Activity Report 130

An Inventory on Malaria Drug Resistance in Bangladesh, Bhutan, India and Nepal

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June 2004

Prepared under EHP Project 26568/E.X.5.ANE.MDRCOORD

Environmental Health Project
Contract HRN-I-00-99-00011-00
is sponsored by the
Office of Health, Infectious Diseases and Nutrition
Bureau for Global Health
U.S. Agency for International Development
Washington, DC 20523

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Abbreviations

ACR	adequate clinical response
ACT	Asian Collaborative Network
AIDS	Acquired Immunodeficiency Syndrome
AVT	Asian Collaborative Training
BBIN	Bangladesh, Bhutan, India, Nepal
b.d.	twice a day
BHU	Basic Health Units
CQ	Chloroquine
CRPf	Chloroquine resistant *Plasmodium falciparum*
DDC	Drug Distribution Center
DoHS	Department of Health Services (Nepal)
EHP	Environmental Health Project
ETF	Early Treatment Failure
EWARS	Early Warning Reporting System
FTD	Fever Treatment Depot
HIV	Human Immunodeficiency Virus
HP	Health Post
I/M	Intramuscular
ITMN	Insecticide-Treated Mosquito Net
LTF	Late Treatment Failure
MDR	Multi-Drug Resistance
MoH	Ministry of Health (Nepal)
NAMP	National Anti-Malaria Program
NCBI	National Center for Biotechnology Information
NE	Northeast
NIH	National Institutes of Health
NLM	National Library of Medicine
NMEP	National Malaria Eradication Program
o.d.	once a day
P. falciparum, Pf	*Plasmodium falciparum*
P. vivax, Pv	*Plasmodium vivax*

PfCP	Plasmodium falciparum Containment Program
PHC	Primary Health Center
Q	Quinine
RBM	Roll Back Malaria
SA	South Asia
SEARO	Southeast Asia Regional Office (of WHO)
SHP	Sub Health Post
SM	Severe Malaria
SP	Sulfadoxine-pyrimethamine
TFM	Treatment Failure Malaria
t.i.d.	thrice a day
UM	Uncomplicated Malaria
VBDRTC	Vector-Borne Disease Research & Training Center
VDC	Village Development Committee
WHO	World Health Organization

About the Authors

Dr. Anand Joshi is presently Associate Professor of Public Health in the Department of Community Medicine and Family Health at the Institute of Medicine, Tribhuvan University, Kathmandu, Nepal. He is responsible for teaching and research in the epidemiological and management aspects of malaria, KA, JE and other vector-borne diseases. Dr. Joshi has been a principle investigator on several research projects such as Entomological and Epidemiological Investigation of Kala-azar in Eastern Nepal, Sero-epidemiology of Visceral Leishmaniasis in Southern Nepal and West Bengal, India, and Review of School Health Programs in Nepal. He has been a co-principal investigator on several projects funded by international organizations such as IDRC/Canada, United Nations, Regional Office for Asia and Pacific, Bangkok, Thailand and WHO/SEARO. Dr. Joshi also worked as a consultant and coordinator periodically with EHP/Nepal for the assessment of "Laboratory Diagnostic Capacity of Five Regional Laboratories," and "Case Control Study to Identify Risk Factors of Visceral Leishmaniasis in Nepal." Dr. Joshi holds a Ph.D in Tropical Medicine and a masters degree in Tropical Medicine from Mahidol University, Bangkok. In addition, he holds a masters in Zoology—Parasitology from Tribhuvan University, Kathmandu, Nepal. He has also received post doctoral training from Liverpool School of Tropical Medicine, University of Liverpool. Dr. Joshi has 23 publications to his credit.

Ms. Sabeena Pandey is the Cross-border Activity Coordinator at EHP/Nepal Infectious Disease Program, where she has been working with Dr. Panduka Wijeyaratne in implementing Objective 5 related cross-border activities and the USAID/ANE supported inter-country component activities. The principle activities included developing and maintaining a network of neighboring countries; Bangladesh, Bhutan, India and Nepal (BBIN), a BBIN website, malaria and Japanese encephalitis surveillance diagnosis and drug resistance common approaches and inventories on insecticide resistance and malaria drug resistance. Several inter-country conferences and workshops have been conducted in the implementation program that included numerous regional and international technical consultants as well as institutional networking. Ms. Pandey has a Master's Degree in Economics from University of Bombay, India, and has experience in developmental studies in and outside Nepal.

Ms. Deepika Singh has worked with EHP/Nepal since March 2000, she started her work with EHP, as an Editorial Associate and later took on the position of the Program Officer up to April 30, 2004. Ms. Singh has extensive experience in producing, editing and writing various reports. At EHP, she has contributed significantly in designing, writing, producing and editing program related activity reports including several write-ups on vector-borne disease programs in Nepal. She holds a masters in English Literature from University of Dhaka, Dhaka, Bangladesh.

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Dr. Panduka M. Wijeyaratne is Resident Advisor to HMG Ministry of Health EHP/Nepal Infectious Disease Program, where he directs a multifaceted program for the control and prevention of vector-borne diseases, particularly malaria, kala-azar, and Japanese encephalitis. Before joining the Environmental Health Project in 1994, Dr. Wijeyaratne was Principal Program Officer (Health, Society, and Environment) with IDRC in Ottawa, Canada, for ten years. As Senior Tropical Disease Specialist at EHP, Dr. Wijeyaratne managed activities (focused on control of vector-borne diseases) in Zambia, Eritrea, Jordan, Nigeria, Malawi, Mozambique, and other countries. He has been a member of several advisory groups and technical steering committees for the World Health Organization and Rockefeller Foundation and the Canadian and Nigerian governments. Dr. Wijeyaratne has extensive experience with work in at least 35 countries including the United States, Canada, Sri Lanka, and Nigeria. His work also includes teaching, research and publications.

Executive Summary

Antimalarial drug resistance has emerged as one of the greatest challenges facing malaria control today. The last decade has seen the spread of drug-resistant malaria in the Indian subcontinent also. The resistance of *Plasmodium falciparum* to chloroquine was first observed half a century ago. By the late 1980s, the parasite showed increased resistance to sulfadoxine-pyrimethamine and mefloquine. It is thus highly likely that the parasite will eventually develop resistance to any drug that is used widely. In addition, the development of new drugs takes much longer than development of parasitological resistance (Bloland, 2001). While this has complicated the control of *P. falciparum,* it has also led to several studies on the efficacy of antimalarials.

The aim of this inventory is to document the status of drug-resistant malaria in four countries: Bangladesh, Bhutan, India and Nepal (BBIN). Within this geographic purview, the inventory has attempted to meet the challenge of consolidating information on malaria drug resistance in the form of a ready reckoner. Studies documented in India point to 15% chloroquine resistance in 1993 and increasing incidence in subsequent years, thereby suggesting that resistance to chloroquine is one of the causes of resurgence and sustenance of malaria. A 17-year long study on monitoring chloroquine resistance of *P. falciparum* in Orissa reveals that of a total of 1,165 *in vivo* tests conducted, RI level of resistance was detected in 12% of the cases, RII in 4.4% cases and RIII in 1.9% of the cases. Fifty-one percent of the samples tested using the *in vitro* method showed *P. falciparum* resistance to chloroquine (Sathpathy et al., 1994). National Program and research institutions monitor resistance in the country, and necessary changes are made in the drug policy based on this information.

In Nepal, *in vivo* and *in vitro* tests of "imported" cases prior to 1984 confirmed that *Plasmodium falciparum* is resistant to chloroquine. In 1984, the first-ever recorded resistance to chloroquine in indigenous cases was from Makawanpur district of the Central Region. Since then, chloroquine resistance has been reported from Udaypur district of the Eastern Region; Dhanusha, Mahottari and Sindhuli districts of the Central Region; Nawalparasi district of the Western Region, and Kailali and Kanchanpur districts of the Far Western Region. While systematic drug monitoring activities have not been carried out during the past few years, reports of failure in *falciparum* malaria treatment with sulfadoxine-pyrimethamine are received from time to time from *falciparum* prevalent areas of the country, indicating the possible emergence of *falciparum* resistance to the antimalarials.

In Bangladesh, 88% of the population is at risk for malaria. The strategy for early diagnosis and treatment has been defined and attempts are being made to monitor drug resistance. Bhutan has a special problem of cross border malaria cases. The drug policy has been effectively revised and monitoring of drug resistance is done regularly.

It has been revealed that the current empirical treatment policy with first-line antimalarials in the different countries has altered the clinical profile of drug resistant *Plasmodium falciparum.* Hence, there is a need to identify and establish a network of institutions working on drug-resistant malaria in the BBIN countries, with possible exchange of visits and sharing of findings that will help in designing and developing future activities. Lack of systematic early diagnosis and proper treatment, change in malaria paradigms, population movement, and developmental activities are a few of the causes for the increase of malaria in some areas of the region. The inventory concludes that there is a need to conduct regular monitoring of treatment practices through standardized and comparable drug efficacy testing methodologies across the South Asian region to prevent the increase of drug resistant malaria, as is the case in the Southeast Asian region including the Mekong countries. Consistent information exchange is also very essential among the countries involved.

Introduction

Worldwide, there are almost 300 million reported cases of acute malaria each year of which an estimated 0.7–2.7 million succumb to the disease (Wongsrichanalai *et al.* 2002). Over 75% of these occur in tropical and subtropical regions of Africa and the rest in Asia. Among the most vulnerable populations are children under five and pregnant women. The disease is a burden particularly for the poor countries. Amid this scenario, the development of drug resistance exacerbates the spread of the disease to epidemic proportions. Along with several other health problems—HIV/AIDS, tuberculosis, and maternal ill health and malnutrition—the risk of malaria is a constraint to economic development of communities, regions, and nations (WHO 1998). It is imperative, therefore, to review the status of antimalarial drug resistance.

In the South Asian region, *Plasmodium vivax* and *Plasmodium falciparum* are the predominant species causing human malaria (WHO 2001). For the last decade, chloroquine-resistant *P. falciparum* has spread explosively in sub-Saharan Africa, Southeast Asia, and South Asia (Table 1). Control of *falciparum* malaria is becoming a challenge especially in Multi-Drug Resistant (MDR) areas. *P. falciparum* is also responsible for complications like cerebral malaria etc, prompting more than one million deaths per year. The other species of mosquito responsible for malaria (*P. vivax, P. ovale* and *P. malariae*) also produce high morbidity but are usually susceptible to chloroquine, which is a good blood schizontodicidal drug.

Table 1. Dates of First Reports of Antimalarial Drug Resistance

Antimalarials	Introduced	1st Reported Resistance	Difference (Years)
Quinine	1632	1910	278
Chloroquine	1945	1957	12
Proguanil	1948	1949	1
Sulfadoxine-pyrimethamine	1967	1967	0
Mefloquine	1977	1982	5
Atovaquone	1996	1996	0

Source: (Wongsrichanalai et al. 2002)

In Bangladesh, 60% of the malaria cases are *P. falciparum*. Malaria is also a health problem in the southern belt of 30–50 km and a few valleys in Bhutan, where 50% of the cases are *P. falciparum*. In India, resurgent malaria has invaded new ecotypes created by the green revolution, growth, and development resulting in a paradigm shift towards man-made malaria. In Nepal, the malaria situation has generally improved since 1992. *P. falciparum* is at about 15%, which is the lowest in the region. In a significant number of countries, initial success in malaria control was followed by a resurgence of the disease. The reasons for this are complex, and include

vector resistance to insecticides, vector exophily, parasite resistance to drugs, and factors related to human ecology.

In Asia, overall mortality rates due to malaria have declined. However, progress is now threatened as a result of the emergence of drug-resistant forms of parasites and new epidemics, which reflect climate change, population movements, or breakdown in control measures. The problem of multi-drug resistant *falciparum* malaria is spreading. *Falciparum* malaria resistant to chloroquine and sulfadoxine-pyrimethamine (SP) is widespread, and mefloquine and quinine resistance has also been reported (Misra, 1996). Uncontrolled population migration both across borders and within countries due to sociopolitical reasons, employment, and other economic activities in forests and endemic areas has made disease transmission more complex. A range of interventions has proven to be effective in reducing the malaria burden, but further work is required to promote these strategies and to build the capacity to implement them. This brief review attempts to identify the gaps in malaria drug resistance research and its relation with cross-border malaria issues. Attempts will also be made to explore potential partners and collaborating institutions for future malaria research activities.

It is important to understand the resistance patterns in each geographical region. Many factors contribute to the development and spread of resistance. In the BBIN countries, one factor is the close proximity of the Mekong region, which is the global epicenter of malaria and from where many drug-resistant parasite strains are transferred to other parts of the world (see Map overleaf).

Objectives

The objectives of this review are:

- To compile documents on malaria drug resistance studies and information on BBIN countries through literature and document searches and personal contacts in Nepal
- To establish contacts by telephone, e-mail or fax with experts and related agencies in Bangladesh, Bhutan, India and Nepal for assimilation of information necessary for compilation
- To identify major gaps in the information collected and to develop a work plan to fill these gaps and conduct a site visit, particularly in India, to collect relevant documents and related information
- To compile collected data, carry out an analysis, and prepare a report

This report will make tangible conclusions and recommendations for the issues that need to be addressed for cross-border follow-up activities.

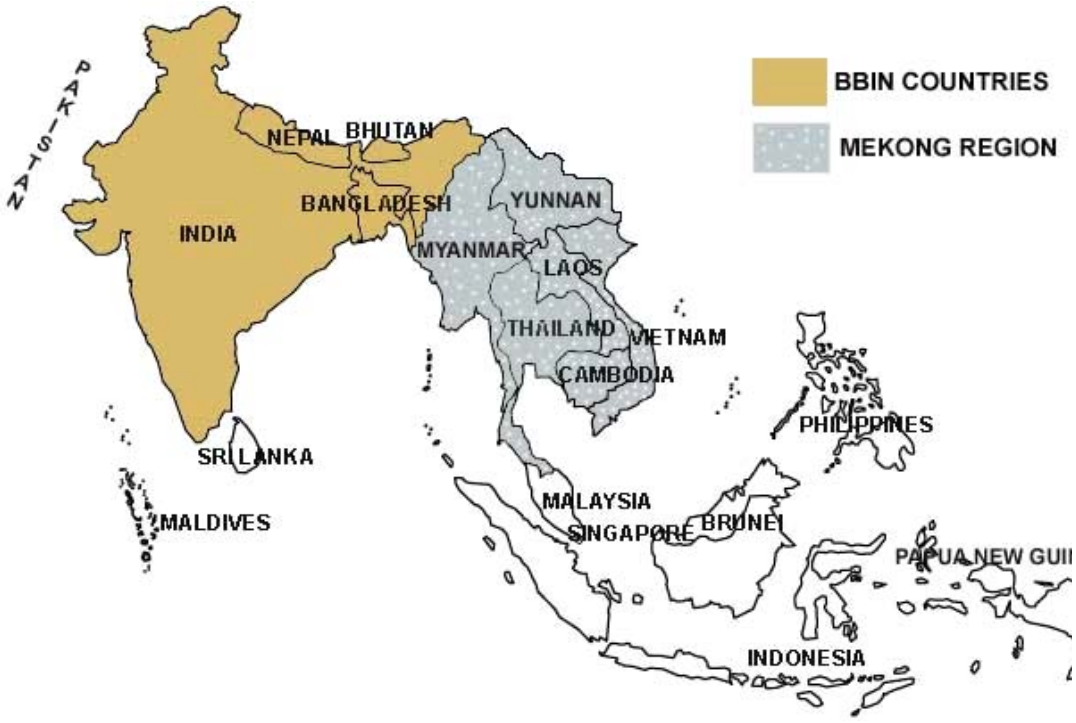
Methodology

A review of existing documents, Internet search, and personnel communication by telephone and e-mail were made to prepare an inventory regarding malaria drug resistance in Bangladesh, Bhutan, India and Nepal.

The Malaria Drug Resistance inventory draft was presented at the Informal Consultative Meeting on Development of South Asia Surveillance Network for Malaria Drug Resistance, where discussions were held on Networking and Information Exchange for Malaria Drug Resistance. The consultation was jointly organized by the Southeast Asia Regional Office of the World Health Organization (WHO/SEARO) in collaboration with the Environmental Health Project (EHP) in Nepal, Jan. 9–10, 2002, in New Delhi, India. Participants included 25 experts on vector-borne diseases from BBIN and Myanmar; WHO representatives from Geneva, Thailand and New Delhi; USAID Cambodia; US Armed Forces Research Institute of Medical Sciences; EHP-sponsored Nepali participants; and representatives from ACT Malaria Coordination, Malaysia. This Asian Collaborative Training (ACT) network for malaria is actively working in the Mekong region.

Dr. Panduka Wijeyaratne, Resident Advisor for EHP/Nepal, presented the inventory. The purpose of the presentation was to highlight the status of the draft inventory on malaria drug resistance undertaken by EHP/Nepal through USAID's Asia and Near East (ANE) bureau for funding and to draw further inputs from the countries towards the finalization of the document. The initiative on compiling the inventory was appreciated and there was a consensus to proceed with the finalization of the inventory. All suggestions made by the experts at the meeting have been incorporated.

Figure 1.


BBIN COUNTRIES
MEKONG REGION
NEPAL
BHUTAN
BANGLADESH
INDIA
YUNNAN
MYANMAR
LAOS
THAILAND
VIETNAM
CAMBODIA
PHILIPPINES
SRI LANKA
MALDIVES
MALAYSIA
SINGAPORE
BRUNEI
INDONESIA

Background

Pub-Med, available via the National Center for Biotechnology Information (NCBI) Entrez Retrieval System, was scanned for papers on malaria published from all countries. This was developed by the NCBI at the National Library of Medicine (NLM) and is located at the National Institutes of Health (NIH), U.S.A. The information retrieved has been tabulated below (Tables 2,3, and 4).

Table 2. Global Malaria Publications Based on PUB-MED National Library of Medicine (Jan. 1, 1994–Aug. 1, 2001)

Total Malarial Publications	**Asia**	**Africa**	**Latin America**
	1200	**2287**	**33**
Falciparum Malaria	530	962	7
Vivax Malaria	228	44	5
Ovale Malaria	16	17	No
Malariae Malaria	16	38	No
Total Drug Resistant Malaria	206	311	2
Drug Resistant Falciparum Malaria	164	235	2
Border Malaria	12	30	-

Table 3. Malaria Publications Based on PUB-MED National Library of Medicine (Jan. 1, 1994–Aug. 1, 2001)

ASIA	**Total Malaria Publications**	**Pf**	**Pv**	**Po**	**Pm**	**Malaria Drug Resistance**	**Drug Resistance Pf**
Indonesia	97	43	62	1	2	11	7
Thailand	305	187	47	3	4	76	63
Sri Lanka	52	16	13	-	-	5	3
Pakistan	47	25	18	-	1	4	4
China	94	32	20	1	4	15	13
Saudi Arabia	25	8	1	-	-	3	3
Philippines	19	9	4	-	-	3	2
Burma	36	23	24	1	1	8	7
Bangladesh	15	3	2	-	-	-	-
Bhutan	-	-	-	-	-	-	-
India	428	192	69	5	6	23	15
Nepal	25	3	7	-	-	1	1

Many malaria drug resistance studies have been carried out in India and other parts of the world. However, very few studies have been conducted in Bangladesh, Bhutan and Nepal.

Table 4. Malaria Incidence in BBIN Countries in 1999

Country	Malarious Population	Positives	Pf Cases	Pf %	Malaria Deaths
Bangladesh	111,638,000	63,723	44,363	69.6	552
Bhutan	419,000	12,237	6,531	53.4	16
India	929,192,000	2,031,781	989,351	48.7	972
Nepal	15,879,497	8,959	622	6.94	7

Sources: WHO 2001, Malaria Situation in SEAR Countries, Internet Search, and Proposed Five Year Plan (2001-2005), Nepal, 2001

1. Inventory by Country

1.1. Bangladesh

1.1.1. Epidemiology

Malaria is a major public health problem in Bangladesh. About 88% of the 128 million people in the country are at risk. Of the two prevalent species *Plasmodium falciparum* is predominant over *Plasmodium vivax*. The majority of cases are reported from 13 out of 64 districts in the country. These have a total population of 24 million, and 10 million are considered at highest risk. Thirty-four Upazilla (smaller divisions) in these districts are in prone border belt areas. Focal outbreaks are also common.

Table 5. Malaria Situation

Year	Positive Cases	*Pf* Cases	*Pf* %	Confirmed Deaths Due to Malaria
1996	100,864	54,307	53.8	447
1997	68,594	42,342	61.73	447
1998	60,023	42,222	70.3	491
1999	63,738	44,306	69.5	551
2000	55,599	39,536	71.1	469

Source: Report on Malaria and kala-azar in Bangladesh (Huq et al. 2002)

Although improvement in the malaria situation has been reported recently in Bangladesh (Table 5), the data must be interpreted with caution because of the decline in surveillance activities in the country over the past few years (WHO 1999). The burden, *Pf* proportion, severe cases, mortality, and treatment failure have remained high. Five major epidemiological types—namely malaria in forest hills, forest fringe, plain border belt areas, rural, and urban malaria—have been identified. Reported prevalence/incidence rates are higher for males than for females in Bangladesh. The prevalence of malaria in 1994–95 was 9.26 per 1,000 males and 8.89 per 1,000 females (Bangladesh Bureau of Statistics 1995). Of the 150,000 cases reported annually, 60% are *P. falciparum* and 80% are from forest areas along the border with Myanmar and India. *Pf* infection has become increasingly dominant in some focal areas (over 90%). In one study in the forest dwelling community *Pf* percent was found to be 70% (Rosenberg et al., 1982).

Regarding malaria control, there is a strong relationship among health development partners as a result of the Sector Wide Management Approach. This approach also

facilitates the accessibility to and utilization of an "Essential Services Package" for the entire population. The country has guidelines to implement revised strategy for malaria control.

1.1.2. Treatment

The following strategies have been defined for diagnosis and treatment:

a. The adoption of the three malaria clinical case definitions of Uncomplicated Malaria (UM), Severe Malaria (SM) and Treatment Failure Malaria (TFM) for Early Diagnosis and Prompt Treatment (EDPT)
b. The adoption of revised reporting forms for Malaria Epidemiological Surveillance, which allow for the reporting of malarial deaths
c. Establishment of a community based Insecticide Treated Mosquito Net (ITMN) program
d. Monitoring of TFM cases and TFM trends, strengthening of malaria laboratory services, and monitoring of the therapeutic efficacy of standard antimalarial drug regimens
e. Strengthening of the epidemic preparedness and response capacity at the National, District and Upazilla levels

The treatment of uncomplicated *P. falciparum* malaria and *P. vivax* cases is done by chloroquine (total dose = 25 mg/kg body weight) in a three-day regimen followed by primaquine (45 mg of primaquine for adults) in a single dose. For severe malaria cases, treatment with parentral quinine (Quinine di-hydrochloride 10 mg/kg body weight) followed by oral quinine for three days and a single dose of SP has been reported to be effective in all cases. During an epidemic the multipurpose health workers are also trained to detect severe malaria cases and to give first dose of Intramuscular (I/M) quinine prior to referral to a hospital or nearby temporary treatment center. This has been reported very effective in the prevention of deaths in a large proportion of cases where longer time is taken for transportation to hospitals due to difficult communication. The drug schedule is as follows:

1. Treatment of *P. falciparum*

Uncomplicated		**Treatment Failure**	**Severe Malaria**	**Pregnancy**	
Unconfirmed	**Lab-confirmed**			**Treatment**	**Prevention**
CQ 25mg/kg Primaquine 0.75 mg/kg (Adult 45 mg, Single dose)	CQ 25 mg/kg Primaquine 0.75 mg/kg (Adult 45 mg, Single dose)	Q 3 days+ SP, Q 7 days	Q 3 days+ SP or Q 7 days	CQ/Q	-

2. Treatment of *P. vivax*

Chloroquine	Treatment failure	Primaquine
CQ 25 mg/kg	Q 3 days + SP Q 7 days	O.75 mg/kg (Adult 45 mg, Single dose)

Q : Quinine CQ : Chloroquine SP : Sulfa-pyrimethamine combination

1.1.3. Drug Resistance

Emergence of drug resistance in some places is posing serious problems. Some of the causes are indiscriminate use of antimalarials, over-the-counter availability, and non-compliance with existing treatment protocols. Chloroquine resistance was first detected in the bordering districts of Haluaghat of Mymensingh district during 1970 and at Chaklapunji Tea Estate in Habigonj district in 1976. Chloroquine resistance has increased from 10% in 1979 to 45% in 1987 and 57% in 1992 (RII + RIII) (Rosenberg et al., 1977; Rosenberg et al., 1982).

Collaborative studies with WHO have attempted to determine the extent of chloroquine resistant *Pf* malaria in the hill and forest areas of Chittagong, Sylhet and Mymensingh. Reports from a randomized controlled trial (sponsored by Integrated Control of Vector Borne Diseases project) in one of the high-risk malaria zones (Ramu Thana of Cox's Bazaar district) have shown a parasitological failure rate of 72% (95% CI, 65–79%) and an early treatment failure rate of 34% (95% CI, 26–41%) to the existing first-line agent chloroquine. The second-line regimen (Q3+SP) for treatment failure cases has also shown a clinical failure rate of 21% (95% CI, 15–29%) in Ramu Thana of Cox's Bazaar district.

In vitro studies also demonstrated high degree of Chloroquine resistance: 84% of the *P. falcip*arum isolates out of 44 collected from Bangladesh showed IC 50 of 114.25 nm (Geometric man). The IC 50 for quinine and Mefloquine were 291.52 and 60.3 nm respectively (Neodl et al., 2001). Cure rates observed in therapeutic efficacy studies (14 day test) for second line treatments viz Q3+SP and CQ+SP were 84% and 79% respectively in Barachara under Sadar Thana of Cox's Bazaar district (Rahman et al., 1998).

Status of mefloquine resistance is similar to that in Thailand. Artemether and Artesunate are as effective as is quinine.

1.1.4. Special Issues

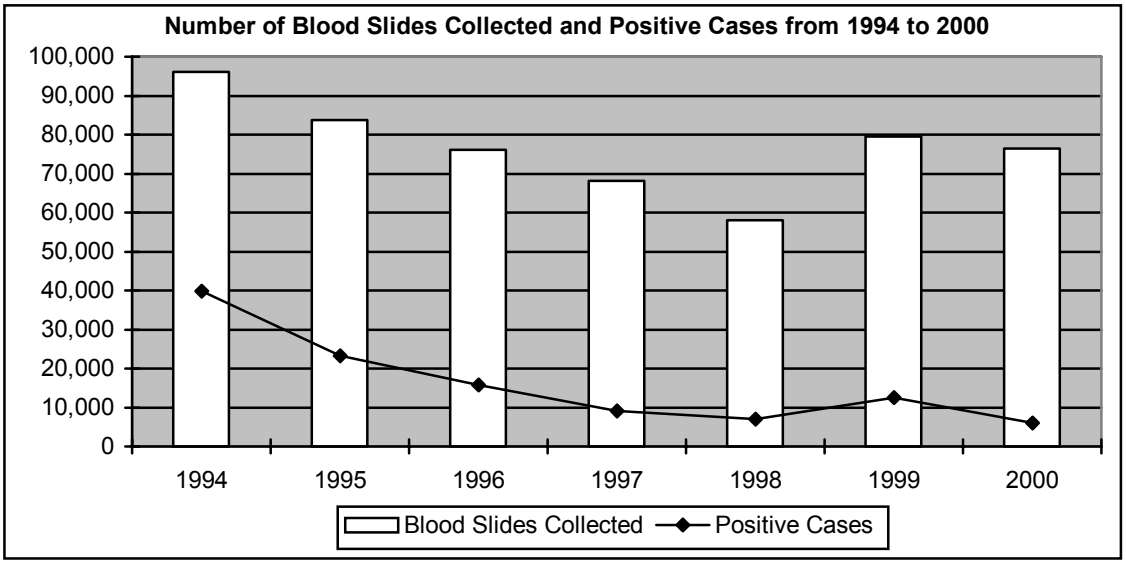
The reported malaria cases are underestimated due to shortcomings in the surveillance. Focal outbreaks are common. Population movement is an additional reason for outbreaks. The cost of insecticides and drugs is a limiting factor in control (Bangladesh Country Report, 2001).

1.2. Bhutan

1.2.1. Epidemiology

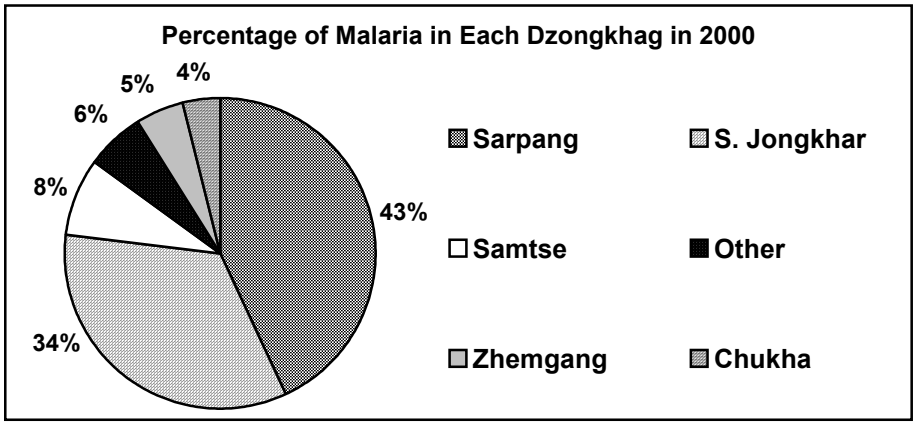
Malaria is a problem in Bhutan and has been appearing as endemic in the southern belt of 30–50 km and in a few valleys. The mountainous northern and central zone of the country is free from malaria. Estimated population at risk is 170,000–180,000 (Fig. 2). About 60% of the population lives in malaria transmission areas, although 95% of cases are reported from the southern lowland Dzongkhags (districts), namely Sarpang, Samdrup, Jongkhar, Samtse, Zhemgang, and Chukha (Fig. 3). Systematic malaria control was started in 1962, and cases dropped in 1966. However, in 1976 the incidence increased to 8,035 and fluctuated subsequently. Use of pyrethroids from 1995 to 1998 also affected the incidence. The number in 1998 was 8,000 as compared to 39,000 in 1994. The reduction was 41% in 1999 and 85% in 2000 as compared to 1994. The decrease may be due to improved surveillance and better treatment (Health Division, Thimphu 1994, 95, 96 and WHO 1999; Zangpo, 2002).

Figure 2. Number of Blood Slides Collected and Positive Cases from 1994 to 2000



Source: http://www.bbin.org

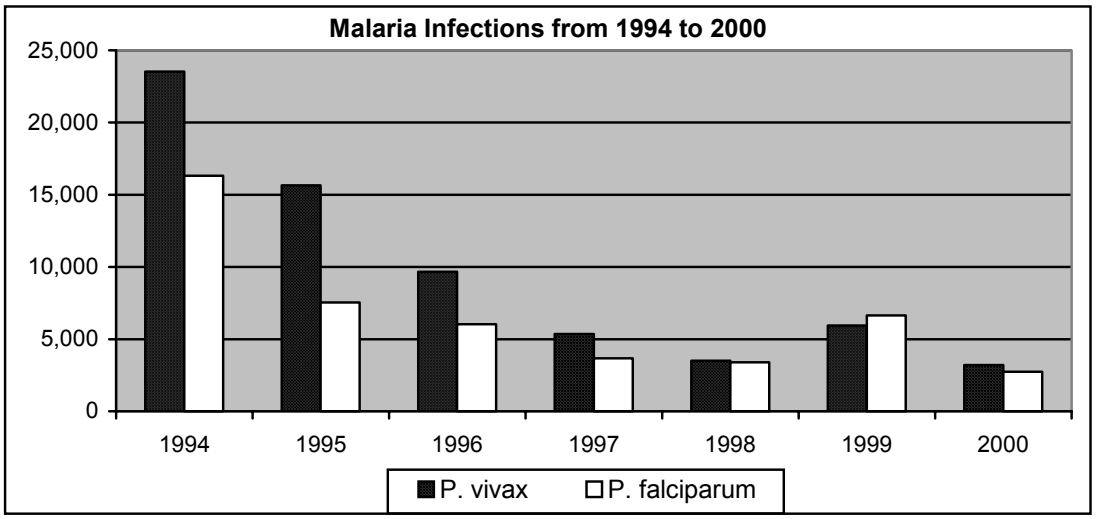
Figure 3. Percentage of Malaria in Each Dzongkhag in 2000



Source:http://www.bbin.org

Of the total malaria cases, approximately 50% are *P. falciparum*. *P. vivax* was predominant through the 1990s. However, *Pf*-positive cases showed a sudden increase to 12,966 in 1991 compared to *Pv*-positive cases of 9,160. The falciparum again showed a rising trend from 1998 and overtook vivax in 1999 with the positive caseload of 6,665 compared to 5,937 positive cases for vivax. But in 2000, it declined to 2,738 cases compared to 3,197 positive for *P.vivax* (Fig. 4). Some foci of *P. falciparum* resistant to chloroquine and SP have been documented.

Figure 4. Malaria Infections from 1994 to 2000



Source: http://www.bbin.org

No epidemic has been reported during the last three years. The reported prevalence/incidence rates were higher for males than for females in Bhutan. The sex ratio of malaria cases from health services data for 1998 was 1.39:1 male to female (WHO 1999). The 15 to 49 year-old age group is most vulnerable. Mortality also decreased over the period from 1993 to 1997, but a deteriorating trend was observed in 1998 coinciding with withdrawal of ITMN program (Zangpo, 2002).

1.2.2. Treatment

Following the national drug policy, the treatment regimen was Chloroquine and Primaquine for *P. vivax* and SP compound for *P. falciparum* as first-line drugs until 1998 (Zangpo,2002). For resistant *P.falciparum*, the drug of choice was Quinine. The drug policy was revised in 2000, and schedules are as follows:

i. P.falciparum

a. Patients of greater than 15 years of age
   - Days 0,1 and 2: Artesunate 100 mg b.d.
   - Days 3: Doxycycline 200 mg o.d. + 30 mg primaquine
   - Days 4, 5, 6, 7, 8, 9: Doxycycline 100 mg

b. Women in the first trimester of pregnancy
   - Days 0,1 and 2: Quinine 600 mg t.i.d.
   - Days 3, 4, 5 and 6: Dapsone 50 mg b.d. and proguanil 200 mg o.d.

c. Women in the second and third trimester of pregnancy
   - Days 0, 1 and 2: Artesunate 100 mg b.d.
   - Days 3, 4, 5 and 6: Dapsone 50 mg b.d. and proguanil 200 mg o.d.

d. Infants below four weeks (neonates)
   - Days 0,1 and 2: Quinine 10/kg 8-hourly by I/M Injection (for 7 days if needed) (Patient should be hospitalized)

e. Children between one month and eight years of age

Age	**Artesunate** **Day 0,1,2**	**Dapsone** **Days 3,4,5,6**	**Proguanil** **Days 3,4,5,6**	**Primaquine**
1-11 Months	12.5 mg b.d.	6.75 mg b.d.	25 mg b.d.	—
1-4 years	25 mg b.d.	12.5 mg b.d.	50 mg b.d.	—
5-8 years	50 mg b.d.	25 mg b.d.	100 mg b.d.	15 mg

f. Children 9-14 years of age
   - Day 0, 1 and 2: Artesunate 75 mg b.d.
   - Day 3: 100 to 200 mg doxycycline o.d. and 22.5 mg primaquine
   - Day 4, 5 and 6: 50 to 100 mg doxycycline o.d.

g. Severe and complicated *falciparum* malaria
   - Adults: Artemether I/M 80 mg b.d. for three days
   - Children: Artemether I/M 1.6 mg/kg b.d. for three days

ii. P. vivax

The standard treatment of vivax malaria consists of chloroquine and primaquine, except in pregnant women and children under five years of age (who are given chloroquine only). The adult doses of chloroquine (base) are 600 mg on Day 1, and 300 mg on Day 2. The adult dose of primaquine (base) is 15 mg daily from Day 0 to Day 13. For children, the chloroquine dose is adjusted to 10 mg/kg of body weight on Day 0 and Day 1, and 5 mg/kg on Day 2. The daily primaquine dose (Day 0 to Day 13) is 7.5 mg for children of 5–8 years, and 11.25 mg for children of 9–14 years.

However, considering the problems with patient compliance due to the 7–10 day required regimens, introduction of co-artemether (a fixed combination of artemether and lumefantrine) has been suggested in the drug policy.

1.2.3. Drug Resistance

Chloroquine resistance in *P. falciparum* was reported in 1984 for the first time, and it reached 63% in the Dzongkhags of Sarpang and Samdrup Jonkhar in 1996. Resistance to SP was first observed in Sarpang Dzongkhag in 1989. Since then, the problem has increased and in 1998, late treatment failure (LTF) reached 35% by day 28. The therapeutic efficacy studies of mefloquine showed S-response in 90% RI 7% and RIII 3% (Table 6).

In therapeutic studies at Sarpang and Gelephu Hospitals and Kalikhola Basic Health Units (BHU), 11 patients showed adequate clinical response (ACR), 17 LTF, one ETF out of 29 cases treated with artesunate. This tends to confirm the high recrudescence rates associated with artesunate monotherapy observed elsewhere. Observations with the combined regimen of artesunate 200 mg daily for three days and doxycycline 100 mg for seven days were carried out at Kalikhola and Daifam BHUs. Out of 49 patients, 43 showed ACR responses (88%), and six LTF (12%).

Table 6. *In Vitro* and Therapeutic Efficacy Drug Sensitivity Tests Conducted from 1995 to 2000

Year	Drugs	SC	*In Vitro* Test				Therapeutic Efficacy Status					
			S	%	R	%	ETF	%	LTF	%	ACR	%
1995	CQ	16	4	25	12	75	-	-	-	-	-	-
	SP	31	8	73	3	27	-	-	-	-	-	-
1996	CQ	11	3	27	8	73	-	-	-	-	-	-
	SP	12	4	57	3	43	-	-	-	-	-	-
1997	CQ	115	-	-	-	-	13	11	73	64	29	25
1998	SP	23	-	-	-	-	0	-	8	35	15	65
1999	MQ	41	-	-	-	-	1	3	3	7	37	90
	SP	13	-	-	-	-	0	0	3	23	10	77
2000	Artesunate Combination	38	-	-	-	-	-	0	4	11	34	89

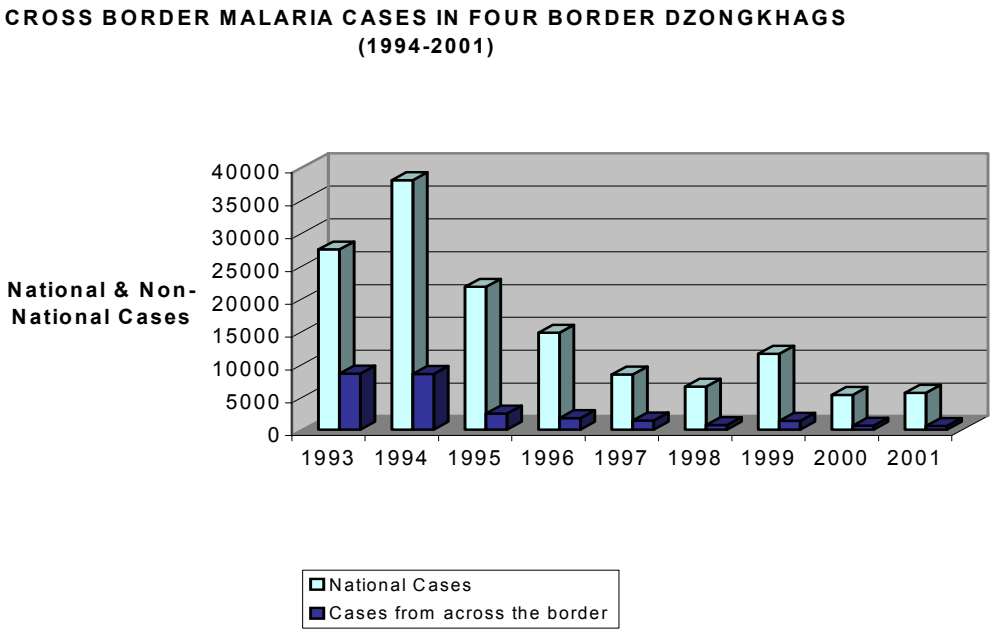
Source: Brief Report of malaria Situation in Bhutan (Zangpo 2002)

1.2.4. Special Issues

The annual statistics indicate that the total non-national malaria cases is proportional to the total indigenous cases, indicating similar epidemiology of the disease in the vicinity of border areas (Fig. 5). Therefore, cross-border malaria transmission needs special attention (Zangpo, 2002).

In addition there are operational problems with the revised drug policy, which involves 7–10 days therapy and a number of regimens for different age groups. Recently, suggestions have been made to simplify the dose schedules by using co-artemether.

Figure 5.



Source : Zangpo, 2002 India

1.2.5. Epidemiology

India is endemic for malaria except in areas above 1,500 m and some coastal areas (Valecha, 1996; Sharma, 1999). Prior to launching the National Malaria Control Program in 1953, 75 million cases with 0.8 million deaths were reported annually. With the introduction of DDT, the cases dropped to 0.1 million in the 1960s and the entire country was brought under the National Malaria Eradication Program (NMEP) (Sharma, 1996; Sharma, 1999). Thereafter, there was a resurgence and 6.47 million cases were reported in 1976. Major changes were introduced by initiating a modified plan of operation (Pattanayak and Roy, 1980; NMEP, 1995). The concept of voluntary managed drug distribution centers and fever treatment depots was introduced. This led to improvement in the malaria situation, and malaria cases stabilized at around 2–3 million cases from 1983 onwards. However, the decline was in vivax malaria and the proportion of *P. falciparum* has gradually increased to about 45% (NMEP, 1996). The increase in *Pf* percentage could be due to any number of causes: environmental changes, inadequate treatment, and inadequate/ineffective intervention measures for transmission control, for example. A committee of experts indicated that a proportion of *Pf* cases 30% and above was one of the criteria for high-risk areas. The proportion of *Pf* cases of the national total came down from 41.31% in 1992, 38.90% in 1995, and 38.28% in 1997. The proportion of *Pf* cases to total malaria positive cases during the period 1996–2001 is shown in Tables 7 and 8.

Table 7. Malaria situation in India

Year	Positive Cases	*Pf* Cases	*Pf* %	Deaths Due to Malaria
1996	3,035,588	1,179,561	38.86	1,010
1997	2,660,057	1,007,366	37.87	879
1998	2,222,748	1,030,159	46.35	664
1999	2,284,713	1,141,359	49.96	1,048
2000	244,070	115,853	47.47	97
2001*	206,807	88,569	42.83	46
* Up to June 25, 2001				

Source: National Antimalaria Program, Malaria Situation in India, 2000

Table 8. Proportion of *P. falciparum* Cases in Affected States

Name of State	Proportion of *P. falciparum* Cases
Andhra Pradesh	33.12 to 44.29
Assam	65.27 to 61.29
Bihar	66.08 to 61.62
Madhya Pradesh	56.87 to 46.85
Manipur	43.23 to 45.98
Meghalaya	60.83 to 49.06
Mizoram	55.19 to 63.42
Orissa	84.73 to 86.44
Tripura	74.55 to 85.48

WHO SEA Regional Office estimates six times more cases of malaria. This wide disparity in the figures for positive malaria cases reported by the Indian National Malaria Eradication Program may be partly because the bulk of malaria cases are treated by the private sector and not reported to health departments (Sharma, 1999).

Presently there is varied distribution of malaria in the country. The northeastern states contribute the majority of *Pf* cases in the country. The population of NE region is 3.7% of Indian population and the region contributed 8–12% of malaria positives; 10–20% of *Pf* and 13–41% of deaths in the country's average between 1991–1995 (Mohapatra, et al., 1998). Outbreaks have also been reported from different parts of country since 1994.

1.2.6. Treatment

The salient features of the national drug policy adopted by the National Antimalaria Program (NAMP) are as follows:

1. All fever cases should be presumed to be malaria, and an antimalarial drug be given, preferably after taking a blood smear.

2. Chloroquine is to be used as the first-line treatment for uncomplicated malaria.

3. In high-risk areas, presumptive treatment of 25mg/kg of body weight of chloroquine base is to be given on three consecutive days with a single dose of Primaquine 0.75 mg/kg on the first day.

4. In the low risk areas, Drug Distribution Centers (DDCs), and Fever Treatment Depots (FTDs), presumptive treatment will be with a single dose of chloroquine at 10mg/kg of body weight.

5. Resistance should be suspected if in spite of full treatment and no history of vomiting or diarrhea, the patient does not respond within 72 hours parasitologically. Such patients should be given an alternative drug (SP combination) and reported to the concerned District Malaria/State Malaria Officer for pursuing drug sensitivity studies.

6. SP combination is the antimalarial drug of choice in *Pf* resistance cases. The dose is 25mg/kg of body weight of sulfadoxine + 1.25 mg/kg of pyrimethamine, which is three tablets for the adult (single dose).

7. The dose of Primaquine is 0.25mg/kg of body weight daily for five days to prevent relapse for *P. vivax* and for *P. falciparum* 0.75 mg/kg single dose for gametocytocidal action. Where presumptive treatment with primaquine has already been given in the chloroquine sensitive high-risk areas, no further antimalarial treatment is required for *Pf* cases. A 14-day Primaquine treatment in *P. vivax* is not advocated in the program because of toxicity and operational feasibility. However, the treating physicians may opt for the 14-day regimen under close supervision so as to detect any complication, which may be very serious.

8. Any area showing more than 25% of RII + RIII or RII or RIII level of resistance to the tested drug in the minimum sample of 30 cases should be switched over to the alternative antimalarial drug, e.g., from chloroquine to SP combination.

9. Amodiaquine has no advantage over chloroquine in chloroquine resistant areas, as there is cross-resistance between these two drugs. Therefore considering the toxicity associated with it, amodiaquine has been withdrawn from the program.

10. In severe and complicated *Pf* malaria cases intravenous quinine/parenteral artemisinin derivatives (for adults and non-pregnant women only) is to be given

irrespective of the chloroquine resistance status of the areas. In case of non-availability of the above drugs, chloroquine 10mg/kg of body weight in isotonic saline should be infused over eight hours followed by 15mg/kg in the next 24 hours. This treatment may continue till such time quinine/artemisinine derivatives become available.

11. Artemisinine derivatives may only be used in injectable form for the treatment of severe and complicated *Pf* malaria in adults. The capsule and tablet forms of these derivatives are not recommended for use in the country so as to prevent misuse of this group of drugs.

12. Mefloquine can be given to chloroquine/other antimalarial-resistant uncomplicated *Pf* cases only. This drug is to be made available through the depot system and is only to be provided to patients with the prescription of medical practitioners supported by a laboratory report showing asexual stages of *P. falciparum* in the peripheral smear.

13. Halofantrine is not recommended due to its erratic absorption, and the toxicity associated even with therapeutic doses, as well as its cross-resistance with mefloquine.

14. In pregnant woman, primaquine is contraindicated. As no data is available to suggest the safety of artemisinine derivatives in pregnancy, it is also not recommended.

15. In infants primaquine is contraindicated. Artemisinine derivatives are not recommended at present.

16. Chemoprophylaxis is recommended for (a) pregnant women in high risk areas and (b) travelers, including service personnel, who temporarily go on duty to high areas of high malaria prevalence. In chloroquine-sensitive areas chloroquine is given weekly, but in chloroquine-resistant areas, chloroquine should be supplemented by daily proguanil. Chemoprophylaxis should not exceed three years due to the cumulative toxicity of chloroquine. Also considering the limitations of chemoprophylaxis personal protection measures should be encouraged.

17. Migratory labor/project population: these populations are to be screened weekly and treated accordingly. The labor coming from resistant areas who are positive for *P. falciparum* should be treated with SP combination and radical treatment should be ensured.

1.2.7. Drug Resistance

i. P.falciparum

Resistance to chloroquine first appeared on the Thai-Cambodia border in 1959. In subsequent years resistant strains were recorded moving north and west, and they entered India in 1973 (Sharma, 2000). Mutant strains multiplied in Assam due to the presence of three highly efficient vectors—*Anopheles dirus, An. minimums* and *An. fluviatilis*—and poor vector control. Monitoring of resistance in *P. falciparum* revealed that the drug-resistant mutants spread to high falciparum transmission areas in Orissa and from there moved to Madhya Pradesh and southern states. Drug resistant strains are more pronounced in the project areas with the aggregation of tropical labor resulting in outbreaks of resistant malaria (Sharma, 1984; Sharma, 2000). In 1977, the Government of India launched the *Plasmodium falciparum* Containment Program (PfCP) with the main objective to contain the spread of *P. falciparum* and more particularly resistant strains to the plains of India. Monitoring of resistance in *P. falciparum* was taken up systematically in the country by six *Pf* monitoring teams (Sharma, 2000). Subsequently, the number of *Pf* monitoring teams was increased to 12. These teams conducted the studies using an extended 28 days or a standard WHO 7-day test in randomly selected villages in pre-selected Primary Health Centers (Misra, 1996). This information has been used to change drug policy and to initiate focused spraying for eradicating drug resistant foci. Table 9 shows the results of in vivo drug resistance studies and the foci of drug-resistant malaria detected by the NAMP.

Table 9. Monitoring *P. falciparum* Sensitivity to Chloroquine in the Year 2000

State/District	BSC/Exam	Total Positive	Pv	Pf	Pm	Mix	S	S/RI	RI	RII	RIII
Andhra Pradesh	2,305	100	4	96	0	0	0	53	0	2	0
Arunachal Pradesh	736	18	4	14	0	0	-	-	-	-	-
Assam	1,250	118	5	113	0	0	0	36	0	0	0
Bihar	301	50	3	47	0	0	-	-	-	-	-
Gujarat	2,066	7	1	6	0	0	-	-	-	-	-
Goa	226	85	47	38	0	0	13	17	3	1	1
Punjab	236	0	0	0	0	0	-	-	-	-	-
Rajasthan	1,157	92	23	66	0	3	0	6	0	0	1
Uttar Pradesh	1,845	319	118	200	0	1	0	47	18	5	0
West Bengal	1,230	436	96	336	0	4	0	80	7	7	6

Source: Annual Report of National Anti Malaria Program, Malaria Situation in India, 2000; BSC: Blood Slide Collected; Pm: *P.malariae*

Subsequent to detection of the first case of *P. falciparum* resistant to chloroquine in Assam in 1973 (Sehgal et al., 1973) several reports of resistance were confirmed from Arunachal Pradesh, Andhra Pradesh, Bihar, Gujarat, Madhya Pradesh, Maharashtra, Meghalaya, Mizoram, Orissa, Tripura, Uttar Pradesh, Karnataka, West Bengal, and Andaman Nicobar Islands (Chakravarty, 1979; Raichowdhuri, 1984; Mohapatra et al., 1989; Prasad et al., 1990; Barkakaty et.al. 1992; Dua et al., 1993; Giri, 1994; Sathpathy et al., 1997; Sahu, 1994; NMEP, 1996; Valecha, 1996; Misra, 1996; Lal et al., 1998) (Tables 10, 11). As such there is wide variation in the distribution of resistance. In high and intense transmission areas like tribal areas of Orissa, Bihar, and Madhya Pradesh, a high degree of chloroquine resistance is slowly but constantly increasing (Ghosh et al., 1992; Singh et al., 1989; Singh and Shukla, 1990). Resurgence of malaria in Mumbai in Maharashtra is being attributed to the increasing level of chloroquine resistance (Garg et al., 1999; Gogtay et al., 1999; Potkar et al., 1995). The RII/RIII level of resistance was highest in the northeastern region and during 1978–84 the NE region recorded 9.8% of RII and RIII resistance followed by eastern region (4.9%), north central (3%), western region (1.8%), and southern region (1.3%) (Misra, 1996; Gogoi et al., 1995). Isolated cases of resistance were observed in Delhi, which could be explained due to population movement (Chaudhury et al., 1987).

A recent USAID/EHP-supported study conducted by the Malaria Research Center of India (Oct 2003–2004) in India and Nepal (Valecha 2004) followed the recently established WHO 28-day treatment protocol of 2001 for moderate/low transmission areas and the standardized methods for collection and analysis of data. The total of 91 subjects were enrolled in two sites of Darjeeling district, West Bengal. Standard

chloroquine treatment was followed through on *Pf* malaria. The cumulative success incidence in one of the sites (Sukna) was 34% (66% treatment failures) and in the second site (Naxalbari) the cumulative success incidence was 66.7% (treatment failures 33.3%). This study has indicated that the drug policy in this area and across the border in Nepal needs to be reviewed.

Table 10. Status of Malaria Drug Resistance up to 1997

Drug	*In Vivo*						*In Vitro*		
	No. of Cases	**S**	**S/RI**	**RI**	**RII**	**RIII**	**No. of Cases**	**S**	**R**
Chloroquine	12,863	3814	5984	1932	653	480	627	331	296
Amodiaquine	333	116	99	61	35	22	36	4	32
Sulfadoxine/Pyrimethamine	915	256	639	10	6	4	8	8	0
Sulfalene/Pyrimethamine	160	135	23	2	0	0	-	-	-
Mefloquine	-	-	-	-	-	-	104	97	7
Quinine	209	171	23	13	2	0	21	19	2

Source: Drug Resistance and Chemotherapy of Malaria in India An update December 1997 (Lal et al. 1998)

Table 11. *In Vivo* Chloroquine Sensitivity Studies

Year	Total Cases Tested	Sensitive	S/RI	RI	RII	RIII	RII + RIII	Pf %
1978	526	473	44	4	3	2	1.0	13.24
1979	704	572	64	43	15	10	3.6	18.22
1980	644	452	89	74	26	3	4.5	20.29
1981	392	252	45	76	17	2	4.8	21.83
1982	457	253	71	95	31	7	8.3	25.25
1983	289	146	87	46	9	1	3.5	29.77
1984	434	227	160	36	11	0	2.5	30.01
1985	484	89	311	61	22	1	4.8	29.23
1986	568	183	121	217	39	8	8.3	35.61
1987	763	300	85	319	31	28	7.7	37.19
1988	600	185	76	250	27	62	14.8	36.95
1989	498	92	250	87	20	49	13.8	36.87
1990	679	137	298	158	48	38	12.7	37.25
1991	541	102	311	50	34	44	14.5	43.38
1992	1,045	134	646	135	61	69	12.5	41
1993	864	64	603	63	67	67	15.5	38.5
1994	793	6	663	34	62	28	11.3	39.4
1995	1,096	59	872	59	74	32	9.7	39.7
1996	888	73	689	82	26	18	5.0	37.5
1997	598	15	499	43	20	21	6.8	35.4

Source: Drug Resistance and Chemotherapy of Malaria in India An update December 1997 (Lal et al. 1998)

The second-line drug sulfadoxine-pyrimethamine (SP) has been introduced in many districts/PHCs in regions where RII/RIII resistance exceeds 25%. Resistance to this drug combination when used in the adult dose of two tablets was reported in a limited number of studies (Ghosh et al., 1992; Yadav et al., 1995) while Garg et al. (1996) reported RII resistance with three tablets of SP in three out of 17 cases. Low-level of resistance has also been reported from West Bengal, Karnataka, Bhopal, and Tripura. However, the development of resistance to SP is slower than is expected with use antifolates. Molecular studies show that mutations of the *DHPS* gene were less frequent while *DHFR* point mutations were very frequent in 89 clinical isolates from India (Biswas et al., 2000). Resistance to mefloquine was observed in 23.6% isolates in Surat in Gujarat.

P. vivax

P. vivax is the predominant parasite in the country, and although deaths are rare, it causes high morbidity. In addition, it is a relapsing parasite and second-line drugs of the sulfa group are not effective in treatment of chloroquine-resistant cases (Kshirsagar et al., 2000). Thus, monitoring of resistance in vivax malaria is also essential. The problem of drug resistance in *P. vivax* may be only the tip of the iceberg as there are reports of drug failure in the treatment of vivax malaria from many parts of the country (Table 12). Garg et al., (1995) reported two cases from Mumbai that did not respond to a full dose of chloroquine (1500 mg) and peripheral smears continued to be positive despite adequate blood concentration of the drug. The case reported by Dua et al. (1996) from Mathura, Uttar Pradesh, did not respond to standard antimalarial treatment as confirmed by repeated blood examination. At Chennai, out of 20 patients administered 1500 mg chloroquine, 14 were sensitive and four showed RI and each RII and RIII level of resistance in the *in vivo* test (C. Nagaraj 1999, personal communication). Recently 16% RI and 6.7%, RII resistance was reported in a study conducted in 75 patients in Bihar (Singh, 2000). In addition, multidrug resistance to quinine and sulfadoxine-pyrimethamine has also been reported (Khirsagar et al., 2000). Since *P. vivax* produces a relapsing type of infection and is the predominant species in India, chloroquine resistance in this parasite may have serious repercussions for public health.

Table 12. Annual Report on Monitoring *P. vivax* Sensitivity to Chloroquine in Year 2000

State/District	BSC/Exam	Total Positive	Pv	Pf	Pm	Mix	S	S/RI	RI	RII	RIII
Karnataka	201	86	31	53	0	2	10	0	1	0	0
Goa	226	85	47	38	0	0	10	3	0	0	0

Source: National AntiMalaria Program, Malaria Situation in India, 2000

Recently the studies on therapeutic efficacy of antimalarials in *Pf* and *Pv* malaria have been initiated in the country, supported by the WHO Tropical disease network. These will generate systematic data using recent WHO protocols for evaluation of drug resistance.

1.2.8. Special issues

Resurgence of malaria has the charateristic features of refractory nature of anopheline vectors, increase in *P. falciparum* proportion, resistance to antimalarials, and invasion of new vectors in some areas (Sharma, 1996). The problem is also compounded by the high cost of new drugs andinsecticides, man-made environment degradation, new malaria paradigms, and population movement (Sharma, 1996).

Considering the above issues and present limitations, improved management of malaria should address a number of priority issues: management of serious and complicated malaria, prevention of mortality, control of outbreaks, reduction in *Pf*

incidence, containment of drug resistant malaria, reduction in morbidity, and maintenance of low incidence status (National Malaria Control Strategy, 1994).

1.3. Nepal

1.3.1. Epidemiology

The first attempt to control malaria in Nepal was initiated in 1954 through the Insect Borne Disease Control Program supported by the U.S. Agency for International Development (USAID). In 1958, the malaria eradication program was launched as a vertical program with an ultimate objective of eradicating malaria from the country, but due to technical, operational and administrative constrains it could not be achieved, and consequently the program reverted back to malaria control in 1978. In Nepal, 15.6 million people (70% of the total population) are at risk to malaria. The conditions for transmission of malaria exist in the low lines of southern belt, which is known as the terai region and borders India, and middle hills below 1,000 m elevation. Most of the malaria in the middle hills is imported by local Nepalese arriving from the terai, with almost all cases confined to the work force around big engineering projects. The majority of malaria transmission in Nepal occurs in 12 districts and these have been labeled as priority districts. These districts are Dadeldhura, Kanchanpur, Kailali, Kavrepalanchowk, Bardia, Nawalparasi, Sindhuli, Mahottari, Dhanusha, Morang, Jhapa and Ilam (Table 13).

Table 13. Malaria Situation in Nepal

Year	Positive Cases	*Pf* Cases	*Pf* %
1996	9,020	951	10.40
1997	8,957	1,150	12.84
1998	8,498	520	6.12
1999	8,959	622	6.94
2000	7,981	836	10.47

Source: The Annual Internal Assessment of Malaria and Kala-azar, DoHS 2001

The *Pf* proportion is about 15%, which is the lowest in the region. Certain foci of chloroquine resistant *Pf* malaria have been reported. Reported malaria cases have been ranging between 25,000-30,000 annually, but now have dropped to 7,000-9,000 annually. During 1996 and 1997, there were focal outbreaks in the Western and Far-western Regions with around 11,000 clinical cases and 17 deaths. An improvement in the malaria situation has been reported recently in Nepal, but the data must be interpreted with caution because of the decline in surveillance activities in the country over the past few years (WHO 1999). The research to date indicates that more males than females are affected by malaria. This is evident in the reported prevalence/incidence rates, which were higher for males than for females in Nepal.

During the past three years, the number of cases of malaria caused by *P. falciparum*, the most lethal species of parasite, has been increasing.

Outbreaks of malaria, which resulted in a few deaths, were reported from different districts. *P. falciparum* is the predominant strain in these focal outbreaks (more than 65% of the cases), and a poor response to sulfadoxine-pyrimethamine (SP) was observed in the epidemic foci. Predisposing factors that have contributed to these outbreaks include:

- migration to adjacent endemic areas
- inadequate or poorly organized surveillance system
- absence of indoor residual spraying activities for the last five years previous to the epidemics as there were no cases of *P. falciparum* in affected areas
- untimely or nonexistent treatment
- inaccurate collection of information
- ecology and physical environment (Annual Report, Department of Health Services, 1999/2000).

1.3.2. Treatment

There is no national antimalarial drug policy, but there are specified drugs for different levels of care and guidelines for the use of antimalarial drugs. Antimalarial drugs have been dispensed to patients free of cost through all levels of health care facilities. They cannot be made available without prescription. There are constraints in effective application and monitoring of quality assurance of drugs (Roll Back Malaria: Proposed five year strategic plan 2001–2002).

There is a list of essential drugs developed by the Department of Drug Administration. Sub Health Posts (SHP) and Health Posts (HP) can prescribe first-line antimalarial drugs such as chloroquine and primaquine and second-line treatment such as SP for uncomplicated malaria. Primary Health Centers (PHC), district centers, and other upper level health institutions with medical officers can also prescribe quinine injection or tablets for severe and complicated malaria. The dose schedule is as follows:

- *P.vivax*: Chloroquine 25mg/kg over 3 days + Primaquine for 5 days (Lab confirmed)
- *P.falciparum*: Chloroquine 25mg/kg over 3 days + Primaquine (Single dose) (Unconfirmed)
- *P.falciparum*: SP + Primaquine (Single dose) (Lab Confirmed)
- Severe malaria & Treatment failure: Quinine 10 mg/1kg 8days x 7 days

1.3.3. Drug Resistance

The studies on drug resistant malaria began in 1978 under the Regional Collaborative Studies on Drug Resistant Malaria. Before 1984, the sensitivity status of locally transmitted *Pf* cases could not be determined by *in vivo* and *in vitro* methods because of the sporadic nature of the incidence of such cases. *Pf* cases both imported and indigenous began to increase only in 1981. Up until then only imported cases originating from the northeastern parts of India were tested and found to be resistant to chloroquine, confirmed by both *in vivo* and *in vitro* tests, e.g., in Jhapa District, Eastern Region, 1979–1983. However, in 1984, indigenous *Pf* cases were recorded as resistant to chloroquine in Makawanpur district in the Central Region for the first time. Since then chloroquine resistance has been recorded in Udaypur, Eastern Region in 1984, Nawalparasi Western Region in 1986, Kanchanpur and Kailali, Far Western Region in 1987, and Dhanusha, Mahottari and Sindhuli, Central Region in 1988 (Table 14).

Table 14. Drug Resistance (Cumulative Test Carried Out from 1984 to 1990)

Drug	In Vivo				In Vitro		
	Number of Pf Cases Tested	***S***	***S/RI***	***RII***	***Number of Pf Cases Tested***	***S***	***Number of Resistance***
Chloroquine	84	52	26	6	178	43	74
SP	-	-	-	-	38	9	0
Quinine	-	-	-	-	-	54	-
Mefloquine	-	-	-	-	133	-	0
Total	**84**	**52**	**26**	**6**	**349**	**106**	**74**

Source: DoHS 1999

From 1984 to 1990, 84 *Pf* patients were subjected to *in vivo* tests after administration of 25mg/kg body weight of chloroquine. Fifty-two cases were susceptible, while 26 cases (30.9%) showed S/R1 level and six cases (7.1%) showed resistance at RII level. The RII level resistant cases were imported from northeastern states of India. No *in vivo* tests were performed for mefloquine and SP.

During the period 1984–1990, a total of 178 micro *in vitro* tests for chloroquine, 38 for sulfadoxine and 133 for mefloquine were performed. Out of the successful tests (117) for chloroquine, 36.7% (43 cases) were sensitive to chloroquine, while 63.2% (74 cases) were resistant. No resistance was evident in mefloquine and sulfadoxine-pyrimethamine.

During 1993 to 1995, data of suspected sulfadoxine-pyrimethamine resistant *P. falciparum* were collected from high *P. falciparum* prevalent areas. The data is based on regular surveillance reports, and the cases were classified and verified by epidemiological investigation as recrudesced cases after the administration of SP treatment. The recrudescence cases were recorded in Ilam, Jhapa, Morang, Sunsari, and Udaypur districts of Eastern Region; Dhanusha, Sindhuli, Mahottari districts of

Central Region; Lamjung district of Western Region and Kailali and Dadeldhura districts of Far Western Region.

In 1996, during the episode of focal outbreak in Parasan Health Post of Kanchanpur district and in 1997 during an episode of local outbreak in Pratappur Health Post of Nawalparasi district, many cases after administration of SP (1,500mg/75mg) were recrudesced. Therefore, in 1997, the Vector-borne Disease Research and Training Center (VBDRTC) launched a special study to find out the therapeutic efficacy of SP in *P. falciparum* (Chand 1997*)*. The results of the study are discussed below.

Parasan Village Development Committee (VDC), Kanchanpur District

A total number of 192 cases with fever or with recent history of fever were screened for malaria infection by parasitological examination of peripheral blood smears between January and March 1997. Out of the total, 75 were positive for malaria infection among which 65 had falciparum malaria. Of the total 65 *Pf* cases, only 23 met the study protocol and enrolled for the study. Twenty-two cases developed treatment failure (one was lost during follow-up).

Guthiparsauni VDC, Pratappur Health Post, Nawalparasi District

A total number of 287 cases with fever or with recent history of fever were screened for malaria infection by parasitological examination of peripheral blood examination between August and November 1997. Of these, 171 (59.6%) were positive for malaria infection and 150 (52.3% of the total screened and 87.7% of the total positives) had falciparum malaria. Out of 150 falciparum malaria patients, 66 met the selection criteria of the protocol and were enrolled for the study, out of which 51 cases completed the study. An early treatment failure to SP was recorded to be four out of 51 cases. The late treatment failure to SP was recorded in 41 (80.4%) of 51 cases. Altogether, 45 (88.0%) cases showed treatment failure and only six cases presented adequate clinical response to the drug (Bastola *et al.* 1998).

The results of first stage sample in Parasan VDC of Kanchanpur district revealed a high degree of late treatment failure of falciparum cases. However, there is an early alleviation of clinical symptoms and probably decreased severity of the disease with SP treatment.

In order to better understand the epidemiology of malaria and the effectiveness of case management of P. falciparum, a 14-day in vivo drug efficacy trial was conducted from July through October 2000. SP, the first-line treatment for malaria according to national policy, was evaluated using a standardized protocol from the World Health Organization (WHO). The trial, which was conducted on four sites in Dhanusha district, screened 2,031 persons, of which 5% or 101 were pure Pf cases. The study enrolled 58 subjects. Five were excluded for various reasons leaving 53 subjects, ranging in age from 1–60 years. Fifty-five percent of these participants resided in one ward, as did 30% of all Pf cases that were identified through the screening process (EHP 2000-2001).

After measuring clinical and parasitological parameters on scheduled follow-up days, the clinical response to treatment was determined. Preliminary analysis shows that no patient was classified as an early treatment failure. Thirty (57%) patients were classified as late treatment failures, with 19 having met the criteria on Day 7 and the remainder on Day 14. Twenty three (43%) were without parasites on Day 14 and were classified as adequate clinical responses. Early and late treatment failure (ETF and LTF) were detected in 2% and 30% cases respectively while 69% had adequate clinical and parasitological response.

While the finding of only one ETF is encouraging, the presence of LTF warrants improved and continued surveillance in these and other malaria endemic areas in order to better understand the picture of resistance in these communities and to direct development of national drug policies. The slide positivity rate of 20% overall and 5% for Pf illustrates the need for accurate diagnosis as an integral part of case management, and as a guide for appropriate drug treatment. The estimated population at risk to develop drug resistant malaria is shown in Table 15 and Fig. 6.

Table 15. Estimated Population (000) at Risk to P. falciparum Resistant to Anti Malarial Drugs

Drugs	Year				
	1992	1993	1994	1995	1996
Chloroquine	1,483	1,803	1,840	1,890	1,930
SP	690*	701*	717*	733*	15**
Quinine	0	0	0	0	0
Mefloquine	0	0	0	0	0

*/ Suspected resistance

**/ Confirmed resistance

Source: Country Report of Malaria Control Program, Nepal (Bista et al. 1999)

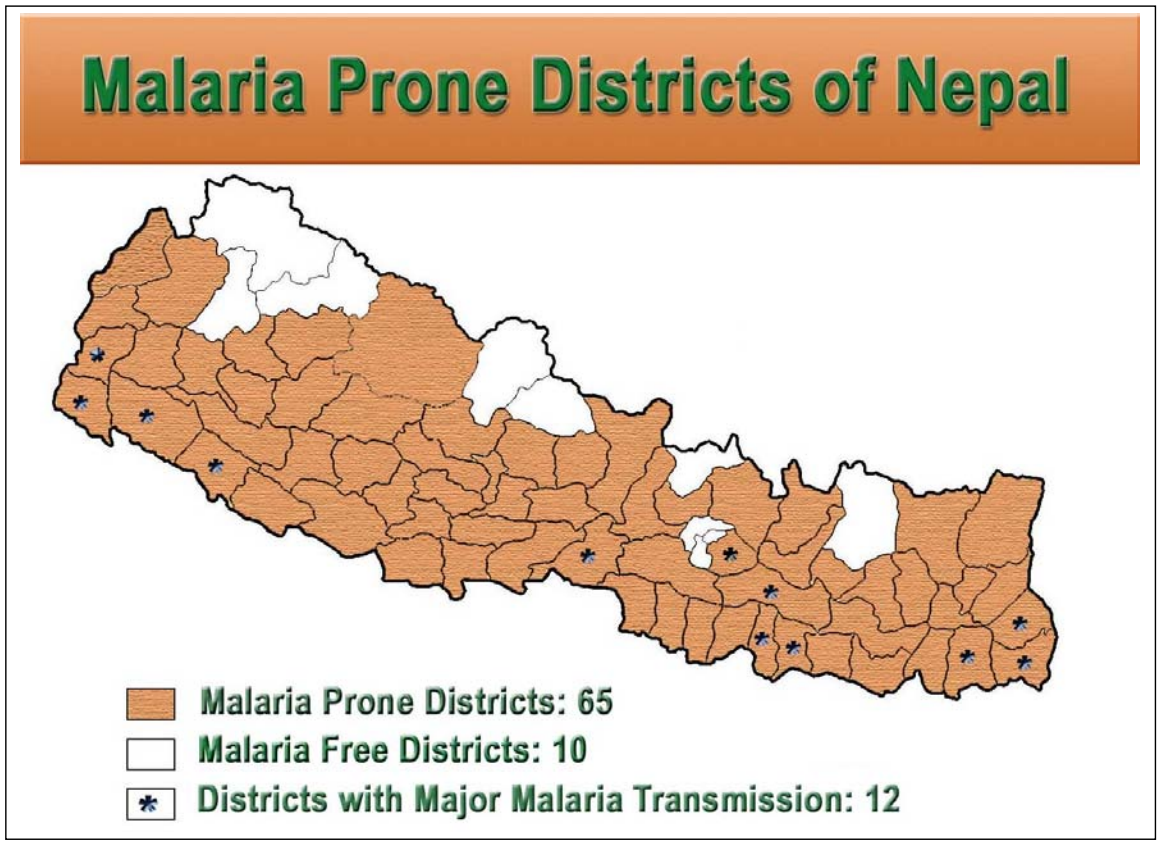
A recent study (2003) by the Government of Nepal in the Jhapa district of far Eastern Nepal conducted as part of an Indo-Nepal cross border Malaria Drug Efficacy assessment through USAID/EHP sponsorship has revealed the following information (Chand et al. 2004): The methodology followed the standard WHO 2001 protocol for 28 days, and the study was conducted at two sites with 107 enrolled *Pf* cases and 102 completing the study. The drug evaluated was SP. Overall treatment failure (early and late) was observed in 21 (20.6% patients) calling for a systematic review of *Pf* treatment policy in this particular area of Nepal in coordination with appropriate actions in bordering districts in India as well.

1.3.4. Special Issues

According to the Ministry of Health, Epidemiology and Disease Control Division, most of the terai districts, mid hills, and mountainous areas of Nepal have been identified as malaria epidemic and endemic areas. However, distribution of different

types of malaria in these geographical areas has not been well defined. Mixed dwelling, bad housing conditions, low socio-economic level, failure to use mosquito nets, and migratory behavior are considered to be contributing factors for the occurrence of the disease. No active case detection, late reporting to the health centers, treatment failure, drug resistance (not well documented) of malaria have been identified as the main causes of growing incidence and mortality of the disease in the recent years. Very recently, the Early Warning Reporting System (EWARS) has been further expanded with 26 participating sentinel reporting institutes, mostly zonal and district hospitals, and it is anticipated that EWARS will strengthen the whole reporting system. However, this reporting system is based only on hospital reports. Adequate information on the status of drug resistance and border community malaria information is not available. But now, a process is underway to extend this reporting system up to the community level.

Figure. 6


Malaria Prone Districts of Nepal
Malaria Prone Districts: 65
Malaria Free Districts: 10
Districts with Major Malaria Transmission: 12

2. Trends in Drug Resistant Malaria in BBIN Countries

A critical review was conducted to address the trends in malaria drug resistance in BBIN countries. Several reports have confirmed the existence of chloroquine-resistant *Plasmodium falciparum* malaria in the Indian subcontinent. Strengthening the monitoring of drug resistance in *P. falciparum* in the region is indicated.

The drug resistance status of Bangladesh and Bhutan needs to be reviewed to some extent to determine the resistance trend of the parasite. However, epidemiologically the resistance of malaria parasite in both the countries has been determined.

An increase in the incidence of malaria in the cities of India in the 1990s has made drug resistance, especially for *P. falciparum*, a problem. Previous studies documenting 15% chloroquine resistance in 1993, and the increasing incidence in subsequent years suggest resistance to chloroquine as one of the causes of resurgence and sustenance of malaria.

P. falciparum resistant to chloroquine in Nepal has been confirmed by *in vivo* and *in vitro* tests. Over the years, chloroquine resistance has been seen distributed across a wide range of areas involving previously hyper-endemic and currently moderate receptive areas of all regions, except the mid-west. Systematic drug monitoring activities have not been carried out during the past in the country. Nevertheless, reports on falciparum malaria treatment failure with sulfadoxine-pyrimethamine are received time and again from falciparum-prevalent areas of the country, indicating the possible emergence of falciparum resistance to drugs. In some parts of Nepal, such as the Bankey district, every year a 5% increment has been seen in *Pf* cases. The existing community-based drug distribution scheme might lead to slow progression of the disease and treatment failure and/or a drug resistance problem in the future.

In the last decade, chloroquine resistant *P. falciparum* (CRPf) has spread rapidly in the Indian subcontinent (Bangladesh, Bhutan, India and Nepal). There is emerging evidence that CRPf is linked with increased incidence of mortality, severe disease, and emergence of epidemics.

In the BBIN countries, *P. falciparum* is increasing. The current empirical treatment policy with first-line antimalarials alters the clinical profile of *P. falciparum* resistance: It makes it milder temporarily, delays confirming the diagnosis, and leads to high mortality. There is an urgent need for more diligent early treatment for these patients who linger on with moderate pyrexia, progressive hepatosplenomegaly,

anemia, and jaundice after empirical treatment until better diagnostic methods are available to avoid prolonged illness and high mortality.

2.1. Gaps in the Review

In Thailand, Myanmar, Cambodia, and Laos, the increasing prevalence of chloroquine resistant *P. falciparum* has complicated the control of falciparum malaria. In this regard, many studies have addressed the drug resistance problem in these countries. Given the recent steep increase in incidence of falciparum malaria in different endemic areas of the BBIN countries, it is important to study the causes for the same as well as analyze the resistance pattern of *P. falciparum* in different areas. Absence of adequate information on drug resistance in these countries was found to be a major problem that needs immediate attention.

Several reports have confirmed the existence of chloroquine-resistant *P. falciparum* malaria in India. Many studies have been conducted in India on the epidemiology, drug resistance, environmental and other aspects of the disease. However, scarcely any studies have been carried out in Bangladesh, Bhutan and Nepal. With increasing reports of *falciparum* malaria resistant to SP from Thailand, Myanmar and Africa, a study needs to be conducted to determine the efficacy of SP, quinine, and other combination therapy in chloroquine resistant *Pf* malaria in border areas of India, Myanmar, Nepal, Bhutan and Bangladesh. Standardized drug efficacy testing methodology will be helpful for guiding effective antimalarial chemotherapy and policy. Additionally, studies on current treatment practices, exact status of *Pf* and *Pv* malaria, and their transmission dynamics will also be important to design better malaria prevention and control programs along with regularizing monitoring and surveillance.

In addition, problems in surveillance mechanisms, proper and early diagnosis, rational use of drugs, patient compliance, and private sector involvement need immediate attention in all these countries.

2.2. Possible Next Steps

- Identification of regional institutions working on drug-resistant malaria in the BBIN countries and exchange of visits among key institutions
- Information exchange on drug-resistant malaria that will guide the design and development of future strategies
- Implementation of updated policy guidelines on chemoprophylaxis and treatment
- Strengthening of drug resistance monitoring for *P. falciparum* along with a review of drug policies in the BBIN countries
- Establishment of standardized and comparable approaches to assessing drug efficacy where data can be readily compared

- The development and conducting of operational research programs on drug resistant malaria in border communities of the BBIN countries and establishment of surveillance networks with regular information exchanges.

3. Development of a South-Asia Surveillance Network for Malaria Drug Resistance

Excepts from the WHO report of an Informal Consultative Meeting New Delhi, India, Jan. 9–10, 2002; (SEA-MAL 231)

3.1. Introduction

In South-Asia (SA), information on drug-resistant malaria is not routinely collected, nor is data shared between the Member Countries. Considering the increasing trend of drug resistance, the establishment of a coordinated network for monitoring drug-resistant malaria in the region is important. This issue was also addressed in March 2000 during the Roll Back Malaria Technical Support Network meeting in Chiang Mai, Thailand, and in June 2001 in Yangon, Myanmar. An Intercountry Cross-Border Collaborative Meeting of South-Asian Countries (Bangladesh, Bhutan, India and Nepal) held in July 2000 in Hetauda, Nepal also pointed out the importance of monitoring malaria drug resistance and exchange of information among the countries. This meeting also emphasized the potential for cross-border collaboration on prevention and control of drug resistant malaria. As a follow-up of this meeting, Bangladesh, Bhutan, India, and Nepal established the BBIN website with the support of the Environmental Health Project (EHP) of USAID. Myanmar, which is also a member of the Mekong group, has shown interest in joining the website in view of its common borders with Bangladesh and India.

The envisaged “Drug Resistance Surveillance Network” would be mandated to accelerate the implementation and monitoring of drug resistance as a pre-requisite for rationalization and updating of antimalarial drug resistance and policy. In addition, surveillance would further elucidate the causative epidemiological factors of drug resistance with a view to developing a comprehensive malaria control strategy.

To address the issue of drug resistance malaria, an informal consultative meeting was held in New Delhi, from Jan. 9–10, 2002. Senior researchers, officers, and principal investigators along with the program managers from Bangladesh, Myanmar, India and Nepal participated in the meeting.

3.2. Purpose of the Meeting

The following were the objectives of the meeting:

1. To update the current status and major trends of malaria drug resistance and its control in the countries of South-Asia

2. To standardize the guidelines on monitoring therapeutic efficacy of antimalarial drugs for uncomplicated falciparum malaria (and chloroquine against vivax malaria)

3. To discuss the strategies for inter-country cooperation on surveillance networking for malaria drug resistance in the SA Region leading to a consensus on framework and focal point for coordination

4. To development a country plan of action for the monitoring of malaria drug resistance through a sentinel system

3.3. Framework on Monitoring and Networking

In the SA Region, the monitoring of drug-resistant malaria has been carried out mostly by mobile teams and in different selected localities depending on epidemiological criteria such as high preponderance of *P. falciparum* in high endemic areas, epidemic outbreaks, and suspected drug resistant malaria foci. Practically no attempt was made to monitor changes in the status of resistance after the primary survey was conducted. Information sharing between cross-border countries is almost non-existent. Antimalaria drug policy in one border country may not be mirrored in the bordering country.

The purpose of the proposed "Drug Resistance Surveillance Network" is:

1. To accelerate the implementation monitoring of drug resistance as a prerequisite for rationalization and regular updating of antimalarial drug resistance

2. To determine a minimum package of standardized methods to be used at the sentinel sites by establishing a balanced, epidemiological representative network of sentinel sites in SA countries for routinely monitoring drug resistant malaria

3. To agree on the strategies for intercountry cooperation on surveillance

   – networking for malaria drug resistance in the SA Region

   leading to a

   – consensus on framework and a focal point for coordination.

During discussions in the meeting, participants agreed to establish a network for drug-resistance surveillance, adopting the latest WHO protocol as a standardized methodology for monitoring drug resistance through the sentinel system. The new protocol will facilitate in the development of an evidence-based drug policy. Participants also expressed the view that monitoring of drug-resistant malaria through selection of sentinel sites would be a better approach to update the current status and major trends of malaria drug resistance in the member countries. There was a strong consensus among the countries on establishing these sentinel sites on either side of the border in the problem areas. First- and second-line antimalarial drugs will be a priority for monitoring, leading to an easy exchange of information and matching the results of the either side. The criteria for selection of sentinel sites, their number, staffing pattern, training, supervision, and related matters were discussed at length.

It was agreed by the countries to use similar forms for recording and reporting and to send the reports to the agreed focal point at specified frequency.

There will be an annual meeting of member countries to review the data generated through drug resistance monitoring sentinel surveillance system. The meeting will have the advantage of comparing the obtained data of corresponding districts of two bordering countries and on the basis of the information available; in this way, an evidence-based decision on updating the drug policy of the particular districts can be made. However, the changes or adjustments or updating will be locus/sentinel area specific. A broader review of drug policy at the country level can be carried out at an interval of 2–3 years.

The member countries agreed that a nodal (focal) point—preferably with the Epidemiology and Disease Control Division, MoH, Nepal—should be established with the support of EHP/Nepal in coordination with WHO. BBIN under the Vector-Borne Disease Research and Training should be strengthened for training in surveillance of vector-borne diseases including drug resistance and in the management of malaria control. EHP/Nepal may continue support for this activity.

3.4. Development of Country Plan of Action

Member Countries prepared a blueprint of the plan of action for malaria surveillance network and monitoring therapeutic response. The draft plan of action required certain inputs for it to be complete and ready for implementation. It was decided to complete the plan of action within three months and submit a copy to SEARO.

3.5. Recommendations to Member Countries

1. Countries should prepare a plan of action for surveillance and therapeutic efficacy monitoring and submit it to SEARO within three months for follow up action by WHO.

2. Member countries should strengthen monitoring of drug resistance in malaria using the WHO guidelines for assessment of therapeutic efficacy of antimalarial drugs for uncomplicated falciparum and/or vivax malaria.

3. Member countries should establish a surveillance network for malaria drug resistance monitoring. This should include the status of malaria drugs by establishing a sentinel system for monitoring drug-resistant malaria for evidence-based changes in the national drug policy. Monitoring will focus on first- and second-line antimalarial drugs.

4. Member Countries should exchange information on cross-border malaria control as part of inter-country collaboration.

5. Member Countries should identify focal (contact) persons (institutions/program managers) to coordinate the joint efforts of the VBDRTC, Nepal in collaboration with Environmental Health Project (EHP) and WHO. The format and frequency of reporting will be worked out by the VBDRTC secretariat in consultation with EHP and WHO for adoption by the member countries.

References

Bloland, P.B. 2001. Drug resistance in malaria WHO/CDS/CSR/ 4.

Bangladesh Bureau of Statistics, 1995.

Barkakaty, B. N., and M. V. Narasimham. 1992. Problem of anti malarial drug resistance in *Plasmodium falciparum* in Mizoram. Indian Journal of Malariology. 29 (2): 89-93.

Bastola, S. P, P. B. Chand, M. K. Banerjee, M. B. Bista, and J. N. Giri. 1998. Outbreak of falciparum malaria in Pratappur ilaka health post of Nawalparasi district of Nepal JNMA.

Bista, M., M. Banerjee, and K. Shrestha. 1999. Country Report of Malaria Control Program, Nepal. A report prepared for Inter-country Meeting of National Malaria Control Program Managers, Pattaya, Thailand. Epidemiology and Disease Control Division, Department of Health Services, Teku, Kathmandu.

Biswas, S., A. Escalante, S. Chaiyaroj, P. Angkasekwinai, and A. A. Lal. 2000. Prevalence of point mutations in the dihydrofolate reductase and dihydropteroate synthetase genes of Plasmodium falciparum *isolates from India and Thailand.* Tropical Medicine and International Health *5: 737-743.*

Chakravarty, S. C., S. R. Dwivedi, S. Das, D. Phukan, R. G. Roy and S. Patanayak. 1979. *Indian J. Med. Res.* 70: (suppl.) : 34-39.

Chand, P. B. 1997. Therapeutic efficacy of sulfadoxine/pyrimethamine against uncomplicated *P.falciparum* malaria in Nepal, Unpublished document.

Chand, P. B., P. Wijeyaratne, M. B. Bista, S. Pandey, M. A. Ansari, and N. Valecha. 2004. Assessment of therapeutic efficacy of anti-malarial drugs against uncomplicated p. falciparum malaria in the Indo-Nepal border, Jhapa District (Nepal) & Darjeeling District, West Bengal (India) (Unpublished report – EHP/MoH Nepal)

Choudhury, D. S., S. Sinha, S. K. Ghosh, Usha Devi and V. P. Sharma. 1987. Report of a case of *P.falciparum malaria.* Resistant to Chloroquine and combination of Sulfalene and Pyrimethamine in Delhi. *Indian Journal of Malariology* 24: 95-96.

Dua, V. K., P. K. Kar, S. Kumar, and V. P. Sharma. 1993. In vivo and In vitro sensitivity of Plasmodium falciparum to chloroquine at Indian Oil Corporation, Mathura, India. Indian Journal of Malariology *30 : 29-35.*

Dua, V. K., P. K. Kar, S. Kumar, and V. P. Sharma. 1996. Chloroquine resistant *Plasmodium vivax* Malaria in India.*Tropical Medicine and International Health* 1: 816-819.

Garg, M. R., N. J. Gogtay, R. N. Kotwani, P. V. Bodhe, and N. A. Kshirsagar. 1999. Resurgence of malaria in Mumbai—Is escalating chloroquine resistance a cause? Journal of Association of Physicians India *47 : 377-379.*

Garg, M. R., N. J. Gogtay, and N. A. Kshirsagar. 1996. Efficacy of Sulfadoxine-pyrimethamine in chloroquine resistant falciparum Malaria in Bombay. Journal of Association of Physicians India *44 : 683-685.*

Garg, M., N. Gopinathan, P. Bodhe, and N. A. Kshirsagar. 1995. Vivax malaria resistant to chloroquine. case reports from Bombay. *Trans. Roy. Soc. Trop. Med. Hyg.* 89 : 656-657.

Ghosh, S. K., R. S. Yadav, and V. P. Sharma. 1992. Sensitivity Status of Plasmodium falciparum to chloroquine, amodiaquine, quinine, mefloquine and sulfadoxine/pyrimethamine in a tribal population of District Sundargarh, Orissa. Indian Journal of Malariology *29 : 211-218.*

Giri, A. and M. K. Das. 1994. Response of P. falciparum to chloroquine in Car Nicobar Island. Indian Journal of Malariology *31: 27-30.*

Gogoi, S. C., V. Dev, B. Choudhury, and S. Phookan. 1995. Susceptibility of *Plasmodium falciparum* to chloroquine in tea garden tribes of Assam, India. *Southeast Asian Journal of Tropical Medicine and Public Health* 26: 228-230.

Gogtay, N. J., A. R. Chogle, J. S. Sorabjee, S. N. Marathe, and N. A. Kshirsagar. 1999. Poor gametocytocidal activity of 45 mg primaquine in chloroquine-treated patients with acute, uncomplicated Plasmodium falciparum malaria in Mumbai. Annals of Tropical Medicine and Parasitology *93 (8): 813-816.*

His Majesty's Government/Nepal. 1994. Department of Health, Ministry of Health, Report of the situation of *P. falciparum* drug resistance problem.

His Majesty's Government/Nepal. 1998-99. Department of Health Services, Ministry of Health. Annual Report.

His Majesty's Government/Nepal. 1999-2000. Department of Health, Ministry of Health, Annual Report.

His Majesty's Government/Nepal. 2001. Department of Health Services, Ministry of Health. The annual assessment of malaria and kala-azar control activities.

His Majesty's Government/Nepal. 2001. Department of Health Services, Ministry of Health. Bankey District Health Report. District Health Office, Bankey.

Kshirsagar, N.A., N.J. Gogtay, D. Rajgor, S.S. Dalvi, and M. Wakde. 2000. An unusual case of multidrug-resistant *Plasmodium vivax* malaria in Mumbai (Bombay), *India. Annals Trop. Med. Parasitol.* 94(2) : 189-190.

Lal, Shiv., G. P. S. Dhillon, G.S. Sonal, Usha Arora and J. Nandi 1998. Drug resistance and chemotherapy of malaria in India an update December 1997, .

National Malaria Eradication Programme, (Enhanced Malaria Control Project). Directorate General of Health Services Ministry of Health and Family Welfare, 22-Sham Nath Marg, Delhi – 54, Govt. of India. Publication.

Misra, S. P. 1996. *In-vivo* resistance to chloroquine and sulfa pyrimethamine combination in *Plasmodium falciparum* in India. *Proc. Nat. Acad. Sci. India* 66(B) 123-128.

Mohapatra, P. K., Anil Prakash, D. R. Bhattacharya, and J. Mohanta. 1998. Malaria Situation in North-Eastern Region of India. *ICMR Bulletin* 28 No 3 21-30

Mohapatra, S. S. S., L. K. Das, and S. P. Pani. 1989. Chloroquine sensitivity of *P.falciparum* in Koraput district, Orissa. *Indian Journal of Malariology* 26: 33-39.

NMEP. 1985. In-depth evaluation report of the modified plan of operation under National Malaria Eradication Program of India. *NMEP Publ.* Delhi-54.

NMEP. 1996. Epidemiology and control of malaria in India Eds. R.S. Sharma, G.K. Sharma and G.P.S. Dhillion. Shakeen Enterprises.

Noedl, H., M. A. Faiz, E. B. Yunus, M. R. Rahman, M. A. Hossain, R. Samad, R. S. Miller, L. W. Pang, and C. Wongsrichanalai. Draft 2001. *Antimalarial drug resistance in Bangladesh*.

Pattanayak, S, and R. G. Roy. 1980. Malaria in India and the modified plan of operations for its control. J.Com Dis *18: 21-7.*

Potkar, C. N., N. A. Kshirsagar, and R. Kathuria. 1995. Resurgence of Malaria and Drug Resistance in *Plasmodium falciparum* and *Plasmodium vivax* species in Bombay. *JAPI* 43: 336-338.

Prasad, R. N., H. Prasad, K. J. Virk, and V. P. Sharma. 1990. Application of a simplified *in vivo* test system for determining chloroquine resistance in *Plasmodium falciparum. Bull of WHO* 68: 755-758.

Rahman, M. R., M. R. Hassan, M. A. Faiz, R. Samad, B. Paul, and M. A. Jalil. 1998. Monitoring efficacy of commonly used antimalarials by a 14-day in-vivo test in a new settler's camp in endemic zone at Cox's Bazar. *Bangladesh Med Res Counc Bull* 24(3):67-74.

Raichowdhuri, A. N., S. Sinha, , A. Gajanana, and K. K. Baishya. 1984. Chloroquine resistance of *Plasmodium falciparum* in Sonapur PHC Area (Assam) detected by micro *in vitro* and *in vivo* tests. *Indian Journal of Malariology* 21: 25-30.

Rosenberg, R. and N. P. Maheswary. 1977. Chloroquine resistance *Plasmodium falciparum* in Bangladesh. *Trans R Soc Trop Med Hyg* 70: 533.

Rosenberg, R. and N. P. Maheswary. 1982. Forest malaria in Bangladesh. Parasitology. *Am J Trop Med Hyg* Mar; 31(2): 175-182.

Sahu, G. C. and A. P. Pandya. 1994. *Plasmodium falciparum* sensitivity in in vivo and its distribution in geo-ecological zones of Gujarat. *J. Commun Diseases* 26(2): 109-115.

Sathpathy, S. K., R. C. Jena, R. S. Sharma, and R. C. Sharma. 1997. Status of *Plasmodium falciparum* resistance to chloroquine in Orissa. *Journal of Commun Diseases* 26: 145-151.

Sehgal, P. N., M.I.D. Sharma, S.L. Sharma and S. Gogai et al. 1973. Resistance to chloroquine in falciparum malaria in Assam state India. *Journal of Commun Dis.* 5 : 175-180.

Sharma, V. P. 1984. in Proceedings of the Indo-UK workshop on malaria, ed. Sharma, V. P., Malaria Research Centre, Delhi.

Sharma, V. P., N. L. Kalra, S. Pattanayak, R. S. Sharma, and V. S. Orlov. 1994. National Malaria Control Strategy published by Malaria Research Centre (ICMR) at 22-Sham Nath Marg, Delhi-54.]

Sharma, V. P. 1996. Re emergence of malaria in India. *Ind. J. Med. Res.* 103 : 26-45.

Sharma, V. P. 1996. Malaria: cost to India and future trends. *Southeast Asian J Trop Med Public Health* 27 : 4-14

Sharma, V. P. 1999. Current scenario of malaria in India. *Parassitologia* 41: 349-353.

Sharma, V. P. 2000. Status of Drug Resistance in Malaria in India. In Multi Drug Resistance in emerging and reemerging diseases. INSA Narosa Publication Ed. R.C. Mahajan.

Singh, N. and M. M. Shukla. 1990. Response of *Plasmodium falciparum* to chloroquine in a tribal area of Madhya Pradesh. *Indian J. Malariol.* 27: 183-186.

Singh, R. K. 2000. Emergence of chloroquine-resistant vivax malaria in South Bihar (India). *Trans. Roy. Soc. Trop. Med. Hyg.* 94 : 327.

Singh, Neeru, M. M. Shukla, V. P. Sharma, and B. N. Saxena. 1989. A focus of high degree chloroquine resistant *P.falciparum* in Mandla District (M.P.). *Indian Journal of Malariology* 26: 45-51.

Valecha, Neena. 1996. Resistance Malaria, Frontiers in Paediatrics 1st edition. Eds. H. P. S. Sachdev and Panna Chaudhry, Jaypee Publications pp. 116-138.

Valecha, Neena. 2004. Assessment of therapeutic efficacy of antimalarial drugs against uncomplicated *P. falciparum* malaria in West Bengal as part of Indo-Nepal cross border activity (unpublished report).

Wongsrichanalai, C., A. L. Pickard, W. H. Wernsdorfer, and S. R. Meshnick. 2002. Epidemiology of drug-resistant malaria. *The Lancet. Infectious Diseases* 2: 209-218.

World Health Organization. 1998. Fact Sheet No. 94.

World Health Organization. 1999. Current situation of malaria provided by the department of communicable diseases, regional office for South-East Asia, New Delhi, India.

World Health Organization. 2001. Women's Health South East Asia. Women's health: disease burden-malaria, New Delhi, India.

World Health Organization. 2001. Malaria Situation in SEAR Countries, Internet Search.

Yadav, R. S., S. K. Ghosh, and V. P. Sharma. 1995. Sulfa-pyrimethamine resistant *P. falciparum* in a malaria endemic zone of India. *Mosq. Born. Dis. Bull* 12: 7-9.

Zangpo Nado. 2002. Brief report of malaria situation in Bhutan. National Malaria Control Program. Public Health Division. Department of Health.

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