New strategies for treating falciparum malaria in Bangladesh

Thirteen out of 64 districts in Bangladesh are seriously affected by malaria. The emergence and spread of antimalarial drug resistance and the resulting increase in treatment failures and case fatality rates due to falciparum malaria have seriously aggravated the malaria problem in Bangladesh. Two regimens for treatment of malaria were evaluated in two separate studies. Among 63 patients with confirmed falciparum malaria who received quinine, three times daily for three days followed by a single dose of sulfadoxine/pyrimethamine, 87% were cured at 42 days. Among 67 patients who received a combination of artemether and lumefantrine, 94% were cured at 42 days. Both combination regimens were effective in Bangladesh. Efforts to make effective antimalarial drugs widely available is vital for malaria control in Bangladesh.

Malaria is a substantial public health problem in Bangladesh. Up to 400,000 clinical cases and more than 57,000 laboratory confirmed malar-
Malaria cases with more than 500 deaths per year have been reported from Bangladesh (1). Thirteen out of the 64 districts in the country are seriously affected by malaria, accounting for about 99% of the country's disease burden (Figure 1). About two-thirds of the laboratory confirmed cases occur in the Chittagong Hill Tracts. However, due to the lack of financial resources and the resulting shortcomings in malaria research, surveillance, and control, the disease burden may be far greater than reported. The most affected of these districts are home to populations and minorities living in the remote hill tract areas and the adjoining districts of the southeast, east, and northeast border of the country. Despite past successes in malaria control, a significant increase in malaria cases and *Plasmodium falciparum* infections has been seen over the years. Particularly the emergence and spread of antimalarial drug resistance and the resulting increase in treatment failures and case fatality rates have turned into a serious problem. Indeed, the vast majority of parasite populations may be resistant to chloroquine (2,3). However, chloroquine remains the most com-

**Figure 1: Thirteen high endemic districts of Bangladesh 2004.**

![Map of Bangladesh showing high endemic malarious areas](image-url)
mon treatment for malaria throughout the country due to inadequate financial means for malaria control and the lack of data on the current drug resistance patterns, as well as the lack of research into affordable alternative treatments.

We evaluated two alternative regimens for treating malaria in Bangladesh. First, we investigated the therapeutic efficacy of the combination of sulfadoxine/pyrimethamine with three days of quinine for the treatment of uncomplicated falciparum malaria at the ICDDR,B field site in Chakaria, Cox’s Bazaar District, Chittagong Division. In parallel, laboratory-based technologies (HRP2 drug susceptibility assay) were used to characterize the intrinsic drug sensitivity of individual patient isolates.

Sixty-three patients were enrolled in the study in 2004 (4). The study design essentially followed the WHO guidelines for the assessment and monitoring of antimalarial drug efficacy with an extension of follow-up until day 42. All patients received the second line treatment with quinine three times a day (10 mg/kg per dose) for three days, followed by a single dose of sulfadoxine (25 mg/kg) coformulated with 1.25 mg/kg of pyrimethamine on the fourth day. The overall cure rate with quinine followed by sulfadoxine/pyrimethamine in uncomplicated falciparum malaria in a 42-day follow-up after PCR adjustment was 87.3% (Figure 2). One patient was classified as early treatment failure, six patients had late treatment failures within a median time of 27 days. Significantly higher ($P =$

![Figure 2: Kaplan-Meier curve for the PCR-adjusted cure rate for the combination of quinine with S/P in 63 uncomplicated falciparum malaria patients in southeastern Bangladesh.](image)

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$^1$Quinine for 3 days plus fansider
in vitro inhibitory concentrations for pyrimethamine in treatment failures reflect the compromised drug sensitivity to this drug.

Parallel in vitro studies were performed to provide background data on intrinsic drug sensitivity for these parasite populations. The in vitro data suggest levels of chloroquine resistance (50% inhibitory concentration: 93.1 nM) comparable to those in Thailand, a country known for its particularly high levels of drug resistance. In contrast, the isolates were relatively sensitive to quinine (73.2 nM) and mefloquine (11.3 nM). The dihydroartemisinin (1.3 nM) inhibitory concentrations were equally low suggesting high sensitivity of the parasites to that drug. Interestingly, close correlations were found between in vitro drug sensitivity of pyrimethamine (1.7 µM) and clinical treatment response parameters, suggesting a significant impact of intrinsic pyrimethamine drug sensitivity on treatment outcome.

The cure rate with quinine plus sulfadoxine/pyrimethamine in the 42-day follow up is comparable to cure rates found in a previous study with a 28-day follow-up from a nearby area (5). These data suggest that the combination of 3 days of quinine with a single dose of S/P is a promising and affordable alternative as long as or whenever artemisinin-based combination therapy is not available.

In 2004/2005 the government of Bangladesh changed its first-line therapy for laboratory-confirmed falciparum malaria to the combination of artemether with lumefantrine (1). We aimed at determining the baseline therapeutic efficacy of artemether-lumefantrine used as a six-dose regimen for the treatment of uncomplicated falciparum malaria (6). Sixty-seven patients were enrolled in the study. The cure rate in a 42-day follow-up after PCR adjustment was 94.3%. The treatment led to rapid fever (25.82 ± 12.14 hrs) and parasite clearance (30.36 ± 19.43 hrs). These data suggest that this combination is a highly efficacious therapy. However, currently its use in Bangladesh is still constrained by relatively high cost and difficulties with supply.

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Comment

Quinine followed by sulfadoxine/pyrimethamine is an effective alternative
for the treatment of uncomplicated falciparum malaria whenever 
atemisinin-based combination therapy is not available. Both quinine and 
sulfadoxine/pyrimethamine are available from local producers and are rel-
avtively inexpensive. Compared to similar regimens (e.g. seven days of qui-
nine plus tetracycline) it is cheaper and due to the shorter duration of 
treatment leads to better compliance. However, the in vitro drug sensitivity 
data demonstrate that some degree of sulfadoxine/pyrimethamine resist-
ance exists among P. falciparum parasites in Bangladesh. Sulfadoxine/ 
pyrimethamine should therefore only be used in combination with faster 
acting antimalarials that have a different mechanism of action to prevent 
a rapid progression of drug resistance.

The combination of artemether with lumefantrine, currently the first line 
therapy for laboratory-confirmed uncomplicated falciparum malaria in 
Bangladesh, results in cure rates considerably above 90%. With its rapid 
fever and parasite clearance this combination also leads to quick clinical 
and parasitological improvement. However, little is known regarding its 
safety in pregnancy and its use in Bangladesh is still constrained by the 
relatively high cost and difficulties with supply. Moreover the first reports 
of failures with artemisinin-based combination therapies in Southeast Asia 
urgently call for research into new alternatives (7).

Consequently, in 2006 we are planning to expand our research efforts to 
Bandarban District in the Chittagong Hill Tracts to evaluate new, safe, and 
avordable combination treatments for falciparum malaria in Bangladesh.

Following the example of malaria research and control in other South-
and Southeast Asian countries, new cost effective intervention strategies 
that meet local needs and that are sustainable are urgently needed in 
Bangladesh. The future development and clinical testing of new, afford-
able, preferably locally produced combination treatments for falciparum 
malaria will therefore be essential.

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### Nutritional status, knowledge and practices of unmarried adolescent girls in rural Bangladesh

The 2004 baseline survey of the Bangladesh National Nutrition Programme examined nutritional status, knowledge and practices of never married adolescent girls (aged 13-19) living in rural Bangladesh. Adolescents were of poor nutritional status; 9% were severely thin and 16% were moderately thin. More than half did not know the names of energy-dense and protein-rich foods. Most (65%) reported understanding of the need to take extra nutrients during adolescence to attain potential growth. On average adolescent girls ate 4.7 servings of protein rich and 3.3 servings of fat rich foods in the preceding week. Adolescents in the highest asset quintile (a proxy for economic condition) were 54% more likely to have had fish or meat and 91% more likely to have had egg or milk in the preceding week than those in the lowest asset quintile. Strong community-based nutrition counselling backed by basic services may improve adolescent nutrition knowledge and practices and address under nutrition 'carried-over' from childhood.

Adolescence is a period of rapid physical growth and additional nutrition is needed during this period to attain potential growth. Improved adolescent nutrition knowledge and practices offer an opportunity to address the nutritional problems 'carried over' from childhood, and set the stage for healthy adulthood. Available evidence suggests that adolescent girls in Bangladesh are of poor nutritional status. One survey reported that 27%