



Strategic Framework for Artemisinin Resistance Containment in Myanmar (MARC) 2011-2015

April 2011

There is a finite window of opportunity to contain artemisinin resistance before it spreads. If the current foci of artemisinin-resistant parasites are not contained or eliminated, the costs, both human and financial, could be great¹.

¹ WHO (2011): Global Plan on Artemisinin Resistance Containment
(http://www.who.int/malaria/publications/atoz/artemisinin_resistance_containment_2011.pdf)

Acknowledgment

The containment framework is the result of intense collaborative effort of several partners and organizations engaged in health and malaria control in Myanmar, in the Greater Mekong Sub-region and outside. The initial draft has been prepared by Dr Allan Schapira, senior researcher, Swiss Tropical and Public Health Institute, Basle, with the financial support from the Bill and Melinda Gates Foundation. The Vector borne Disease Control Division, Department of Health, Myanmar, jointly with the World Health Organization (Global Malaria Programme, Regional Office for Southeast Asia, Mekong Malaria Programme and Office of the WHO Representative in Myanmar) has finalized the containment framework towards its immediate implementation with field staff and support from international donors.

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Abbreviations

3DF	Three Diseases Fund for AIDS, tuberculosis and malaria in Myanmar
ACT	Artemisinin-based combination therapy
AL	artemether-lumefantrine
AMFm	Affordable Medicines Facility for malaria
AMT	Artemisinin mono-therapy
AP	atovaquone-proguanil
ARC3	Artemisinin resistance: pilot studies to confirm, characterize, and plan for containment
AS7	Seven day Artesunate treatment
BCC	Behaviour change communication
CBA	Community Based Activities
CBO	Community Based Organization
CQ	Chloroquine
DHA-PIP	dihydroartemisinin-piperaquine
EPI	Expanded Programme on Immunization
FDA	Food and Drug Administration
FDC	Fixed dose combination
GAVI	Global Alliance for Vaccines and Immunization
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
GPARC	Global Plan for Artemisinin Resistance Containment
GMS	Greater Mekong Sub-region
G6PD	Glucose-6-phosphate dehydrogenase deficiency
HU	Health Unlimited
IOM	International Organization for Migration
LLIN	Long-lasting insecticidal net
IRS	Indoor residual spraying
ITN	Insecticide-treated net
JICA	Japan International Corporation Agency
MIS	Malaria indicator survey
NMCP	National Malaria Control Programme
PCR	Polymerase chain reaction
PSI	Population Services International
RDT	Rapid diagnostic test for malaria
SP	Sulfadoxine-pyrimethamine
TA	Technical assistance
TES	Therapeutic efficacy study
ToR	Terms of reference
TSG	Technical strategic group for malaria control in Myanmar
VBDC	Vector Borne Disease Control Division (Department of Health, Myanmar)
WVI	World Vision International

Summary

In the last decade, the global malaria situation has shown substantial improvement following massive deployment of preventive and curative tools including artemisinin-based combination therapy (ACT), which has proven an effective intervention for mortality and morbidity reduction. There is growing evidence that artemisinin resistant parasites, which were first detected around the Thai-Cambodian border, occur also in eastern Myanmar. This has potentially disastrous consequences for global malaria control, given that in the past, resistance to antimalarial drugs has spread from Southeast Asia to the Indian subcontinent and Africa. Cambodia and Thailand have made progress towards elimination of falciparum malaria, but this will be almost to no avail, if there is unbridled transmission of resistant parasites in Myanmar.

The malaria burden in Myanmar is by far the highest among the Mekong countries though there is a lack of precise information. According to WHO's burden estimations, there were in 2006, 870,000-8.5 million (midpoint 4.2 million) malaria cases in the country with around 75 percent of the confirmed cases caused by *P. falciparum*. The national malaria treatment policy adopted the ACT principle in 2002. However, the scale and reach of implementation has been far from sufficient and a large proportion of the population seeks treatment in the private sector.

WHO has now established a Global Plan for Artemisinin Resistance Containment (GPARC) which defines the global objectives in the efforts to protect artemisinin-based combination therapies (ACTs) as an effective treatment for falciparum malaria. The present document is intended to outline priority objectives and interventions in Myanmar and identify target zones and populations. Containment entails concentrated efforts and a high number of activities in a focused area. This means that there is an even stronger need for coordination, monitoring and evaluation. Thus, a key part of this document is to establish suitable coordination mechanisms backed up by a strong monitoring and evaluation system.

Containment can never be a done by a single intervention, but can only be achieved by a strong multifaceted approach focusing both on long and short term solutions

Specific objectives outlined in the documents are:

- 1) To improve access to and use of early diagnosis and quality treatment according to the national treatment guidelines
- 2) To decrease drug pressure for selection of artemisinin resistant malaria parasites by stopping the use of Artesunate Mono-therapies and sub-standard/fake drugs
- 3) To limit the transmission of malaria by vector control and personal protection
- 4) To increase migrant/mobile populations' access to and use of malaria diagnosis, treatment and vector control measures including personal protection
- 5) To support containment of artemisinin resistant parasites through advocacy and BCC/IEC
- 6) To conduct studies and do operational research to support the development of evidence-based containment policies and strategies
- 7) To provide effective management and coordination to enable rapid and high quality implementation of the containment strategy

Based on results from *in vivo* Therapeutic Efficacy Studies carried out in Myanmar, a "Zonation exercise" has been made in an effort to delineate target areas and define priority actions by zone (so-called tiers in the GPARC). An overview can be seen in the table below.

Table 1 - Overview of tiers

<i>Tier</i>	<i>Area</i>	<i>No. of townships</i>	<i>Justification</i>
1	Tanintharyi All 10 townships	21	Strong evidence of suspected resistance. Widespread ecological and social risk factors. Intensive population movement.
	Mon: All 10 townships		
	Bago East: Shwegyin township.		
2	Kayin State: All 7 townships	31	Unclear evidence of suspected resistance; Near suspected resistance areas in Myanmar, Thailand and China
	Kayah State: All 7 townships		
	Bago East: Remaining 13 townships		
	Kachin: 4 townships		
3	Rest of country		

Many of the townships included are difficult to access, especially in the rainy season putting even higher demands on the planning of distribution of supplies, data management and good supervision and reporting by staff located at township and health care levels.

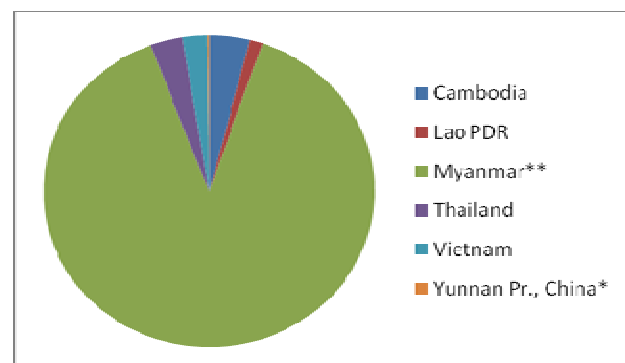
1. Introduction

In the last decade, the global malaria situation has shown substantial improvement following massive deployment of preventive and curative tools. WHO estimates that worldwide, the number of deaths due to malaria has decreased from 985,000 in 2006 to 781,000 in 2009.² The treatment of uncomplicated falciparum malaria with oral artemisinin-based combination therapy has proven an effective intervention, which plays an important role in mortality and morbidity reduction in Southeast Asia and the benefits are beginning to be realized also in Africa, India and South America. Unfortunately, there is growing evidence that artemisinin resistant parasites, which were first detected around the Thai-Cambodian border, occur also in certain other parts of the Greater Mekong Sub-region (GMS), especially eastern Myanmar.

Further spread of artemisinin resistance could jeopardize global efforts to combat malaria. Much progress has been made in Cambodia and Thailand in the last few years, but the efforts will be fruitless if the situation in Myanmar is not handled with the same determination.

The present document intends to support the development of an evidence-based and feasible national response to this acute problem. The containment framework highlights priority interventions by objective and tiers. Increased collaboration and exchange of information between all partners is needed to actually implement and monitor proposed interventions and to successfully contain artemisinin resistant P.f. strains in Myanmar.

Figure 1 – P.f cases in the Mekong region



Purpose of the framework

- Define priority action to contain artemisinin resistance in Myanmar*
- Identify target zones and populations*
- Help mobilize resources to fund containment*
- Increase collaboration among stakeholders and identify coordination mechanisms*
- Define metrics/indicators for assessment of progress towards objectives and outcomes*

It is expected that by significantly delaying the spread of artemisinin resistant *P. falciparum*, the negative health impact in Myanmar and globally can be considerably lessened (Annex 6). Furthermore, the activities will help to drastically reduce the burden of malaria benefitting both Myanmar and the region.

² WHO. World Malaria Report 2010. WHO, Geneva, 2010

2. Artemisinin resistance and containment

2.1. Emergence of artemisinin resistance in the Greater Mekong Sub-region including Myanmar

The following review of the history of artemisinin tolerance and resistance and the response to it is largely based on WHO's recently published report on antimalarial drug efficacy and resistance. The figures in this section are copied from that report.³

The Cambodia–Thailand border area has historically been the initial focus of resistance to antimalarial treatments in Southeast Asia, reporting the first cases of *P. falciparum* resistance to chloroquine, sulfadoxine–pyrimethamine and mefloquine. Resistance to the first two drugs eventually spread across Southeast and South Asia, and then to Africa, rendering treatment as practiced ineffective in most malaria-endemic countries. Artemisinin resistance has now emerged in the same area. The main events in this short history up to end of 2010 are listed in Table 2 and then described in the following.

Emergence on Cambodia-Thai border

Artemisinins (artemisinin and its derivatives dihydroartemisinin, arte-ether, artemether and artesunate) were used on a limited scale since around 1980 in China and its neighbouring countries. Since around 1990 they were used on a large scale in Vietnam. While Thailand used the combination of artesunate and mefloquine in certain areas since the 1990s, Cambodia, where self-administered monotherapy with artesunate had become common, was the first country to adopt an ACT (artesunate + mefloquine) as first-line treatment nationwide in 2000.

In 2002, it was found in Pailin Province in Cambodia that an exceptionally high proportion, 14.3%, of patients treated with artesunate + mefloquine had late treatment failure at day 28, and that about 10% of patients in the study had not cleared parasites by day 3. At about the same time, between 2001 and 2003, in Battambang Province, north-western Cambodia, artemether–lumefantrine was shown to have a high failure rate, with 13.8–32.7% of patients having parasites at day 3. Later, in Pailin, after large scale introduction of rapid diagnostic tests and replacement of artesunate–mefloquine by dihydroartemisinin–piperaquine, the treatment failure rate of artesunate–mefloquine decreased to 0-5% in 2007–2008.

Table 2 - Main events in the history of emergence of artemisinin resistance in Southeast Asia

2001	Routine efficacy studies in Cambodia and Thailand
2002 - 5	High failure rate and increased parasite clearance times with ACTs at Cambodia – Thailand border
2005 September	WHO publishes report warning of artemisinin resistance in Greater Mekong
2006 January	WHO calls for international ban of artemisinin monotherapy

³ WHO (2010). Global report on antimalarial drug efficacy and drug resistance: 2000–2010. WHO, Geneva, 2010

2006	AFRIMS detects two cases of artemisinin resistance in Tسانh, Cambodia
2007 January	Initiation of containment strategy development in Cambodia and Thailand ⁴ .
2007 April	WHA resolution for a ban on artemisinin monotherapy
2007 December	WHO begins coordination of ARC3 project funded by Gates Foundation
2008 February	Relevant partners reach agreement on containment strategy at meeting in Thailand ⁵ .
2008 November	Gates Foundation commits funding for containment; implementation begins
2009 May	WHO press release confirms artemisinin resistance on Cambodia-Thailand border
2011 January	Launch of Global Plan for Artemisinin Resistance Containment

The referenced reports and other documentation are available on <http://www.malaria.who.int> or http://www.whothailand.org/EN/Section3/Section113_269.htm

In Thailand, where the malaria incidence has been drastically reduced over the last 20-30 years, the treatment policy in certain provinces was changed to an artesunate-mefloquine combination. Declining efficacy was later observed in Trat Province on the Cambodian border, where the cure rate decreased from 92.5% in 1998 to 84.6% in 2002. More recently, similar developments were found near the border to Myanmar, for example in the province of Kanchanaburi, where the percentage of patients clearing parasites at day 3 decreased from 100% in 2005 to less than 80% in 2009.

Reports on *in vitro* studies of artemisinins in China and Vietnam published between 2000 and 2005 indicated increasing trends for IC50, IC90 or IC99 values. Subsequently, in a comparison of samples from Bangladesh, western Cambodia and western and eastern Thailand, decreasing susceptibility was observed, and in Cambodia, the highest IC50 was reported in the western part of the country.

The first clear and certain evidence of artemisinin resistance was provided in a study of oral artesunate monotherapy conducted in Cambodia in Tسانh, Battambang Province, where falciparum malaria patients were admitted to hospital for 28 days, and treated with oral artesunate monotherapy (4 mg/kg body weight per day for 7 days) or quinine plus tetracycline. Four treatment failures were observed among the 60 patients who received artesunate. Two of these four patients had adequate drug plasma levels and were consequently classified as having artesunate-resistant infections. They had parasite clearance times of 133 h and 95 h, which are markedly longer than the median parasite clearance time of 52.2 h. The IC50 for dihydroartemisinin for parasites isolated from these patients was four times the IC50 geometric mean for cured patients and almost 10 times that for the reference clone W2.

⁴ WHO (2007). Containment of malaria multi-drug resistance on the Cambodia-Thailand border, Report of an informal consultation, Phnom Penh, 29-30 January 2007. SEA-MAL-246.

⁵ WHO (2008). Development of a strategy towards elimination of *Plasmodium falciparum* parasites with altered response to artemisinins. Report of an informal consultation, Bangkok, Thailand, 13-14 February 2008

Initial response

In January 2006, WHO urged the pharmaceutical industry worldwide to stop the sale of single-dose forms of artemisinins and began monitoring manufacturers of oral artemisinin-based monotherapies (AMT) and the availability of these drugs. WHO called attention to the risks of resistance to artemisinins, citing the reduced sensitivity in the GMS as a possible consequence of the use of oral monotherapy. In May 2007, the World Health Assembly called on Member States to “cease progressively the provision in both the public and private sectors of oral artemisinin monotherapies”. In November 2007, the Bill & Melinda Gates Foundation provided funding to the WHO to coordinate a project entitled ‘Artemisinin resistance: pilot studies to confirm, characterize, and plan for containment (ARC3)’. The information collected in the ARC3 studies led the investigators to conclude that the proportion of patients who are still parasitaemic on day 3 (72 h after the beginning of the treatment) in clinical trials with ACTs is the most appropriate indicator of possible artemisinin resistance. WHO has now established a working definition for artemisinin resistance (Box 1). From 2007, a series of meetings were held to develop a strategy of containment of artemisinin resistance, assumed to be present only in limited areas of Cambodia and Thailand. Consensus on a containment strategy was established in early 2008 and a few months later, Bill & Melinda Gates Foundation committed funding.

Current situation in the Greater Mekong Sub-region

The strongest evidence of artesunate resistance is still in northwest Cambodia, near the Thai border. In Pailin, the proportion of patients who were still parasitaemic after 3 days of treatment with dihydroartemisinin–piperaquine increased from 26% to 33% between 2008 and 2009. In Pailin and Tansanh, over 40% of patients were parasitaemic on day 3 after treatment with 2–4 mg / kg body weight per day of oral artesunate monotherapy.

Box 1. WHO’s working definition for detection of artemisinin resistance

- an increase in parasite clearance time, as evidenced by 10% of cases with parasites detectable on day 3 after treatment with an ACT (suspected resistance); or
- treatment failure after treatment with an oral artemisinin-based monotherapy with adequate antimalarial blood concentration, as evidenced by the persistence of parasites for 7 days, or the presence of parasites at day 3 and recrudescence within 28/42 days (confirmed resistance).

Absolute **confirmation** of artemisinin resistance can be established only when artemisinins are used alone, preferably with measures of the artemisinin blood concentration. A genetic marker of artemisinin resistance has not yet been identified, so that it is impossible to confirm the presence of artemisinin resistance in a molecular marker study.

For details on methodologies and interpretation of results, see WHO’s global report on resistance (footnote 3)

Elsewhere in the region, the situation is less severe but some recent findings are alarming. At the Myanmar–Thailand border, 10–20% of patients are now parasitaemic after a 3-day treatment with ACTs. At the China–Myanmar border, a study of oral artesunate monotherapy (16 mg/kg body weight over 7 days) found that 25% of patients were still parasitaemic at day 3. This study was conducted at the border between Dehong prefecture in China and Kachin State in Myanmar. However, it is possible that high initial parasitaemia

could have been a main contributor to the presence of parasites on Day 3. In contrast, a study of dihydroartemisinin-piperaquine further south on the border near Pu'er prefecture in China gave no indication of resistance.

These results indicate a clear change in the sensitivity of parasites to artemisinins. However, the treatment failure rates with ACTs remain low (< 10%), provided that partner drugs that are effective in the region are selected and used. High treatment failure rates with ACTs have been observed only in those areas where resistance to a partner drug has been confirmed. In those settings, changing to an ACT with a different partner drug resulted in high treatment efficacy. Therefore, the term 'ACT resistance' should be avoided. When the efficacy of an ACT appears to be compromised, reference should be made to that ACT and not to ACTs in general.

Generally, the failure rate with artesunate monotherapy remains low, even if the proportion of patients who are parasitaemic at day 3 is very high. There are, however, two exceptions. In Pailin, the treatment failure rate following treatment with 7-day artesunate was as high as 30% (6/20 patients); reduced artemisinin susceptibility was also reported in Bu Dang district, Binh Phuoc Province, in Vietnam, where, a high treatment failure rate was found after treatment with artesunate 16 mg/kg body weight over 7 days. The focus seems to be limited to this one district in Vietnam. The main population movements are to and from parts of Vietnam, where falciparum malaria is not endemic. The risk of spread of artemisinin resistance from there is therefore relatively low.



Figure 2 - Percentages of patients with *P. falciparum* parasitaemia on day 3 after treatment with an ACT (2006–2010)

The map shows the results of the most recent therapeutic efficacy study per site and per drug only: 1. 2007, artemether–lumefantrine; 2. 2007, artesunate–amodiaquine; 3. 2009, artemether–lumefantrine; 4. 2007, artesunate–amodiaquine; 5. 2007, artemether–lumefantrine; 6. 2007, artesunate–amodiaquine; 7. 2009, artemether–lumefantrine; 8. 2009, dihydroartemisinin–piperaquine; 9. 2007, artemether–lumefantrine; 10. 2007, artesunate–amodiaquine; 11. 2007, artemether–lumefantrine; 12. 2009, artemether–lumefantrine; 13. 2009, dihydroartemisinin–piperaquine; 14. 2009, dihydroartemisinin–piperaquine; 15. 2009, artesunate–mefloquine; 16. 2009, artesunate–mefloquine; 17. 2009, artesunate–mefloquine; 18. 2008, artesunate–mefloquine; 19. 2009, artesunate–mefloquine; 20. 2008, artesunate–mefloquine; 21. 2008, artesunate–mefloquine; 22. 2007, artesunate–mefloquine; 23. 2010, artesunate–mefloquine; 24. 2009, dihydroartemisinin–piperaquine; 25. 2006, artesunate–mefloquine; 26. 2010, dihydroartemisinin–piperaquine; 27. 2010, dihydroartemisinin–piperaquine; 28. 2007, artesunate–mefloquine; 29. 2009, dihydroartemisinin–piperaquine; 30. 2006, artesunate–mefloquine; 31. 2008, artesunate–mefloquine; 32. 2008, dihydroartemisinin–piperaquine; 33. 2009, dihydroartemisinin–piperaquine; 34. 2010, dihydroartemisinin–piperaquine.



Figure 3 - Percentages of patients with *P. falciparum* parasitaemia on day 3 after treatment with oral artesunate monotherapy (2–4 mg / kg body weight per day), 2007–2009 (The map shows the results of the most recent therapeutic efficacy study per site only.)

In contrast, the affected area on the Thai-Myanmar border is home to millions of people. It is only tentatively delimited and has extensive population movements: across the border, to and from the epicentre of resistance on the Thai-Cambodia border and to and from other parts of Myanmar, endemic as well as non-endemic. The emergence of artemisinin resistance in this area has magnified and complicated the containment challenge.

The data on artemisinin resistance within **Myanmar** is reviewed in Annex 4, together with historical data on resistance to other antimalarials and relevant recent data from Bangladesh and India. In general, resistance to antimalarials emerged earlier in the east than in the west of Myanmar and earlier in Myanmar than in Northeast India, which was clearly the entrance of at least chloroquine resistance to India as a whole.

Until 2009, there were no clear signs of artemisinin resistance in Myanmar. In 2009, TES studies with ACTs showed the following main results:

Table 3 - Selected TES results 2009, Myanmar

Day 3 positivity rate in TES studies with two ACTs	Kawthaung, Tanintharyi Division	Shwe Kyin, Bago East Division	Kalay, Sagaing Division
Dihydroartemisinin-piperaquine	19%	4.2%	-
Artemether-lumefantrine	4.8%	10%	0%

In principle, these results, seen in isolation, only raise a suspicion. However, when considered together with elevated day 3 positivity rates in Kanchanaburi, Tak and Ranong on the Thai side of the border (Fig.1), there is no doubt that artemisinin resistance has emerged in eastern Myanmar. As mentioned, worrying results have also been found on the border to China in Kachin State, but these need further investigation.

Unpublished results from Myanmar in 2010 suggest that so far, there are no signs of artemisinin resistance in the Shan States (2 sites), in Myitkyina, Kachin State, or in Rakhine State. In contrast, results from Mon and Kayin States close to areas of suspected resistance in Thailand, give rise to concern, but no final conclusions can be drawn until the results have been PCR corrected. A study with artesunate monotherapy is to take place in Kawthaung in 2011. So far, there is no indication of artemisinin resistance in Bangladesh or in India.

While definitive proof of the presence of artemisinin resistance in Myanmar is awaited, time must not be lost. Containment needs to be initiated to minimize the risk of spread of artemisinin resistance within Myanmar and from Myanmar, minimize the risk of *de novo* emergence in the country and mitigate the effects of the problem on the health of the population of Myanmar.

Considering the geography and the history of spread of chloroquine-resistance, it can be said with a high degree of certainty that if artemisinin resistance will emerge in India or Bangladesh, it will be imported from Myanmar. It could arrive in Africa with a traveller from any country in South or Southeast Asia. However, given the very small populations affected by artemisinin resistance in Cambodia, Thailand and Vietnam and the likelihood that these countries will still be able to contain these foci (artemisinin resistance has not spread to eastern Cambodia), the risk of a traveller taking artemisinin-resistant parasites from one of these countries to Africa is not high. The risk of a traveller getting infected in Myanmar or India would be much higher.

The strategy for containment of artemisinin resistance in Myanmar needs to be seen as part of a regional strategy with global implications and draws on the experiences accumulated over the last few years in Cambodia and Thailand. A review of these experiences is presented in annex 2. Furthermore, annex 3 includes summaries of the current plans (approved Global Fund Round 10 proposals) of China and Thailand for malaria control near and on the borders to Myanmar.

3. The malaria situation and its determinants in Myanmar

3.1. Geographic, demographic and social features

Myanmar is the largest country in mainland South-East Asia with a total land area of 676,578 km². It stretches 2,200 km from north (28°31'N) to south (09°32' N) and 925 km from west (92°10' E) to east (101°11' E) at its widest point.

There are three well marked natural divisions: the western hills, the central belt and the Shan plateau on the east, with a continuation of this highland in the southern region of Tanintharyi. Three parallel mountain ranges from north to south divide the country into

three river systems: Ayeyarwaddy, Sittaung and Thanlwin. Myanmar has abundant land, water, forest, coal, mineral and marine resources as well as natural gas and petroleum. Great diversity exists between the regions. The rugged terrain in the hilly north makes communication difficult, while numerous rivers and tributaries criss-cross the southern plains and marshlands.

The climate is tropical with three main seasons: The rainy season comes with the southwest monsoon, lasting from mid-May to mid-October, the cold season is from mid-October to mid-February and the hot season from mid-February to mid-May.

The country is divided into 17 States and Regions, and comprises 66 Districts, 325 Townships, 13,714 Village Tracts and 64,910 Villages. The first level administrative area is the Region or State. The Townships are the core planning and implementation units for health. The population of Myanmar was in 2009 estimated at 59 millions. About 70 percent of the population resides in the rural areas. The population density for the whole country is 77 per km². There is some variation in demographic estimation, as can be seen from for example UN publications.⁶ In this document, like in the Global Fund Round 9 proposal, the estimation published by the Ministry of Health is applied.



Figure 4 - Topography of Myanmar

⁶ WHO (2010). World Malaria Report 2010. World Health Organization, Geneva, 2010

The Union of Myanmar is made up of 135 national groups speaking over 100 languages and dialects. The major ethnic groups are Kachin, Kayah, Kayin, Chin, Mon, Bamar, Rakhine and Shan. About 89.4% of the population is Buddhist whilst the rest are Christians, Muslims, Hindus and animists.

3.2. Health System and Financing in Myanmar⁷

The Ministry of Health (MOH) has seven Departments as seen in the figure below. Hierarchically, the health system is organized in accordance with the country's administrative structure with health departments at State/Regional, District and Township level.

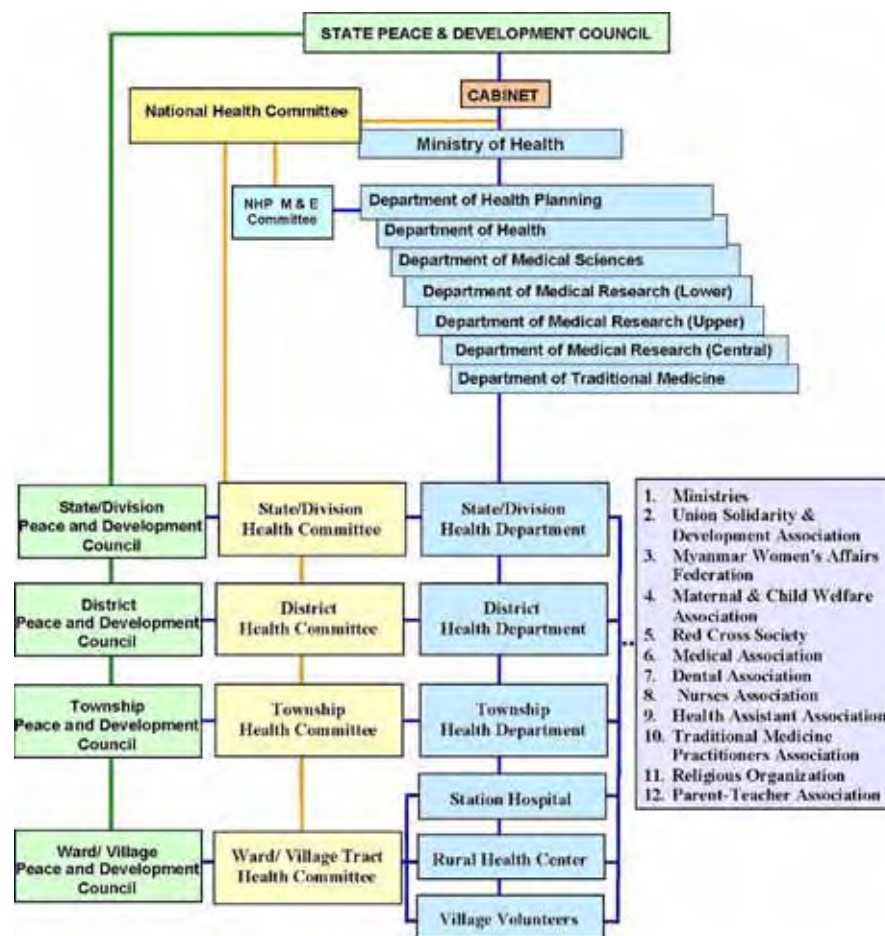


Figure 5 - Organogram of Health Service Delivery System in Myanmar
Source: Health in Myanmar 2010

Delivery of health care in the townships

A Township Health Department has the following health facilities and manpower complement: a Township Hospital managed by the Township Medical Officer, 1 to 3 Station Hospitals managed by a Medical Officer, 4 to 5 Rural Health Centers (RHCs) led by Health Assistants, and 4 to 5 Sub-rural Health Centers per Station Hospital and RHC. A public health supervisor is assigned to Township Hospital, Station Hospital and in each RHC. A Lady Health

⁷ GFATM Round 9 proposal for malaria control in Myanmar

Visitor is assigned to each RHC. Each sub-center has a midwife who delivers basic health services including malaria prevention and control. Each sub-center covers between 5 to 15 villages.

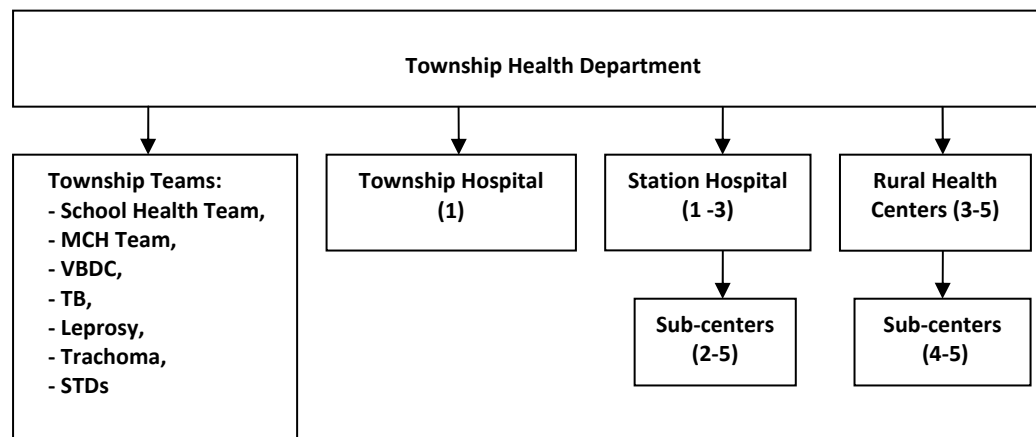


Figure 6 - Organogram of Township Health Department

Vector Borne Disease Control Programme (VBDC), Ministry of Health

The National Malaria Control Programme (NMCP) is part of the VBDC Programme, under the Division of Disease Control, Department of Health of the Ministry of Health.

At Central Level, the VBDC programme is mandated to formulate plans, policies, standards and norms related to malaria control, provide training, conduct operational research, control of outbreaks, and provide consultative and advisory services to other implementing agencies. In recent years, VBDC issued a national antimalarial treatment policy, standard case definitions, core epidemiological and operational indicators and implementation strategies for scaling-up insecticide-treated nets (ITNs).

At State/Divisional level VBDC is responsible for the control of malaria, under the supervision of the State/Divisional Health Director. The Medical Officers lead the State and Divisional level VBDC teams which have responsibilities for supervision, and monitoring of implementation at lower levels.

At District/Township level, the malaria control programme is integrated into the Basic Health Services, where the Township Medical Officers supervise the implementation of malaria control and prevention interventions within the Townships, station hospitals, RHCs and sub-centers. The VBDC staff allocation in each endemic Township comprises a malaria assistant, malaria inspector, malaria supervisor, malaria spray man and sometimes laboratory technician. However, not all of these positions are filled. Overall nationwide about 60-70% of the allocated sanctioned posts for VBDC are filled.

Health Financing

According to 2001-2002 estimation of national health expenditure, the funding sources for health care services are: private out-of-own-pocket (73.4%), government (13.6%),

external aid (12.1%), community contribution (0.54%) and social security system (0.36%)⁸. Government health expenditure in Myanmar was about 886 Kyats (USD 1.0) per capita in 2008-2009⁹. Myanmar receives only \$4 per person per year (2007) in humanitarian aid. This is 15 times less than what nearby Lao People's Democratic Republic receives. Myanmar does not currently access resources from the World Bank or the Asian Development Bank.

A US\$33 million **Health Systems Strengthening Programme supported by GAVI is expected to start in 2011**. It will initially target 180 of the 325 townships in the country. The approach is centred on the development of integrated annual township health plans and budgets which show the contribution to service delivery by both government and non-government service providers. The development of the plan and reports against it will support coordination between service delivery partners at township level. Plans will identify specific health systems strengthening needs to service delivery, such as support for training and supervision, facility renovation and equipment and supplies. The program will also examine and pilot incentives for health workers (particularly midwives) in remote and hard-to reach areas. **Innovative health financing schemes** will also be piloted.

3.3. Malaria epidemiology

Ecological and social determinants and geographical distribution

Like in other countries in Southeast Asia, malaria in Myanmar is mainly associated with **forests**. It has been estimated that 60% of malaria cases in Myanmar are forest-related. Most forests are located in highland areas; above 600m above sea level, transmission reduces and it is usually absent above 1000-1200m. Plantations can often create conditions for breeding of forest vectors¹⁰.

Malaria also occurs as **coastal** malaria transmitted mainly by *An. sudaicus* in Rakhine State.

In the **plain areas** of Myanmar, malaria is highly unstable, and tends to cause outbreaks, for example among road and construction workers. There are several weak vectors in these areas, the most important probably being *An. annularis*. Like elsewhere in Southeast Asia, malaria is rare in areas dominated by river- irrigated rice-fields.

A phenomenon that is peculiar to Myanmar is the tendency of the efficient forest vector *An. dirus*, to breed in deep wells, as has been observed in Mon State. Also, *An. minimus* has been observed in wells, in Sagaing State.

Most malaria cases and deaths are likely to occur among people residing in **villages near or in the forests**. These people are usually national races (ethnic minority groups) living from subsistence agriculture supplemented by forest activities, such as cutting bamboo or rattan or production of charcoal. Generally, residence within 2 km distance from the forest means that malaria transmission can occur in the village at least during part of the year, with all age-groups being at risk. If the village is located at somewhat greater distance from the forest, the risk is usually somewhat more confined to adult men, who enter the forest periodically. These men usually go in groups and stay in the forest for several days in makeshift shelters that offer no protection from mosquito bites.

Malaria risk also occurs in **plantations**, which offer forest-like environments such as rubber trees and oil palms. In such situations, it is usually relatively easy to organize control,

⁸ Source: Health in Myanmar 2006, MoH

⁹ Source: Health in Myanmar 2010, MoH

¹⁰ VBDC - WHO (2009) ITN Policy and Implementation Strategy in Myanmar

but this then meets with technical obstacles in rubber plantations, where workers need to start before sunrise, when anophelines are highly active.

Apart from forest-dwellers, and people residing in forest-fringe villages, the major risk group is **migrants**¹¹, who are often induced by economic opportunities such as logging or mining in forested areas or road or dam construction and maintenance. Displacement caused by dam construction may also lead to exposure. These population movements may be organized, in which case it is relatively easy to organize prevention and curative services. However, often the migrant groups are small, spontaneous and even clandestine and illegal, and this makes it difficult to protect them. In relation to containment, at present, the most important migrants may be those moving back and forth between Thailand (or Cambodia) and Myanmar. There is an estimated 1.2-1.6 million migrants workers from Myanmar in Thailand¹². Within Myanmar, there are large numbers of migrant workers in plantations, mainly palm oil; alone in the Kawthaung and Boke pyin areas in Tanintharyi, where artemisinin resistance is suspected, there are an estimated 30,000 migrant workers. Another important group of migrants in Tanintharyi Division are fishermen, who often go to Thailand. Population movement in Myanmar has not yet been mapped sufficiently for exact planning of health services targeting these risk groups.

Box 2. Malaria control in migrants in Bago

The malaria control project supported by JICA in 16 townships in Bago has focused on the migrants' malaria problems for some years. In 2009, it was found that 94% of a total of 60,623 persons examined for malaria and 97% of 28,332 positive (confirmed) cases were internal migrants. The reasons for the presence of these internal migrants were extremely diverse. In order of magnitude, the most important were:

- Bamboo cutting
- Taungya* (agro-forestry)
- Forest visit
- Wood cutting
- Farm
- Charcoal production
- Timber
- Plantation

JICA's projects show that a high number of migrants can be reached through health facilities though the activities focused on migrants and inter-sectoral collaboration needs to be increased.

Burden and recent trends

According to the burden estimations of World Malaria Report 2008 (WHO), there were in 2006 870,000-8.5 million (midpoint 4.2 million) malaria cases in the country, around 75 percent of the confirmed cases were caused by *P. falciparum*, and the estimated number of malaria deaths was 2,400-17,000 (midpoint 9100). The estimated number of fever cases, which would be considered as suspected malaria was 2.8 million-38.1 million (midpoint 18.8 million). Of these, 2.2 million would be in children under 5 years.

¹¹ VBDC - WHO (2009) ITN Policy and Implementation Strategy in Myanmar

¹² R. Sciortino & S. Punpuing (2009). International Migration in Thailand, IOM, Thailand Office. ISBN 978-92-9068-471-8

Between 2002 and 2009 there has been a continuous gradual reduction in the number of reported malaria deaths, from 2634 to 1088. At the same time, the number of reported malaria admissions went down from 82,193 to 47,772; the number of all-cause admissions increased; the number of reported all-cause deaths decreased; the number of reported and confirmed malaria cases increased.¹³ These figures suggest that it has been possible to reduce severe malaria and malaria deaths; the reductions in malaria-attributable deaths and admissions are not likely to be due to more specific diagnosis only, given the concomitant increase in both reported and confirmed malaria cases. However, it is not easy to explain exactly which changes led to these improvements, as the trends started already in the 1990s.¹⁴ There was a marked increase in the number of cases tested, mainly because of increased use of rapid diagnostic tests (RDTs), from 173,096 in 2002 to 980,640 in 2009; over the same period, the test positivity rate increased from 37.0% to 43.3%, suggesting that the RDTs were used to a larger extent in high risk populations than microscopy; there is no indication that the incidence of malaria has been reduced. It is not unlikely that there has been a reduction in incidence, which has been counterbalanced by increased recording and reporting by health facilities. Between 2006 and 2008, a total of 1.5 million ITNs were delivered. This scale-up to protect less than 10% of the eligible population (see below: Stratification and quantification) would not be sufficient to have a discernible impact on malaria incidence at national scale. Likewise, the scale up in the use of ACTs through services supported by the public would not be sufficient to reduce transmission.

It is thought that the progress in control, which is reflected in fewer malaria admissions and deaths, has been mainly in central areas, where access is easier. In the areas with the highest burden, infrastructure is not well developed and transport often has to be on foot. Furthermore, the control of some areas by local ethnic groups, constrains the operation of public services.

In 2009, approximately 591,000 malaria patients, confirmed and unconfirmed, were treated in the government health facilities. 68% of cases were adults; 19% 5-14 years old and 13% under 5; among adult cases, 61% were males and 39% females (VBDC).

The 591,000 patients constitutes only 14% of WHO's midpoint estimate of malaria cases in 2006 (but 68% of the lower bound). Approximately, 60-75 percent of people in Myanmar are thought to use the private sector for health care. When this assumption is combined with knowledge about difficult access especially in highly endemic peripheral areas, it is plausible that the fraction of malaria cases recorded by the Department of Health is in fact only around 14% of all the cases occurring in the country.

The persistence of the high malaria burden can be ascribed to a combination of the following factors:

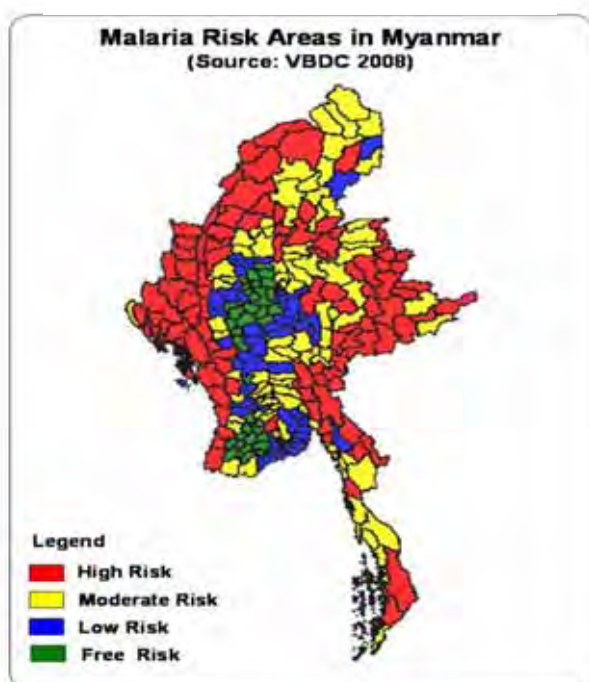
- A relatively large proportion of the population may still live in or near forested areas or are still occasionally exposed to forested areas.
- Access to health facilities is difficult especially in the areas with the highest malaria burden.
- Specific malaria control investments have been inadequate and much lower than in neighbouring countries

¹³ WHO (2009). World Malaria Report 2009. WHO, Geneva, 2009.

¹⁴ VBDC (2010). National Strategic Plan for Malaria Control in Myanmar (2010)

Stratification and quantification of populations at risk

Figure 7 – Stratification by township



Based on an understanding of ecological determinants of malaria and long-term malaria data, the country has been divided into areas of no risk and low, moderate and high risk for malaria. However, within the high risk areas there are villages with little or no transmission, hence there is a need to undertake micro-stratification for more effective targeting of malaria prevention and control interventions.

Micro-stratification done with the support of UNICEF in 2007 – 2008 in 80 townships classified as high risk indicated that 75% of the population in these townships reside in malaria risk villages.¹⁵ This may or may not reflect the situation in other townships, so micro-stratification in other townships should be done for better planning and targeting of interventions. The national level estimations resulting from

stratification exercises can be summarized as follows:

Out of a total of 325 townships in the nation, 284 are endemic for malaria. Of these, 180 are targeted as priority for prevention, but there are villages, which should be protected also in the remaining 104. For planning, the following figures are applied (2009):

- **National population in 325 townships:** **59.1 million**
- **Population in 284 endemic townships:** **51.4 million**
- Thereof:*
- ✓ **High (25%)** **12.9 million**
- ✓ **Medium risk (27%):** **13.9 million**
- ✓ **Low risk (23%):** **11.8 million**
- ✓ **Potential risk (13%):** **6.7 million**
- ✓ **No risk (12%):** **6.2 million**

Availability and use of antimalarial drugs

Summaries of relevant recent studies are presented in Annex 5. It has been common knowledge for years that in the GMS the majority of patients with malaria symptoms with the possible exception of Thailand, use medicines bought from shops or pharmacies with little regard to official recommendations. Around 1999, several studies showed that a large proportion of the presumed antimalarials sold were counterfeits containing no active ingredient; fatalities resulting from this situation were reported.¹⁶ In the following years, many of these products were modified to include trace amounts of artesunate so as to make it more difficult for field laboratories to show that they were fake. Thanks to intense,

¹⁵ UNICEF & JICA. Malaria Risk Micro-stratification in UNICEF 80 Townships

¹⁶ Newton, P. et al. (2002). Fake artesunate in Southeast Asia. *BMJ*, 324: 8000-1

interdisciplinary, international collaboration it became possible to clamp down on major manufacturers of these products in China.¹⁷

A study on practices of medical practitioners indicates that they were also prone to use artemisinin monotherapy in arbitrary doses and combinations. A study on the available antimalarial medicines indicated substantial mark-ups in the retail sector. For example, a pack of artesunate 12 tablets was reported to cost Kyat 3000 (over USD 3), about 2-3 times as much as it should be, as the ex factory price in recent years has been only about USD 1-1.25 (Annex 5 section 1).

A study on the supply chain conducted in 2010 in Kayin State¹⁸ indicated that the great majority of antimalarial treatments provided through the informal private sector were with one medicine, artesunate, belonging to a single brand and sold through a single commercial network. This brand of artesunate, AA, is believed to be a *bona fide* product (Annex 5 section 2). If these findings can be generalized, then the counterfeits now play a much lesser role than 5-10 years ago. While this is an improvement from a clinical viewpoint, the benefits are limited, because most treatment courses are inadequate. As a consequence, most patients are likely to suffer recrudescence after treatment.

3.4. Malaria control in Myanmar including lessons learnt

Malaria control in Myanmar is based on case management and vector control.

Case management

For many years, most cases, also in the public sector, have been managed based on clinical criteria. Since around 2002, efforts have been made to expand the use of rapid diagnostic tests for *P. falciparum*. In 2010, polyvalent rapid tests, which can also diagnose *P. vivax* have been adopted. In 2002, ACT was adopted as first line treatment. In 2010, it was decided to use primaquine single dose as an adjunct to treatment of falciparum malaria in order to kill gametocytes and thereby reduce transmission. The treatment for vivax malaria is chloroquine and primaquine (for 14 days). Sporadic cases of chloroquine-resistant vivax malaria have been found, but have not yet become a major problem. The programme promotes case management through three channels:

- Public sector health facilities
- Community volunteers, who are sometimes remunerated, sometimes not, and who are sometimes general health volunteers, sometimes malaria volunteers. These are supported in some cases by the VBDC, in others by various NGOs or by IOM or UNICEF.
- Private practitioners, who are supported through among others Myanmar Medical Association (MMA) (see box 3) and PSI.

¹⁷ Newton, P. et al. (2008) A collaborative epidemiological investigation into the criminal fake artesunate trade in South East Asia. *PLoS Med.* 2008 Feb;5 (2):e32.

¹⁸ The private sector distribution chain for anti-malarial drugs in Myanmar: Findings from a rapid assessment, PSI July 2010

Box 3. MMA's "franchised clinics"

Myanmar Medical Association (MMA) is professional organization of doctors. It has 7,000 members and 72 branch offices across the country. In collaboration with VBDC and WHO, it has established a network of 50 general practitioners in Mawlimyi, Pathien, Taungoo, Taungyi, and Pyinmana in 2005. The "franchised clinics" called *Quality Diagnosis and Standard Treatment of Malaria (QDSTM)* aim to improve case management of malaria among private general practitioners, educate the vendors on rational use of antimalarial drugs, promote the use of insecticide treated nets for malaria prevention, improve early treatment seeking behavior and improve adherence to treatment.

In addition, MMA promotes proper case management of malaria in accord with national malaria policy to the general practitioners in other parts of the country. They also initiated a review of the training curriculum in medical schools to help ensure that it is updated to respond

The supply of RDTs is still inadequate relative to the needs of the services, which are functional at present, and which are far from sufficient to cover the populations at risk. Also, only around 60% of the 700 malaria microscopy centres are functional and quality is an issue.

Vector control and personal protection

The main method is **insecticide treated nets**. Traditionally people in Myanmar own mosquito nets; in eastern part of the country 81 to 97 per cent of families owned mosquito nets, and on average each family owns 2 mosquito nets of various sizes and materials; a survey in 160 malaria endemic and hard to reach villages in Chin State, Kachin State and Sagaing Division showed that 91% of households own mosquito nets and on an average each household has two; a study in 2008 in Mandalay Division and Northern Shan State showed that of the 1,859 households surveyed, 87.8% used at least one bednet, 68% - 85% slept inside mosquito net the night before the survey and 85.8% of the nets used were purchased with private money (i.e., not provided by the project).

Given the high levels of ownership in some areas, a key intervention that has been used is net treatment even though not all nets owned are in a condition that makes them suitable for impregnations. In addition, LLINs are distributed in other communities aiming at full coverage through a norm of 2 LLINs per household. Hammock nets have been discussed, but field observers indicate that hammocks are very rarely used in Myanmar and have yet to be tested.

However, the coverage of insecticide treated nets (either ITNs or LLINs) has remained modest, given the limited scale of implementation. In 2008 only 2.3 million people (5.7% of the total population in malaria risk areas, 8.5% of population in high/moderate risk areas) were protected with ITNs/LLINs. Around 8 million ordinary mosquito nets are already owned by the people in malaria endemic areas but only 531,400 were treated with insecticide.

Indoor residual spraying (IRS) is presently used to respond to outbreaks and occasionally also in development projects where newly arrived workers are to be protected with this method for three years after their arrival.

Larval control is not used systematically for malaria control in Myanmar at present.

A small trial of **repellents** has been conducted by IOM. According to information presented at a TSG meeting on 9 December 2010, the malaria attack rate was lower in migrants provided with repellents than in the control group. This encouraging finding needs to be scrutinized.

Planning of malaria control, especially vector control is mainly based on stratification and micro-stratification. The main interventions are supported by behaviour change communication activities.

Malaria control resources

For the malaria control program, the Government provides around US\$ 200,000 per year for salaries of VBDC staff and around US\$60,000 for drugs and supplies. VBDC has more than 2300 approved posts, though only around 1600 are filled.

Myanmar obtained a round 3 grant from GFATM, but hardly had implementation started before it was terminated by GFATM in 2005. The \$125 million Three Diseases Fund (2006-2011) was then set up to help address the funding shortfall (see Box 4).

Other major sources for funding include UNICEF that supports the national programme in 80 townships and in the period 2006-08 supported with \$5.2 million. In the same period, JICA/Japan grant Aid gave \$3.8 million for national malaria control.

Box 4. The Three Diseases Fund

3DF is a donor consortium supported by Australia, the European Commission, the Netherlands, Norway, Sweden, the United Kingdom and Denmark. The fund was set up to support HIV/AIDS, TB and malaria. Since the termination of the Global Fund Round 3, 3DF has been the most significant source of funding for malaria activities in Myanmar and has in the period 2007 till June 2010 given 15.48 million USD for malaria projects.

3DF gives support through to the National Programme (through WHO), to WHO and to 5 International NGOs and 4 local NGOs working with malaria. With the support of 3DF, more than 1.1 million confirmed and probable malaria cases have been treated. In addition, more than 230,000 LLINs have been distributed and more than 880,000 nets have been treated with insecticide.

With the coming of GFATM round 9, it is expected that 3DF will broaden its scope and give more support to maternal and child health.

In 2011, the Global Fund (Round 9) will return to Myanmar. The GFATM Round 9 proposal for malaria control has a total budget of 74 million dollars over five years and an annual budget of USD 13-19 million per year. This budget included delivery of more than 730,000 LLINs in 2011 and insecticide treatment of more than 1,015,000 nets. GFATM round 9 also aims to cover 890,000 microscopy slides taken and 920,000 RDTs read in 2011 and treatment of 750,000 *P.f* cases and 510,000 *P.v* cases. While these are huge numbers, a high proportion of the estimated burden of 4.2 million malaria cases remain undiagnosed and possibly treated with sub-standard of fake medicine privately purchased.

In annex 10 are maps giving an overview over townships where malaria activities have been planned using funding by Global Fund Round 9. That a township is included is obviously not the same as saying that the needs for malaria control activities in the township are met. Shifting focus towards containment will obviously put a high demand for additional resources.

4. Discussion on options for moving from malaria control to containment

While the ultimate goal of containment operations is to eliminate *P. falciparum* strains resistant to artemisinins, the enormity of the malaria burden in Myanmar, the complexity of malaria epidemiology as well as the operating environment does not make it feasible to reach elimination goal at present except possibly in certain areas of the country. It is however considered feasible to prevent or at least further delay the spread of resistant parasites until such point, when it becomes irrelevant or obsolete, because new control tools will become available and can be scaled up. Delaying the spread and mitigating the damage caused by Pf resistant strains will be beneficial to Myanmar, to the Region and to the World (See Annex 6).

Containment in Myanmar, understood as delay of spread of resistant parasites within the country and beyond its borders, will only be possible through a broad strategy incorporating both an intensification of the current malaria control response and adoption of additional interventions. Clear demarcation between interventions aimed at malaria control, malaria elimination and containment is not possible and interventions included in a containment project must be dependent on local malaria epidemiology and environmental socio-economic conditions. Table 4 summarises interventions applied under malaria control in general and as part of containment operations.

Table 4 - Relationship between malaria control and resistance containment in a country

Area	Malaria control	Resistance containment	
		Basic	Advanced
Case management and chemotherapy	Diagnose cases Treat with ACT + PQ	Diagnose all cases Treat with ACT + Primaquine emphasizing compliance	Follow-up all treated cases for 28 days; treat failures with alternative, follow-up again
	Eliminate monotherapy	Eliminate monotherapy urgently as soon as replacement with ACT can be ensured	Eliminate treatment based on symptoms as soon as 100% access to diagnostic services can be ensured
		Screen and treat migrants from resistant areas on exit and on entry to receptive areas	Eliminate residual parasite reservoir by general screening and treatment and/or mass drug administration. - - - <i>Currently <u>not</u> envisaged for Myanmar.</i>
Vector control and personal protection	Reduce transmission by LLIN/ITNs and other appropriate vector control	Achieve 100% coverage of risk populations as soon as possible with priority to resistant areas. In resistant areas, maximize effectiveness e.g. by combining LLIN/ITN + IRS.	
		Provide migrants with adapted personal protection: repellents etc. <i>Comprises various options to be validated by local field research</i>	

Case Management

There is no question about the primordial role of case management. The use of antimalarial treatment only on the basis of confirmatory diagnosis limits drug pressure; this is particularly important for synthetic partner drugs which often have a long half-life. The use of ACT (with synergistic compounds) in preference to artemisinin monotherapy will prolong the useful life of artemisinin. It may be possible to control malaria without vector control, by making adequate medicines available for treatment, thereby preventing severe disease and death. Such a strategy can also contribute to the reduction of transmission - if the transmission intensity is not too high at the outset, and primaquine is included.¹⁹ However, in Myanmar, where the resistance clock has manifestly started ticking, case

¹⁹ Okell et al. Modelling the Impact of Artemisinin Combination Therapy and Long-Acting Treatments on Malaria Transmission Intensity. PlosMedicine 2008 | Volume 5 | Issue 11 | e226

management alone would lead to increasing proportions of resistant infections and therefore diminishing effects on transmission to a point, where transmission would increase again,²⁰ and the direct effects of case management only on morbidity and mortality would also gradually be reduced. Attempting to contain Artemisinin resistant parasites in Myanmar only through ACT case management without including other activities such as vector control would not be advisable.

The addition of a single dose of primaquine to ACT will help further reduce transmission.²¹ Current evidence in Myanmar does not give cause for concern over the safety of a single dose of Primaquine (45 mg in adults).

The evidence from Cambodia, where the situation has improved when mefloquine was replaced by piperazine lends some support to the theory indicating that multiple first line ACTs will help slowing the development of resistance. The current consensus in Myanmar is to promote artemether-lumefantrine (AL) as the standard first line treatment in the public sector and in the informal private sector as well. Encouraging the use of dihydroartemisinin-piperazine (DHA-PIP) in areas where it is not associated with high Day 3 positivity rate or high therapeutic failure rate could be a possibility, for example in military health services. It is of course essential to ensure that the product is of good quality and conforms to WHO recommendations on dosages.

The option of using a non-artemisinin-based first line treatment is being applied in 3 districts in Thailand (tier 1) and is under consideration in Cambodia. The selected medicine is atovaquone-proguanil (AP), which is considered very vulnerable to resistance development through a single point mutation. The use of AP in Thailand seems rational because the reservoir of parasites is becoming small and the correct use of AP monitored (e.g. Direct Observed Treatment), so that the risk of emergence of atovaquone-proguanil resistance is considered negligible. This is not the situation in Myanmar. In some years ahead, if malaria transmission in tier 1 can be significantly reduced with well defined population groups at risk and well documented endemic areas with reduced artemisinin-resistant parasite population such a strategic change could be then considered as appropriate. In the meantime, more will be learnt about Pf resistance to atovaquone-proguanil and about combining AP with other drugs in Cambodia and Thailand.

From a public health perspective, there is no question that case management should be promoted through public health facilities and village health/malaria workers/volunteers and formal private services backed up by performing private or public referral hospitals.

Active case detection (ACD) can play a role in providing a minimum service by somebody visiting and asking about fever cases, for example every fortnight in areas and communities, where there is no fixed service provider. This can be done with many variations; in some situations, there may be little practical difference between ACD and an offer of screening for migrants.

There are discussions about the role of the informal private sector. Compared to functional, comprehensive public health services including a network of fully supported and accessible community-based services, there is no doubt that the unsupervised, profit oriented, uneducated drug vendor is less than a second best. However, establishing a well-performing public sector supported network takes years. Consequently, involving the informal private sector and promoting the use of RDTs is an option that should be explored and piloted. Officially engaging recognized or accredited private providers and private health care facilities is definitely a scenario to be considered and monitored. Ongoing Public-Private

²⁰ Historical data from Thailand has shown that whenever the efficacy of first line treatment for falciparum malaria decreased, the first epidemiological sign was an increase of the falciparum ratio.

²¹ Smithuis F. et al. Effectiveness of five artemisinin combination regimens with or without primaquine in uncomplicated falciparum malaria: an open-label randomised trial. *The Lancet Infectious Diseases*, 2010. www.thelancet.com/infection Published online September 9, 2010 DOI:S1473-3099(10)70187-0

mix strategies have to be documented and properly framed to strengthen the performance of health care delivery systems in Myanmar.

As shown in table 4, advanced containment interventions should include 28-day **follow up of all infected patients**. The yet large number of cases in Myanmar and the limited human resources mean that approach can only be considered at a later stage of the project.

Mass screening and treatment aiming for elimination has proven impractical in Cambodia (see Annex 2). Focused screening in contrast has proven useful at least to elucidate and monitor malaria surveillance at the most peripheral level. This might also be of interest in Myanmar, but rather at a point, where malaria has become less intense than it is now, given that in most parts of the country, about 40% of malaria tests are positive.

Mass drug administration has been used in some countries in the terminal phase of eradication to “mop up” last foci of malaria transmission. The scale of MDA has then usually been limited in a few villages at a time. It is now envisaged as a tool to be piloted to eliminate falciparum resistant malaria from tier 1 in Cambodia and Thailand. The total population in those tier one areas is 380,000 and the parasite rate is around 2%. This is very different from tier 1 in Myanmar where the SPR in fever cases is still much higher than the pre-elimination threshold of 5%. Mass drug administration can therefore not play any role in Myanmar at present, but this could change in the future, if resistance can be delimited to a small human population harbouring a small parasite population. Consequently, in the short term in Myanmar, the goal must be to rapidly increase access to quality diagnosis and quality treatment with ACT and primaquine single dose putting emphasis on compliance.

Enforced ban of mono-therapies

At present, the importation and sale of registered Artesunate Monotherapy (AMT) is legal and widely available through the private sector. Though the goal must be that AMT should be banned, a ban and enforcement of it cannot be deemed ethically sound before access to diagnosis and ACTs has improved. An immediate effective ban could furthermore be counterproductive, because it could lead to a growth in the market for non licensed drugs including fake and sub-standard. The current registration of AMTs will expire in 2012 and no new AMTs will be registered. Once a ban is in place, support must be given to FDA and other competent entities to monitor the availability of AMT in particular and sub-standard/fake drugs in general; advocacy will also be needed to ensure that such a ban is enforced.

Vector control

Vector control is the only intervention, which can reduce parasite biomass without exerting an undesirable selection pressure on the parasite population. According to experience from other Asian countries, a combination of chemotherapeutic and anti-vector measures can reduce malaria burden and transmission to the extent that the disease becomes more focal; this makes it possible to concentrate efforts on adapting strategies to local specifics, making continued, progress possible.

Among vector control options, it is generally thought that the use of insecticide treated nets especially LLINs is the best. However, a main problem is with forest / plantation vectors, which tend to be exophilic limiting the efficacy of IRS and to some extent LLINs/ITNs. Some studies in Myanmar have suggested very little effect of LLINs/ITNs, due to early biting, but this was mainly a problem of *An. sundaicus* in Rakhine State,²² which is an important vector in coastal areas there, but not very important at national level in Myanmar. However, early biting is also often a problem with the more widespread *An. minimus*. Other unpublished studies in forested areas in Myanmar have suggested an

²² Smithuis, F. Malaria in Myanmar. Thesis

effect of LLINs/ITNs on morbidity and mortality.²³ A cluster-randomized trial of conventional ITNs in Cambodian forest villages suggested a reduction of around 30% of malaria incidence and prevalence,²⁴ while an entomological trial of long-lasting insecticidal hammock nets indicated good protection against the bites of *An.minimus*, but much less against *An.dirus*.²⁵ In Vietnam, a community-randomized trial in forest and forest fringe villages found that incidence in villages provided with long lasting insecticidal hammock nets was reduced twice as much as in villages without this intervention.²⁶ Two of the three studies indicate the advantage of hammock nets, but unfortunately in Myanmar, people in general do not use hammocks. The most relevant study may therefore be that published by Sochantha et al. (2006), which suggested about 30% protection of people living in forest villages. This level of protection would not necessarily apply to people, who only stay temporarily in forests, and for whom the essential issue is whether it is worth the effort carrying a net to the sleeping place in the forest. However, it might well apply to plantation workers especially those working during nights (in rubber plantations). There is a lively discussion in Myanmar about the priority which should be given to LLINs/ITNs given the high cost and variable effect. In this it should be considered that LLINs/ITNs has been part of the control package in the countries, which have made most progress in recent years, Cambodia, Laos and Vietnam; ITNs/LLINs have the additional effect of making malaria control visible, palpable and attractive for all involved;²⁷ pervasive promotion of ITNs/LLINs also conveys the message: *Malaria is dangerous and to prevent it, you must avoid mosquito bites.*

The prioritisation between distribution of LLINs and retreatment of conventional nets has been a topic of discussion in Myanmar and elsewhere. A WHO position statement on Insecticide-treated mosquito nets²⁸ strongly recommends distribution of LLIN over treatments of conventional nets. It furthermore recommends full coverage of all people at risk of malaria in areas targeted for malaria prevention with LLINs. However, the position paper does not exclude other approaches that have been successfully developed and implemented in specific contexts. It is recognised that full coverage with LLINs will not be achieved over a short period of time. To reach the best possible coverage with the available resources, supplementing the distribution of LLINs with retreatment of conventional nets can therefore be an option especially in areas where access is not difficult and where net ownership is high.

IRS is currently mostly used for outbreak control. However, in situations, where the effect of ITNs/LLINs is constrained, it is worthwhile considering a combination of IRS and ITNs. This is done in Vietnam, and there is evidence suggesting additive effect from studies in Africa and from models.²⁹ This would be particularly relevant in high priority situations, i.e. among migrants in areas affected by artemisinin resistance. The insecticide malathion usually runs into rejection by the target populations because of the horrible smell. In practice, this leaves synthetic pyrethroid as the only (inexpensive) option; this reality further

²³ Yadav, R. Insecticide Treated Nets for Control of Malaria in South-East Asia. WHO, SEARO, 2005

²⁴ Sochantha T. et al.: Insecticide-treated bednets for the prevention of Plasmodium falciparum malaria in Cambodia: a cluster-randomized trial. *Trop Med Inter Health* 2006,11(8):1166-1177.

²⁵ Sochantha T, et al. Personal protection by long-lasting insecticidal hammocks against the bites of forest malaria vectors. *Trop Med Inter Health* 2010,15(3):336-341.

²⁶ Thang ND, et al. Long-Lasting Insecticidal Hammocks for Controlling Forest Malaria: A Community-Based Trial in a Rural Area of Central Vietnam. *PLoS ONE* 2009,4 (10):e7369.

²⁷ Ettlting, M. Malaria in Vietnam – what went right. WHO/WPRO Unpublished, 2002.

www.wpro.who.int/malaria

²⁸ Insecticide-treated mosquito nets <http://www.who.int/malaria/publications/atoz/itnspospaperfinal.pdf>

²⁹ Chitnis et al. Comparing the Effectiveness of Malaria Vector-Control Interventions Through a Mathematical Model. *Am. J. Trop. Med. Hyg.*, 83(2), 2010, pp. 230–240

strengthens the case for insecticide resistance monitoring, as ITNs/LLINs are also impregnated with synthetic pyrethroids which are largely used in agriculture as well.

Personal protection by repellents has been neglected for too long. For rubber plantation workers, who start work before dawn, it may be the best option. For those who stay overnight in forests or are exposed, when they approach breeding sites to wash etc., it may also be the case. The Thai programme uses repellents on a large scale, seemingly with little supportive evidence. They provide migrants with 3 kits to last for 21 days at a cost of USD 0.45 per person. Protection for 6 months would therefore cost USD 3.6. Thus, this method is more costly than any form of ITN. Undoubtedly, the effectiveness should be expected to be present in some scenarios and not others. In some situations, repellents alone may prove to be the best option, in others they could be combined with ITNs.³⁰

Other options, which are being discussed for personal or small scale community protection, include impregnated uniforms and scarves for soldiers and impregnated curtains or blankets in video parlours and similar places.

Targeting migrants

Few activities have previously explicitly focused on migrant/mobile populations. As outlined in table 4, containment must include activities specifically targeting migrants/mobile populations to provide adequate case management as well as ensuring appropriate vector control/personal protection. The number of internal migrants in Myanmar is very high as a large number of people mainly from the central parts of Myanmar migrate for work especially in the eastern States/Regions.

Screening of migrants is a logical strategy for preventing people from acting as vectors. There are however few examples of such systems being effective except in the case of highly organized groups crossing international borders. Some countries, which have eliminated malaria, but are still receptive, screen organized groups of people from endemic countries, but have not been able to institute such screening for tourists and other individual travellers. Nonetheless, such schemes should be piloted and could be set up in collaboration with employers and screening coupled with IEC/BCC can be offered as a free service, where migrants congregate, especially at places, where they may need to wait for transport etc. Screening focused on high risk groups such as migrants can furthermore help raise the general awareness of the risk of malaria and the availability of diagnosis and treatment. Recent experience from Thailand indicates that it is essential that screening is voluntary.

Supporting activities

Containment entails concerted efforts and a high number of activities in a focused area. This means that there is an even stronger need for coordination, monitoring and evaluation to support high quality rapid implementation of the containment project. In addition, there is an urgent need to increase our understanding both on the precise spread of artemisinin resistant parasites and the best way to tackle it. This requires additional studies and operational research.

Section 5 describes the specific objectives of the containment project in eastern Myanmar. They follow naturally from the discussion above. These objectives are consequently close to those set in the ongoing Cambodian-Thailand containment project though due to the different context and scale there are naturally differences in main activities.

³⁰ Prakash, et al. Malaria control in a forest camp in an oil exploration area of Upper Assam. *Natl Med J India*. 2003, **16**:135-8

5. The goals and objectives of containment in Myanmar

The **overarching goal of malaria control in Myanmar is to reduce malaria mortality and morbidity** (MDG6). The aim of the containment project is to build on and strengthen existing control efforts **to prevent, or at minimum, significantly delay the spread of artemisinin resistant parasites within the country and beyond its borders**. This implies intensification of present activities and an expansion of specific interventions also to pay more attention to migrants and mobile populations, set up extra sentinel sites to monitor efficacy of antimalarial medicines, increasing advocacy to engage local authorities and relevant stakeholders, engaging the private sector and bridging interventions with neighbouring countries.

The seven specific objectives listed below thus include activities that are a part of malaria control and some additional activities that must be initiated as part of containment project.

Project goal: To prevent or at minimum significantly delay the spread of artemisinin resistant parasites within the country and beyond its borders

To reduce transmission, morbidity and mortality of *Plasmodium falciparum* malaria, with priority to areas threatened by artemisinin resistance

Project specific objectives:

- 1- To improve access to and use of early diagnosis and quality treatment according to the national treatment guidelines
- 2- To decrease drug pressure for selection of artemisinin resistant malaria parasites by stopping the use of artemisinin mono-therapies and sub-standard/fake drugs
- 3- To limit the transmission of malaria by vector control and personal protection
- 4- To increase migrant/mobile populations' access to and use of malaria diagnosis, treatment and vector control measures including personal protection
- 5- To support containment of artemisinin resistant parasites through advocacy and BCC/IEC
- 6- To conduct studies, especially operational research to support the development of evidence-based containment policies and strategies
- 7- To provide effective management and coordination to enable rapid and

Below is a description of main activities under each objective. In addition, key indicators and critical milestones measuring the progress towards the objective are given. More details on measurement of the indicators can be found in section 7.

5.1 Description of activities under each specific objective

Objective 1: Improving access to and use of early diagnosis and quality treatment according to the national treatment guidelines

Objective 1 seeks to expand the access to and use of services in targeted areas. By increasing coverage of services offering diagnosis and treatment (and through the support of BCC), it is expected that it will be possible to progressively crowd out the use of quacks and self-treatment. Though the quality of microscopic diagnosis will be strengthened, the expanded services will mainly rely on polyvalent RDTs. Treatment of P.f. will be co-formulated, quality assured ACT (presently, artemether-lumefantrine³¹ in public sector) along with one single dose primaquine (45mg for adults). Including primaquine in combination with ACT will clear mature gametocytes from the blood faster contributing to a reduction of transmission. The risk of haemolysis in patients with G6PD deficiency must be taken into account but is considered minimal in Myanmar with the use of a single dose of primaquine.

Depending on access and capabilities, in some areas it will be beneficial to work mainly through the government health service while in other areas, local or international NGOs and CBOs may do a significant part of the project implementation. The efforts done to improve access should to the extent possible build on past and existing work to strengthen health systems in Myanmar e.g. through the GAVI, EPI and existing volunteers.

Main activities:

- 1.1 Improve access to and use of performing health care facilities.** Additional health clinics can be established in remote areas, but the main activity will be improvement of quality of services and continuity of supplies in the existing health facilities. An estimated 70% of the population have geographical³² access to these health facilities.
- 1.2 Expansion of the use of village health volunteers.** This channel is vital for securing better access. In tier 1, the norm will be one volunteer per village, though with priority to villages located more than 5 km or 1 hour walk from a performing health care facility; however, in the case of villages with small populations, it will be more rational to deploy one volunteer per 2-3 villages, if located close together. In tier 2, only villages farther than 5km or 1 hour walk from a health facility will normally be supported for a malaria curative service. In targeted villages, the strategy is to post volunteers giving diagnosis by RDT and treatment free of charge in addition to basic health education. At present, it is estimated that in tier 1, at least 30% of the villages can be defined as “hard to reach” but these numbers need to be further consolidated through a baseline survey and cross-checked information. When deciding where to place a volunteer, geographical access is important but other aspects that can act as a barrier, such as language differences, should also be considered. If a village already has a health volunteer this person will be the malaria volunteer, and it is always the aim to develop integrated health services.

In the TOR for the volunteers will be screening patients with fever/malaria symptoms using combo RDTs³³, treating with ACTs+Primaquine/ chloroquine and referring patients

³¹ However, at a later stage it may be pertinent to consider the possibility of introducing a multiple first line treatment policy in the country with different ACTs deployed to different areas.

³² Maximum one hour walking distance or 5km distance as per WHO guidelines

³³ http://www.wpro.who.int/sites/rdt/who_rdt_evaluation/

with non-malaria fever or severe symptoms to nearest health facility. Management and supervision of volunteer networks is essential to increase and maintain performance. This is done in various ways by the many organizations (VBDC, IOM, UNICEF and NGOs) which are scaling up this approach through CBA. Though it is not possible to define one management system that will be functional across all partners it is crucial that the reporting lines and supervision responsibilities are clearly defined and agreed upon. A supervisor should normally meet with all volunteers in his or her area once a month and visit each one at least every second month which could be very challenging in remote areas. The government volunteers will ideally be supervised by BHS but these must be supported by VBDC/township staff that equipped with motorcycles can be supervisors (TORs to be finalized) and responsible for re-supplying and reporting from volunteers that cannot easily be monitored by the BHS. Though volunteers working as part of the public sector cannot received official salary, incentives and "in-kind" prizes should be given to well-performing volunteers for example based on the number of diagnostic tests done and quality treatment and reporting. It should be ensured that they provide diagnosis and treatment for malaria, which is free (normally) or so inexpensive that their services are more attractive than those provided through the private sector.

1.3 Improve case management through private medical practitioners.

There are good experiences in Myanmar for engaging private medical practitioners for quality case management. Their reach among high risk populations may be limited, but they may also play a role as role models and possibly as trainers. There is a need to map and do a situation analysis to form a strategy on how best to engage and use the role of private practitioners. Ideally, there should be a concerted strategy on the engagement of private practitioner among partners. Currently, PSI and MMA are main partners working with private practitioners.

1.4 Improvement of storage facilities and support to transportation of drugs and RDTs. As part of the preparation for Global Fund, work will commence on improving and supporting the storage facilities at national and state³⁴ level. Additionally, support should be given in ways of improving the storage facilities at township level. A situation analysis for the capacity of storage at less than 30 degrees Celsius must be undertaken to estimate the needs. Additionally, cooling boxes should be procured for the health facilities and for the volunteers³⁵.

Supporting activities:

Supportive supervision and monitoring is crucial and will be described in more details under objective 7 and in chapter 7. Additionally, **Behavior change communication** must also be an integrated part of the strategy and is described separately under objective 5. Ensuring that not only the population permanently residing in the targeted areas but also the **migrant/mobile population** benefits from the improved access is essential to the containment strategy and is described under a separate objective (4).

Indicators of success and critical milestones:

1.1. *Percentage of persons with a history of fever in the last two weeks that have been tested for malaria (RDT or Microscopy)*

The target is that in 2015, 90% of fever cases are tested for malaria.

³⁴ At present, the plan is to renovate the VBDC warehouse in Yangon and build new storage facility in Tanintharyi and Northern Shan

³⁵ L. Chanthap et al (2010). Low-technology cooling box for storage of malaria RDTs and other medical supplies in remote areas. *Malaria Journal* 2010, 9:31

1.2. Percentage of villages that are within one hour walk of a functioning health facility or a trained volunteer delivering diagnosis and treatment.

A key output of the first year of operations would be better information making planning and targeting easier. The aim is that by 2015, 90% of villages are within one hour walk of a functioning health facility or a trained volunteer delivering quality diagnosis and treatment.

1.3. Percentage of confirmed P.f cases treated with ACT plus primaquine in accordance with national treatment guideline

Primaquine are being introduced as treatment together with ACTs to reduce the number of gametocytes carriers and thereby reduce transmission. The aim is by 2012, 100% of treatments for confirmed P.f. are ACT plus primaquine.

1.4. Percentage of confirmed malaria cases treated in accordance with national malaria treatment guidelines within 24 hours of onset of symptoms

Presently around 15% of confirmed cases are treated within 24 hours of onset of symptoms. The aim is that in 2015, in the areas targeted for containment, 75% are treated within 24 hours

1.5. Number of RDTs taken and read

1.6. Number of people with malaria (by gender and age group) treated with recommended ACT

1.7. Number of volunteers trained and supported

Objective 2: To decrease drug pressure for selection of artemisinin resistant malaria parasites by stopping the use of Artesunate Monotherapies and sub-standard/fake drugs

Presently, Artesunate mono-therapies are widely available through private channels. The private sector needs to be engaged through a comprehensive strategy aiming both at addressing objective 1 (increasing access to diagnosis and quality treatment) and objective 2 of reducing drug pressure.

The production, importation and sale of mono-therapies should be banned though doing so before adequate amounts of ACTs are available would not be advisable.

Main activities:

2.1 Ensuring that affordable quality-assured ACTs are available through the private sector

in combination with diagnostics A high proportion of patients seek treatment through the private sector and unfortunately most of these patients access almost exclusively artesunate mono-therapies or sub-standard/fake drugs. It is therefore important to promote the use of quality assured ACTs in the private sector given on the basis of a diagnosis confirmed by RDT or Microscopy. To safely stop the use of oral artemisinin based monotherapy for most suspected malaria, as a first step, oral artemisinin based monotherapy will be replaced in the private sector market channel with an approved ACT (FDC) + primaquine regimen subsidized to be affordable to malaria patients in remote areas. This will be supported by communication of the need for specific diagnosis, treatment and adherence to a full course of ACT plus primaquine, in order to discourage treatment based on only clinical signs. Quality-assured, affordable RDTs will be promoted at the lowest possible level of the private sector supply chain, in support of public, community-based and private services.

It is emphasized that while the provision of improved malaria diagnosis and treatment through the informal private sector is a necessary early measure to eliminate monotherapy, effective control and resistance containment should, in the long term, rely on public sector and community-based services.

2.2 Banning the sale of oral AMTs and strengthen the regulatory capacity, action and enforcement of the ban. According to the investigation summarized in Annex 5, the informal sector currently sells about 2.4 million packages of 12 artesunate tablets per year, which are used by 10 million persons, of whom up to 40% might have malaria. Though a ban on oral monotherapy should in principle be introduced and enforced as soon as possible, the given situation of the private market means that there is a risk that an immediate, effective ban could lead to an influx of all kinds of counterfeits or substandard antimalarials. The FDA does not intend to renew the licences for importation or production of artesunate monotherapy. These will expire in 2012. Any ban must be followed up by regulatory actions and law enforcement (inspections and action) by the local authorities. **Monitoring of the quality of antimalarial medicines, available in public and private facilities including the informal private sector.** Support must be given to the Food and Drug Administration which is in charge of national regulatory procedures and registration of medicines and laboratory equipments for supplies, supervision visits, training and regular reporting followed by action. Additional mini-labs are needed for field screening of drug quality so that only few drug samples have to be sent to the central level to be further tested / cross-checked through more sophisticated methods³⁶.

Supporting activities:

In addition to the activities described above it will also be important to do **advocacy towards retailers, improve training of and corporation with private practitioners and conduct BCC** to inform patients on the risk of ATMs to reduce demand.

Indicators of success and critical milestones:

2.1. Percentage of private drug outlets selling AMTs

The aim is that by 2015, no more private drug outlets are found to sell AMTs

2.2. Percentage of sampled antimalarial drugs that are fake or sub-standard

The aim is that by 2015 less than 5% of the sampled antimalarial medicines are fake or of sub-standard quality

2.3. Number of drug inspections carried out and reported by local authorities/FDA in target areas

From 2012, the aim is annually to carry out 1 drug inspection per township

Objective 3: To limit the transmission of malaria by mosquito control and personal protection

Vector control in general and use of suitable personal protection measures in particular are important interventions of the containment strategy as per the GPARC guideline. The aim must be to achieve the highest possible ownership and use of insecticide-treated nets by people at risk.

³⁶ S Phanouvong et al. (2010) Strengthening National Capacity in Medicine Quality: Five-year Summary (2005-2009). <http://www.usp.org/worldwide/dqi/resources/technicalReports.html>.

Presently, it is estimated that approximately 75% of the population are living in areas with malaria transmission (high, moderate or low risk). Essential to the effectiveness of vector protection measures is effective targeting including high risk populations.

The main group of people at risk is those working in forests and plantations (outside villages) for short or longer periods of time. Providing them with adequate personal protection has always been a challenge. A review of experience gained in neighboring countries and defining operational research needs are necessary to find the best way of protecting those mobile people in forest or plantations or on their move.

Main activities:

- 3.1 Treating bed nets already owned by the community with insecticides.** At present, the coverage of LLINs/ITNs nationwide is below 10% in the eligible populations. The aim under the containment project is ensure that each household in villages or areas classified as high, moderate and low risk own a minimum of two LLINs/ITNs.
- 3.2 Distribution of LLINs.** In addition to the impregnation of existing bed nets, LLINs will be distributed.
- 3.3 Increase the use of other personal protection.** VBDC will carefully review experiences in use of other personal protection in Myanmar and other countries in the Mekong region. This will lead to the development of a strategy on the identification and scale up of suitable personal protection measures and the development of a strategic research agenda (see objective 6).
- 3.4 Increasing the use of Indoor Residual Spraying (IRS).** IRS, especially in combination with LLINs/ITNs, is expected to be useful in areas where people, especially migrants, sleep in rooms with sprayable walls. The most critical sub-areas in Tier 1 will need to be assessed for rational planning and use of IRS. If intensive activities are planned in tier 1, priority should be given to villages or private companies experiencing high number of migrants infected for *P. falciparum*. The effectiveness should be evaluated through operational research, e.g. in conjunction with selective spraying. IRS is also used during the initial phase of malaria epidemics to reduce transmission and limit the extension of the disease. The choice of insecticide is not easy: As LLINs/ITNs depend on pyrethroids, this class of insecticide should be avoided for IRS so as to diminish the risk of development of pyrethroid resistance. However, most alternative insecticides are considered less acceptable to the population and/or are more expensive. There is an urgent need for initiating monitoring of insecticide resistance, especially where IRS will be implemented on a large scale, and to identify the most suitable non-pyrethroid insecticide for IRS, at least for the long term.

Supporting activities:

As always, distribution and treatment of nets with will be combined with **Behavior Change Communication** to ensure that importance of using LLINs/ITNs is widely understood in particular by the most at risk population (migrants). Additionally, it is essential to invest again in **micro-stratification**.

Indicators of success and critical milestones:

3.1. Percentage of households with at least one ITN/LLIN per two inhabitants

The aim is by 2013 in tier 1, 100% of households in malaria risk areas owns at least one ITN/LLIN per two inhabitants

- 3.2. *Percentage of population at risk sleeping under an ITN/LLIN the previous night*
The aim is by 2013 in tier 1, 90% of the population at risk are sleeping under an ITN/LLIN the previous night
- 3.3. *Percentage of population protected through (i) other personal protection measures (not LLIN/ITN) (ii) IRS*
The aim is that from 2013, 10% of the population is protected through other personal protection measures
- 3.4. *Number of LLINs distributed (i) total population and (ii) migrant/mobile population*
- 3.5. *Number of nets treated/retreated with (i) regular insecticide treatment or (ii) long lasting insecticide treatment*

Objective 4: To increase migrant/mobile populations' access to and use of malaria diagnosis, treatment and vector control measures including personal protection

This separate objective has been formulated to ensure that sufficient focus is placed on reaching and covering migrant/mobile populations. The reasoning behind the special attention paid to migrant/mobile populations is that they are more likely than other groups to carry and spread resistant parasites. Moreover, these populations often live in border regions with high malaria transmission and they have limited access to malaria prevention, diagnostics and quality-assured ACTs. Migrant populations are probably more likely to seek care from any private vendors and are thus more often exposed to use of AMTs, substandard or even counterfeit medicines. Their mobility makes them difficult to reach them, using standard health interventions, they are more difficult to monitor, and ultimately they are more likely to spread parasite resistant strains into new areas. Currently, only very few activities are explicitly targeting mobile/migrant populations. In Thailand, IOM with MOH has developed an innovative Migrant Health Programme Model of great interest in the region and in Myanmar³⁷.

Mobile and migrant populations are very heterogeneous groups. In the containment areas they encompass both migrants coming from different States/Divisions (mostly internal migrations) to work on plantation or in mining; they also include seasonal migrants and those only moving for a few days or weeks to work in the forest.

Main activities:

- 4.1 Mapping migrants and developing townships plans for targeting migrants/mobile population.** The information on the location and type of migrants present in every township is limited, making targeting and planning difficult. Therefore, a key output the first year of activities would be a detailed mapping of the migrant / mobile population in each township and the access they have to diagnosis, treatment and prevention. This will be prioritized initially for tier 1. The methodology for this has yet to be developed together with key partners.
- 4.2 Improve migrants/ mobile populations' access to diagnosis and treatment through health care facilities and volunteers.** Based on information collected, a plan will be developed for each township to reach migrants through outreach activities in specific locations of interest (markets), mobile clinics, additional (migrant) volunteers (who may be recruited from among migrant groups), ACD (screening) targeting migrants and other relevant channels to be explored.

³⁷ IOM & MOPH Thailand (2009). Healthy Migrants, Healthy Thailand: A Migrant Health Programme Model, IOM – MOPH Thailand, ISBN 978-92-9068-551-7

4.3 Strengthening of malaria prevention and treatment through work-site. For organized groups such as plantation workers it will be important to work with the employers to set up agreed upon system that ensures that all workers have access and are actually using LLINs/ITNs and knowledge on where to get tested and treated for malaria. Advocacy towards employers / private company owners is an important part of the containment strategy (part of objective 6).

4.4 Targeted screening of migrants. Screening of mobile/migrant populations could be arranged by setting up a malaria stand offering voluntary malaria control and diagnosis at for instance private companies, bus-stations, ports and at official border crossings.

Supporting activities:

To **incorporate targeting of migrants into all training activities** and to do **operational research** in the best ways to ensure that also migrant/mobile populations have access to quality diagnosis and treatment and are covered by vector control measures. Additionally, **BCC activities targeting migrants** through culturally appropriate messages and methods must be designed at national level for mass media and at township level to encourage use of local curative and preventive services.

Indicators of success and critical milestones:

4.1. *Number of township where mapping of migrant/mobile populations have been completed/updated*

The aim is in the first year of operation to map migrants Tanintharyi, Mon, Shwe Kyin, Kayin and Kayah.

4.2. *Number of people tested through a) tested at worksite, b)tested at malaria screening points, c) Others*

4.3. *Number of volunteers trained specifically for serving migrants/mobile populations*
The aim is that minimum 10% of the volunteers trained should be trained and supervised specifically for targeting migrant/mobile populations

4.4. *Percentage of migrants/mobile people sleeping under an ITN/LLIN*

Objective 5: Support to containment of artemisinin resistant parasites through advocacy and BCC

The aim of objective 5 is through advocacy and behavior change communication to accelerate the implementation of the objective 1-4. The strategy for BCC and advocacy must be consolidated across activities, areas and partners.

Main activities:

5.1 Advocacy

- **Toward local authorities** to ensure support for the containment effort
- **Towards related departments**
- **Towards retailers** to inform them on the risk of AMTs, the importance of compliance and how emergence of resistance would affect patient outcomes.
- **Toward companies and private owners**, especially those companies employing migrants to ensure they access needed “culturally adjusted”

information and understand the importance of malaria prevention and control and understand how they can contribute.

5.2 Behavior Change Communication is not seen as a separate component but an integral part of all health interventions. It serves both to improve use of the available health services offering quality diagnostics and ACT, to reduce the demand for AMT in the private sector and to improve adherence to the 3-day ACT regimen. For preventive activities it will help increase the use of LLINs/ITNs. The main component of BCC is inter-personal or peer communication, but it will be necessary to use a variety of channels, including mass media. Collaboration with various sectors, especially transport companies (malaria messages through loudspeakers of bus stations and buses etc.) will be explored. Formative research, involvement of advertising professionals and dialogue with other sectors will allow the development of strategies for reaching various mobile groups. A specific BCC component to be designed targeting the private sector needs to be coordinated with other BCC activities, especially to make sure that messages are perfectly consistent. Overall there needs to be developed a BCC strategy. Part of the development of this is to gather information on the BCC used targeting migrants in neighbouring counties and ensure that the messages are not contradictory.

Indicators of success and critical milestones:

5.1. Percentage of private drug sellers aware of drug policy

The aim is that by 2013, 90% of sampled drug sellers are aware of key components of the drug policy (use of diagnostics and ACTs and importance of compliance)

5.2. Percentage of respondents that is aware of key messages (to be clearly defined under BCC).

The aim is that by 2013, 90% of the respondents are aware of key messages.

5.3. Number of advocacy meetings held

Objective 6: To conduct studies and do operational research to support the development of evidence-based containment policies and strategies

The purpose of objective 6 is to ensure that implementation of the previous objectives is evidence based. Therapeutic Efficacy Studies (TES) and setting up sentinel sites looking at day 3 parasitemia will show the geographical extent of the problem while strategic operational research will help fine tune strategies and guide implementation approaches. An agenda listing operational research priorities will be developed at a workshop in March/April 2011.

Main activities:

6.1 In vivo Therapeutic Efficacy Studies (TES). There are a total of nine sites where TES are currently carried out. To adequately map the resistance in Myanmar there can be a need to do additional TES (described in chapter 8).

6.2 Sentinel sites for monitoring parasitaemia on Day 3. In addition to the TES, sentinel sites will be set on to monitor the proportion of patients still positive for P falciparum infection on Day 3 (after 72-hour on-set treatment) (described in chapter 8).

6.3 Operational research. There are in number of areas where additional operational research is needed to inform the strategies and policies for containment. A tentative list of topics that should be considered is included in chapter 8. Particular attention must be given to studies looking at suitable personal protection measures.

Indicators of success and critical milestones:

- 6.1. *Number of TES completed to define artemisinin resistance in Myanmar*
- 6.2. *Number of functional Day 3 parasitaemia sentinel sites*
- 6.3. *Number of operational research done in line with the research agenda*
- 6.4. *Number of operational research that has contributed to refinement of containment policy/strategy*

Objective 7: To provide effective management and coordination to enable rapid and high quality implementation of the containment strategy

This objective focuses on the structures needed to carry out the project successfully. This includes monitoring and evaluation, surveillance, management, human resources, logistics and infrastructure.

As compared to both previous malaria control activities in Myanmar and to malaria activities planned under Global Fund Round 9, the containment project has a greater reliance on precise geographical and epidemiological information and must aim at higher levels of intervention coverage and higher penetration of activities to hard-to-reach populations.

The first year of operation will focus on the collection of baseline information / assessment of needs and on the strengthening of the surveillance system, conducting additional monitoring and evaluation, surveys and ensure proper supervision. The activities that are part of this are merely mentioned in the section below but are described in more details in the section on Surveillance, Monitoring and Evaluation (Section 7). A project of this magnitude should not be thought of in isolation but should ideally be put in a context of general health system strengthening (HSS). The baseline assessment will be inspired by current information and formats developed for GAVI which is expected to start in 2011.

The success of the project will definitely rely on sufficient skilled and motivated human resources at decisional and operational levels. An outline of the needed human resources is in chapter 11. Strong coordination will be needed in planning as well as in implementation phases. The suggested mechanism for this is described in chapter 9.

Main activities:

- 7.1 Strengthening the routine surveillance system.** Provided that information systems and data quality assurance are implemented in tandem, strengthened case management as described above will by itself lead to progressively improved malaria surveillance as a much larger proportion of suspected cases are confirmed. There is a need for recruiting more staff at national level to strengthen the data management as well as quality assurance of surveillance. The required actions are described in detail in *(Draft) Monitoring - Evaluation Plan Malaria Prevention & Control, Union of Myanmar 2010-2015*, prepared the VBDC in collaboration with WHO.
- 7.2 Monitoring and Evaluation.** The Monitoring and evaluation is described in more details in the chapter 7. It will encompass the following activities:
 - **Continued monitoring of activities in the field** by staff located and central, divisional and township level

- **Strengthening of M&E capabilities at central and State level** through hiring additional staff and training. Survey tools have to be designed and agreed and implemented with trained staff. Data management is a crucial component to be seriously considered in order to get data collected, computerized, screened and analyzed in a timely basis.
- **External evaluation of the project after two years** to ensure that the project performs as intended and make necessary adaptations for later stages.
- **Household and health facility surveys:** Existing protocols have to be fine tuned with necessary training and supervision
- **Survey of private drug vendors**
- **Expanded Micro-stratification with prevalence/MIS+** of targeted townships. This will require training and supervision of township staff and collaboration and support of the NGOs and other organizations supporting malaria control in various areas.

7.3 Supportive supervision

- **Additional support and training of Township staff and BHS.** To ensure that supervision is of the quality needed, additional training will be warranted. Travel even within townships can be expensive. An option is to procure motorbikes and support fuel cost for staff at township level. Additionally, travel cost for BHS visiting volunteers working more than one hour travel from their duty stations should be included.
- **Support to supervision of State/regional and central level staff.** Regular supervision using appropriate reporting forms throughout the project will be needed.

7.4 Strong partner coordination. A strong focused effort in targeted areas requires stronger coordination and information sharing than the present activities. Management of the project will be described in chapter 9.

7.5 Improved Supply Chain Management to ensure that RDT and ACT and other commodities are where needed when they are needed and have not been damaged by for instance long exposure to unusual high temperatures.

7.6 Continued strong cross border corporation. As much resistance in the region has occurred in the less accessible regions along country borders, regional network and information sharing across countries are crucial. The “*in vivo* Mekong therapeutic efficacy network” has 32 active sentinel sites in six countries in the Greater Mekong Sub-region with corporation being coordinated by WHO Mekong Malaria Programme located in Bangkok³⁸. It is important that Myanmar participate in regional and international meetings on containment, case management and prevention especially in connection with on-going and planned containment activities in the western provinces of Thailand bordering Myanmar (GFATM R10).

7.7 Strengthen human resources at all levels for management and implementation including adequate staffing and training. The HR of the national programme needs to be strengthened primarily through training and capacity building. Additional HR are also

²⁶ WHO (2010) Workshop to review and plan therapeutic efficacy studies to monitor *P. falciparum* and *P. vivax* resistance to anti-malarial drugs in the Greater Mekong Sub-region, Mandalay, Union of Myanmar, September 30 - October 2, 2009 SEA-MAL 263
http://www.whothailand.org/EN/Section3/Section113_269.htm

needed to support, manage and monitor the project. This is described in more details in chapter 11.

7.8 Provide support for essential operation expenses including transportation and infrastructure

Indicators of success and critical milestones:

7.1. Routine data from the containment areas consolidated and shared between all partners quarterly (Functional surveillance system in place in containment tiers)

The aim is that from 2012 data from a minimum of 80% of health facilities and volunteers has been encoded and analysed

7.2. Surveys carried out as planned, and results are analyzed and disseminated within 6 months from the end of fieldwork

7.3. Number of quarterly reviews of any new surveillance data and new survey finding at MARC Task Force and/or TSG meeting

7.4. Percentage of VBDC positions filled at each operational level relative to plan in containment tiers

6. Zonation

Based on available data and results from in vivo therapeutic efficacy studies of ACTs, tiers have been geographically defined in accordance with WHO's latest recommendations (Annex 1). Extra attention and effort will firstly focus on tier 1 where there is credible evidence of artemisinin resistance and secondly in bordering areas (tier 2) with yet unclear evidence, but close to areas with suspected resistance in Myanmar and Thailand. Additionally, the surveillance system and monitoring should be strengthened in the rest of the country (tier 3)

The proposed zonation in Myanmar can be seen in the table below. More details with names and population of the targeted townships can be seen in annex 8.

Table 5 - Zonation for resistance containment operations in Myanmar according to the three-tier classification of GPARC based on in vivo TES data available

<i>Tier</i>	<i>Area</i>	<i>No. of townships</i>	<i>Justification</i>
1	Tanintharyi Region: All 10 townships Mon State: All 10 townships Bago East: Shwegyin township (East Bago Region)	21	Strong evidence of suspected resistance. Widespread ecological and social risk factors. Intensive population movement. Ongoing big development projects
2	Kayin State: All 7 townships Kayah State: All 7 townships Bago East: Remaining 13 townships Kachin State: 4 townships	31	Unclear evidence of suspected resistance; Very near suspected resistance areas in Myanmar, Thailand and China
3	Rest of the country		

This zonation is based on the available information and is neither perfect nor can it be static. It has been updated based on the preliminary data of in vivo TES studies in 2010 and may have to be updated again once the final PCR corrected results are available. The preliminary data from 2010 showed a very high Day 3 parasitaemia (24%) from the study in Mon state. For this reason, Mon State has been included in tier 1. The preliminary result of the study in Kayin State did not actually show the same high day 3 parasitaemia. That southern Kayin have nevertheless been included in tier 1 is partly due to the proximity to the Mon study site and partly due to the fact that Mae Sot in the neighbouring Tak province in Thailand has become a hot spot for artemisinin resistant P.f. malaria. Containment efforts on the Thai side of the border will be covered under Global Fund Round 10 (annex 3) but as there is significant cross-border movements the situation on the Myanmar side of the border can not be ignored.

There is substantial evidence of resistance along the southern part of Thai-Myanmar border. The status in terms of resistance further north along the Myanmar-Chinese border is more unclear. One study in 2009 done by Chinese scientist on the Chinese border to the southern part of Kachin State with AS7 monotherapy, showed high day 3 positivity rate (25%). However, preliminary results from the 2010 studies with DHA-PIP from both Kachin (Myitkyina) and the Chinese side of the border show a therapeutic efficacy rate above 90% and a day3 positivity rate much less than 10% (yet to be confirmed). An AS7 monotherapy study is expected to start in Menglian, further to the south bordering Myanmar, in March 2011. Until there is more clarity on the situation, it has been decided to include also the southern part of Kachin in the targeted areas.

The preliminary results from an on-going study in Eastern Shan do not raise cause for concern nor has there been found any evidence of suspected resistance in the provinces bordering Shan states. Consequently, Shan States have not been included in the targeted areas.

Table 6 compares the sizes of tiers 1 and 2 in Cambodia and Myanmar, indicating how much greater the challenge is in the latter, already in terms of populations.

Table 6 – Comparison of populations of tiers 1 and 2 in Cambodia and Myanmar

	CAMBODIA	MYANMAR proposed in MARC
Zone 1	0.27 million (in 4 provinces)	4.8 million
Zone 2	4.02 million (9 provinces, excluding town areas)	6.0 million
Total	4.29 million (10 provinces)	10.8 million

Figure 8 - Maps of townships in tiers 1, 2 and 3



The proposed above zonation provides a basis for prioritization of interventions which are presented in the table below.

Table 7 - Proposed containment interventions by tier in Myanmar from 2011 onwards

Tier	2011	2012	2013
1	<ul style="list-style-type: none"> • Collection of baseline information • Strengthening the malaria surveillance system • Set up of day3 sentinel sites • improve access to diagnosis and treatment (resident & migrant population) • Pilot screening and treatment of migrants • Increasing coverage of population protected by ITN/LLIN • Engaging actors from the private sector to provide quality diagnosis and treatment • Strengthening supply chain management including good condition storage 	<ul style="list-style-type: none"> • Expansion of 2011 interventions and fine-tuning according to results from baseline surveys and 2011 achievements • Increasing the coverage of population through other personal protection based on results from operational research 	<ul style="list-style-type: none"> • Consolidation and re-orientation of interventions as needed • Focal screening and treatment depending on (a) performance of surveillance system especially day3 surveillance, (b) lessons from experiences in CAM &THA; (c) operational feasibility • Real-time endemicity mapping from surveillance data at village level
2	<ul style="list-style-type: none"> • C • Collection of baseline information • Strengthening the malaria surveillance system • Set up of day3 sentinel sites 	<ul style="list-style-type: none"> • Improve access to diagnosis and treatment (resident & migrant population) • Screening and treatment of migrants • Increasing coverage of population protected by ITN/LLIN and other protective measures • Engaging actors from the private sector to provide quality diagnosis and treatment • Strengthening supply chain management including good condition storage 	<ul style="list-style-type: none"> • Scaling up and fine-tune 2012 interventions according to survey results and surveillance data
3	<ul style="list-style-type: none"> • Set up of day3 sentinel sites Scale up and strengthen malaria control as planned under GFATM Round 9 		
Nation wide	<ul style="list-style-type: none"> • Consolidation of partners' involvement (data/info sharing consolidation and set up of common planning and M&E Surveillance mechanisms) • Strengthen cross-border operations, exchange of information and coordinated actions • Do operational research in accordance with an agreed research agenda • Engaging private sector into good practices in quality diagnosis and treatment • Artemisinin monotherapy effectively banned (2012) 		

Intensive control interventions will be quickly set up in tier 1 and progressively in tier 2 with additional containment interventions. Additional advanced “specific containment interventions” will focus on high demanding day3 surveillance through sentinel sites which include a strong QA microscopy system, setting up a performing volunteers’ network expected to deliver quality diagnosis and treatment backed up by strong management, supervision and monitoring at Township and State levels and extra routine attention to migrants and mobile population. Epidemiological tier 1 and 2 are quite similar. In both tiers there is a widespread high transmission and there is a high number of migrant/mobile

populations. As tier 1 is the areas where the clearest evidence of resistance, the choice is, to the extent possible, to focus the efforts on collecting information and scaling up activities in tier 1 first. Implementation activities can be started in tier 2 the first year with all partners involved as long as it does not divert human and financial resources away from implementation in tier 1.

The most urgent action is to improve the baseline information (see section 7) and support the functioning of a MARC task force working on the coordination and planning and monitoring and reporting (see section 9) with clear agreed upon TORs and nomination of active technical / implementation members. The baseline information will both aim at providing epidemiological data and basic information on HR gaps by operational level as well as on managerial capacity by level of care, gaps on equipments and supplies including supply management issues, managerial gaps at State, township and HCF levels, basic Health Systems issues, gaps in M&E and surveillance including data management, survey method and consolidated reporting, etc.

7. Surveillance, Monitoring and evaluation

As part of the containment project there is an urgent need to strengthen the surveillance, monitoring and evaluation. The lack of good baseline data makes this one of the top priorities in the first year of operation.

The National Monitoring and Evaluation Plan (draft) 2010-2015 includes indicators, procedures and formats for data collection, aggregation, analysis, storage, reporting and feed-back; standards, formats, check-lists for supervision and procedures for a programme review. Some of the forms need to be updated and revised for the project and a few additional indicators need to be included but otherwise, this plan, if implemented, will provide adequate M&E also for containment.

In addition, given the need for partner mobilization and considerable external resources, a **joint programme review** should take place in 2013.

7.1 Containment Monitoring and Evaluation framework

In the table below are all indicators suggested to be used to report on the progress of the containment project. More details on the indicators can be seen in Annex 9.

Table 7 - Suggested project indicators (Indicators marked * are also used for reporting on Global Fund Rd. 9)

PROJECT GOALS:
<ul style="list-style-type: none"> To prevent or delay the spread of artemisinin resistant <i>Plasmodium falciparum</i> parasites To reduce transmission, morbidity and mortality of <i>Plasmodium falciparum</i> malaria, with priority to areas threatened by artemisinin resistance
<ul style="list-style-type: none"> Artemisinin resistance in Myanmar in tier 3 remains at low level of resistance so that the % of patients positive on day 3 are <10% at all sentinel sites Malaria prevalence and incidence decline toward pre-elimination targets
Objective 1: Improving access to and use of early diagnosis and quality treatment according to the national treatment guidelines
1.1. Percentage of persons with a history of fever in the last two weeks that has been tested for malaria (RDT or Microscopy)
1.2. Percentage of villages that are within one hour walk of a functioning health facility or a trained volunteers delivering diagnosis and treatment
1.3. Percentage of diagnosed <i>P.f</i> cases treated with ACT plus primaquine
1.4. Percentage of confirmed malaria cases treated in accordance with national malaria treatment guidelines within 24 hours of onset of symptoms*
1.5. Number of RDTs taken and read*
1.6. Number of people with malaria (by gender and age group) treated with recommended ACT*
1.7. Number of volunteers trained and supported*

Objective 2: To decrease drug pressure for selection of artemisinin resistant malaria parasites by stopping the use of Artesunate Mono-therapies and sub-standard/fake drugs
2.1. Percentage of private drug outlets selling AMTs
2.2. Percentage of sampled anti-malarial drug that are fake or sub-standard
2.3. Number of drug inspections carried out and reported on
Objective 3: To limit the transmission of malaria by mosquito control and personal protection
3.1. Percentage of households with at least one ITN/LLIN*
3.2. Percentage of population at risk sleeping under an ITN/LLIN the previous night*
3.3. Number of people protected through other personal protection measures (i.e. not LLIN/ITN)
3.4. Number of LLINs distributed*
3.5. Number of nets treated/retreated*
Objective 4: To increase migrant/mobile populations' access to and use of malaria diagnosis, treatment and vector control measures including personal protection
4.1. Number of township where mapping of migrant/mobile populations have been completed
4.2. Number of people tested through a) tested at worksite, b) tested at malaria screening points, c) Other
4.3. Number of volunteers trained targeting migrants/mobile populations
Objective 5: To support containment of artemisinin resistant parasites through advocacy and BCC/IEC
5.1. Percentage of private drug sellers aware of drug policy
5.2. Percentage of respondents that are aware of key messages (to be clearly defined under BCC)
5.3. Number of advocacy meetings held
Objective 6: To conduct studies and do operational research to support the development of evidence-based containment policies and strategies
6.1. Number of TES completed to define artemisinin resistance in Myanmar
6.2. Number of functional Day 3 parasitaemia sentinel sites
6.3. Number of operational research done in line with Operational Research agenda
6.4. Number of operational research that has contributed to refinement of containment policy/strategy
Objective 7: To provide effective management and coordination to enable rapid and high quality implementation of the containment strategy
7.1. Functional surveillance system in place in containment tiers (data from a minimum of 80% of health facilities and volunteers have been encoded and analysed)
7.2. Surveillance data from the containment areas are shared and consolidated between all partners
7.3. Surveys are carried out as planned, and results are analysed and disseminated
7.4. All operational levels (from central to township level) are fully staffed according to the human resource plans in containment tiers
7.5. Number of cross-border meetings held
7.6. MARC task force meetings organised according to plans

To be able to report on these indicators, the surveillance system needs to be strengthened and additional surveys needs to be carried out.

7.2 Surveillance

The success of the containment project will be dependent on a strong routine surveillance system. Strengthened case management, with improved access to diagnosis and treatment, will be the most important source of information if the data is quality assured and the reporting coverage is high. The expected rapid increase in number of patients tested and treated will require additional resources to the reporting system at all levels.

The surveillance system of the different partners needs to be aligned to the degree that it is possible to make a consolidated report of key outputs from all partners (a process that has commenced for partners involved in the Global Fund round 9)

7.3 Surveys

A number of surveys are needed to provide the containment project with key information and to monitor the progress and any need for adjustment of the approaches.

The list of surveys is in the table below

Table 8 - List of surveys

	2011	2012	2013	2014	2015
Health facility survey	X*	X*	X*	X*	X*
Household survey	X*	X*	X*	X*	X*
Drug outlet survey	X	X	X	X	X
Township mapping of migrants	X	X			
Micro-stratification with prevalence survey	X* (Tier 1/2)	X* (Tier 2)			

Some surveys (marked with *) have already been partly planned with funding from the Global Fund. However, to get the sufficient information for reporting on the containment project it will require additional funding for oversampling in the targeted areas it. Micro-stratifications have been planned under Global Fund Round 9 but for the containment project, the plan is to include prevalence survey in the targeted township and thereby both get a better estimation for the size of the malaria burden and the distribution. Combining this with the mapping of migrants in the townships and additional township assessments will significantly augment the ability to do well targeted implementation with better identification of risk groups, risk factors and risk areas. In addition to the listed surveys, there is also the possibility of doing a nationwide prevalence survey in 2012, though the focus at present is to get better information on the epidemiological situation in the areas targeted for containment.

7.4 Data consolidation

All partners taking part in the project needs to commit themselves to help facilitate the data consolidation by timely sharing of information on key output and outcome information including reporting on relevant indicators. The flow of information will mainly be through the State/Regional VBDC staff and WHO national consultants. Standard reporting formats will be developed for reporting on activities carried out by partners. At a later stage of the project when the staff at township level has been strengthened, it is conceivable that the township will play a more central role in the data consolidation process.

8. Studies and operational research

8.1 In vivo TES

The TES studies carried out since 2007 are shown by site in the table below.

Table 9 - TES studies since 2007 by site

State/Division	Locality	Year		
		2007	2009	2010
Kachin	Myitkyina	X		X
Sagaing	Kalay		x	
Mandalay	Mandalay	X		
Rakhine	Ponnargyun	X		X
Eastern Bago	Shwegyin		x	
Kayin	Myawaddy	X		X
Mon	Thanphyuzayat	X		X
Tanintharyi	Kawthaung		x	X
Eastern Shan	Kyaingtone			X

The sites are well distributed geographically, covering areas under threat as well as those, where the emergence of artemisinin resistance in the near future is less likely. A confirmatory study using artesunate mono-therapy will be done in Kawthaung, Tanintharyi in 2011. To ensure information is available to revise zoning according to the epidemiological realities, and thereby target containment interventions correctly, surveillance of resistance will be intensified. Part of this is to conduct additional TES studies. The location of the study sites will depend on the previous results. At the sites two ACTs will be selected from the three ACTs recommended in the National Treatment Guidelines, artemether-lumefantrine, artesunate-mefloquine and dihydroartemisinin-piperaquine.

8.2 Studies of Day 3 parasitaemia

In addition to the TES, sentinel sites will be set up to monitor the proportion of patients still positive for *P. falciparum* infection on Day 3 (72-hour after start of treatment). Once artemisinin resistance has been found in a country, the purpose of D3 monitoring is primarily to obtain a better mapping of the extent of artemisinin resistance. The studies should therefore be conducted as priority in tiers 2 (especially) and 3. This mapping should then lead to improved targeting and adaptation of interventions. In the D3 sentinel sites, the full treatment course will be directly observed and microscopy will be quality controlled, as in TES.

8.3 Operational research

A workshop focusing on the priorities for research will be organised March/April 2011, to help develop a research agenda. Among operational research the following topic could be considered:

- **Studies on distribution of vector species, characterize vector behavior and ecology** in areas in Tier 1, where IRS could be envisaged.
- **Research on feasible, cost-effective methods of increasing the vector control and personal protection coverage for containment**

- **Research on surveillance of artemisinin resistance**
- **Research on ways of increasing the access of migrant/mobile populations to prevention and treatment**
- **Research on methods, systems and technologies that can be used in Myanmar improving the quality and accessibility of diagnosis and treatment.** This could include areas such as storage facilities for RDTs in the field.
- **Research on methods of engaging to private sector in the delivery of quality diagnosis and treatment**
- **To gain knowledge on ways of increase compliance to ACT treatment course and increasing the use of LLINs/ITNs/personal protection though BCC and advocacy towards patients, health workers and other stakeholders.** Ensuring compliance is important to prevent the development of resistance though not much is known on the level of compliance in Myanmar or the best way to address the issue.

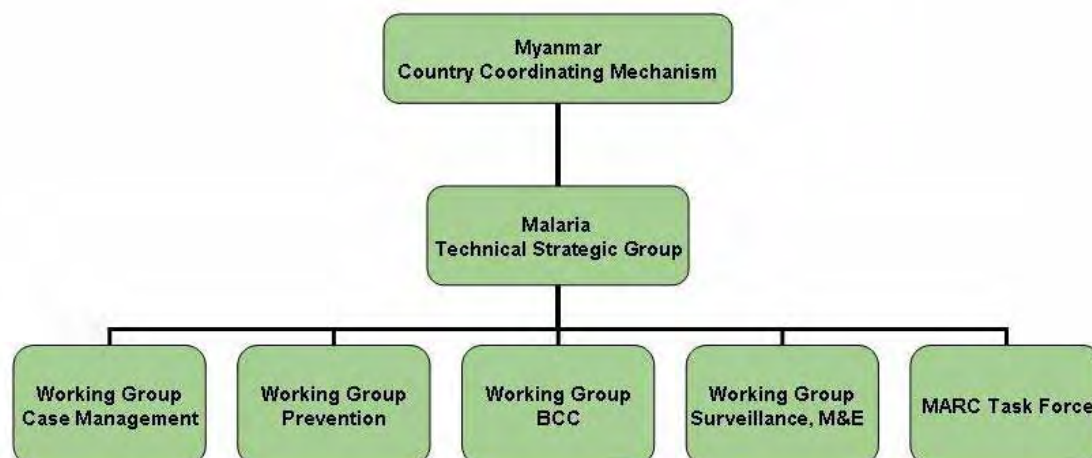
9. Partner coordination, planning, management

Containment requires a sense of unified purpose, shared vision and well coordinated efforts. The essential task is to ensure that there are no gaps and no overlaps.

A coordination mechanism for the national malaria control programme already exists - the Malaria Technical Strategic Group (TSG), which includes VBDC and its partners in the country. At a meeting of the Technical Strategic Group (TSG) for Malaria on February 18, 2011 it was agreed that the containment project should be overseen by a MARC Task Force which would include selected members of the TSG (see Figure 9). The composition and the ToR for the Task Force can be seen in annex 7.

It is likely that the containment effort will be funded by various donors so to keep track of implementation; there is a need for a strong support unit under the MARC Task Force. At the TSG meeting on February 18, 2011 it was agreed this support unit should be under the Malaria unit in WHO.

Figure 9 - Malaria Technical Strategic Group



10. International collaboration

Containment efforts in Myanmar have to be connected to existing interventions currently implemented in the Greater Mekong Sub-region (GMS) especially in western provinces of Thailand and southern provinces of Yunnan Province in China. There is already increasing engagement of the national malaria programme and research institutions in Myanmar into in vivo therapeutic efficacy studies carried out in the GMS and coordinated by WHO. Results gathered from sentinel sites across the GMS are driving a focused response by documented tiers starting intensive containment operations in 17 provinces on the Cambodia-Thailand border³⁹. Cambodia and Thailand have set up national containment task forces (TF) involving high ranking decision-makers, representatives from non-health sectors and partners engaged in operations. Those national TF are superseded by one International Task Force (ITF) with 9 officially nominated international experts looking at progress made and providing technical advices to partners engaged and WHO. As per Cambodia-Thailand bi-country operations, cross-border or cross country workshops have to be regularly

³⁹ http://www.whothailand.org/EN/Section3/Section113_278.htm

organized to exchange information towards concerted planning and reporting. Containment operations are also supported by the GFATM in Cambodia (R9), Thailand (R10) and China (R10). Annex 3 includes summaries of the current plans (approved Global Fund Round 10 proposals) of China and Thailand for malaria control near and on the borders to Myanmar. The project elaborated in China by the Yunnan Institute for Parasitic Diseases (YIPD) and Health Unlimited includes activities which could be described as intensified malaria control with policies and case management and vector control interventions, which are well aligned with those of VBDC for malaria control. However, the R10 proposal from China has as one of its objectives to minimize the importation of falciparum malaria cases to China, so as to support China's elimination efforts. Thus, in addition to village services providing diagnosis and treatment, similar services will be set up specifically for Chinese migrant workers in Myanmar.

The Thai project aims directly at falciparum elimination in Thailand. To a large extent, the activities are focused on the (mobile) populations in the border areas with Myanmar and Cambodia, and on migrants. Progress towards elimination in China and success in containment in Thailand and Myanmar will require intense supra-national collaboration and coordination between countries. WHO is expected to facilitate this collaboration towards the development of a regional response building on regular informal consultations and technical workshops with national programmes and stakeholders.

In summary, in the medium-long term it will be essential that mechanisms are set up for:

- Regular exchange of operational and epidemiological data including results from operational research
- Harmonization of case management, vector control approaches backed up by similar BCC/IEC messages provided in different languages and culturally appropriate
- Intensive Collaborative activities in specific border areas
- Exchange of experiences and lessons learnt
- Advocacy and communication through relevant media channels

Participation of national experts in International meetings and symposium are also important to gather opinions, consolidate science and access peer-review information on innovative malaria elimination and containment strategies.

11. Human resources

Implementation, monitoring and reporting of all programmatic and research containment activities by objective are either routine tasks to be done faster than currently planned or are extra tasks on top of routine malaria control. Those high demanding activities are placing extra burden on existing limited health and managerial staff at all levels and might require extra human resources and/or skills to ensure performance and quality of operations from communities to State and Central levels. Capacity building of national experts with appropriate staff TORs by level of care and adjusted training curriculum is certainly a critical component of containment operations to be appropriately factored in the overall containment activities and budget. International staffing has also to be seriously considered to meet international donors' and MOH / VBDC requirements including to push for an increasing connectivity with the international regional and global containment community.

Containment is a highly information-driven variant of malaria control/elimination. It needs to

- strive for higher degrees of perfection than “standard” malaria control,
- be conducted with greater urgency than “standard” elimination, and
- to include exceptional flexibility and innovation.

National staffing (during 5-year project duration)

To meet these demands for increasing performance, the MOH/VBDC will need a variety of skills and capabilities at all levels (central as well as in the States, Regions, Townships, health care facilities and communities of Tiers 1 and 2). To ensure the growth of national capabilities and a minimal critical mass at central level, there is also a need for increased technical collaboration within and outside the MOH. From preliminary analysis, the main needs to fill the gap are as follows (in addition to what already exists and is planned under GFATM Round 9):

- 1 officer / consultant at national level to pilot / develop and implement a performing malaria surveillance system from communities to central level involving private providers and beyond to match national and international institution requirements e.g. from WHO.
- 2 officers / consultants for monitoring and evaluation which is a critical component of any control programme including containment operations. Baseline information is important to be collected starting in tier one with surveys conducted at regular intervals to complement routinely collected data. Existing survey methodologies (MIS, Health care facilities, outlets, household / population surveys ...) have to be updated to gather information needed as part of containment operations.
 - It is suggested to post one national M&E consultant at central level (Nay Pyi Taw) and one at State level in tier one.
- 1 officer/consultant for supply chain management at central level. The containment project requires substantial extra laboratory equipments like microscopes, reagents and commodities such as LLINs, insecticides tablets, RDTs and cooling boxes, ACTs, training equipments etc. If procurement of such goods need intense follow up, there is also a need to ensure that all above goods reach their final field destination in good order which includes appropriate storage facilities at all levels. The procurement / supply chain management officer will collaborate with international procurement officer and State / Division and Township management staff toward the set up of a performing procurement / chain delivery system
- Data assistants will be posted as follows: 2 at central and State level and one in each township of tier 1 with appropriate IT skills and additional training on data management. Additional data assistants will be posted in tier 2 from year 2.
- BCC and IEC activities are considered strategic interventions to ensure proper use of diagnosis, ACTs and LLINs/ ITNs by prescribers and end-users. Innovative methods need to be field tested targeted migrants and mobile population.
 - It is proposed to post a BCC / IEC specialist at central level with extra TORs looking at partnership facilitation and inter-sectoral coordination

International staffing (long and short term technical assistants / consultants)

WHO is expected to play a major coordinating and facilitating role in containment operations with focus on convening technical and partnership meetings with MOH and partners and donors, liaising with similar activities in Thailand and beyond, day-to-day technical work with the MOH/VBDC including raising sub-contracts and ensuring financial accountability, special focus on M&E and surveillance [many surveys are planned] with all actors (MOH, NGOs and donors), and overall consolidated reporting to MOH and donors. This is highly demanding extra tasks with deadlines which put extra stress and burden on existing staff in the WHO country office Myanmar and WHO in general.

In addition to the international staff as malaria team leader in malaria control in Myanmar overseeing all malaria activities including research and partnership building, it is suggested to have

- 1 international specialist in M&E and surveillance, with experience in large-scale population surveys and surveillance with expertise in data management and up-to standard reporting
- 1 international project coordinator looking at overall project managerial task and project reporting.
- 3 programme assistants to support day-to-day above described tasks
- One international staff at State level tier one to collaborate and monitor activities in collaboration with national staff
- Extra short term consultant from one month to 6 months is needed to address specific technical or managerial issues (to be decided)

Annex 1. Global Plan for Artemisinin Resistance Containment (GPARC)

WHO has now established a Global Plan for Artemisinin Resistance Containment (GPARC) published in early 2011⁴⁰. Following excerpts are particularly relevant to the situation in Myanmar.

The **goal** of the GPARC is to protect artemisinin-based combination therapies (ACTs) as an effective treatment for *Plasmodium falciparum* malaria. Experts agree that there is a limited window of opportunity to contain or eliminate the resistant parasites before they spread to areas of higher transmission, putting at risk recent progress in malaria control. The urgency is increased by the fact that no other antimalarial agents are available that offer the same level of efficacy and tolerability as ACTs, and few promising alternatives are available in the immediate research and development pipeline. While efforts to contain and prevent artemisinin resistance at global and local levels have begun, they are not sufficient and must be expanded, intensified and better coordinated.

The **objectives** of the GPARC are to:

- define priorities for the containment and prevention of artemisinin resistance;
- motivate action and describe responsibilities by constituency;
- mobilize resources to fund the containment and prevention of artemisinin resistance
- increase collaboration and coordination for artemisinin resistance containment and prevention among relevant stakeholders; and
- define governance mechanisms and indicators for continual assessment of progress made in implementing the Plan.

As part of a coordinated effort to contain or eliminate artemisinin resistance where it exists and to prevent resistance where it has not yet appeared, WHO recommends the following activities:

1. **Stop the spread of resistant parasites.** In areas for which there is evidence of artemisinin resistance, an immediate, comprehensive response with a combination of malaria control and elimination measures is needed to stop the survival and spread of resistant parasites. In areas without known resistance, malaria control can reduce transmission, lowering the risk that resistant parasites will spread into those regions and minimizing the potential public health effect if resistance were to take hold. Increased coverage with preventive measures, especially vector control, is a priority, as are programmes to control malaria in mobile and migrant populations. Where artemisinin resistance is confirmed, national malaria control programmes may also consider a range of epidemiological or transmission-reduction tools, including focused screening and treatment, active case detection, mass screening and treatment or mass drug administration, in accordance with the latest evidence and guidelines, if and when they become available.
2. **Increase monitoring and surveillance to evaluate the threat of artemisinin resistance.** Regular monitoring and surveillance are critical to identify new foci rapidly and to

⁴⁰ WHO (2011): Global Plan on Artemisinin Resistance Containment
(http://www.who.int/malaria/publications/atoz/artemisinin_resistance_containment_2011.pdf)

provide information for containment and prevention activities. WHO recommends that countries endemic for malaria perform routine monitoring of antimalarial drugs at sentinel sites every 24 months in order to detect changes in their therapeutic efficacy.⁴¹ An immediate priority is to assess ACT therapeutic efficacy in countries where no studies have been performed in the previous 2 years. Emphasis should be placed on data quality. Regions for which there is evidence of resistance should consider adding further sentinel sites to facilitate early detection of additional foci. In high-risk areas, especially in those with no active sentinel sites, routine surveillance of confirmed malaria cases, deaths and (especially) treatment failures should be strengthened.

3. **Improve access to diagnostics and rational treatment with ACTs.** Increasing access to affordable, quality-assured diagnostics and treatment with ACTs improves patient outcomes and limits opportunities for resistance to both artemisinins and partner drugs.⁴² Programmes should include complementary activities to ensure consistent, accurate diagnostic testing, better access to ACTs for confirmed cases, compliance with ACT treatment and removal of oral artemisinin-based monotherapies and substandard and counterfeit drugs. Education and communication campaigns focused on diagnosis and treatment, with messages tailored to patients, providers and retailers, should be a component of these efforts.
4. **Invest in artemisinin resistance-related research.** Research is important to improve understanding of resistance and the ability to manage it. Research in five disciplines should be a priority: laboratory research (e.g. to identify a molecular marker for artemisinin resistance), research and development (e.g. of novel non-artemisinin-based antimalarial combinations), applied and field research (e.g. pilot studies of transmission reduction tools, such as mass screening and treatment or mass drug administration), operational research (e.g. scalable⁴³ programmes for mobile populations) and mathematical modelling (e.g. of the potential impact of resistance on the malaria burden).
5. **Motivate action and mobilize resources.** Successful implementation of the GPARC will depend on motivating many stakeholders at global, regional and national levels to support or conduct the recommended activities. Additional funding will be required, and leadership and sustained cooperation in the malaria community will be needed to stimulate relevant individuals, organizations and governments to support artemisinin resistance containment and prevention.

Applying recommendations at country level

In view of regional differences and varying levels of artemisinin resistance, each endemic country is expected to evaluate its level of risk and then to apply the GPARC recommendations accordingly in designing a containment or prevention programme. Different levels of response may be required for different areas in a country.

⁴¹ WHO. Methods for surveillance of antimalarial drug efficacy. Geneva, World Health Organization, 2009.

⁴² WHO. Guidelines for the treatment of malaria. 2nd Ed. Geneva, World Health Organization, 2010.

⁴³ In the context of this document, 'scalable' refers to expanding the scope of a tool or programme to reach a larger population or area

Criteria for identification of three tiers for containment planning at country level

Tier I	Areas with credible evidence of artemisinin resistance
Tier II	Areas with significant inflows of mobile populations from Tier I areas, including those immediately bordering Tier I
Tier III	Areas with no evidence of artemisinin resistance and limited contact with Tier I areas

TIER I AREAS

In areas for which there is credible evidence of artemisinin resistance, defined as ‘tier I’, an immediate, multifaceted response is recommended to contain or eliminate resistant parasites as quickly as possible. Tier I areas include several suspected foci in the Greater Mekong sub-region in November 2010.

The recommended response for tier I areas is a combination of intensified malaria control and tools for elimination:

Intensify and accelerate malaria control to reach **100% coverage** of at-risk populations as soon as possible, including:

- parasitological diagnosis for all patients with suspected malaria;
- a full course of quality-assured ACTs plus primaquine for confirmed cases, in compliance with current WHO treatment guidelines (when the risk for glucose 6-phosphate dehydrogenase deficiency is considered low or testing for deficiency is available);⁴⁴ and
- vector control, as locally appropriate, to lower transmission and minimize the spread of resistant parasites.

Launch specific activities to contain or eliminate resistant parasites:

- intensified monitoring of therapeutic efficacy near current foci to track the spread of artemisinin resistance and ensure that the recommended first-line treatments remain effective;
- education and enforcement to eliminate use of oral artemisinin-based monotherapies and substandard and counterfeit antimalarial agents;
- programmes to reach mobile and migrant populations with adequate prevention, diagnosis and treatment; and
- epidemiological or transmission-reduction tools, which may include mass screening and treatment, focused screening and treatment, active case detection or mass drug administration, in accordance with the latest evidence or guidelines, if and when they become available.

TIER II AREAS

Tier II areas are those with significant inflows of mobile and migrant populations from tier I areas or shared borders with tier I areas. The specific recommendations for tier II areas are:

Intensify and accelerate malaria control activities, including:

- parasitological diagnosis for all people suspected of having malaria;
- a full course of quality-assured ACTs plus primaquine for confirmed cases, in compliance with current WHO treatment guidelines (see above); and

⁴⁴ *Guidelines for the treatment of malaria*, 2nd Ed. Geneva, World Health Organization, 2010.

- vector control, as locally appropriate, to lower transmission, prevent the spread of artemisinin resistance or limit the potential impact of resistance if it were to emerge.

Implement specific tactics to manage the potential spread of resistant parasites from tier I areas, including programmes to reach mobile and migrant populations, especially those moving between tier I and tier II areas, with effective prevention, diagnosis and treatment.

Launch activities specific for the prevention of resistance, including:

- intensified monitoring of therapeutic efficacy to track the spread of artemisinin resistance and ensure that the recommended first-line treatment remains effective; and
- education and enforcement to eliminate the use of oral artemisinin-based monotherapies and substandard and counterfeit antimalarial agents.

TIER III AREAS

In tier III areas, defined as *P. falciparum* endemic areas which have no evidence of artemisinin resistance and limited contact with tier I areas, prevention and preparedness should focus on scaling up control measures to increase coverage with parasitological diagnostic testing, quality-assured ACTs and vector control to limit malaria transmission. In addition, tier III areas should undertake two other components of good control:

Monitor the therapeutic efficacy of first- and second-line treatments every 24 months, as recommended by WHO. This is an immediate priority for any *P. falciparum*-endemic country with a sufficient number of malaria cases in which studies of the efficacy of ACTs have not been conducted in the past 2 years

In areas in which there is extensive use of oral artemisinin-based monotherapies or poor-quality drugs, introduce or enforce actions to eliminate their use.

Roles of different actors

Successful implementation of the GPARC will depend on the support and cooperation of many groups, including research and academic institutions, funding agencies, including the Global Fund and bilateral donors, nongovernmental organizations and, the private sector.

Financial costs

Given the overlap between malaria control and artemisinin resistance containment, a fully funded and implemented malaria control agenda, as outlined in the Global Malaria Action Plan, would address many of the needs for the containment and prevention of artemisinin resistance. Nonetheless, additional funding will be needed for specific initiatives to manage artemisinin resistance, the immediate priority being funding for programmes in current tier I and II areas.

On the basis of experience with the programme for artemisinin resistance containment and elimination in Cambodia and Thailand, tier I and II containment and prevention programmes are estimated to cost US\$ 10–20 and US\$ 8–10 per person at risk annually, respectively. Additional funding will be needed for tier III programmes, where modest additional costs are anticipated for increased monitoring of drug efficacy and enforcement of bans on monotherapies and substandard and counterfeit drugs. These additional costs are estimated to be US\$ 50,000–100,000 per country per year for monitoring⁴⁵ and roughly

⁴⁵ WHO/GMP estimate; assumes US\$ 50 000–100 000 for three studies per year or six studies in a given 24-month period.

US\$ 500,000 per country per drug quality enforcement programme, depending on the sophistication of the national drug regulatory authority.

The estimated cost for accelerating research and development of non-artemisinin antimalarial agents and high-priority laboratory research is US\$ 60–65 million annually. In total, full funding of artemisinin resistance containment and prevention would be upwards of US\$ 175 million per year globally. These estimates are based on the assumption that tier I and II areas are limited to those in and around the currently suspected foci in Cambodia, Myanmar, Thailand and Viet Nam.

Measurement and evaluation

Measurement and evaluation should be conducted at all levels—global, regional, national and area (tier)—and should include regular, formal reporting. Data quality should be a strong focus, as a useful assessment of the progress of GPARC will rely on good data. WHO/GMP will lead global coordination in tracking and communication of key indicators. In order to ensure independent, transparent evaluation of progress and achievements, WHO/GMP will establish a technical expert group on drug resistance to review and evaluate progress reports regularly.

Evaluation will cover a mix of process, outcome and impact measures. To minimize resources, the measures will, where possible, be based on data that are already collected for malaria control and elimination. Continued cooperation with the research community will further widen and deepen the pool of available information. In some cases, new indicators, and processes to measure them, will be identified and developed.

Annex 2. Containment of artemisinin-resistant malaria parasites in Cambodia and Thailand

After the containment strategy had been developed at a meeting in early 2008, the Bill & Melinda Gates Foundation committed US\$ 22.5 million towards the project. Additional contributions were made by the Global Fund to Fight AIDS, Tuberculosis and Malaria and the United States Agency for International Development. The goal of the project was to stop the spread of artemisinin-resistant parasites by removing selection pressure and by ultimately eliminating *P. falciparum* or at least all resistant parasites.

The containment project is currently ongoing in certain tiers on the Cambodia–Thailand border area. In tier 1, where artemisinin resistance has already been detected, intensive activities are aimed at **local elimination** of *P. falciparum*. In Cambodia, tier 1 covers about 270,000 people in four provinces (all of Pailin and parts of Battambang, Pursat and Kampot). In Thailand, about 110,000 people live in tier 1 in the border areas of Trat and Chantaburi provinces. Tier 2 borders tier 1, and its residents are considered at high risk for infection by artemisinin-resistant parasites. In Cambodia, tier 2 covers nine provinces with a total population of more than 4 million (excluding towns). In Thailand, tier 2 comprises seven provinces with a population of nearly 7 million, about 150 000 of whom live in areas at risk for malaria (See Fig.3).

More than 500,000 long-lasting insecticidal nets have been distributed and more than 200,000 nets re-treated. Village health care workers were recruited and trained to improve case detection and treatment; they provide free rapid diagnostic testing, and patients with a positive test receive free treatment and follow-up. In Thailand, all malaria cases are followed up for 28 days. In Cambodia, the patients are monitored during the 3 days of treatment, and those who are still parasitaemic after day 3 are followed for up to 28 days. The provision of free treatment and care helps to undermine the sale of counterfeit and substandard antimalarial drugs by the private sector. Treatment is available at health facilities established to diagnose and treat malaria, which are open 24 h a day.

In addition to vector control and case management, education programmes inform villagers about the importance of using treated nets and about appropriate treatment. A special campaign has been launched to include the mobile population. Migrants come to the Cambodia–Thailand border area to work on farms and construction projects and in military postings, forestry, land development and gem mining. **The strategies used to address mobile populations in containment activities** include:

- engaging mobile malaria workers to seek out transient workers;
- providing mosquito nets to farm owners for distribution to seasonal workers;
- distribution of free repellents, in Thailand
- establishing diagnosis and treatment stations in construction camps and temporary villages of military families;
- operating mobile malaria clinics at all border crossings; and
- providing all educational materials in both Thai and Khmer and designing them to ensure that the messages and appearance are the same in both languages.

Efforts have also been made to **stop the sale of counterfeit and substandard drugs**, which are a major factor in the development of resistance. The Government of Cambodia has prohibited the sale of oral artemisinin-based monotherapies, and the ban is enforced by justice police, who systematically visit pharmacies, shops and markets. Workshops and education materials are used to inform both medicine sellers and residents.

- According to a population survey in late 2009, the deployment of LLINs has worked well in zone 1 leading to coverage rates for treated nets above 70%. The rates are lower in tier 2, presumably because distribution there was more focused.
- Success is reported in scaling up case management through village workers. In late 2009, by far most people still preferred either health centre or private provider; it will be interesting to see, what the situation looks like in 2010.
- Official ban on monotherapy combined with social marketing in Cambodia has not been entirely successful, in that the population avails itself of a variety of antimalarial products. Nonetheless on the plus side, it may be noted, that people like to get a confirmatory diagnosis, that the great majority of fever cases are not treated with any antimalarial, and that artesunate monotherapy seems less common than in the past.
- Mass screening and treatment has proven technically possible, but the human resource constraints make this intervention impossible on a large scale with the objective of eliminating the parasite reservoir. However, a rapid and highly sensitive PCR has been developed in Cambodia, making focused screening a useful tool for micro-epidemiological studies.
- There have been solid efforts at engaging migrant populations; in particular, collaboration with employers seems promising. Considerable information on types of migrants and movements between Cambodia and Thailand has been generated.
- Preliminary data generated by health centres and village workers in Cambodia referring to 39 targeted villages in Cambodia suggest a marked decrease in *P.falciparum* incidence. It is however so far impossible to say, which intervention(s) may have caused this.
- Senior WHO staff involved in the malaria containment efforts has noted the need for
 - Emphasizing ongoing monitoring and surveillance, so that data can be used continuously for programme adjustment.
 - Extensive operational research, especially on migrants, but also on other aspects of malaria control.
 - Coordinating and harmonizing research and control related to migrant malaria across borders.
 - Ensuring that containment activities in part of a country do not weaken the implementation of malaria control in areas classified as Tier 3 by pulling most human resources in one direction.

Review of experiences from containment efforts in Cambodia and Thailand

A variety of formal and informal reports have been reviewed in an attempt to answer questions about the experiences accrued since containment activities started in 2008.

1. Overview of target populations.

Targeted populations in Zones 1 and 2

	CAMBODIA	THAILAND
Zone 1	267,748 (8AD in 5OD in 4 provinces)	112,153 (3 districts in 2 provinces)
Zone 2	4,023,241 (9 provinces, excluding town areas)	841,436 (risk areas A1+A2+B1 in 7 provinces)
Total	4,290,089 (10 provinces, 5 OD, 8 AD)	953,589 (7 provinces, 3 districts)

2. How well have vector control and personal protection worked?

More than 500,000 long-lasting insecticide-treated mosquito nets have been distributed, and more than 200 000 nets have been re-treated in mid-2009. In tier 1, all villages were targeted, in tier 2 only high risk.

A probability random sampling household cluster survey in tiers 1 and 2 in December 2009 found 80% of people sleeping under a net and 51% under a treated net. Use of treated nets was much higher in tier 1 than tier 2. Thus, 65% of households in tier 1 had an Olyset™ net against 42% in tier 2. In tier 1, 71% had slept under an ITN and 62% under an LLIN against 46% under ITN and 36% under LLIN in tier 2. If the campaign was more intense in tier 1 than in tier 2, then there was according to these data a marked effect in terms of coverage.

Hammock nets have also been distributed on a large scale to migrants found in tier 1 and 2 and survey data indicate that these are also used on a large scale.

3. What are the lessons on case management?

Many village health care workers were recruited and trained in order to improve case detection and treatment; they are equipped to provide free screening with a rapid diagnostic test, and patients with a positive test result for malaria receive free treatment and follow-up. In Thailand, all malaria cases are followed up for 28 days. In Cambodia, the patients are monitored during the 3 days of treatment, and patients who are still parasitaemic after day 3 are followed for up to 28 days.

It seems that it was possible to make a large number of village health workers functional over a short period. However, through 2009, more cases were still seen in health centres than by village health workers. Only data from the 2010 survey can show the results of the efforts.

4. Stopping monotherapy through regulation and social marketing – has it worked?

Efforts have been conducted very professionally, but the donor support has fluctuated. So far it has been difficult to change the widespread irrational polypharmacy including artesunate monotherapy in Cambodia.

Efforts have also been made to stop the sale of counterfeit and substandard drugs, which are a major factor in the development of resistance. The Government of Cambodia

has prohibited the sale of oral artemisinin-based monotherapies, and the ban is enforced by justice police, who systematically visit pharmacies, shops and markets. Workshops and education materials are used to inform both medicine sellers and residents.

These efforts included, in Cambodia from 2001 nation-wide deployment of co-blistered ACTs. Artesunate-Mefloquine co-blisters which were pre-packed for the public sector as "A+M" and for the private sector under the trade mark of Malarine™. This new drug policy was combined with mass deployment of rapid diagnostic tests (Parasight F™) throughout the public and private sector. The IEC campaigns for the new ACTs included mass media campaigns against monotherapy and other forms of inadequate treatment. Fake antimalarials were identified and publicly denounced followed by an effective police crack-down on sales of fakes. All these efforts were completed with the massive deployment of treated mosquito nets through community distribution combined with the social marketing of impregnated hammock nets.⁴⁶

By 2003, studies had revealed the ACT usage of only 11% despite good availability of ACTs in the public sector and private sector and well monitored market penetration of Malarine™. The main obstacle that remained was the general practice of pharmacists and drug vendors to also sell a host of cheaper but inadequate alternative treatments for fevers.

By 2009, according to the survey carried out in Cambodia, the great majority of fever cases were treated with paracetamol and not with an antimalarial. Shopkeepers and the general population stated that artesunate-mefloquine ("Malarine") or various formulations of dihydroartemisinin-piperaquine were preferable for treating malaria.

Thus, it seems that over the years, social marketing and persistent BCC through various channels had an effect, but so far the picture is not clear as regards the relative proportions of patients treated with ACT or AMT.

5. How are migrants and mobile populations engaged?

Migrants come to the Cambodia–Thailand border area to work on farms and construction projects and in military postings, forestry, land development and gem mining. The strategies used to include the mobile population in containment activities include:

- engaging mobile malaria workers to seek out transient workers;
- providing mosquito nets to farm owners for distribution to seasonal workers;
- establishing diagnosis and treatment stations in construction camps and temporary villages of military families;
- operating mobile malaria clinics at all border crossings; and
- providing all education materials in both Thai and Khmer and designing them to ensure that the messages and appearance are the same in both languages.

Some useful information is available in *Summary from the Technical Workshop on Cross-Border IEC/Behaviour Change Communication Strategies "A Strategy for the Containment of Artemisinin resistant Malaria Parasites in Southeast Asia"*. Malaria Consortium, 2009.

The IOM definition of **migration** is the process of moving across borders or within a state.

Migration can be regulated or unregulated (includes trafficked and smuggled migrants). The majority of migrants are irregular and do not appear in government statistics.

⁴⁶ Doung Socheat, Stefan Hoyer *Country update on malaria control Kingdom of Cambodia/ 4th*. RBM Global Partners' meeting, World Bank Washington, DC 18-19 April 2001

Thailand has memorandums of understanding (MOUs) with neighboring countries but the legal process is complicated and expensive. Recruitment agencies can make large profits from unregulated migrants.

There are an estimated 1.3 million migrants in Thailand: 80% from Myanmar, 13% from Cambodia, and also from Laos, China and Vietnam.

Migrants can be men, women or children (travelling with families or alone). Migrants are predominately men in agriculture and construction, while mostly women in domestic work. Interestingly, the proportion of migrants is increasingly women.

At least 50% of migrants are unregistered. This is especially true for those migrants outside migrant camps where 80-90% are unregistered.

- In 2004, the total number of migrants was 1,847,525, which includes those possessing work permits (1,012,051) and those with health insurance (817,245).
- Demand for migrant labour is high - 1.2 million people passed through the official borders last year.
- 25% of migrants in the Thai/Cambodia border area are from Myanmar
- Data collection does not distinguish between legal and illegal migrants
- There is good cooperation between MOPH, IOM and other NGOs
- Epidemiological survey tool used to conduct a survey in three provinces of Tak, Ranong and Samut Sakorn to gather data on migrants. Data collected included sleeping under a bednet, use of health services, symptoms experienced and diagnosis. When the survey tool is used regularly, it can detect trends in migrant health.

The main risk groups for malaria in Cambodia include the following:

Risk group	Ethnic group	Composition	Access to health care	Immunity	Highest at risk
(A) <i>Traditional forest inhabitants</i> (montagnards)	Mixed non Khmer minority groups	Families	Little due to remoteness and linguistic barrier	Adults only	Children and pregnant women
(B) <i>Forest fringe inhabitants</i> . Make overnight visits to the forest to hunt & to collect construction wood /other products.	Khmer	Villagers (predominantly young men)	Relatively good in recent years	None	All age groups but the majority of cases are found in adult males.
(C) <i>Temporary migrants</i> . Individual forest workers, gem-miners, hunters, and others	Khmer and foreigners	Mostly adult males	Inadequate, but better than in (A) due to high mobility and more cash; private sector often preferred	Little or no immunity	Adult males
(D) <i>Organized groups</i> : plantation-workers, road-workers, military, police-forces	Khmer and foreigners	Mostly adult males	Usually good, as employers want to protect workers	None	Adult males, sometimes females or entire families
(E) <i>Refugees, displaced persons</i>	Khmer	Families	Relatively good in recent years	None	Children and adults alike
(F) <i>New forest settlers</i> , sometimes aftermath of (E)	Khmer	Families	None, not even private sector	Usually low	Children and adults alike

A. Definition of “migrant” versus “mobile population”

Thailand and Cambodia use different definitions for migrants and mobile populations but generally they can be defined with regard to:

- Temporary vs permanent (time)
- Internal vs external
- Reasons for migration
- Operational definition (easy to reach, intermediate, hard to reach)

Migrant: The general definition of a migrant is any person who moves from one place to another. "External migration" refers to moving across international borders. On the other hand, "internal migration" refers to movement from one area (province, district or municipality) to another within one country.

For our purpose which is containment of resistant malaria parasites, it was proposed that a migrant be described as anyone who moves out from their permanent residence and stays in a malaria endemic area for whatever purposes with regards to targeting malaria intervention. Therefore, operational definitions can be used to describe migrants as those who can be classified as **easy-to-reach** (e.g., within 5km of a health centre), **intermediate to reach** (e.g., within reach of VMWs or MMWs), and **hard-to-reach** migrants (e.g., those who engage in illegal activities in the forest).

Mobile population: Any person who moves from one area to another (whether internally or externally) usually for a short period of time (less than one month)

There is a large Myanmar migrant population working in the orchards of Trat province in Thailand that may have contact with the populations in Pailin or *visa-versa*. Asymptomatic parasite carriers of MDR resistant strains contracted in Pailin may already be travelling back and forth from Trat to Myanmar. Gem mining has become less of a factor in population movements but logging and expanding agriculture have since lead to continued intense and sustained population movements. Despite the widespread logging malaria, transmission remains intense in many hilly areas (Personal information; Dr S.Hoyer).

In conclusion, a lot has been learnt about migrants and malaria. The intense exchange of information between Cambodia and Thailand has been of value and experience has been gained in assessing migration and malaria through various kinds of surveys and in engaging migrants for example by collaboration with employers (which has not always been easy or straightforward). Concrete data on the size of the migrant populations have been generated and exchanged between the two countries.

6. What are the experiences with mass screening and treatment?

An efficient PCR has been set up in Cambodia, so that it is possible to get results back to a village within the country in 4 days. However, mass screening is too labour intensive to work as a key strategy for reduction of the parasite reservoir. In contrast, focused screening can help elucidate micro-epidemiology.

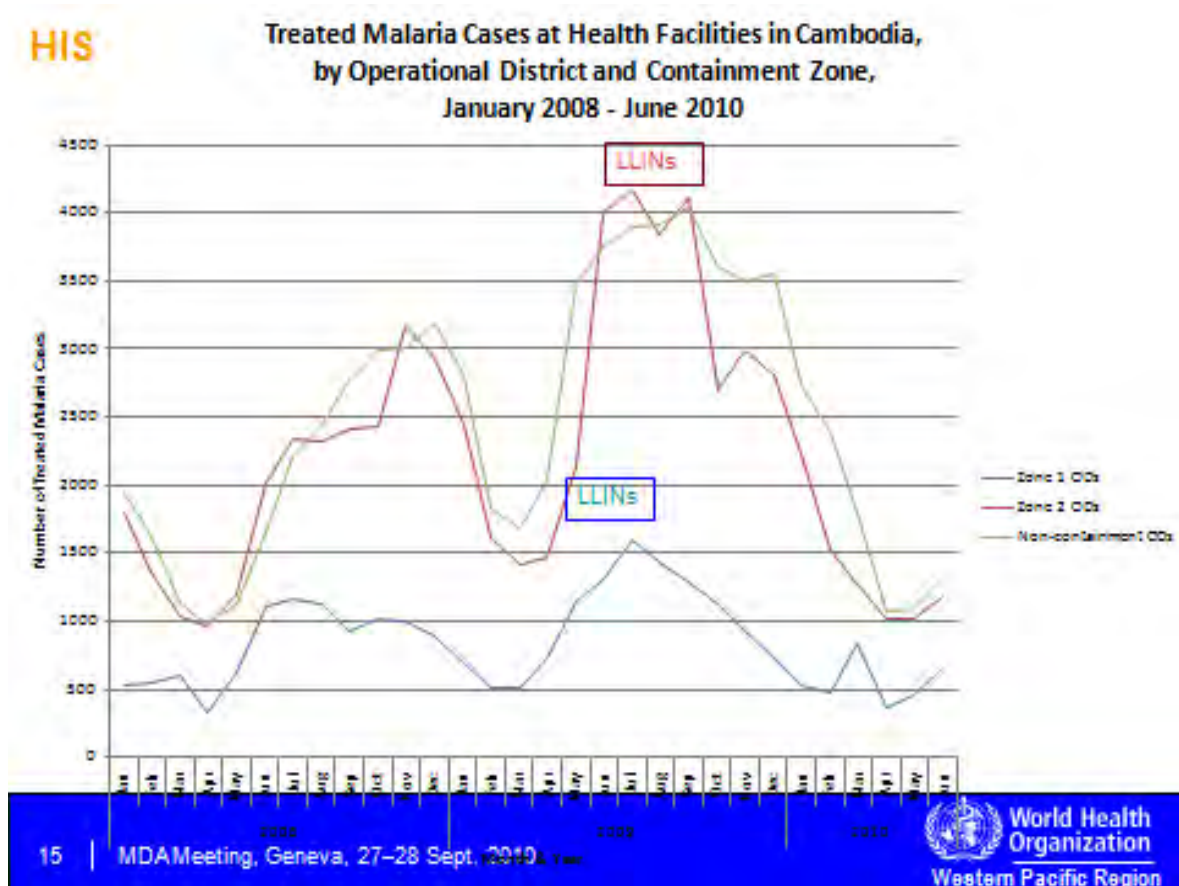
A first test of mass screening and treatment (MSAT) feasibility was carried out in March 2008 in Pailin, Cambodia. It concluded that a mass screening and treatment campaign was possible after a preparation period of nine months, if the human and material resources could be provided, which was not the case. Village-based, cross-sectional surveys could use the rapid PCR technique developed at the Pasteur Institute of Cambodia (IPC). The high sensitivity of PCR allowed for the detection of 56 asymptomatic parasite carriers within one village, 34 of which had parasitaemia levels below those detectable by microscopy or RDT. Furthermore, the PCR screening was so rapid that 94.7% of previously undetected parasite carriers could be retrieved within 4 days of screening and receive radical, directly observed treatment. The insights gained by being able to detect and classify all asymptomatic carriers present has become more important than the goal of the limited and local reduction of parasite biomass. The human resource constraints in Cambodia allowed for of a maximum of one village screened per week (among 109 in Pailin). The current speed of operations is 40 persons/hr and 5 hrs/ workday.

The initial goal of rapid and sustained reduction of malaria transmission by means of MSAT was further rendered impossible by the fact that Pailin has very high rates of immigration and internal migration, that the maximum attendance levels obtained under optimal conditions were about 2/3 of the resident village population and that, finally, even PCR could not detect all cases, as could be demonstrated in the second MSAT test. (Personal information: Dr S. Hoyer)

7. What has been the effect on malaria transmission and morbidity?

1. Examining data on patients treated at health centres as well as by village health workers, it was found that in 39 villages in Tier 1 in Cambodia with a population of 34368 the number of Pf in 2009 was 521; in Jan-Oct 2010 it was 117. At the same time the number of PV cases increased from 248 to 391. (Data analysis in progress, unpublished). This suggests that from 2009 to 2010 there was in target areas in Tier 1 in Cambodia a marked reduction in the incidence of falciparum malaria.

The data shown in the following graph is more difficult to interpret, because it includes only data from health facilities.



8. Has artemisinin resistance become worse, better or unchanged?

The below presentations indicate that it may have gotten worse in Pailin, but not elsewhere. Even in Pailin, a change of the partner drug seems to keep the situation in check. The possible increasing artemisinin resistance in Pailin must be seen on the background of a decreasing parasite reservoir and should be expected according to Maude et al., 2009.

Annex 3. Plans for malaria control and containment in China and Thailand along the borders to Myanmar

1. China

Activities have been planned in China by the Yunnan Institute of Parasitic Diseases in collaboration with the INGO, *Health Unlimited*. A proposal was submitted to Global Fund Round 10 and was approved. The following is excerpted from the summary of the proposal.

Title: Intensified malaria control along the Myanmar-China border.

Round 10 targets 586,000 residents of the five Special Regions of Myanmar which border China's Yunnan province, plus 100,000 longer term migrants from China based in this target area, and an estimated 1.5 million shorter-term migrants who frequently cross the Sino-Myanmar border into the target area. Sub-populations within these groups will be targeted with different services according to their characteristics and malaria risk.

There are currently no national malaria prevention, treatment, care or support strategies in the five special regions of Myanmar targeted by this application. The public sector is rudimentary at best, and in many areas completely absent. Effective reliable access to these regions is only possible from China.

The five Special Regions have a high burden of disease (estimated incidence for the resident population as a whole is 134/1,000) and are home to some of Myanmar's most at risk populations. The epidemiological situation is very heterogeneous with a mixture of hypoendemic, mesoendemic, hyperendemic and even holoendemic communities. Reliable epidemiological data is however scarce and so a stratification of malaria risk is to be an important activity in phase 1.

In 2009, 63 percent of Yunnan's malaria cases (1,832/ 2,987) were imported from Myanmar and more than 95 percent of these are believed to have come from the five Special Regions. Minimizing the number of cases imported from the area targeted by this application will therefore make a crucial contribution to China's NSA funded malaria elimination effort.

The goal of this programme is to improve the health status and life expectancy of people living in the five Special Regions of Myanmar bordering China, to contribute to the regional effort to prevent the further development and spread of artemisinin resistance, and to indirectly support the NSA funded elimination programme in China. Efforts will focus on strengthening malaria control in the target area, reducing the selection pressure for artemisinin resistance by preventing the use of fake and substandard antimalarials (including artemisinin monotherapy), and preventing the import of malaria into China by means of expanded border controls and special interventions targeting migrants in Myanmar.

The programme has four major objectives. Each will be achieved through the implementation of a series of activities as presented below:

Objective 1 is to improve access to diagnostic and treatment services. Health Unlimited (HU) will manage a series of interventions to dramatically increase the coverage of diagnostic and treatment services: it will improve the capacity and services of 80 public sector malaria diagnosis and treatment stations in the five Special Regions; in order to address gaps in public sector coverage, it will support malaria diagnostic and treatment services through 102 selected private sector healthcare providers (one in each township with no public sector malaria diagnosis and treatment station); and, it will establish

community based diagnostic and treatment services for malaria in 475 remote and highly endemic local communities (Village Malaria Workers - VMWs) and in 30 Chinese migrant communities in the target area (Migrant Malaria Workers - MMWs). HU will also continue to run outreach services incorporating BCC activities and supportive supervision of health facilities and VMWs/MMWs. The Yunnan Institute of Parasitic Diseases (YIPD) and China's Centre for Disease Control (China CDC) will establish 30 new border malaria posts at informal border crossing points in the 7 border counties not yet covered under the NSA grant (these posts will provide diagnosis and treatment for malaria and target migrants crossing into Myanmar with LLINs and BCC).

Objective 2 is to improve access to long-lasting insecticidal nets (LLINs) for Myanmar residents and Chinese migrant populations. HU will provide LLINs to all residents of villages in Myanmar with a high malaria burden. 146,000 and 196,000 large polyester LLINs will be supplied through mass distributions in years one and four respectively. HU will also manage a scheme to provide an additional 20,700 large LLIN to pregnant women in villages with high malaria burden. This scheme will be implemented through the existing network of traditional birth attendants (TBAs). In addition, HU mobile teams will provide 32,000 LLINs to Chinese workers based in Myanmar (through annual mass distributions coordinated with the employers of large migrant groups). YIPD/China CDC will provide 180,000 large polyester LLINs to Chinese workers migrating to Myanmar through the 30 new border malaria posts created under objective 1.

Objective 3 is to maximize the utilization of preventive, diagnostic and treatment services through the production of IEC materials and through communication for behaviour change. HU will conduct formative research and then develop BCC strategies and develop and produce user-friendly and ethnically appropriate IEC materials based on the outcomes of this research (this will be achieved with technical support through WHO). Community health education will be provided by HU through the training of 350 village volunteer peer group educators each year. In addition HU outreach teams will carry out sessions of community health education in 550 villages and Chinese migrant gathering sites each year. China CDC will provide IEC materials and BCC to Chinese workers migrating to Myanmar through the 30 new border malaria posts created with R10 support. In addition China CDC will set up 17,302 billboards to provide migrants with key malaria messages (one billboard in every poor village in the 7 border counties not supported by NSA).

Objective 4 is to strengthen project implementation, management and information exchange and enhance the efficiency of cross-border malaria control. YIPD will provide intensive residential training for malaria professionals from China and Myanmar. In order to improve the targeting of malaria control interventions, HU will develop a village level stratification of malaria risk in target regions of Myanmar (with TA through WHO). As a part of its technical activities, YIPD will carry out surveillance of drug sensitivity and vector bionomics and insecticide resistance in the five Special Regions. In an effort to support the regional strategy for the containment of artemisinin resistance, HU will support local authorities in Myanmar to decrease drug pressure for selection of resistant malaria parasites by introducing and enforcing a new regulation banning the sale of fake and sub-standard antimalarials (including monotherapy). The grant will support routine annual management and planning meetings for programme staff at PR, YIPD and HU levels. In order to coordinate migrant specific malaria control activities HU will establish regular communication with enterprises in the target area which employ Chinese workers. In an effort to coordinate Round 10 activities with those being implemented in other parts of Myanmar, the PR will support the strengthening of information exchange between China and the Myanmar Union. YIPD will undertake operational research in collaboration with international partners to support technical direction of the programme. The PR and the two SRs will supervise and

monitor implementation of interventions at each level. A financial audit of the entire programme will be carried out annually and an external evaluation will be conducted in year 2 (to support the Phase 2 request for continued funding) and in year 4 (to inform the development of a follow-on funding application). The grant will support the necessary resources (financial, human and commodity) for implementation of programme interventions. A technical assistance call-down facility will be established with WHO to provide quality technical support to all programme areas as and when needed. HU's London office will provide technical and administrative management of all components of the Round 10 grant implemented by HU.

The activities described in this proposal will contribute to the overall strengthening of the 80 public sector health facilities in Myanmar already covered by the Round 6 grant and extend support to these facilities for another 4 years after Round 6 ends. Activities will result in the dramatic strengthening of the malaria diagnostic and treatment services of selected private sector healthcare providers in townships with no public sector health facility, and result in the establishment of community based malaria diagnostic and treatment services in the most endemic communities in the five Special Regions, and in Chinese migrant communities in endemic areas. This multi-pronged public, private and community based approach will ensure that basic malaria diagnostic and treatment services are available in every township and in the 475 most endemic and remote communities in the five Special Regions. On the prevention side, HU will raise LLIN coverage in endemic areas from 1 net per 3.3 people to at least 1 net per 2 people. This will lead to high coverage and result in the bednets having a 'community effect' whereby even those not using them will receive some protection (thus increasing the cost effectiveness of the LLIN intervention). HU managers and mobile teams will coordinate the activities of the public, private and community based systems, to maximize their effectiveness. Together these activities will ensure dramatically improved malaria diagnostic and treatment service delivery, and greatly improved outcomes.

At the impact level: Malaria prevalence amongst residents in the five Special Regions is expected to fall from 7.5% in year 1 to 3% in year 5; API in the five Special Regions is expected to fall significantly (targets will be set once a baseline has been established in Phase 1); and, the number of malaria cases amongst Chinese migrant workers returning to China from Myanmar is expected to fall from 1,600 in year 1 to 650 in Year 5.

The budget requested for Phase 1 is US\$8,942,362 and the budget requested for Phase 2 is US\$12,944,967.

Total Budget requested: US\$ 21,887,329.

2. Thailand

The following is an excerpt from Summary the Round 10 proposal from Thailand, which was approved. It covers all containment activities in the country including Cambodian and Myanmar borders. Introductory paragraphs on earlier activities and the failed Round 9 proposal are omitted as redundant.

Title: CONTAINMENT OF ARTEMISININ RESISTANCE AND MOVING TOWARDS THE ELIMINATION OF *PLASMODIUM FALCIPARUM* IN THAILAND

The programme's overall objective is **to move towards the elimination of *Plasmodium falciparum* malaria parasites in Thailand**. Strengthening of systems to detect and respond to all *P. falciparum* cases will also address the urgent need for containment of artemisinin resistant parasites which threatens to undermine regional and global malaria control efforts.

This will be achieved through the implementation of strategic activities aimed at removing selection pressure and reducing and ultimately eliminating falciparum malaria through the implementation of a range of activities associated with the following four specific objectives with special attention on migrants and mobile populations:

1. To eliminate artemisinin resistant parasites by detecting all malaria cases (both asymptomatic and symptomatic) in target areas and ensuring effective treatment and gametocyte clearance using combination therapies.
2. To prevent transmission of *P. falciparum* parasites through vector control and personal protection measures.
3. To support containment/elimination of *P. falciparum* parasites through comprehensive behaviour change communication, community mobilization and advocacy.
4. To provide an effective management system (including surveillance, monitoring and evaluation) to enable rapid and high quality implementation of the strategy.

The PR will be the Department of Disease Control (Ministry of Public Health) which has extensive experience in program management (responsible for seven successful GF grants). The PR will be supported by the following identified sub-recipients (SRs) with complementary skills and geographical areas of operation:

1. **Bureau of Vector-borne Diseases (BVBD)** in collaboration with provincial health teams (22 provinces) will focus on strengthening existing public health and malaria delivery facilities including community activities and overall data management, reporting and measurement of outcomes; provincial teams will manage and supervise NGO-run health facilities expected to provide health care to migrants but will also set up new Malaria Posts (MPs) on the border with Myanmar
2. **International Rescue Committee (IRC)** will contribute to their health facility network inside and outside 9 camps along the Thai-Myanmar border to provide malaria diagnosis and treatment on Directly Observed Therapy (DOT) to migrants as well as IEC/BCC
3. **American Refugee Committee (ARC)** will implement a migrant health worker (MHW) and migrant health volunteer (MHV) network in Kanchanaburi, Petchaburi, Chumphon and Ranong provinces
4. **International Organization for Migration (IOM)** with their experience in increasing access to the health for migrants, will conduct formative assessments and focus on specific interventions (e.g., BCC/IEC package, LLIN/LLIHN distribution, etc) targeting migrants and mobile populations from a community perspective in 7 provinces (Chiang Rai, Chiang Mai, Mae Hong Son, Tak, Sa Kaew, Chantaburi, and Phang Nga)
5. **Raks Thai Foundation (RTF)** will develop community mapping focused on migrant and mobile populations in 9 provinces (Ratchaburi, Prachaubkirikhan, Si Saket, Ubon Ratchatani, Trat, Chonburi, Songkla, Surathani, and Rayong).
6. **Kenan Institute Asia (K.I. Asia)** through United States Pharmacopoeia (USP) will focus on monitoring drug quality and supporting remedial action against substandard drugs, quality assurance of long-lasting insecticide treated nets (LLIN), and school-based BCC/IEC interventions.
7. **Centre of Excellence for Biomedical and Public Health Informatics (BIOPHICS)** together with the Geographical Unit of Mahidol University will focus on increasing the performance of the internet-based surveillance system countrywide and with

inputs from BVBD, Malaria Consortium, and other partners develop and implement this Management Information System (MIS) for surveillance and M&E.

8. **Shoklo Malaria Research Unit (SMRU)** will strengthen its technical support to 8 clinics on the border under R7 and will provide extra technical assistance to nongovernmental organizations (NGOs) managing health care facilities targeting unrecorded displaced persons in case management, day3 follow up, quality of care (severe malaria) and surveillance.
9. **Malaria Consortium Asia (MC Asia)** will provide technical assistance support for overall monitoring and evaluation of the programme, including household malariometric surveys and support for operations research.

In addition WHO will use its existing country and sub-regional network (mainly supported by USAID) to ensure links and cooperation between concerned Member States and, together with the Malaria Consortium Asia (based in Mahidol University), provide inputs into the M&E and surveillance system. WHO will support an antimalarial drug policy review meeting in Thailand in November 2010 to select an alternative ACT to the current one (which is provisionally budgeted in this proposal) and potential treatment options to manage *P. falciparum* malaria.

The total requested budget under this R10 proposal is approximately **US \$101 million** over five years.

Annex 4. Antimalarial drug resistance and therapeutic efficacy for *P. falciparum* malaria in Myanmar and selected neighbouring countries

As the subject of antimalarial drug resistance has been extensively reported in journal literature and WHO reports on Thailand, as the importance of China per se as a reservoir (and therefore conduit) for falciparum malaria is dwindling, it has been decided to quote some pertinent studies and data only from India and Bangladesh. A huge amount of information on drug resistance has been compiled in a monograph on antimalarial drug resistance in Myanmar, the latest version of which is a draft dated May 2009. This is presented in section 1 of this annex. Section 2 includes results obtained in Myanmar in 2009-10. Section 3 focuses on India and Bangladesh. The results are discussed in the main text.

1. Edited excerpts from Monograph of Drug Resistant Malaria in Myanmar (Draft, May 2009)

In deciding which sections to excerpt from this thorough review, it was decided to give priority to *in vivo* studies and to newer studies, especially those concerning artemisinins. The two maps in this Annex are sourced from Ye` Htut: *Update on drug resistant malaria and the activities and challenges in monitoring therapeutic efficacy of antimalarial drugs in Myanmar*: Presented at the Malaria Centre, London School of Hygiene and Tropical Medicine, 2 May 2007.

Abbreviations

ACPR	Acceptable Clinical and Parasitological Result
AS	Artesunate
AM	Artemether
DMR	Department of Medical Research (of Department of Health)
DSGH	No.1 Defence Services General Hospital, Mingaladon
MH	No. 2 Military Hospital, Yangon
MQ	Mefloquine
R	Resistance/resistant
SP	Sulfadoxine-pyrimethamine
TSN	Technical Support Network
VBDC	Vector-borne Disease Control Programme of Department of Health

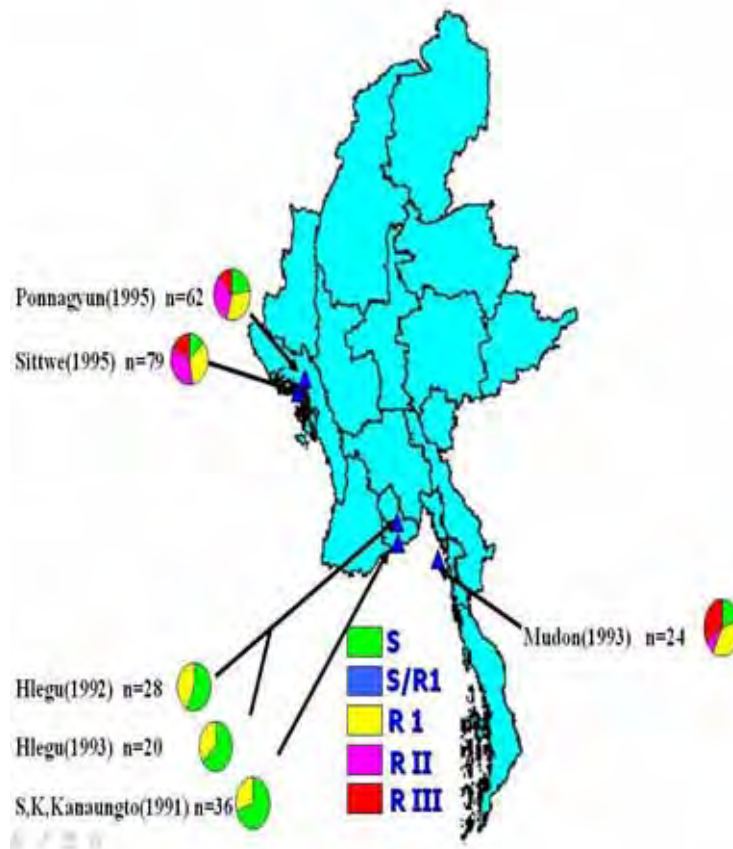
Chloroquine

In **1969**, it was first noticed that patients with malaria frequently had recrudescences soon after a standard dose of chloroquine. A small clinical trial in Bago in 1969 indicated that chloroquine resistant *P. falciparum* existed in Myanmar. Map 1 shows the situation of chloroquine resistance, 1991-5.

Amodiaquine

In 1980 Franco Tin & Nyunt Hlaing reported resistance to standard dose of amodiaquine in Thandaung to be 14/33 (42 %), all at R1 level; and at six other areas (R1:R2/R3=93:7). A study on amodiaquine 1500mg over 3 days in the Shan States, on 19, 24 and 104 patients in 1985, 1986 and 1987, followed up for 7 days, reported sensitivity (S/R1) of 94.7%, 62.5% and 49% respectively.

Fig. 1. *In vivo* 28 day tests with chloroquine in Myanmar, 1991-1995



Sulfadoxine-pyrimethamine (SP)

SP was introduced as a **therapeutic drug** during early 1980's in Myanmar and was recommended as the second line drug for falciparum malaria.

In 1971, SP resistance was first reported by F. Tin & N. Hlaing when single dose SP was used a trial basis for 40 patients, 21 of whom were resistant to standard doses of chloroquine at R1 level. 1/40 was found to be resistant to SP. In 1979, a hospital based study on 30 patients followed up for 28 days also reported 20% resistance (including R1, R2 and R3). In 1980, a comparative study using sulfadoxine-pyrimethamine (SP) on 244 patients and sulfalene-pyrimethamine on 221 patients with *P. falciparum* followed for 2 months, reported R1 resistance of 3.7% and 9.2% within one month and 9.1% and 8.3% respectively between one and two months follow up period.

In 1995 at Dabine and Kuntaung villages in Rakhine State a 28 day trial on 296 patients reported sensitivity of 30% in Dabine and 36% in Kuntaung (*Trans. Roy. Soc. Trop. Med. &*

Hyg. 1997). In **1997**, a 14 day trial of SP at Katha (Sagaing Division), Hsipaw (Northern Shan States) and Tarchileik (Eastern Shan States) showed S/R1 of 50%, 83.3% and 37.5% respectively. (*WHO Bulletin*, 1999, 77/3).

According to VBDC reports on the therapeutic efficacy of chloroquine, SP and mefloquine in Myanmar in 14 day tests (**1999-2002**), the SP treatment failures were generally higher on the eastern border. The failure rates were 35% in Shan East (1999) and 100% in Kayin state in 2002.

Technical Support Network studies were done by DMR in collaboration with VBDC in **2002/2003** and showed ACPR of SP as 85.9% in Kalay (Sagaing Div), 67% in Myitkyina (Kachin State) and 70% in Myeik (Tanintharyi Div).

Mefloquine

In Myanmar, mefloquine was not generally recommended for prophylaxis, but in 1985, in special situations in south-eastern Myanmar, it was used for that purpose at dosage of 250mg/week. It had also been used for the treatment of hospitalized falciparum malaria patients, and it was included as the third line therapeutic drug for chloroquine resistant falciparum malaria at a dosage of 20mg/kg in 2 doses 8 hours apart (children 25mg/kg single dose), if available. (Malaria as a clinical problem today; *Proceedings of a Symposium at 35th Burma Medical Conference*, January 1988, page 42 and page 19). Initially, the malaria control programme used it in fixed-dose combination with SP (MSP) since 1990. After 1993, it was found that the MSP had no superior efficacy over mefloquine alone, so it was no longer used afterwards.

Studies were done in No. 2 Military Hospital, Yangon (MH) and No.1 Defence Services General Hospital, Mingaladon (DSGH) since **1984** using 28 day test. Mefloquine was given as a total dosage of 750 mg or 1000 mg in the early years. After 2001, the dose was increased to 1250 mg in divided doses. The earliest study in **1984** showed sensitivity 100%, followed by 94% (1990) and 80% (**1991**). Dose finding studies showed sensitivity 80% with 1000 mg and 94% with 1250 mg in **1996**. The lowest rate was found among patients from Kayin State, showing sensitivity of 36% in **1991**.

Vector-borne Disease Control Programme and Civilian hospitals conducted studies as follows. In Thandaung township (Kayin State) in **1980**, S/R1 in children was 91% and in adults 98.3% using Mefloquine (750mg total dose) (*WHO Bulletin* 1988). Another study in Mong tone (Eastern Shan State) showed S/R1 of 100% in **1988** and 75% in **1991**. A study in Rakhine state during **1995** showed S/R1 of 92%. Studies found declining efficacy of Mefloquine between **1987 and 1992** (*Ye` Thwe et. al.* 1997) especially in patients who had contracted malaria from the Kayin and Kayah States (*Kyaw Win et. al.* 1993).

A dramatic example of rapid spread of drug resistance has been reported in the period of **1991-1992**, when migrant gem miners returning from the Pailin gem fields in Cambodia carrying drug resistant malaria, spread the resistant strains to Trat (east) and Tak (west) provinces of Thailand, as evidenced by a precipitous fall in MSP cure rate over a short time frame in the two provinces, (*Thimasarn et. al.* 1995). From Tak the resistant strains spread rapidly to Myanmar. Fig. 2 shows the east-west gradient observed during that period.

A multicentre study of mefloquine (750mg total dose) in Katha (Sagaing Division), Hsipaw (Northern Shan State) and Tarchileik (Eastern Shan State) in **1997** showed S/R1 100%, 100% and 77.80%, respectively. However, S/R1 declined to 68% in Tarchileik in **1999**. (*WHO Bulletin* 1999, 77/3). According to studies by Technical Support Network (**2002-2003**), the efficacy of Mefloquine (1000 mg) was reported as ACPR 94% in Myeik (Tanintharyi Division), 81% in Myitkyina (Kachin State) and 91% in Kalay (Sagaing Division).

From DMR field studies, mefloquine treatment failure at R1 in a 28 day trial was first recorded in **1992** in Tarchileik near the Thai-Myanmar border (Fig. 2). Subsequent studies documented mefloquine failures (R2 & R3) at 12.4% in Shan East in **1997**, increasing to 17%

in **1999**. Kayin state documented 26% mefloquine treatment failures (R2 & R3) in **1999**. All documented studies of mefloquine treatment failures (R2 & R3) came from districts bordering with Thailand on the east: 15% in Mon State, 21% in Kachin State and 45% in Myawaddy- Kayin State in **2002**.

The drug efficacy status of CQ, SP and MQ from **1999 to 2000**, using mainly the 14-day *in vivo* test shows that MQ sensitivity was 75% at Myawaddy (Kayin State) and 83% at Tarchilek (Eastern Shan State), 90% in Kawthaung (Tanintharyi Division) and more than 90% in all other sites.

Quinine

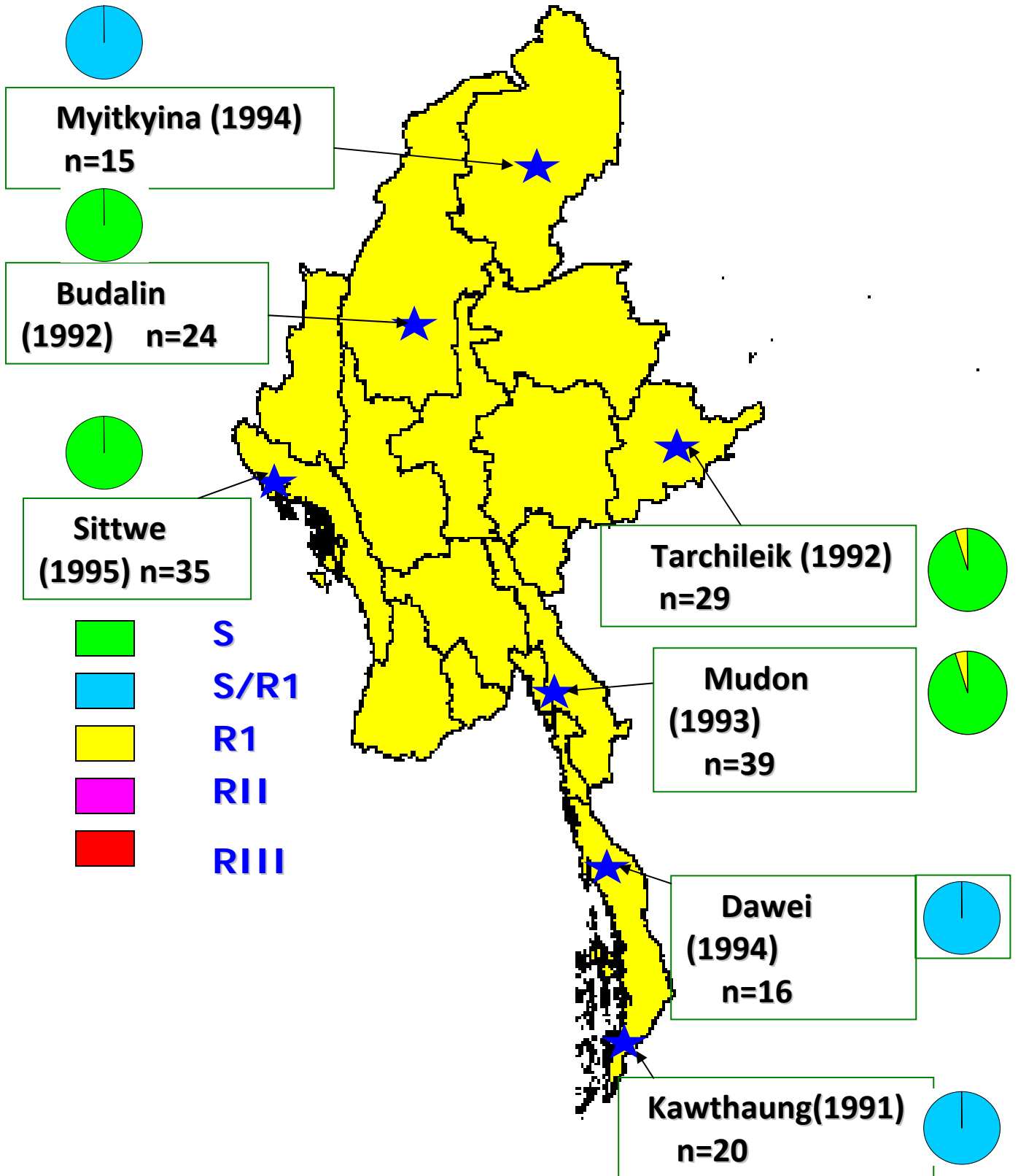
Many clinical efficacy studies were done on alternative drug regimens using oral quinine as the standard drug to compare with.

In **1993**, sensitivity using the standard 7 day regimen was found to be 85.7% in Lashio (Northern Shan States) and another hospital based study reported 55% on 20 patients in **1998-99**. A study in **1997-98** at Intagaw (Bago Division) using oral quinine plus tetracycline for 7 days reported 100% sensitivity. Field studies showed 42% S/R1 at Hlelangu, Thayawaddy district in Bago Division in **1983** and 83.87 % in Thayawaddy (Bago Division) in **1986**.

Atovaquone –proguanil

At DSGH Mingaladon in **1998-99** a 28day clinical efficacy trial on 12 patients, reported a Sensitivity of 100%. In **1999-2000**, at DSGH comparing atovaquone–proguanil on 22 patients with artemether on 24 patients, followed up for 28 days reported PCTs of 90.57 ± 39.32 and 84.43 ± 66.66 hours; and sensitivity of 100% and 95.85% respectively .

Mefloquine 28 day *in vivo* tests in Myanmar 1991-1995



Piperaquine

In **1995**, at DSGH, 61 adult male patients were given Piperaquine Composite Tab (piperaquine phosphate 250mg + sulphadoxine 50mg) 4 tablets followed by 2 tablets after 8-12 hours (total dose 1500mg). The parasite and fever clearance times were 36.49 ± 18.5 hours and 24.76 ± 16.18 hours respectively. The 7 days, parasite clearance rate (S/R1) was 98.21%. However, at 28 days the R1 recrudescence rate was 53.57%. No adverse clinical or laboratory effects were noted.

Artemisinin and its derivatives

Monotherapy

In **1983**, at DSGH intramuscular artemether compared to intravenous quinine in 60 uncomplicated falciparum malaria patients followed up for 28 days reported cure rates of 83.4% and 76.7% respectively. In **1985**, at Tharyawaddy Civil Hospital, comparing intramuscular artemether with intravenous quinine on 31 pairs of complicated and severe falciparum malaria, followed up for 28 days; reported all survived and 2 died ; with R1 resistance of 39.1% and 9% in the artemether and quinine groups respectively. (*Transactions Roy. Soc. Trop. Med & Hyg.* 1987, Vol.81). Further studies from the same hospital site in **1986** and **1987** reported the efficacy of artemether in cerebral malaria patients with coma. (*Transactions Roy. Soc. Trop. Med & Hyg.* 1988, Vol.82 and 1989, Vol 83). At MH in **1994/95**, the same dosage of intramuscular artemether on 40 patients reported that 73.33% of patients cleared parasitaemia by 18 hours, 87.5% by 24 hours and 100% by 30 hours. Average parasite clearance time was 20.2 hours. Cure rate at 28 days was 100%. However, 2 cases had recrudescence on Day 30. No serious side effects were encountered.

Artemisinins in combination with other antimalarials including comparative studies

In **1992-1994**, dose-finding studies on artemether monotherapy at 360-960mg over 7 days showed 60-70% Sensitivity, improving to 94-100% when given in combination with mefloquine. Artemether + doxycycline were also shown to be effective with 97% sensitivity and artesunate + doxycycline over 5 days had 94% Sensitivity.

In the mid-to late 1990s, when these trials were conducted, mefloquine monotherapy was still highly effective in some sites in Myanmar (95% sensitivity in 14 day field trials). However, a 28 days clinical trial in DSGH in **1991**, comparing artesunate and mefloquine as single agents to artesunate + mefloquine combination, showed that there was increased sensitivity of the combination therapy (96.43%) compared to mono-therapy of each drug (Artesunate 75% and Mefloquine 78.45%) (*Kyaw Win et. al.*1994). The patients were kept in hospital for the entire 28 days and hence there was no chance of re-infection. This study was done on non immune military population who had received ineffective SP prophylaxis.

Between **1994-2000**, using suppository artesunate (*Plasmotrim caps™*), studies in uncomplicated as well as in severe falciparum malaria it was found that higher dose artesunate 1200mg + mefloquine 1500mg regimen gave better cure rates 93-96% sensitivity compared to the lower dose Artesunate 800mg + Mefloquine 1500mg regimen 83-84% sensitivity.

A field trial using artesunate plus mefloquine, at Intagaw (Bago Division) in **1997-98**, reported 100% sensitivity and in **2002**, 96.9% sensitivity.

Twenty-eight day clinical studies in DSGH in **2002**, comparing artemether + lumefantrine (AM +L) with mefloquine (MQ) showed 100% ACPR with AM-L, and 85% with MQ. In **2005**, the efficacy of five different brands of artesunate was tried in loose combination with mefloquine and all showed 100% ACPR. Comparing co-formulated dihydroartemisinin + piperazine and dihydroartemisinin + mefloquine in **2006-2007** also showed 100% ACPR. Comparing 2 and 3 doses of a co-formulated preparation of artemisinin + piperazine showed 92.2% and 94% ACPR, respectively.

To provide baseline data on ACTs, prior to the nationwide use of these in the new treatment guidelines, according to the change in antimalarial drug policy, TSN field-based trials with artemisinin-based combination therapy were conducted by VBDC team and DMR Lower Myanmar at Indagaw (Bago Division) in **2002 and 2003** using artesunate in combination with tetracycline, doxycycline, clindamycin or SP, and in **2004**, at several other sentinel sites using artesunate plus mefloquine or amodiaquine and artemether. The results showed ACPR above 93%. Field based studies on co-formulated artemether + lumefantrine between **2004 and 2008** carried out by VBDC and DMR lower Myanmar all showed efficacy above 90%. A trial at Pyin Oo Lwin (Mandalay Division) by VBDC Upper Myanmar in **2007**, using co-formulated artemisinin + naphthoquine also reported 94.5% ACPR.

A study at the sentinel sites in **2007**, comparing artesunate + amodiaquine with artemether-lumefantrine at 4 sentinel sites: - Rakhine (70,85), Kayin (33,40), Mon (45,40) and Kachin States (79,72) patients followed up for 28 days revealed that 2 cases in the artesunate + amodiaquine group (one each from Kayin and Mon States) and 2 cases in the artemether -lumefantrine (both from Mon State) were LTF confirmed by PCR technique to be true recrudescences (*Myat Phone Kyaw et. al. 2008*). It is possible that AM+L may not have been absorbed properly. Pharmacokinetic support was not feasible in this study.

In a clinical efficacy study in DSGH (**2008**), prolonged PCT was observed 49.96 ± 34.28 hours with Artequick™ (artemisinin + piperazine fixed dose combination) 3 dose regimen on 50 patients, with directly observed treatment and follow-up for 28 days in hospital. Percentage parasite clearance was 36.7% at 24 hr, 61.2% at 48 hr, 79.6% at 72 hr and 93.9% on Day 7, (*Khin Phyu Pyar, et. al. 2009*). The findings suggest that increased tolerance of *P. falciparum* maybe developing to Artemisinin – piperazine. It is also possible that drug metabolism may be the problem, as artemisinin needed to be metabolized to the active form of dihydroartemisinin in the body.

2. Studies on therapeutic effectiveness and efficacy of artemisinins and ACTs conducted in 2009-10

In a randomised trial in Rakhine, Kachin and Shan states in 2009, the **effectiveness** of fixed-dose ACTs (artesunate–mefloquine, artesunate–amodiaquine, dihydroartemisinin–piperazine, artemether–lumefantrine) and loose artesunate–mefloquine was compared in adults and children with uncomplicated *Plasmodium falciparum* malaria or mixed infection

All patients were also randomly assigned to a single dose of primaquine 0.75 mg /kg or not. Patients were followed up for 63 days. 155 patients received artesunate–amodiaquine, 162 artemether–lumefantrine, 169 artesunate–mefloquine, 161 loose artesunate–mefloquine, and 161 dihydroartemisinin–piperazine. By day 63 of follow-up, 14 patients (9.4%; 95% CI 5.7–15.3%) on artesunate–amodiaquine had recrudescence *P falciparum* infections, a rate significantly higher than for artemether–lumefantrine (two patients; 1.4%; 0.3–5.3; $p=0.0013$), fixed-dose artesunate–mefloquine (0 patients; 0–2.3; $p<0.0001$), loose artesunate–mefloquine (two patients; 1.3%; 0.3–5.3; $p=0.0018$), and dihydroartemisinin–piperazine (two patients 1.3%; 0.3–5.2%; $p=0.0012$). The addition of a single dose of primaquine reduced *P falciparum* gametocyte carriage substantially: rate ratio

11.9 (95% CI 7.4–20.5). All regimens were well tolerated. Adverse events were reported by 599 patients, most commonly vomiting and dizziness.⁴⁷

The excellent effectiveness of three ACTs is encouraging; the high failure rate of amodiaquine-artesunate is what would be expected given the poorer results with this combination in the past. It should be noted that the study was conducted relatively far from the areas in Thailand and Myanmar, where there is now evidence of artemisinin resistance. It should be noted that the study was an effectiveness trial. High cure rates were achieved in a scenario, where only the first dose was given under supervision and the remaining self-administered on the basis of careful guidance to patients and caretakers. This confirms several studies from Africa: It is possible to achieve high levels of compliance with ACTs, in a health service setting, where due attention is given to instruction and education. The most striking finding of this study is the very marked reduction of gametocyte carriage by adding a single dose of primaquine – despite the fact that artemisinins have a degree of gametocytocidal effect.

In 2009, Therapeutic Efficacy Studies (TES) were done at three sites in Myanmar examining the efficacy of ACTs (Artemether-Lumefantrine and Dihydroartemisinin-Piperaquine). The results from these studies can be seen below.

ACT studies, Myanmar 2009	Artemether - Lumefantrine (Coartem)			Dihydroartemisinin-Piperaquine (Duocotexin)	
	Shwe Kyin, Bago East	Kawtaung, Taninthayi	Kalay, Sagaing	Shwe Kyin, Bago East	Kawtaung, Taninthayi
Adequate Clinical and Parasitological Response	84 (98%)	74 (92.5%)	72 (99%)	100%	76 (95%)
Early Treatment Failure	1 (1.1%)	0	0	0	0
Late Clinical Failure	0	5 (5.7%)	1	0	2 (2.5%)
Late Parasitological Failure	1 (1.1%)	1 (1.1%)	0	0	2 (2.5%)
Withdrawal	0	2	0	0	1
Loss to follow-up	2	0	4	0	0
Day 1: % parasitemia	53 (60%)	48 (60%)	0	48 (67%)	56 (69%)
Day 2: % parasitemia	34 (39%)	18 (22%)	0	10 (14%)	28 (35%)
Day 3: % parasitemia	9 (10%)	4 (4.5%)	0	3 (4.2%)	15 (19%)
Day 0: % gametocytemia	18 (20%)	27 (34%)	0	16 (22%)	7 (9%)
Day 7: % gametocytemia	0	4 (4.5%)	0	0	5 (6%)

Especially the data from the study in Kawthaung is worrisome as 19% of patients treated with dihydroartemisinin-piperaquine and 4.5% of patients treated with artemether-lumefantrine were positive on day 3. The results of these studies unfortunately show that it is highly probable that resistance has developed. To confirm that it is true artesunate resistance it is necessary to do a study which includes testing of blood drug concentration. One such study testing artesunate monotherapy will be conducted early 2011 in Kawthaung.

In 2009, a study was conducted near Yingjiang, Dehong Municipality in Yunnan, China. This study site is located at a clinic on the border to Kachin State, Myanmar, about 78 km south of Myitkyina, and nearly all the patients were from Myanmar. Here 25% of the patients treated with 7-day artesunate were positive on Day 3, but there were no late failures after PCR correction. The initial parasite density in this study was 24,120 per μl , which is unusually high. This might have contributed to the high Day 3 positivity rate. Thus,

⁴⁷ Smithuis F. et al. Effectiveness of five artemisinin combination regimens with or without primaquine in uncomplicated falciparum malaria: an open-label randomised trial. *The Lancet Infectious Diseases*, 2010. www.thelancet.com/infection Published online September 9, 2010 DOI:S1473-3099(10)70187-0

the findings in this study do suggest a suspicion of artemisinin resistance, but further evaluation would be necessary. Other studies by Myanmar researchers in Kachin State have not indicated a resistance problem.

In 2010, the following TES were done:

- Kawthaung, Tanintharyi (Drug: AL, CQ)
- Myawaddy, Kayin (Drug: AL, CQ)
- Kyauk Taw/Ponnargyun, Rakhine (Drug: AL, DHA-Pip, CQ)
- Myitkyina, Kachin (Drug: AL, DHA-Pip, CQ)
- Thanphyuzayat, Mon (Drug: DHA-Pip, CQ)
- Kyaing Tone, Eastern Shan (Drug: AL, DHA-Pip, CQ) (On-going)

Only the preliminary results from these studies are available. These results have contributed to an adjusted zonation.

3. Studies from selected neighbouring countries: Bangladesh and India

Bangladesh

Bangladesh adopted an ACT treatment policy around 2005. WHO Global malaria database (2010) findings indicate no problems with artemisinin resistance up to 2008 in Bangladesh (excerpt from Table A.1.2. below).

Bangladesh					
Artemether-lumefantrine [42 d]	2003-2007	3	2.9	0.0	5.7
Artesunate-mefloquine	2003-2003	1	0.9	0.9	0.9
Chloroquine	2004-2004	1	57.7	57.7	57.7
Chloroquine-sulfadoxine-pyrimethamine	2002-2003	6	28.3	12.9	33.0

In Chittagong Hill Tracts, around 2004, 364 *P. falciparum* patients were recruited and randomly assigned to either CQ + SP, mefloquine + artesunate (MQ + AS) or lumefantrine + artemether (Coartem™). Results showed that CQ + SP therapy was less effective than the two artemisinin-based combination therapies. The day 42 PCR-corrected efficacy rate was 62.4% for CQ + SP, 100% for MQ + AS and 97.1% for artemether + lumefantrine.⁴⁸ A later study found a cure rate of artemether + lumefantrine of 94.3%.⁴⁹ Thus, so far there seems to be no problem of artemisinin resistance in Bangladesh.

India

India adopted an ACT treatment policy for Northeast and selected other areas in 2008 and nationwide in 2010. WHO Global malaria database (2010) findings indicate no problems with artemisinin resistance up to 2008 in India (excerpt from Table A.1.2. below).

⁴⁸ van den Broek IV et al. Efficacy of chloroquine + sulfadoxine-pyrimethamine, mefloquine + artesunate and artemether + lumefantrine combination therapies to treat *Plasmodium falciparum* malaria in the Chittagong Hill Tracts, Bangladesh., *Trans R Soc Trop Med Hyg.* 2005 Oct;99(10):727-35. *Wien Klin Wochenschr.* 2006;118(19-20 Suppl 3):58-61.

1 ⁴⁹ Haque et al. Therapeutic efficacy of artemether-lumefantrine for the treatment of uncomplicated *Plasmodium falciparum* malaria in Bangladesh.

India						
Artemether-lumefantrine	2007-2008	3	0.0	0.0	1.4	
Artesunate-sulfadoxine-pyrimethamine	2005-2007	9	0.0	0.0	4.0	
Chloroquine	2001-2008	85	37.5	0.0	100.0	
Sulfadoxine-pyrimethamine	2001-2007	22	13.6	0.0	56.7	

Sehgal et al. (1973) first documented chloroquine resistant *P. falciparum* in Northeast India in the Karbi-Anglong district of Assam, in the north-east in 1973. At 5 year intervals different regions show a similar trend of increasing chloroquine resistance but with different speeds. Drug resistance has been consistently high in the Northeast area and lowest in the North-central area.

The first reports of SP resistance emerged, again from Karbi-Anglong in Assam in 1979 (Das, 1981). SP resistance increased from 12% in 1984-92 to 23% in 1997-07, largely in Northeast India. Between 1978 and 2007, 17 studies of SP efficacy with 891 patients of SP were conducted. One study used sulfalene-pyrimethamine (Karbi-Anglong, Assam, 1984), while the rest used sulfadoxine-pyrimethamine. SP resistance increased from 12% (18/147, 95%CI 7.9-18.5) in 1984-92 to 23% (170/744 95%CI 20.0-26.0) in 1997-07 (Table 2). Most of the studies were conducted in North-eastern states with Arunachal Pradesh, which is along the China and Burma borders, displaying the highest SP failure rate.

Fig.3

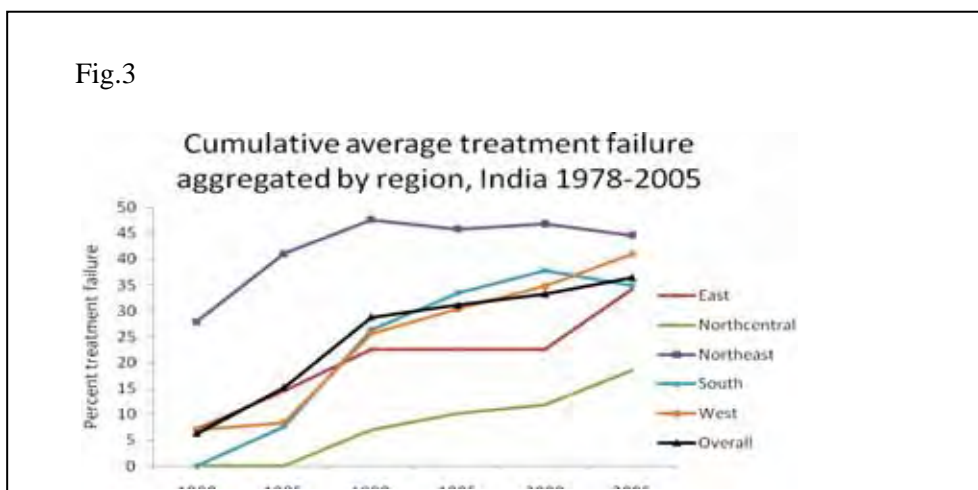


Table 1. SP resistance in India

State (district)	Year	n	total failures	%
Arunachal Pradesh				
Changlang	1992	57	4	7
Changlang	1999	43	19	44
Changlang	2002	65	35	54
Lohit	2002	70	12	17
Assam				
Karbi-Anglong	1984	30	8	27
Karbi-Anglong	2001	51	18	35
Nagaon	2002	78	0	0
Nagaon	2003	32	0	0
Sonitpur	2001	49	21	43
Sonitpur	2003	32	0	0
Darrang	2004	37	4	11
North Lakhimpur	2007	47	6	13
Madhya Pradesh				
Mandla	1997	114	42	37
Orissa				
Sundargarh	1991	60	6	10
Keonjhar	2002	61	0	0
West Bengal				
Purulia	2000	30	7	23
Bankura	2005	35	6	17
Total		891	188	21

Scientists from National Institute of Malaria Research, New Delhi, report “lack of” *falciparum* cases in North-east following massive deployment of LLINs and RDTs + ACTs; such a state does not indicate a problem of spreading artemisinin resistance.

⁵⁰ All of the following information about India has been excerpted from published and unpublished reviews by Dr N. Valecha *et al.*, National Institute of Malaria Research, New Delhi. Some of it is now published in Shah *et al.* Antimalarial drug resistance of *Plasmodium falciparum* in India: changes over time and space. *Lancet Infect Dis* 2011; 11: 57–64

Annex 5. Studies on provider behaviour, treatment-seeking, and antimalarial usage and availability in Myanmar

1. Excerpts from Monograph on Antimalarial Drug Resistance in Myanmar

Studies on general medical practitioners

The following study was conducted before the initiation of a special project for involving general practitioners in correct diagnosis and treatment of malaria. It probably still illustrates the situation of management of malaria in the informal private sector.

In a study using telephone interviews carried out on GPs from 6 selected Divisions in Myanmar, less than 5% of uncomplicated falciparum malaria cases treated by the GPs received ACTs (Artemether / Artesunate + Mefloquine) because of the high cost of the regimen. Only 7.2% of GP's used microscope and 2.9% used RDT kit and 5.8% referred to a laboratory for the diagnosis of malaria. The GPs understood the importance of giving complete course of antimalarials but because of socio-economic constraints they had to prescribe on a daily basis. Self medication and buying direct from road side sellers was very common. Patients sought treatment only when their own treatment did not work. Artemisinin derivatives were widely available over the counter in districts. GPs were enthusiastic and ready to help the population if they received relevant support, (*Chit Soe, 2004*).

In another KAP study fifteen GPs each from 10 malaria endemic districts (total 150) were interviewed between July and October 2005. It was reported that 35% of GPs used Artemisinin, out of which 20.3% gave treatment with ACT and 14% with Artemisinin alone. 33% gave a prescription and 98.6% used an injection, (*Chit Soe. 2007*).

In a study from the QDSTM project of MMA on the ACT usage among GPs it was found that only 26/39 (38%) used either RDT or Microscope for the diagnosis of Malaria and 32/69 (46%) used ACT for clinically uncomplicated malaria. From a qualitative telephone survey, the reasons for not using ACT were given as: *"ACT is not available for GP, only for basic health staff (before project), ACT cannot be bought in market, Patients had already taken artesunate tablets by themselves. Only Quinine injection can impress them. Available artesunate are not reliable, may be fake drugs. We don't know how to differentiate fake drugs. Guidelines are changing frequently. I doubt whether it is necessary. They recovered well with our current treatment. We don't know the sensitivity tests. We mostly rely on clinical diagnosis. So, cannot use expensive combinations. Doxycycline is cheap compared to mefloquine. Natives don't think malaria as deathly disease and they look for cheapest treatment, even self treatment. So I can't use expensive blood test or ACT. Although there is lab with microscopy service, the results are doubtful. So I use middle regime which will also cover bacterial infection (Artesunate + Doxycycline)"* – (*MMA - QDSTM Presentation made at the Technical Meeting on Antimalarial drug resistance in Myanmar 13th March, 2009, Yangon.*

Study on general population

According to various documents, health-seeking studies suggest that only around 25% – 40% of suspected malaria cases seek care in the public health facilities due to various factors such lack of diagnostics and drugs, geographic barriers and easy availability of malaria treatment, albeit inappropriate, in endemic villages; however, the number of detected cases

(about 0.5 million) is only about 10% of the estimated burden. The discrepancy is explained by poorer access among those at highest risk.

In one KAP study it was reported that over 60 percent of the respondents took self treatment for malaria and only 22% took complete course and 10% said they omitted by themselves once symptoms were relieved (*Myat Htut Nyunt et. al. 2008*)

In a study exploring the context of family decision-making in response to malaria, it was reported that the husband alone decided on the first action at home and gave chloroquine to a child under 10 years of age in over 20% of cases (*Tin Oo et. al. 2007*). In rural areas, most people self-medicate with various drugs bought from shops given in various dosages and combinations.

Cost and convenience of Artemisinin formulations available in Myanmar

Table 1, compares the approximate retail prices and the convenience, in terms of total number of tablets, the frequency of dosing and the duration of therapy, of each Artemisinin combination currently available in the market. The value of 900 Kyat is approximately 1 US\$; the prices for the different products are generally twice as high as those for the same drugs, if they were imported in bulk at competitive prices, indicating a considerable mark-up.

Table 1. Comparing the Cost & Convenience of Different Brands of Artemisinin formulations in Myanmar between 2004 and 2008
(* Approximate price - Source from local drug stores)

ACTs (Generic)	Trade Name & Formulations	Total Tabs / Doses per course	Duration of therapy hrs	Retail price* (Kyats)
ARTEMETHER (Tabs/ Caps) Single	Artemether - Kunming- PRC	10/5	96	2500/ 12tab
ARTEMETHER (Inj.) ampoules	Artem - Kunming- PRC Larither - IPCA –India			1500/amp
ARTESUNATE (Tabs) Single	Artesunate - Guilin phar -PRC Plasmotrim lactab Mepha-Switz Dawnasunate -MPFMyanmar	12/3 NA NA	72 NA NA	3000/12tab
ARTESUNATE (Inj.) ampoules	Artesunate -Guilin phar -PRC			2000/amp
AM +Lumefantrine (Tabs) FDC	Co-oartem –Beijing Novartis Artefan – Ajanta India	24/6 18/6	60 60	NA 5000
AS + Mefloquine (Tabs) Blister packs	Arfloquine -Kaledoscope Vietnam Artequin - Mepha-Switz	3+3/3 3+6/3	48 48	2000 NA*
AS + Amodiaquine (Tabs) Blister packs	Amonate –Dafra Phar. Belgium Arsumon - Guilin phar -PRC Artekam - XL Lab India Larimal - IPCA –India Artemodi –Beijing Holley Cotec	NA 6+6/3 NA 6+6/3 3+3/3	NA 48 NA 48 48	3000 to 4000/ pack
DHA + Piperaquine (Tabs) FDC	Duo-cotecxin -Beijing Holley Cotec Artekin - Beijing H Cotec Artepip - Holleykin,Nanjing Real Piperamisinin - MPFMyanmar	8/4 8/4 8/4 12/6	32 32 32 48	3200 NA NR NA
AMSN + Piperaquine (Tabs) FDC	Artequick 2 doses <i>Artepharm</i> Guangzhou China 3 doses	4/2 or 6/3	24 or 48	NA
AMSN + Naphthoquine (Tabs) FDC	Arco AMMS Beijing China (KPC)	8/1	stat	NA

(AM = Artemether, AS = Artesunate, DHA = Dihydroartemisinin, AMSN = Artemisinin, MQ = Mefloquine,

L= Lumefantrine, AQ = Amodiaquine, PPQ = Piperaquine, NTQ = Naphthoquinone)

(FDC = Fixed dose combination, NA = Not available yet in market, NR = Not registered yet)

2. Study by PSI on supply chain in the private sector

In August 2010, PSI conducted a study of the supply chain for antimalarials in the private market in two townships in Kayin state, (Kawkraik and Hlaingbwe). The investigators themselves point out that the scale of the study was small, its geographic range very limited

and that the findings must be interpreted with all caution. The key findings were as follows (verbatim):

- 1. Client behaviour** The vast majority of clients consume artemisinin monotherapy in loose form (i.e. as individual pills rather than in strips) and do not complete the full course. Clients tend to consume 2- 3 pills and then stop when they feel relieved of symptoms of suspected malaria.
- 2. Provider behaviour** Providers/retailers typically report giving clients 'what they want'. Their self-reported behaviour is based on servicing client demand (which appears to be entrenched with regard to brand preference). Providers/retailers typically give clients artemisinin in tablet form in a form which is not a full treatment course. Providers tend to dispense incomplete doses of artemisinin monotherapy because clients are not willing to pay for a full course.
- 3. Market size** Based on data from two of the largest pharmaceutical businesses for the anti-malarial category, and assuming a typical behaviour of incomplete treatment of suspected malaria with 2-3 pills of artemisinin, the total number of suspected cases treated with an incomplete course is estimated to be between **6,888,000 and 10,332,000** cases
- 4. Market share** According to importer distributors, Monotherapies constitute **97%** of the total category of anti-malarials. AA Artesunate constitutes **70%** of all monotherapies in the monotherapy category. AA Artesunate constitutes **67%** of all anti-malarials in the market. Data at the level of pharmacies indicates that AA Artesunate constitutes **81.7%** of all anti-malaria drugs sold at this point in the supply chain. This is followed by Chloroquine and Artemether however their sales are much lower than AA Artesunate. If Chloroquine is removed from the market analysis (i.e. with only AA Artesunate's share of monotherapies being the focus of analysis) AA Artesunate comprises 94.5% of all monotherapies on the market.
- 5. Market structure** AA Pharmacy not only controls the monotherapy market it has a sophisticated distribution mechanism that penetrates to a very low-level of the supply-chain. Many pharmacists in towns/cities are supplied directly by AA's distribution mechanism. Approximately half of AA's sales are funnelled through wholesalers and a further half is transported directly to pharmacists and other providers (in towns and cities). The monotherapy market is therefore relatively centralized.
- 6. Brand loyalty** Clients are described by a wide assortment of providers as displaying considerable brand loyalty to AA Artesunate. In addition to this, providers believe that clients prefer AA Artesunate because it is more affordable than other antimalarials, has less side-effects associated with consuming the drug, and is more effective. AA Artesunate is therefore a strong brand and conveys a powerful series of ideas in the minds of both providers and clients. This suggests that displacing AA Artesunate will be a challenging task unless a compelling new behaviour can be marketed. Providers additionally described clients as not being favourable to changing drugs or changing behaviours.
- 7. Market price** The average POS price for AA Artesunate is 2,400 Kyats for a course of 12 tablets. This equates to 200 Kyats per pill or 400 Kyats to 600 Kyats (for 2 to 3 tablets which is associated with the predominant behaviour at present).
- 8. Market functionality** Markets are efficient and supply lower-level actors with Artemisinin when, and in the form they want in an efficient fashion.
- 9. Policy and legal framework** Artemisinin monotherapy is legal and is registered by the GOUM (although the government guideline encourages the use of combination therapy). There is therefore a high degree of contradiction and ambiguity within the policy and legal frameworks. AA (for instance) supplies AA Artesunate with a registration number.
- 10. Key market actors and ACT watch** AA Pharmacy presently includes ACTs in its product portfolio. ACTs constitute a small proportion of its overall product portfolio.

Annex 6. Assessment of the potential losses of lives, if artemisinin resistance spreads west of Myanmar

Comparing the periods 1982-89 and 1990-98, malaria mortality in children 0-59 months in southern and eastern Africa increased from 6.5/1000 to 11.9/1000, or by 80%. According to the authors, "the most parsimonious explanation for the changing mortality patterns in Africa over the past 20 years remains failing drug efficacy, possibly compounded by deterioration in health systems able to manage clinical drug failures."⁵¹

According to WMR 2009, there were an estimated 863,000 malaria deaths in the world in 2008. Of these, 89%, or 773,000 were in Africa.

According to the same report, the proportion of children under 5 years in Africa receiving ACT for malaria in 2008 was probably below 15%. Given current efforts at strengthening deployment, lowering of prices and mechanisms such as AMFm, it would be reasonable to expect coverage to increase to at least 70% over the coming 5-10 years, and on the basis of the historical data to assume that this would lead to a further reduction in current malaria mortality by at least 25%. The reduction could be less, because there are competing causes of improvement and increasing urbanization, but, in some areas with moderate transmission, there is a possibility for synergy between ACTs and vector control in reducing transmission, so that the effect could be greater than the historical chloroquine effect. In fact, if the Global Malaria Action Plan's objective of reaching near 0 preventable malaria deaths in the world by 2015 will be only approximately reached, it will to a large extent be a result of massive ACT deployment. Given expected population growth, it is not an exaggeration to assume that around 2015, ACTs could lead to 200,000 saved lives per year in Africa manifesting as a reduction compared to the currently estimated 773,000.

If artemisinin resistance should emerge in Africa (through spread or local emergence) in 2011, it would probably take about 10 years time before it would possibly manifest by greatly increasing the malaria mortality burden. This development took about 10 years from when chloroquine resistance first appeared in Kenya, in 1978. For ACT, the combination principle could help slow and mitigate the effects. The question is to what extent artemisinin resistance would be accompanied by resistance to partner drugs, of which, fortunately, there are several. As long as it is possible, in a given area, to identify an ACT with a highly effective synthetic partner drug, it should be possible to limit morbidity and mortality, as has in fact been the case so far in Cambodia and Thailand. The problem with rotation of partner drugs is that it requires very good resistance surveillance and very dynamic and responsive policy-making. Furthermore, with some likely cross-resistance among these synthetic drugs, the options may become exhausted at some point in time. Thus, given the pessimistic state of the pipeline (See Box) the loss of more than 100,000 lives per year in Africa starting from around 2020 is a possible scenario, and this figure could well increase, until a new class of antimalarials have become available. Losses in India could come earlier, but would be smaller and more difficult to estimate, as there is uncertainty about the true malaria mortality in India (estimates varying between 15,000 and 200,000 deaths per year according to recent publications in *The Lancet*). Malaria modellers will be able to prepare much better estimations. The important point in this analysis is that every year of postponement of spread to countries west of Myanmar during the next few years

⁵¹ Korenromp, E.L. et al. Measurement of trends in childhood malaria mortality in Africa: an assessment of progress toward targets based on verbal autopsy *The Lancet Infectious Diseases* 3 June 2003 <http://infection.thelancet.com> 349

could save the lives of many thousand people, in Africa per year in about 10-15 years from now. It could be argued that as long as we cannot eliminate falciparum malaria from Myanmar, spread will happen sooner or later, so why be so concerned with containment? Further into the future, the effects of spread would be less dramatic, because – also sooner or later - it is likely that other interventions including other antimalarial medicines will be available to reduce the burden. Also, the odds of *de novo* emergence of artemisinin resistance in Africa or India will also increase over a longer time horizon. In conclusion: the time to act is now.

The pipeline for development of new antimalarial medicines including transmission-blocking. Source: WHO (2011). Global plan for Artemisinin Resistance Containment

Currently, about 30 antimalarial drugs are under development from the preclinical stage to phase IV, and an additional 13 candidate drugs are in early stages of research. Much of the development is coordinated by the Medicines for Malaria Venture. Only 14 of the drugs in development are potential alternatives to artemisinin-based therapies. Six of these 14 candidates are endoperoxides or synthetic artemisinins, including Arterolane/OZ277 (phase IIb/III) and OZ439 (phase IIa). It is not known whether synthetic artemisinins will be effective against artemisinin-resistant parasites. If endoperoxides prove to be ineffective, three antibiotic combinations are the next most promising candidates. Clindamycin–fosmidomycin is in phase II, and another antibiotic combination, azithromycin–chloroquine, is being developed for intermittent preventive treatment of pregnant women and not specifically to address artemisinin resistance. Apart from endoperoxides and antibiotics, there are only five other candidates in the pipeline, and the earliest any of them could be available is 2016. The most promising candidate in this group is NITD 609. If its safety and tolerability are acceptable, it would be the first non-artemisinin non-peroxide to be studied for proof-of-concept.

At present, primaquine is the only transmission-blocking drug available, and tafenoquine is the only other candidate in the pipeline. Primaquine causes variable haemolysis in glucose 6-phosphate dehydrogenase-deficient people and is therefore not recommended for those with severe deficiency of this enzyme. Most patients are, however, not aware of their deficiency status. Thus, although WHO recommends the use of primaquine against *P. falciparum* malaria, particularly in low-transmission settings and in the context of pre-elimination or elimination programmes, more widespread use to prevent transmission is limited. In addition, primaquine is contraindicated for pregnant women and infants in the first months of life. As tafenoquine is in the same chemical class as primaquine, similar limitations would apply if it were eventually licensed and recommended for use.

Annex 7. MARC task force composition and ToR

MARC Task Force - composition

- Chair – DOH (Deputy DG, Disease Control)
- Co-Chair – WHO (Medical Officer, Malaria)
- Secretary – DOH (Director, Malaria)
- Members:
 - Deputy Director, VBDC, DOH
 - Principal Investigator, Department of Medical Research (Lower Myanmar) / WHO Collaborating Centre for Research and Training on Malaria
 - Representatives (2) from National NGOs
 - Representatives (2) from International NGOs (based in MMR)
 - Representative (1) from Ministry of Defense
 - Representative (2) from UN agencies (UNICEF, IOM)
 - Representative (1) from Donors (based in Myanmar)
 - Independent national experts (2)
- Observers:
 - Representative (1) from Fund Manager, 3 Diseases Fund
 - Representatives (2) from Principal Recipients of GFATM (1 from each PR)
 - National Malaria Control Programme Manager, MOPH, Thailand
 - WHO Mekong Malaria Programme Coordinator

MARC Task Force - ToR

The Technical Group appointed by the Technical Strategic Group (TSG) Malaria to:

- provide overall guidance in planning, implementation, monitoring and evaluation of MARC;
- review project proposals on MARC and recommend for funding;
- review MARC project progress and technical achievements;
- mobilize political commitment and financial support thru advocacy;
- regular update the TSG; and
- through the TSG update the M-CCM and seek their guidance

Annex 8. Population and townships by tier

Population, villages and health facilities by tier

	Estimated population 2011 (millions)	Number of villages	Total number of government health facilities	Total number of village based government health facilities*	Square kilometers
Tier 1	4.8	2660	734	646	53,958
Tier 2	6.0	9298	1090	999	77,390

*Includes Rural health centers, Station hospitals and sub-centers

Source: MoH and MIMU (Myanmar Information Management Unit)

Names of targeted townships

	State/Region	Township
Tier 1	Bago(E)	Shwegyin
	Mon	Beelin
	Mon	Chaungzon
	Mon	Kyaikhto
	Mon	Kyaikmayaw
	Mon	Mawlamying
	Mon	Mudon
	Mon	Paung
	Mon	Thanpyuzayat
	Mon	Thaton
	Mon	Yae
	Tanintharyi	Boke Pyin
	Tanintharyi	Dawei
	Tanintharyi	Kawthaung
	Tanintharyi	Kyun Su
	Tanintharyi	Laung Lone
	Tanintharyi	Myeik
	Tanintharyi	Palaw
	Tanintharyi	Taninthayi
	Tanintharyi	Thayet Chaung
	Tanintharyi	Ye byu

	State/Region	Township
Tier 2	Bago(E)	Bago
	Bago(E)	DaikOo
	Bago(E)	Htantabin
	Bago(E)	Kawa
	Bago(E)	Kyaukkyi
	Bago(E)	Kyauktagar
	Bago(E)	Nyaungglaybin
	Bago(E)	Oaktwin
	Bago(E)	Phyu
	Bago(E)	Tanutpin
	Bago(E)	Taungu
	Bago(E)	Waw
	Bago(E)	Yedashe
	Kachin	Bammaw
	Kachin	Mamsi
	Kachin	Momauk
	Kachin	Myitkyina
	Kayah	Bawlahkhae
	Kayah	Demawso
	Kayah	Loikaw
	Kayah	Maeset
	Kayah	Pharsaung
	Kayah	Phruso
	Kayah	Shadaw
	Kayin	Kawkareik
	Kayin	Kyarinseikyi
	Kayin	Myawaddy
	Kayin	Hlaingbwe
	Kayin	Hpapun
	Kayin	Hpaan
	Kayin	Thandaung

Annex 9. Tentative M&E framework

Annex 10. Maps showing GFATM Round 9 coverage

Figure 1- Townships with planned malaria activities by VBDC (MoH), National NGOs and international organizations funded under Global Fund Round 9

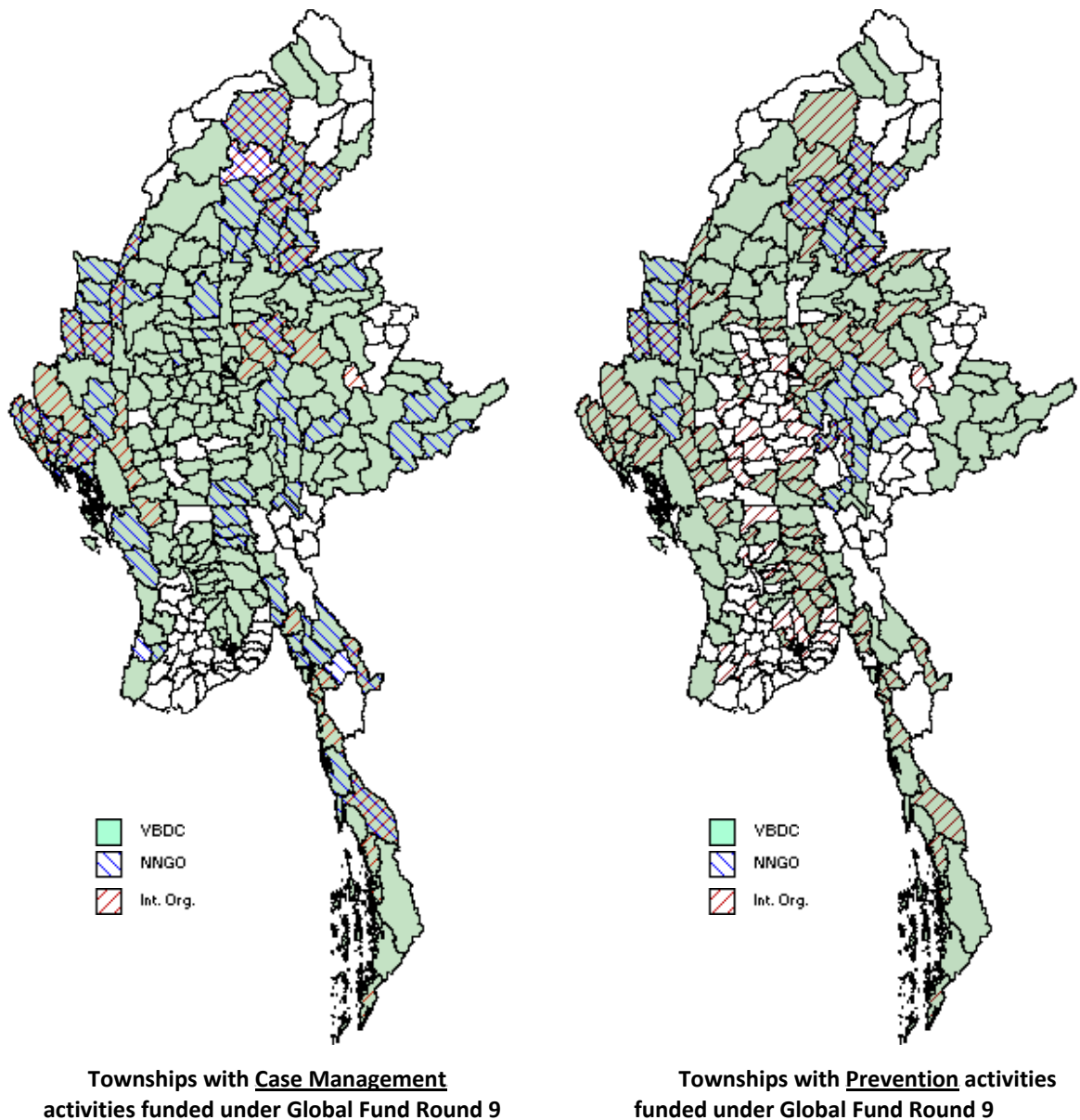
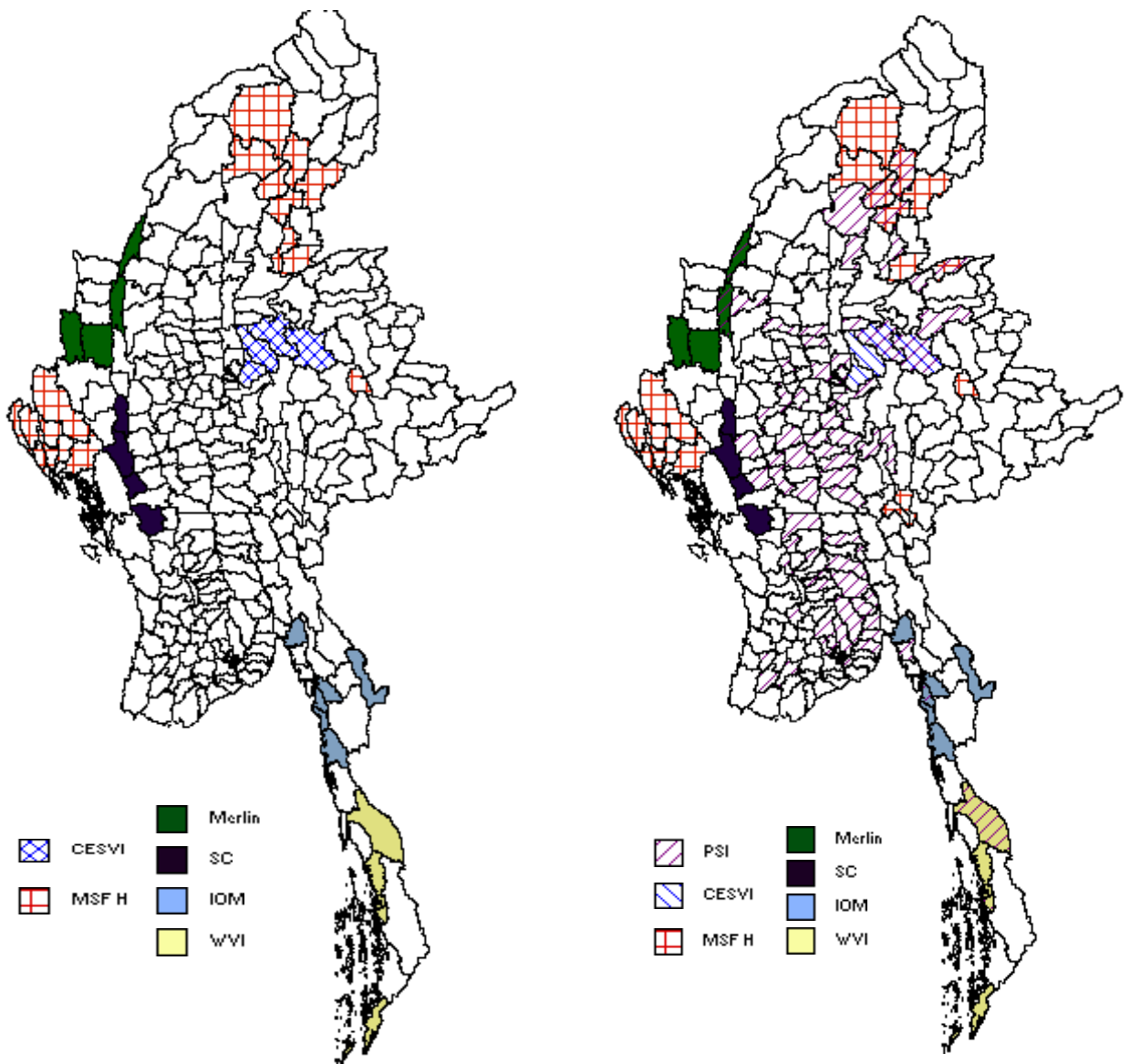


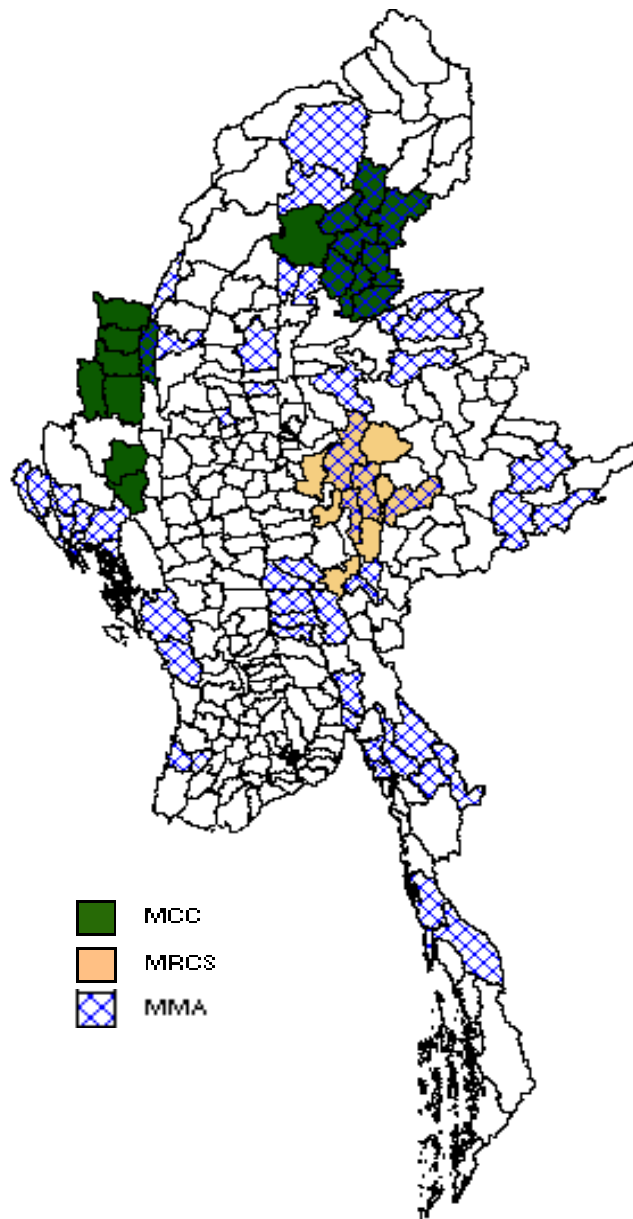
Figure 2 – Malaria activities by International Organizations funded under Global Fund Round 9



Case Management activities by international organizations under GF round 9

Prevention activities by international organizations under GF round 9

**Figure 3: Malaria activities by National NGOs
funded under Global Fund Round 9**



Note: MRCS will do only prevention activities; MMA will do only Case Management mainly through General Practitioners and MCC are doing village based prevention and case management activities through volunteers