Transactions of the Royal Society of Tropical Medicine and Hygiene (2005) **99**, 727—735

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Efficacy of chloroquine + sulfadoxine—pyrimethamine, mefloquine + artesunate and artemether + lumefantrine combination therapies to treat *Plasmodium falciparum* malaria in the Chittagong Hill Tracts, Bangladesh

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Received 9 November 2004; received in revised form 28 January 2005; accepted 1 February 2005

KEYWORDS
Malaria;
Plasmodium falciparum;
Chloroquine;
Sulfadoxine—pyrimethamine;
Mefloquine;
Artesunate;
Lumefantrine;
Artemether;
Bangladesh

Summary Bangladesh faces growing levels of *Plasmodium falciparum* resistance to chloroquine (CQ) and sulfadoxine—pyrimethamine (SP). Alternative antimalarial therapies, particularly combination regimens, need to be considered. Therefore, the efficacy of three antimalarial combination therapies was assessed in Chittagong Hill Tracts. A total of 364 *P. falciparum* patients were recruited and randomly assigned to either CQ + SP, mefloquine + artesunate (MQ + AS) or lumefantrine + artemether (Coartem©). Results showed that CQ + SP therapy was less effective than the two artemisinin-based combination therapies. The day 42 PCR-corrected efficacy rate was 62.4% for CQ + SP, 100% for MQ + AS and 97.1% for Coartem. Failures occurred at a shorter interval after CQ + SP treatment than after Coartem. The artemisinin-based therapies effectively prevented development of

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0035-9203/$ — see front matter
doi:10.1016/j.trstmh.2005.02.007

gametocytes, whereas CQ + SP did not. All three therapies were well tolerated, although reports of mild complaints during treatment appeared higher with MQ + AS. We conclude that CQ + SP is not a viable option for replacing CQ monotherapy as first-line *P. falciparum* treatment in this area of Bangladesh. A change to artemisinin-based combination therapy is recommended. Both Coartem and MQ + AS appear to be good options, effective in curing *P. falciparum* malaria and in preventing recrudescences following treatment.

1. Introduction

Multidrug resistance of *Plasmodium falciparum* parasites has developed in Asia earlier than in other malarious areas around the world. As early as 1957, chloroquine (CQ) resistance appeared, whilst sulfadoxine–pyrimethamine (SP) resistance first emerged in 1967, both at the Thai–Cambodian border. Since then, it has been described in all Asian countries. Drug resistance is enhanced with patterns of drug availability and drug use (Hastings, 2001; Wongsrichanalai et al., 2002). Generally across Asia, pharmacy shops are found at every street corner and people have the tendency to try to cure an infection without proper diagnosis, by simultaneous use of a cocktail of various medicines. In Bangladesh, the national drug policy is quite strict and the list of medicines registered for import is limited. However, these restrictions, together with clear case definitions and treatment guidelines for malaria, have not been able to block the spread of resistance to the country's malaria-endemic areas bordering India and Myanmar (Rahman et al., 1996, 2001).

Changes in national treatment policies of Asian countries in response to rising levels of resistance have been slow at first, but currently the majority of countries in this region have made a switch from CQ to artemisinin-based combination therapies (ACT), such as artesunate combined with mefloquine, amodiaquine or SP, Coartem or a novel combination called CV8 (Bosman, 2004; Giao et al., 2004). Bangladesh lingered over a change in treatment protocols, but recently the Ministry of Health and Family Welfare (MoHFW) decided on implementation of artemether–lumefantrine (Coartem©) as a new national policy to treat uncomplicated falciparum malaria in the future, if the required funding becomes available (JICPD, 2004).

The change in national malaria treatment protocols were planned but not yet decided at the time of this trial. Further insight into the pros and cons of different therapies was needed. ACTs are the preferred option because of their high efficacy, rapid cure and capacity to reduce gametocyte development (WHO, 2001); however, their high cost remains a barrier to implementation. Taking these considerations into account, the MoHFW of Bangladesh, the WHO and Médecins Sans Frontières (MSF) conducted this efficacy trial on three drug combination therapies, namely artemether and lumefantrine (Coartem), mefloquine + artesunate (MQ + AS) and CQ + SP, which could possibly be introduced as alternative antimalarial protocols in the future.

2. Patients and methods

2.1. Study location

Located in the eastern part of Bangladesh, the Chittagong Hill Tracts (CHT) encompasses mountainous, forested land with an elevated yearly rainfall, characteristic for high malaria transmission in Asia. With one case per five inhabitants annually (MoHFW, 2002; malaria cases, clinical and confirmed, reported per district), it is one of the areas of highest endemicity in Southeast Asia. The rainy season is from May to October. The ethnic composition of the population is Chakma, Marma and Tripura tribal groups and Bengali settlers. Health services in the rural areas of CHT were disrupted during preceding periods of instability. These were still understaffed and insufficiently supplied when MSF started a basic healthcare project in 1998, with two outpatient clinics situated in Khagrachari Hill District near the Indian border. The statistics from the MSF clinics confirm the scale of malaria as a threat to public health. More than 30% of all patients are ill from malaria, ~85% *P. falciparum* monoinfection or mixed infections, 15% *P. vivax* and 1% *P. malariae* (MSF-Holland data 2003). Malaria incidence shows a clear seasonal pattern, and young and old as well as males and females are affected at similar ratios.