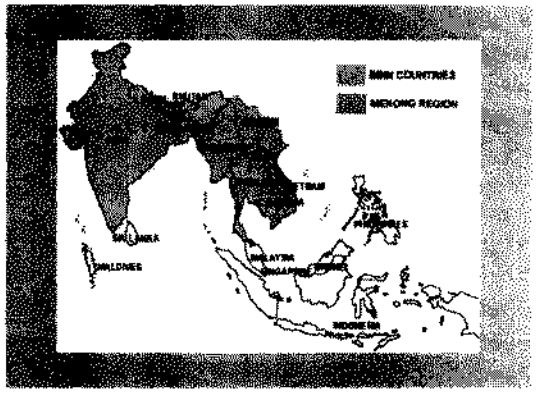
Assessment of Therapeutic Efficacy of Anti-Malarial Drugs Against Uncomplicated *Plasmodium falciparum* Malaria in the Indo-Nepal Border Jhapa District (Nepal) & Darjeeling District, West Bengal (India)

Chand P.B.[a], Wijeyaratne P.[b], Bista M.B.[c], Pandey S.[d], Ansari M.A.[e] & Valecha N.[f]

Malaria has re-emerged as a significant public health problem in countries of South Asia including India and Nepal; strains of *P. falciparum* that are resistant to treatment with chloroquine (CQ) and sulfadoxine-pyrimethamine (SP) are already well established in both these countries. There is extensive migration along the national borders that India shares with countries in the land bridge between South Asia and Southeast Asia, including Myanmar, Bangladesh, Bhutan, and Nepal. There is a predominance of *P. falciparum* in the northeastern states of India adjoining Bangladesh and this forms the pathway for Malaria Drug Resistance (MDR) from Myanmar of Mekong Region. Among South and Southeast Asian countries, India alone contributes more than 80% cases of malaria and *P.falciparum* accounts for nearly half of this burden.

In Nepal, prior to 1981 CQ resistance had been noted only in "imported" malaria cases from northeastern India. Although the number of laboratory confirmed malaria cases are approximately 10,000 annually, the reported clinical malaria cases are more than 60,000 and estimates even higher. The proportion of the more dangerous form of Malaria - *P. falciparum* varies from 6%-20% in different geographic regions of the country.

12 districts labeled as priority districts contribute the majority of malaria cases particularly P. falciparum; sharing borders with India. The intense population movements in these border areas have implications to the epidemiology, transmission and control of malaria. After the emergence of *P. falciparum* resistance to chloroquine, the drug used since the 1950's in Nepal, the malaria drug policy in Nepal was modified in 1988 and sulfadoxine-pyrimethamine (SP) was introduced. This drug was hence established as the first line drug for the treatment of microscopically confirmed uncomplicated *P.falciparum* malaria. A drug efficacy trial in Dhanusha district (Central Region) in 2000 involving 53 patients recorded early and late treatment failures in 2% and 30% respectively among the cases treated with SP while 69% had adequate clinical and parasitological response.



MAP: Malaria Drug Resistance in Mekong Region

In India, the National Anti Malaria Program (NAMP) policy specifies CQ as the first-line drug for treating cases of uncomplicated malaria, and SP as the second-line drug for cases in which parasitemia persists for 72 hours after initial treatment with CQ. The policy also requires that SP be used as the first-line drug in areas where CQ resistance is high (>25% RII + RIII). Resistance to CQ was first detected in 1973 and gradually became

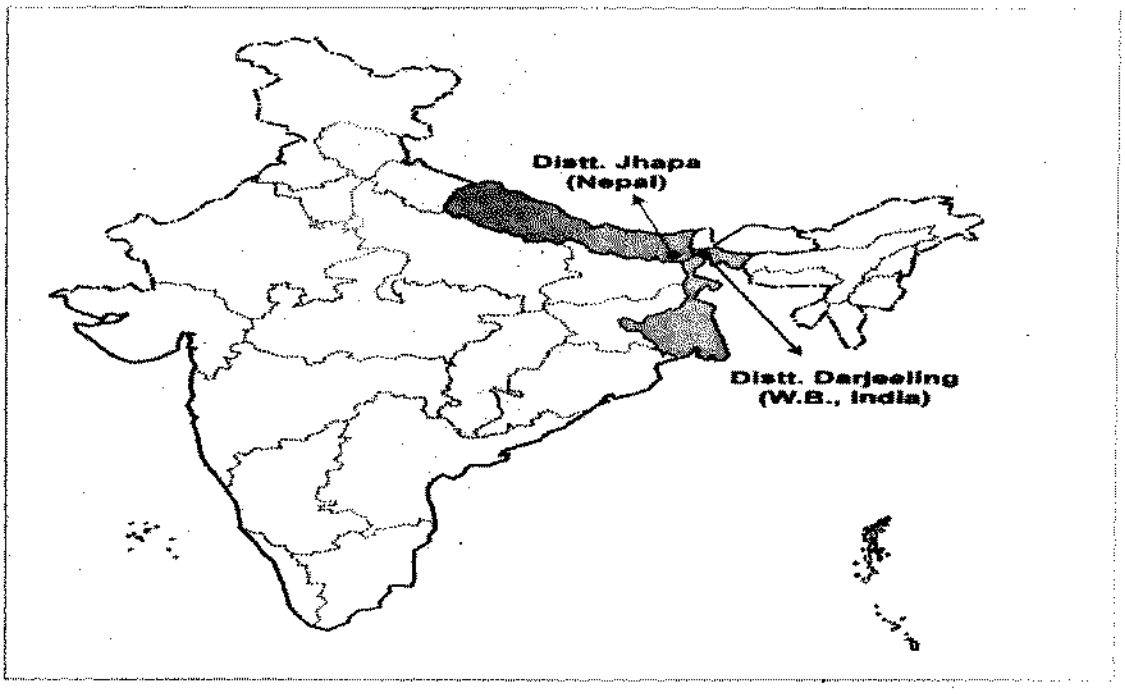
[a] Dr. Padam Bahadur Chand, Management Division, DoHS, /MoH, Teku, Nepal
[b] **Corresponding Author**: Dr. Panduka Wijeyaratne, Resident Advisor, Environmental Health Project, Kathmandu, Nepal, email: panduwij@ehp.wlink.com.np
[c] Dr. M.B. Bista, Director, Epidemiology and Disease Control Division, MoH/Nepal
[d] Ms. Sabeena Pandey, EHP/Nepal
[e] Dr. M.A. Ansari, Director, OIC/ Malaria Research Center, Delhi, India
[f] Dr. Neena Valecha, Deputy Director, Malaria Research Center, Delhi, India

more prevalent, first in Assam state in northeast and later in central and southern states. The NAMP monitors drug resistance routinely, using WHO protocols for in vivo trials. In West Bengal, studies performed in the year 2000-recorded resistance to CQ in 20% of *P. falciparum* cases tested (7% RI, 7% RII, and 6% RIII). Studies conducted in 1997 in four states, including West Bengal and Tripura, reported resistance to SP in about 2% of cases (20 cases total for RI, RII, and RIII, of 915 tested).

In Nepal, a prospective descriptive study using standard protocol of WHO of *in vivo* drug efficacy test (WHO, 1996)[1] showed chloroquine treatment effective in 88% cases, 3.4% early treatment failure (ETF) and 8.6% cases of late treatment failure (LTF)[2].

government regulation or medical practice. Given all these factors, the potential emergence and growth of anti-malarial resistance in South Asia seeks serious attention. Hence, there arose an urgent need to systematically generate scientifically rigorous data on efficacy of currently used drugs in India and Nepal not only for addressing efficacy issues but also to substantiate the findings of previous studies and to generate data on both sides of the Indo-Nepal border for developing uniform policy for effective reduction of the malaria disease burden.

This study conducted in India and Nepal followed the established WHO 28 day treatment protocol (2001) for moderate/low transmission areas and the standardized methods for collection and analysis of



MAP: MDR Study Sites in Jhapa/Nepal and West Bengal/India

Recent history has shown that the distribution and prevalence of drug –resistance forms of parasite can grow quickly. Various anti-malarial drugs are available in the private markets in these countries and their use is not effectively controlled by the

data. The assessment was conducted in two sites each in the West Bengal state of India and in the Jhapa district of Nepal during the period July 2003 to January 2004.

Highlights of Findings

Description	Nepal			India		
	Site A Kakarvitta	**Site B Bahundangi**	**SITE A + SITE B**	**Site A Sukna**	**Site B Naxalbari**	**Site A + Site B**
Drug Evaluated	SP 25 mg + 1.25 mg/kg			CQ 25 mg/kg over 3 days		
Rescue Drug	Quinine			SP; Artesunate + Mefloquine Quinine		
No. Enrolled in the study	56	51	107	50	38	88
No. Completed the study	52	50				
Early Treatment Failure	4	3	7	4	1	5
Late Parasite Failure	3	6	9	14	11	25
Late Clinical Failure	3	2	5	NA	NA	NA

Late Treatment Failure	6	8	14	14	1	15
Total Treatment Failure	10	11	21	32	13	17
No. Adequate Clinical Parasite Response	42	39	81	-	-	-
Loss to Follow-up	2	1	3	-	2	2

The Nepal Study

Following the criteria for selection, a total of 107 *P.falciparum* cases were enrolled in both sites of Jhapa district and 102 completed the study. The selected subjects were administered a strictly monitored regimen of SP as a single dose of 25 mg + 1.25 mg/kg body weight respectively by the team, and were followed up on day 0, 3, 7, 14, 21 and 28 or any other day of illness with symptoms of malaria for clinical and parasitological assessment. Treatment failure (early and late) was observed in 21 (20.6%) patients. Treatment failure and withdrawal patients with signs of severe malaria or co-infections were referred to the Primary Health Center or the Mechi Zonal Hospital for alternative treatment - Quinine was given as the rescue drug. Thirty three percent of treatment failure was reported in a previous study carried out in 2002 in this district, in a much smaller sample of cases.

The India Study

This study was conducted in the Darjeeling district of West Bengal, India and preliminary results show high resistance to Chloroquine in *P. falciparum* malaria. A total of 88 subjects were enrolled in the study in Sukna and Naxalbari sites, 50 in Sukna and 38 in Naxalbari respectively. The treatment course included 25mg/kg doses of CQ over a three-day period. Of the 50 cases in Sukna, 12 were cured, 4 showed early treatment failure, 11 showed late treatment failure and 13 showed late parasite failure. Of the 38 cases in Naxalbari, 20 cases were cured, one showed early treatment failure, one showed late treatment failure, eight showed late parasite failure and two were lost to follow-up.

Conclusions

The results of both studies pose several implications.

1. Up to, 1988, both India and Nepal were still using CQ and Nepal then changed its drug policy to SP, which now is showing degrees of resistance, and its treatment policy needs to be reviewed.
2. The West Bengal state of India, the land bridge to Southeast Asia is the suspected pathway to the spread of drug resistance from Mekong, Myanmar foci is now showing high levels of CQ resistance and hence, this treatment policy in the region would need to be reviewed.
3. Coordination and a standardized approach towards Malaria treatment and case management in the whole West Bengal and Eastern Nepal region would need to be systematically approached in both countries.
4. If the prevalence of SP resistance was to increase dramatically in South Asia, or multi-drug-resistant strains are introduced and become established, the additional burden of adverse health outcomes (deaths and severe cases) and drug costs for effective treatment would increase substantially constituting a significant health, social and economic burden.
5. These and findings of other studies on monitoring efficacy of SP confirm the urgent need to examine the alternative drugs for the treatment of *P.falciparum* malaria in the region. Based on available safety and efficacy data, WHO Technical Consultations have recommended artesunate (ART) or artemesinin based combination therapies (ACT) as alternative therapies for countries.
6. An immediate recommendation is made to establish and conduct systematic surveillance and monitoring to generate data on the efficacy and safety of these drugs as well as treatment practices in national and regional reviews.
7. Timely amendments to localised/area-wide malaria drug policy could then be made to reduce disease severity and prevent mortality from *P.f* malaria as well as to reduce or delay the risk of drug resistance.

References

1. WHO, Assessment of therapeutic efficacy of antimalarial drug for uncomplicated failure malaria in areas with intense transmission. WHO/MAC/96. 1077. Geneva, WHO, 1996.
2. Sherchand JB. In vivo Chloroquine sensitivity test in two malaria endemic districts of Nepal. *Journal of Nepal Association for Medical Laboratory Sciences*, 2003; 5: 1-3.