sulfamethoxazole use	6 (5.8)	7 (6.9)	0.78*
Number (%) with diarrhea on presentation	8 (7.7)	12 (11.9)	0.31*
Mean/median number of days with fever prior to presentation at health facility (range)	2.0/2.8 (1–14)	2.0/2.6 (0–14)	0.38†

* By chi-square test.
† By Wilcoxin rank sum test.
‡ By Fisher's exact test.

TABLE 4

Day 14 clinical and parasitologic response to antimalarial therapy, n = 202*

	Trimethoprim-sulfamethoxazole (%) (n = 102)	Sulfadoxine-pyrimethamine plus erythromycin (%) (n = 100)	*P*
ETF	1.0	3.0	0.37
LCF	2.9	9.0	0.08
LPF	8.8	8.0	1.00
ACPR	87.2	80.0	0.19

* ETF = early treatment failure; LCF = late clinical failure; LPF = late parasitologic failure; ACPR = adequate clinical and parasitologic response.

transported to a referral facility. She had no malaria parasites detectable in a blood film at the time of referral and did not qualify as an ETF or as RIII failure. Because we do not have subsequent blood films on this child, she was excluded from the analysis of clinical and parasitologic response. A third child who received TS developed signs of respiratory distress on day 1, was referred with parasites present, and was classified as an ETF. The first and third child could not be classified for parasitologic response because in both cases, there was no day 2 parasite density measurement.

Clinical response. A total of 202 (98.5%) of enrolled children had their clinical outcome evaluated. Among those 102 children who received TS, 89, (87.2%) achieved ACPR. Among the 100 children who received SP plus E, 80 (80.0%) were classified as ACPR. There was no significant difference in clinical and parasitologic response between the two treatment arms (Table 4 and Figure 1). However, the percentage of children who achieved ACR was higher in the TS arm (98 of 102 [96.1%] than in the SP plus E arm (88 of 100 [88.0%]; $P = 0.03$).

A total of 159 children (78 in the TS arm and 81 in the SP plus E arm) came to the health facility with temperatures ≥ 38.0°C. Of them, only one child in the TS arm and two children in the SP plus E arm had a temperature ≥ 38.0°C on day 14 ($P = 0.97$). Among children with fever at presentation, the median time to fever resolution was 30 hours in the TS arm and 36 hours in the SP plus E arm. Children who received TS resolved fever sooner than those who received SP plus E ($P = 0.03$) (Figure 2).

Parasitologic response. A total of 199 (97.1%) children had data available to assess parasitologic response. Three children who did not meet criteria for parasitologic RIII classification

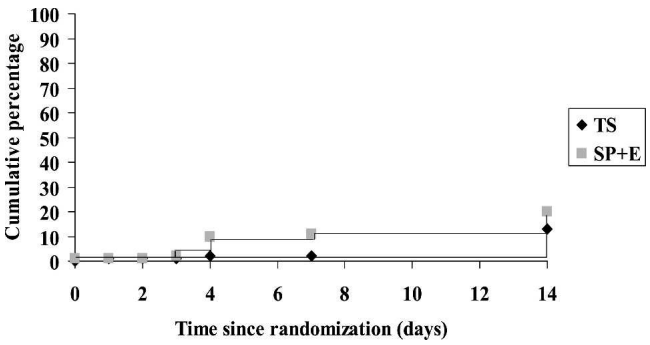

FIGURE 1. Cumulative percentage of treatment failure, trimethoprim-sulfamethaoxazole (TS) versus sulfadoxine-pyrimethamine plus erythromycin (SP + E), n = 202.

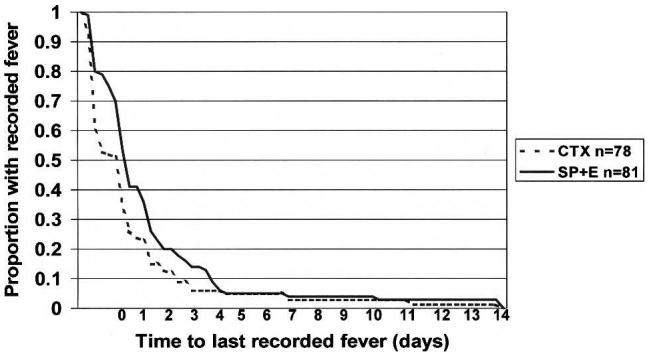

FIGURE 2. Time to last recorded fever by study arm, trimethoprim-sulfamethoxazole versus sulfadoxine-pyrimethamine plus erythromycin (SP + E). CTX = cotrimoxazole.

were classified as ETF. There was no significant difference in parasitologic response to therapy in the two study arms (Table 5).

Factors influencing clinical and parasitologic outcome. Nutritional status was associated with treatment failure (defined as not achieving ACPR): children who had IMCI classifications of very low weight for age, which approximates a z-score < –3, were more likely to fail treatment than better nourished children (relative risk [RR] = 3.34, $P = 0.03$). There was no significant association between treatment failure and having a z-score < –2 (RR = 1.07, $P = 1.00$). There was no evidence that child's age, weight, sex, temperature on admission, initial parasite density, hemoglobin level at admission, administration of iron supplementation, duration of fever prior to presentation, vomiting or diarrhea during illness, or TS or SP administration prior to presentation were associated with an increased risk of clinical or parasitologic failure.

Hematologic response. Hemotologic response was measured in 199 (97.1%) children. Prevalence of anemia was similar at day 0. A total of 42.2% of the children in the TS arm and 49.0% of those in the SP plus E arm had an initial hemoblobin level ≤ 8 ($P = 0.33$). Children in both study arms had an increase from day 0 to day 14 in mean hemoglobin levels. The mean (± SD) hemoglobin increase between days 0 and 14 was 1.0 g/dL (± 1.7) in the TS arm and 1.1 g/dL (± 1.5) in the SP plus E arm ($P = 0.76$). On day 14, 10.8% of children in the TS arm and 13.3% of those in the SP plus E arm had a hemoglobin level ≤ 8 g/dL ($P = 0.46$).

Factors influencing hematologic outcome. Children who achieved ACPR had a greater increase in mean hemoglobin level between days 0 and 14 (1.14 g/dL) when compared with children who did not achieve ACPR (0.39 g/dL) ($P = 0.004$). Children with initial hemoglobin level ≥ 5.0 g/dL and ≤ 8.0 g/dL (46% of enrollees), all of whom received iron, had a

TABLE 5

Parasitologic response to antimalarial therapy among 199 children less than five years of age*

Response	Trimethoprim-sulfamethoxazole, % (n = 101)	Sulfadoxine-pyrimethamine plus erythromycin, % (n = 98)	*P*
RIII	1.0	1.0	1.00
RII	0	2.0	0.24
ERI	12.9	16.3	0.55
S/LRI	86.1	80.6	0.34

* ERI = early RI; S/LRI = sensitive/late RI.

greater mean increase in the hemoglobin level than those with an initial hemoglobin level > 8.0 g/dL (1.99 g/dL versus 0.24 g/dL, respectively) ($P < 0.0001$). A total of 16 children (9%), 8 in each study arm, received albendazole. There was no evidence that child's age, sex, nutritional status, albendazole administration, or initial parasite density was associated with hematologic outcome. Achieving ACPR was not significantly associated with a decreased prevalence of anemia, and having persistent asymptomatic parasitemia (LPF) was not associated with increased risk of anemia at day 14.

Gametocyte response. Gametocyte prevalence on day 7 was high and similar in both study arms. A total of 55% of the children in the TS arm and 64% of the children in the SP plus E arm had gametocytes detectable on day 7. Median (mean) gametocyte density was 320 (723) gametocytes/μL of blood in the TS arm with a range of 40–9,600 gametocytes/μL, and 180 (676) gametocytes/μL in the SP plus E arm with a range of 40–6,600 gametocytes/μL, ($P = 0.23$). Risk factors for gametocytemia on day 7 included an initial hemoglobin level ≥ 5 g/dL and ≤ 8 g/dL when compared with a hemoglobin level > 8 g/dL (RR = 1.26, 95% confidence interval [CI] = 1.01–1.58) and fever duration less than three days prior to presentation when compared with fever of longer duration (RR = 1.30, 95% CI = 1.03–1.64).

Adverse drug effects. One child vomited SP within 30 minutes after administration. A second dose was successfully administered. No child vomited TS. No child had a rash or other notable adverse reaction. Sixteen (15.5%) children administered TS and 11 (11%) children administered SP plus E vomited during their illness ($P = 0.34$).

DISCUSSION

We found that both TS and SP plus E, when used for children with dual IMCI classifications of malaria and pneumonia, are efficacious, well-tolerated options for the treatment of *P. falciparum* malaria. This finding, a full nine years after SP was adopted as first-line antimalarial therapy in Malawi, is encouraging, and suggests that *P. falciparum* antifolate resistance may not be increasing at the rate observed in other east African countries, and that cross-resistance development is not currently jeopardizing the usefulness of TS for treatment of malaria in children with concomitant classification of pneumonia.

Importantly, we still do not know the effectiveness of TS, that is, how well it works when administered at home, outside of the study setting. The effectiveness will depend largely on the caregiver's adherence to a five-day treatment course. In a study of TS antimalarial effectiveness in The Gambia, only 67% of the patients adhered to the TS five-day treatment course.[2] In Uganda, where the clinical efficacy of SP for *P. falciparum* infection is as high as 90%, clinical effectiveness among children with malaria treated with TS varied from 59% to 90%, depending on the study site.[9,10] The investigators speculate one reason for the poor treatment response may have been non-adherence to the five-day drug treatment regimen. There are no recent data on the antimalarial efficacy of a shortened course of TS.

A series of SP efficacy studies conducted throughout Malawi since 1993 show a steady decrease in clinical and parasitologic efficacy. However, in most of these studies, ACR remains greater than 80% (Table 6). The level of SP plus E efficacy found in our study is on the higher end of findings from other SP efficacy studies. It should be noted that erythromycin does have mild antimalarial properties, which may have increased the efficacy of SP in our study.

We found that malnourished children were less likely to achieve ACPR than their well-nourished counterparts. Malnutrition has been described previously as a risk factor for antimalarial treatment failure among children living in a refu-

TABLE 6
Recent studies measuring the efficacy of sulfadoxine-pyrimethamine (SP) in Malawi*

Study year†	SP clinical efficacy % (ACR at day 14, unless otherwise indicated)	SP parasitologic efficacy, %	N	Comments
2001 (1)	88	81	100	SP plus erythromycin (E) children 6–59 months old, 14 day follow-up.
2002 (2)	83	61	138	5 studies conducted yearly at one peri-urban site. Patients > 3 months old, 28 day follow-up.
2001	80	63	386	
2000	82	65	216	
1999	82	64	146	
1998	86	73	77	
1998 (3)	81	65	43	Children < 5 years old, 14 day follow-up.
1998 (4)	–	83	60	Children < 5 years old, 14 day follow-up.
1997–1998 (5)	100‡	85	75	Children < 5 years old, 14 day follow-up. 7 sentinel sites.
	100	81	86	
	98	82	123	
	98	73	103	
	100	91	111	
	100	93	62	
	97	81	81	
1995 (6)	89§	91	78	Children 6–59 months old, 28 day follow-up.
1994 (7)	–	97	69	Children < 5 years old, 28 day follow-up at 2 sites.
	–	99	76	
1990 (8)	100	70	37	Children < 5 years old, 28 day follow-up.
1986 (9)	–	100	34	Children < 5 years old, 21 day follow-up.

* ACR = adequate clinical response.
† 1 = Current publication; SP + E, Parasitologic efficacy defined as sensitive/late RI (S/LRI) at day 14; 2 = Parasitologic efficacy defined as initial parasitemia cleared and all blood films negative by day 14[18]; 3, Parasitologic efficacy defined as S/LRI at day 14[3]; 4, Parasitologic efficacy defined as S/LRI at day 14[19]; 5 = Parasitologic efficacy defined as S/RI at day 14[20]; 6 = Parasitologic efficacy defined as S/LRI at day 14[21]; 7 = Parasitologic efficacy defined as sensitive/RI at day 14[22]; 8 = Parasitologic efficacy defined as sensitive/RI at day 14[23]; 9 = Parasitologic efficacy defined as no parasites present on day 21.[24]
‡ Clinical failure defined as an axillary temperature ≥ 37.5°C with parasitemia on day 7.
§ Clinical efficacy defined as an axillary temperature < 37.5°C on days 7 and 14.

gee camp.[11] Malawi has regular periods of drought and famine; those coming to a health facility with malnutrition and malaria will need close follow-up to confirm adequate treatment of their malaria parasitemia.

Several studies have documented high gametocytemia prevalence associated with SP treatment when compared with other antimalarial drugs, with peak gametocyte prevalence occurring around day 7 following treatment.[12–16] To our knowledge, this is the first study to demonstrate a similar increase in gametocytemia after treatment with TS. Gametocytes, the sexual form of the malaria parasite, are infective to the mosquito and responsible for malaria transmission. A study of gametocyte infectivity following treatment with SP and other antimalarials has documented persistent transmissibility following antimalarial therapy.[17] It remains unknown whether transmission of these gametocytes results in transmission of mutant resistant genotypes. Furthermore, it is unclear if the transmission of mutant resistant genotypes would significantly contribute to drug resistance in an area where transmission is already high. More research will be needed to explore these questions.

In conclusion, we found that at Chilomoni Health Center, both TS and SP plus E are efficacious, well-tolerated treatment options for uncomplicated *P. falciparum* malaria among children with IMCI classifications of malaria and pneumonia. Children with malnutrition are especially prone to fail therapy, and in times of famine, health workers will need to be diligent in reminding caretakers to return for follow-up to confirm the child has successfully responded to treatment or to change the child to a second-line drug therapy. If Ministries of Health continue to choose TS as a treatment choice for IMCI dual classifications of malaria and pneumonia, it will be important to measure adherence to the five-day TS treatment course.

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