Forest Malaria and Poverty
A Study on Improving Effective Access to Care for Forest Populations living with Endemic Malaria along the Thailand-Burma Border by Exploring means of Conserving Protective Premunition and Delaying the Onset of Drug Resistance

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Minor Thesis submitted in part requirement for the degree of Master of Social Science (International Development) at the RMIT University School of Social Science - April 2004

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Abstract

Prevention, Early Detection, Rapid Treatment, and Systems for Epidemic Control are foundation blocks of the Global Rollback Malaria Program. This paper is specifically concerned with aspects of Treatment as they pertain to remote, resource-poor populations without consistent access to anti-malarial drugs living within, and adjacent to, forested areas.

While modern pharmaceutical treatments are widely regarded as the best, albeit imperfect, solution to containing malaria in most bio-regions, this paper will argue that in light of multidisciplinary research on the specific dynamics of Forest Malaria, pharmaceutical anti-malarials are not necessarily the most cost-effective, efficacious or sustainable solution for containing, alleviating or actually healing (as opposed to merely curing) endemic malaria amongst remote, resource-poor populations living within, and adjacent to, forested areas.

This paper is based on the premise that it is crucial that protective premunition be conserved specifically and uniquely for forest populations living with endemic malaria in areas without consistent or timely access to pharmaceutical antimalarials. While effecting only small numbers of people, forest malaria nevertheless represents the strongest nexus between man, insect and parasite. This paper explores the possibility that a whole systems analysis of current parasitological, entomological and immunological evidence will sufficiently demonstrate that forest malaria plays a broader and pivotal global role - as a self-perpetuating reservoir that ensures that malaria will never be totally eradicated. If this reality is acknowledged, it is important from an immuno-epidemiological standpoint that we exercise wisdom in improving our long-term relationship with the malaria parasite by maintaining a sustainable balance of power instead of waging an unwinable war. This paper argues that we need to conserve our power and resources – our only defenses – by deploying them as judiciously and appropriately as possible. We cannot afford to do otherwise. We may be winning the battles, but by overextending ourselves in a misguided fashion, we run the risk of losing the war. Already, the most affected populations cannot carry the financial burden of current strategies without recourse to debilitating outside aid. This paper argues that an ancient non-combative, but complementary strategy that acknowledges the intractable nature of forest malaria exists and needs to be explored further. A brief review of the ethnobotanical underpinnings of modern pharamaceuticals reveals the urgency; all of our anti-malarial drugs have been derived from just two plants. Furthermore, the onset of drug resistance should be delayed so that the efficacy of intravenous, intra-muscular and suppository formulations of pharmaceutical anti-malarials be conserved for emergency treatment in situations where the patient is unable to ingest medicine orally. Neither of these objectives are currently being addressed or served directly.
Under the current strategy, radical cure treatments eliminate parasite residuals resulting in a loss of protective premunition, with grave implications for those without consistent and timely access to care, while clinical cure treatments suppress parasite levels increasing the risk of fostering drug resistance, with expensive consequences for the broader global struggle against malaria.

This paper argues that easy to propagate low-cost suppressive cures that do not compromise premunition, nor foster drug resistance, may already exist and should be further investigated.
Declaration

I declare that this work is entirely of my own creation except where due acknowledgment has been made and that it has not been submitted, in whole or in part, to qualify for any other academic award.

Acknowledgements

This thesis came into being, first in my heart, then in my mind, after a series of visits to the Thai Burma border.

I would like to thank those who encouraged me to question, tear-open and question again, every scrap of information I could get my hands on in order to seek not just answers but better questions.

Firstly, I would like to thank Rohini David, my life partner for her love, support and understanding while I ranted and raved, wrote on the walls, paced up and down and obsessed about how resource-poor peoples living in forested areas could best deal with their malarial burden.

Deep gratitude is also due to Dr Ranil Senanayake, agro-ecologist and systems theorist for inspiring me to tackle complex problems from as many angles as possible no matter what the prevailing consensus was, and for convincing me that paradigmatic shifts required patient and formal not just wild and intuitive expression. For telling me I had all the colors of the rainbow, an undistorted view, that I just needed to turn up the brightness.

Most importantly, I wish to thank Kevin Bunka (Hong Kong), Alex Ackerman (Melbourne), Nazli Anwari (Singapore), Mary Beshid (Los Angeles), and Yung Chu Higgins (Beijing) for lifting my game, for encouraging me to seek, express and accept love in all areas of my life.

Amongst the medical profession, I would like to acknowledge the Directors of GHAP- the Global Health Access Program - one of the small but dynamic NGOs currently implanting a brave malaria program along the Thailand Burma Border in collaboration with a team of Karen back-pack medics. Anusha Dahanayake, Nurse Practitioner, for inviting me to Burma with GHAP and for her silent skepticism that forced me to develop better arguements. Dr Tom Lee of the University of California, Los Angeles for his spirited opposition and subsequent curiosity.
Acknowledgements also go out to the various scientists and doctors who took the time to respond, argue, debate and otherwise engage with someone who was examining a problem across many disciplines – who by definition, would be constrained in his intellectual movements by a lack of experience and formal training in their respective chosen disciplines.

Particular and deep thanks go out to Dr Krongthong Thimasarn (Thailand), head of the World Health Organization’s Rollback Malaria Program – Mekong Delta for his continued interest, correspondence, introductions and encouragements. Sean Stevens (Angola) at Medicines sans Frontiers, for his concern and kind hearted admonishments.

Finally, thanks go out to Dr Peter Annear, my thesis supervisor, for his surprisingly efficacious use of clear, concise, firm yet gentle observations and suggestions.
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1 Introduction

Malaria is a major cause of mortality and morbidity in the developing world. Transmitted from person to person through the bite of a female Anopheles mosquito, malaria kills an estimated one to two million children each year and causes disease in a further 300 to 500 million individuals [World Bank 2001\(^1\)]. Malaria disproportionately affects people living in poverty — specifically those who are most marginalized [Sachs 2002\(^2\)]

Attempts to eradicate malaria have been confounded by a multitude of programmatic, financial, and political factors that are beyond the scope of this paper. However, even if these programmatic, financial, and political factors were be overcome, the situation would still be intractable due to the parasites ability to replenish itself from stubborn reservoirs – areas where most of the population are infected carriers -deep inside remote forested areas.

The existence of these forest reservoirs ensures that malaria can never be totally eradicated globally. Containment is thus the only option. The distinction between eradication and containment is not as subtle as it first appears. The schism between containment and eradication orientated strategies is most dramatically problematic at the treatment level – the focus of this paper. While eradication orientated treatment strategies that seek to eliminate malaria on a host-by-host basis are appropriate for most bioregions, doing so amongst forest dwelling populations living with endemic malaria and without consistent access to drugs may be both cruel and counterproductive.

While modern pharmaceutical treatments are widely regarded as the best, albeit imperfect, solution to containing malaria in most bio-regions, this paper will argue that in light of multidisciplinary research on the specific dynamics of Forest Malaria, pharmaceutical anti-malarials are not necessarily the most cost-effective, efficacious or sustainable solution for containing, alleviating or actually healing endemic malaria amongst remote, resource-poor populations living within, and adjacent to, forested areas.

It is crucial that protective premunition be conserved for populations living with endemic malaria and without consistent or timely access to pharmaceutical antimalarials. It is equally, if not more important, that the onset of drug resistance be delayed, and the efficacy of intravenous, intra-muscular and suppository formulations of pharmaceutical anti-malarials be conserved for emergency treatment in situations where the patient is unable to ingest medicine orally. Neither of these objectives are currently being served.

Under the current strategy, radical cure treatments eliminate parasite residuals resulting in a loss of protective premunition, with grave implications for those without consistent and timely access to care, while clinical cure treatments suppress parasite levels

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increasing the risk of fostering drug resistance, with expensive consequences for the broader global struggle against malaria.

This paper argues that easy to propagate low-cost suppressive cures that do not compromise premunition, nor foster drug resistance, may already exist and should be further investigated.

This paper seeks to answer the question:

"Can Drug Access Problems be Mitigated, Protective Premunition be Conserved, and the Onset of Drug Resistance Delayed, all in a Cost-effective and Sustainable manner?"

.... and question the answer that:

"Easy to propagate low-cost suppressive cures that do not compromise premunition, nor foster drug resistance, may already exist and should be further investigated."
**History of Anti-malarials** - Let us begin with brief overview of the historical context. It is salutary to note that the two most effective pharmacological approaches to malaria originated from plants used as repellent/cures in traditional medicine: The quinines (chloroquine (1934), mefloquine (1970+), pamaquine (1924), mepacrine (1930), amodiaquine (1946), primaquine and pyrimethamine (1952), quinocide (1956), etc) from the bark of the Peruvian cinchona tree *Cinchona succiruba* (*Rubiaceae*). And the artemisinin derivatives (artesunate, a water soluble salt for oral, parenteral and suppository use, and two oil soluble compounds for intramuscular injections: artemether and arteether) from the Chinese antipyretic *Artemisia annua* L. [Kayser 2002³]. All of these drugs, in fact all the 'significant' drugs we have against malaria, came from just two plants: *Cinchona succiruba* and *Artemisia annua*. Moreover, the front-line treatment for multi-drug resistant malaria is made up of artenusate (from *Artemisia annua*) and lumefantrine, which, like halofantrine and mefloquine, is an aryl amino alcohol structurally similar to quinine (from *Cinchona succiruba*).

**Myopic Reliance on Formal Research** - The programmatic evaluation of medicinal plants has been compromised by a sometimes fanatical belief in 'scientific due process', even when these results contradict clinical observation and common sense. The in vivo anti-plasmodial activity of, *Pothomorphe umbellata*, a well known traditional Brazilian anti-malarial plant could not be confirmed using the standard intra-peritoneal Plasmodium berghei mice model [De Ferreira-da-Cruz 2000⁴]. The activity of Cryptolepine, the active constituent of the West African anti-malarial herb *Cryptolepis sanguinoleta* could not be confirmed for a long-time due to the inability of several investigators to observe a positive in vivo result from a *P. berghei* infected mice model treated intra-peritoneally with the compound. Similarly, it took a long time for the now famous *Artemesia annua* to be recognized as a significant anti-malarial, despite the incredibly extensive historical documentation of its efficacy, merely because scientists had problems extracting and evaluating one of the active compounds, artemisinin. Investigators had to resort to an uncommon method; extraction with diethyl ether at low temperatures. Until then, scientific recognition and more importantly, 'acknowledgment of efficacy for programmatic use' was absent despite the fact that it's anti-malarial qualities were first described in 341AD China in *Zhouhou Bei Ji Fang*, the "Handbook of Prescriptions for Emergencies" edited by Ge Hong, and then again by Li Shizhen, in his "Compendium of Treatments", *Ben Cao Gang Mu*, published in 1596AD. Although

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³ Kayser, Oliver (1), AF Kiderlen (2) & SL Craft (3) (2002) Natural Products as Potential Antiparasitic drugs 1 Freie Universität Berlin Institut für Pharmazie, Pharmazeutische Biotechnologie Kelchstraße 31, 12169 Berlin, Germany 2 Robert Koch-Institut Nordufer 20 13553 Berlin, Germany 3 London School of Hygiene and Tropical Medicine Department of Infectious and Tropical Diseases Keppel Street London, WC1E 7HT, United Kingdom Unpublished Book Draft 2002

rigorous, controlled studies are invaluable and perhaps indispensable in determining the therapeutic value of a substance, there is little sense in ignoring information obtained from case studies, which can often provide the basis for more detailed research in an area.

This paper will present a re-evaluation of an ancient treatment strategy to contain malaria as a possible solution to a specific problem: As a cost-effective and sustainable solution for containing malaria amongst remote, resource-poor populations living within, and adjacent to, forested areas. To illustrate the argument, a specific forested region has been chosen.
2 Research Site
The argument that a re-evaluation of an ancient strategy to contain malaria is called for will be explored in the context of Forest Malaria along the Thailand / Burmese border. I have chosen this area because the scientific community recognizes the Forest Malaria in this region as the most intractable. This is borne out by Oxford University’s decision to locate its world renowned Shoklo Malaria Research Unit in the very heart of this region. The motivation is simple: If a solution can be found for this region, its applicability for less problematic areas is almost guaranteed. Furthermore, due to the fact that drug resistance has developed and spread faster and more frequently from this area than any other, the results of this study may have implications on the broader global struggle against malaria.

3 Methodology
The methodology behind this paper, by order of priority, is as follows:

Multidisciplinary Meta-analysis – Medical, Pharmacological, Ethno-botanical, Immunoepidemiological, Anthropological, Parasitological, Entomological, Agro-ecological, Historical and Political resources were consulted to create a portrait of forest malaria along the Thai Burma border.

Literature Searches - I used Lexus-Nexus, Reuters and Dialog database searches as well as general Internet resources. Hard copy material was obtained by visiting libraries at Nanyang University, Singapore; UCLA, Los Angles, Polytechnic University, Kowloon, Hong Kong; Toronto University, Canada; IDEP Yayasan, Ubud, Bali, Indonesia; and Melbourne University, Australia. Additional local language material was translated and mailed to me upon request from Mahidol University, Thailand.

Field Observations – One visit was made in 2001 to a border town within the focus area, Mea Sot, where Oxford University has located its malaria research unit. Another visit was made in 2002 to a Karen rebel stronghold inside Burma, whereupon clinics in adjacent villages were also visited. Interviews were conducted with village elders, KNU (Karen National Union) cadres, the foreign minister of the Burmese NLD (National League for Democracy) government in exile, doctors, backpack medics, as well as a number of NGO’s operating in the area such as Medicines sans Frontiers. Interviews with the Thai Army were conducted while the 3rd division of the 9th Army was operating as part of the UN Peacekeeping Mission in East Timor in 2002. (This division directly controls the border area in question)

Email correspondence was initiated with specialists in tropical medicine at the Shoklo Malaria Institute, Mahidol University, Oxford University, The Liverpool School of Tropical Medicine, to name just a few. In addition, clarification of my assumptions was sought from experts in related fields, including immuno-epidemiologists, pharmacologists,
entomologists, ethno-botanists, and agro-ecologists. I am currently on the internal mailing list of the World Health Organization’s Rollback Malaria Mekong Delta Program. These field observations and interviews were used to verify my understanding of the material I had gathered from the literature searches. Photographs of my visits to these areas are included as a supplement.

**Structure of Argument** - In order to properly evaluate the situation, and in order to cover all of the salient parameters, I have assembled and compacted the necessary data into a very concise and densely packed format. All significant claims have been referenced and come from peer-reviewed journals. To assist the reader in navigating through this complex maze of interrelated information I have attached an outline of the major ideas presented. (see Appendix A). Where possible, basic background material fundamental to a sound understanding of malaria, such as the parasite lifecycle, has been presented in schematic form in lieu of pedantic descriptions. Due to the heavy reliance on cited material, references have been presented in footnote form for easy access.

I shall begin with the relationship between the mosquito vector, malaria parasite, human immune system, existing drug protocols, and drug resistance. I will then examine the impact of this complex relationship between vector, parasite, immune system, and pharmaceutical efficacy on villagers within the forest environment.

I shall show how the villagers’ socio-political and economic conditions impinge on their ability to access modern pharmaceuticals in a timely and consistent manner. As the specific conditions of these resource poor, illiterate and displaced forest dwellers are examined, I shall explain the shortfalls of the current strategy. Why the strategy has worked in other areas, why it cannot provide a cost-effective and sustainable solution to the forest malaria problem along the Thailand Burma border and why this strategy, borne out of the old paradigm of eradication, is inappropriate. In exploring a possible solution to this impasse, I shall demonstrate how recent developments in the field of pharmacodynamics have vindicated certain traditional ethnomedicinal knowledge systems. Finally, I propose that sufficient scientific validation has been accumulated to argue that the micro-propagation of select medicinal plants as a cost effective and sustainable solution to this specific problem deserves further research.

It is assumed that the reader has a basic understanding of the malaria parasite lifecycle (see Appendix 7.6), and can differentiate the significance between the two most significant strains; p. falciparum and p. vivax.
4 Data Analysis

4.1 Forest Malaria - What is Unique and Significant about Forest Malaria?

The goal of totally eliminating Malaria was abandoned by the WHO in 1969, (publicly in 1975), as unachievable in the context of Forest Malaria. This is tacitly acknowledged in the naming of the current global campaign - "Rollback Malaria" as opposed to the earlier "Eradicate Malaria".

Sure, malaria can be controlled. Even eradicated, but only in certain eco-zones. For example, in India, where malaria once infected an estimated seventy-five million and killed eight hundred thousand every year, fatalities dropped to near zero by the early sixties. But not in the 'undocumented' forests. Look at the great Malaria success stories: The Malaria that was conquered in Taiwan, much of the Caribbean, the Balkans, parts of northern Africa, the northern region of Australia, and a large swath of the South Pacific back in the fifties, was not forest malaria.

In other words, the forest - where most of the population are infected carriers - is the reservoir. (see Appendix 7.1)

'Malaria transmission in forests is intense because of highly efficient vectors, multiple vectors and prolonged transmission due to ecological conditions favoring enhanced vector longevity.' [Sharma et al., 1991]

Effective Vectors - Very adaptable, with higher sporozoite rates in response to population pressure resulting in more infective bites.

Vector Longevity - Mosquito populations expand during the rainy seasons from 'mother foci' in deep forests by forming secondary foci and then retreating from the latter during the dry season.

Multiple Vectors - Peripheral zones, usually cleared of forest for cultivation purposes, promote vector diversity due to the existence of adjacent ecosystem habitats, thus facilitating the survival of parasite populations resulting in prolonged seasonal malaria transmission.

Multiple Transmission Intensities - Pockets of intense transmission (>100 annual infective bites/ individual) occur within short distances of low transmission areas (<15 annual infective bites/ individual). It should be noted that while some villages may be located in low transmission areas, adults from these same villages engaged in agricultural activities will be exposed when traveling through high transmission areas.

Forest Populations - Heterogeneous immunity of populations inhabiting the forest setting, ranging from complete absence of immunity among some groups of migrants / settlers to the presence of residual immunity among some other groups, determines

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meso-/ hypo-endemic types of malaria with great possibility of outbreak / epidemics of malaria. [WHO/SEA/MAL/172 1991]

**Analogous Areas** - The similarity between the combined effect of vectors in Madhya Pradesh, India and the vectors Dirus & Minimus along the Thai / Burma border has been established and may prove instructive.[Singh 1999]. Directly analogous areas include North East India. Forest settlement outbreaks have been documented in Dandakarnaya Project located at the nexus between Andhra Pradesh, Orissa & Madhya Pradesh, and Chanderpur in Maharashtra State, India.

**Conclusion:** The *Forest Malaria Bionomics of host, Vector and parasite are unique and distinct from that of other bioregions.*
4.2 Vectors - A basic, programmatic understanding of the vector characteristics in the focus area will assist in the design of appropriate, cost-effective, and sustainable interventions.

Entomological Profile - Out of the 380 species of Anopheline mosquito, only 60 can transmit malaria. The main vector in South East Asian Forest Malaria is Anopheles dirus. Along the Thai-Burma border and spreading west across most of Burma and into Bangladesh and Assam it is A. dirus Species D, spreading east, across Thailand to Cambodia, Vietnam and Laos, it is A. dirus Species A. These two species, A. dirus A and A. dirus D, display little genetic differentiation; they are more similar to each other than other dirus species, they are also more widespread. Anopheles dirus Species C is also implicated in the focus area, but only where there are rocky limestone outcrops. [Walton et al 2000]. (see Appendix 7.5)

The other significant vectors in this area are A. minimus, and A. maculatus [AFPM 1993]. Note that while A. minimus may be responsible for more bites in the area, resident as it is in forest fringe areas adjacent to and within villages, it is A. dirus living inside the forest - up to a 150 metres away - that has the higher sporozoite rate and hence vector capacity. Thus on a village level, adults get malaria from A. dirus OUTSIDE in the forest which is then transmitted to children, the elderly and the infirm NEAR and INSIDE villages via A. minimus.

Anopheles Dirus Species A & D - This vector begins biting at 9pm (earlier during the cool dry period) and bites late into the night until at least 3am, is exophilic (bites outdoors), and is exophilic (rests outdoors after a blood meal). Highly adaptable. Primary habitat is within the forest and recently, in adjoining fruit orchards [Singhasivanon 1999] and mature rubber plantations. Breeds in small, temporary pools of fresh water [Rosenberg et al. 1990], including shaded wells [Thin Thin Oo 2002] and even tiretracks, hoofprints and footprints. More susceptible to drug-resistant malaria than to drug-sensitive malaria [Sucharit 1977]. A silent flyer, its flight range is estimated at 1-3

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kilometers. The geographic distribution and biting behaviour of A. dirus species have been documented. [Baimai 1988\textsuperscript{14}].

**Anopheles Minimus Species C & D** - Highly adaptable. Begins biting at 6pm (before dusk). This vector has adapted to DDT spraying by changing its behavior to resting outdoors and biting even earlier in the day during the cool dry season and the wet season [Ratanatham 1988\textsuperscript{15}]. It is also an early morning biter in the wet season. Breeds in clear flowing water with vegetation [Kondrashin & Rashid 1987\textsuperscript{16}]. Primary habitat is along the forest fringes. Like A. dirus, it also has a higher larval density during the dry season. [Overgaard 2001\textsuperscript{17}]. Flight range is estimated to be less than four kilometers.

**Visualization** - It might help to construct an aerial schema of the disease carriers: the mosquito vector(s) can be viewed as bounded by overlapping microclimatic, ecological and agro-ecological boundaries. Some controllable, and some not. The human vectors can be viewed as carrying the parasite along transportation routes. When an infected individual enters an area where sufficient vector and transmission control is possible, and integrated strategies have been effectively implemented, one can regard that route closed, as if it never existed. This is how malaria is "Rolled Back". Satellite images showing forest cover juxtaposed with transmission and mortality figures [Singhasivanon 1999\textsuperscript{18}], vividly illustrate the success of the various integrated strategies employed by Thai Health Authorities and the World Health Organization's Rollback Malaria Mekong programme outside the forested border areas. Most of central Thailand is now effectively malaria clear and the overwhelming majority of cases 84.2\% occur along the Thai/Burma border (91\% of all Thailand's cases are along its borders). This paper seeks to address these cases and calls for a specific response with a particular focus on Tak province, which carries the biggest burden at 35\% of all cases. (2001 figures cited) [Sirichaisinthop 2002\textsuperscript{19}]


\textsuperscript{19} Sirichaisinthop P (2002) Situation of Vivax Malaria in Thailand, FY 2001 Office of Vector Born Disease Control 1 CDC Thailand
**Conclusion:** Understanding vector characteristics can aid in the evaluation of different strategies. In some instances, *Transmission Control* may not be possible.
4. 3 Transmission Control - Forest Vector Characteristics limit the type of Transmission Control Strategies that can be employed

Rationale - During the approximately 12 days required for sporozoite development, a member of most female tropical Anopheline mosquito species would be expected, if it survives, to re-visit homes three or four times to take bloodmeals and thus initiate new cycles of egg development. If the mosquito can be killed at any one of those three or four house visits it can never develop sporozoites and become a disease vector.

Wall spraying - The majority of households live in structures that are open. Even in the few instances where walls are present such as in a clinic, school or hospital the strategy of spraying is not as viable as in other areas. House spraying pre-supposes that the mosquitoes will rest inside a house before or after feeding, which is not the habit of one of the main vectors in the area - Anapholus dirus is both exophagic and exophilic.

Insecticide Treated Nets - ITNs are used not so much to prevent bites - even though the insecticide coating does act as a repellent and hence makes the net more secure - but to eradicate the mosquito during its most dangerous phase. However, as discussed above, the main vectors, A. dirus, being an outdoor biter, and A. minimus, being an early biter, are largely unaffected by ITNs. The only significant vector that bites late into the night indoors is A. maculatus. Here, a case could be argued for mosquito nets as a means of reducing cluster infections and nuisance bites. But the case for insecticide treated nets, predicated as they are on vector control, needs to be re-evaluated in the context of Forest Malaria vector specifics. Studies of ITN use in Africa are inappropriate to this area. The main vector there is A. gambiae, which bites later in the evening.

Differences between African and Tropical Forest Vectors - Bionomics of Forest Malaria Vectors: the ecological relationship between the mosquito and its environment. Morphological adaptation of vector species in arid / semi arid zones, such as the selective pressure for small spiracular openings, have insulated most African species from humidity variations allowing for wide dispersal opportunities, which are generally indoors to avoid day-time temperatures. In contrast, mosquito populations occurring in regions of high humidity with large spiracular openings are not sufficiently insulated against relative humidity variations. Tropical forest vectors thus tend to be exophilic [rests outdoors after a blood meal] and less likely to disperse as widely. Dispersal is generally in clusters to a couple of hundred metres reflecting the diverse ecosystems within the forest. Tropical forest species thus occupy highly specific niches, displaying variations in outdoor resting and feeding behaviour. Vector survival and inoculation rates in the focus area have been shown to differ between similar sites a mere 800m apart
[Rosenburg\textsuperscript{20}]. Due to the complexity and variety of forest malaria vectors, the cost effectiveness and appropriateness of any intervention will vary by bio-region.

Papers evaluating ITNs in the context of Forest Malaria in Thailand / Burma, with a focus on the main vectors: \textit{A. dirus} and \textit{A. minimus} should be consulted [WHOPES 2001\textsuperscript{21}, Meek 1995\textsuperscript{22}, Dolan 1993 \textsuperscript{23}, Luxemburger 1994 \textsuperscript{24} and Kamol-Ratanakul 1992 \textsuperscript{25}]. The most compelling document in favour of ITBN utilization amongst forest dwelling hill tribes comes from a four-year study conducted in Vietnam [Hung 2002\textsuperscript{26}]. Unfortunately, direct communication with the researchers involved in the aforementioned Vietnam study has led me to question the applicability of their conclusions to the focus area.

**Conclusion:** Vector control strategies employed in Africa are less effective in this tropical forest region. Selective use of ITNs is indicated, as part of an integrated strategy. In areas where transmission control is not meaningfully possible, solutions that have worked in other areas, and other times, need to be re-evaluated.

In areas where transmission control is possible, integrated strategies have been comprehensively implemented and drug treatment has been fast, comprehensive and aggressive. The same strategy may be unwise in a forest setting if it accelerates the development of drug resistance (see next section), and thus minimizes treatment options. It is crucial that the efficacy of intravenous, intra-muscular and suppository formulations of anti-malarial drugs be preserved for emergency treatment in situations where the patient is unable to ingest medicine orally.

IDP camp populations in controlled settings where ingress and egress is severely restricted (such as Ban Mai Nai Soi, Ban Mae Surin & Ban Kwai in Mae Hong Song, Mae Hong Ka & Ban Sa La in Mae Sariang, Wang Nite & Jao Derng in Tavoy, Maela Camp in Tha Song Yang, Tak province, Ban Dong Yang, Mae Ra Ma Luang, Bee Ree Area, Halochanee Area, Uimpie Camp, Tham Hin Ratchaburi and Nu Po Camp in Umphang,

\textsuperscript{22} Meek SR (1995) Vector control in some countries of Southeast Asia: comparing the vectors and the strategies., Malaria Consortium, London School of Hygiene and Tropical Medicine, U.K. 1995 Ann Trop Med Parasitol Apr;89(2):135-47
\textsuperscript{25} Kamol-Ratanakul P & C Prasitsitik (1992) The effectiveness of permethrin-impregnated bed nets against malaria for migrant workers in eastern Thailand. Faculty of Medicine, Clinical Epidemiology Unit, Chulalongkorn University, Bangkok, Thailand. 1992 Am J Trop Med Hyg Sep;47(3):305-9
Tak Province) are exceptions and can be regarded as 'islands' of low and 'controllable' transmission.

In all other areas where neither the vector nor the parasite can be eradicated or meaningfully controlled, current strategies dictate that chemotherapy be administered indefinitely and relentlessly - posing both a macro and micro-economic opportunity cost as well as the risk of Drug Resistance.
4. 4 Drug Resistance  - When Transmission Control Strategies are Compromised, the risk of fostering Drug Resistant Strains Increases

History of Accelerated Resistance - Development of resistance to Sulfadoxine-Pyrimethamine in the focus area, took a mere 5 years [Peterson 199027]. By 1990, treatment failure rates (not the same as resistance, but indicative) for mefloquine s/p combinations had risen to 29% in adults and 50% in children. The treatment failure rate for mefloquine alone is above 50%. Chloroquine resistance is as high as 85% among P. falciparum cases. Reduced drug pressure may allow for the reintroduction of mefloquine and chloroquine at a later date, but the situation is as yet unclear. What is clear, however, is that resistance to all previously introduced anti-malarial drugs has emerged faster along Thailand's borders than anywhere else in the world.

Combination Therapy Rationale - The 'one-two' punch. Fixed-combination and multiple-drug therapies are predicated on exploiting the synergistic and additive potential of individual drugs thus improving efficacy and retarding the development of resistance to the individual components of the combination. Multiple-drug therapies have been used for leprosy, tuberculosis and cancer and, more recently, in anti-retroviral treatments. Examples in the field of malaria include: sulfadoxine-pyrimethamine, atovaquone-proguanil and mefloquine-sulfadoxine-pyrimethamine [WHO 200128].

The most significant combination therapy to date teams artemisinin derivatives with an older drug to form coartemether (artemether-lumefantrine), developed in the early 1980's by the Institute of Microbiology and Epidemiology at the Academy of Military Medical Sciences, China. Globally registered by Novartis of Switzerland as Coartem®/Riamet®, this drug provides faster parasite clearance times and a theoretically lower possibility of generating resistance.

Weak Gatekeepers - It should also be noted that drugs partnered with artemisinin derivatives (which have a short half-life), will be unprotected once the artemisinin derivatives have been eliminated from the body.

As the leading experts in the field say: "In areas of high transmission, where infections occur frequently, and are usually asymptomatic in older children and adults, the rapidly eliminated artemisinin derivative will not protect its more slowly eliminated partner during the elimination "tail" of declining blood concentrations. Infections newly acquired during this tail will therefore be under selection pressure. But, provided (emphasis added) the patients with these infections are treated with the combination if (emphasis added) they

become symptomatic, and provided (emphasis added) the combination partner retains some efficacy against any selected mutants, the infections will usually be cured and the resistant parasites will not be transmitted [White et al 1999\(^2\)]. The 'gatekeeper mechanism' is already breaking down: In vitro studies show cross resistance to lumefantrine from mefloquine, halofantrine and quinine [CDS/RBM 2002\(^3\)].


The Original Combination Therapy - It can be argued that traditional medicines, based on the use of whole plants with multiple ingredients or of complex mixtures of plant materials, constitute combination therapies that may well combat the development of resistance to antimalarial therapy.

The call to combine anti-malarials overlooks the fact that combination existed in the traditional formulations before the process of extraction took place. In view of this, it must be asked whether any pre-existing synergism, and hence challenge to the development of resistance, may have been lost in the process of extraction, isolation and synthesis of new molecules.

Consider the artemisinin drugs (artesunate, artemether, and dihydroartemisinin) derived from *Artemisia annua*, used in traditional Chinese medicine as an antipyretic. Traditional Chinese medical knowledge and practice dictates that this plant be used in combination with others in the treatment of fevers. The original treatment calls for five parts *Scutellaria* sp. (huang-ch'ing) to two parts *Artemisia annua* (Ch'ing-kao) [Barefoot Doctor 1974](31). (*Scutellaria*, presumably for its antispasmodic properties, but there may be other benefits.)

In the development of the new artemisinin drugs, not only has this been overlooked, but the complex of alkaloids in the plant itself have been sacrificed for the purpose of isolating the so-called single active ingredient. Indeed, flavonoids (i.e. the methoxylated flavonoids artemetin, chrysoplenetin, chrysoplenol-D, and cirsilineol) in *Artemisia annua* which are structurally unrelated to the antiplasmodial properties of the sesquiterpene lactones that are largely responsible for the antimalarial activity, actually enhance the in vitro activity of artemisinin (Phillipson et al., cited in Kirby, 1997).

Lending credence to the studies demonstrating 'other' active compounds is the typical dosage of raw ching-hao (*Artemisia annua*) recommended to treat malaria which is 20-40 grams of the dried herb per day in decoction. Based on a content of 0.5% artemisinin in the herb, this amount provides only 100-200 mg of the compound, considerably less than that contained in modern medical formulations of the isolated compound or its synthetic derivatives.

Similarly, chichona bark is still effective as opposed to the isolated compound, quinine, perhaps because it retains the other active isomers: quinidine (a more potent antimalarial, but also more toxic), cinchonidine and cinchonine. Note that treatment failure rates for quinine are over 50% in the focus area.

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Conclusion: Strategies that indiscriminately deploy and squander the effective-life of expensive anti-malarial drugs in an area where resistance develops at an accelerated rate - without even a programmatic possibility of ever controlling malaria - should be reconsidered. Furthermore, it is crucial that the efficacy of intravenous, intra-muscular and suppository formulations of these drugs be preserved for emergency treatment in situations where the patient is unable to ingest medicine orally.

*The very success of certain anti-malarials in effecting a radical cure raises the question of how this might impact on Immunity.*
4.5 Immunity / Premunition – Radical Cure Treatments appear to Erase the Protective Benefits of Premunition

Non-sterilizing Immunity - In tropical zones where mosquitoes do not hibernate, individuals often receive multiple malaria infections that over time develop into a non-sterilizing immunity that suppresses clinical symptoms - a condition called asymptomatic malaria. This state of partial immunity in which parasitemia is lowered, but not eliminated, and parasitemia is better tolerated - both in severity and duration - is referred to as 'premunition'. Premunition refers to a subset of immunity that is contingent upon the parasite being present. Premunition is thus a factor of the number of infective bites, with populations living in high transmission areas ironically experiencing lesser morbidity and mortality to those in low, seasonal transmission areas. Severe disease in the most critical period, early childhood, is also less frequent in areas where transmission is the greatest with infants experiencing increased exposure to infection while protected from disease, possibly by maternal antibodies, thereby emerging from this period of clinical protection with considerably more immunity than those who experience lower transmission intensities. On this basis, [Carme, 32], [Snow and Marsh, 33], [Snow et al., 34], and [Trape & Rogier, 35] have all suggested that malaria transmission control may not reduce overall mortality rates. [Explains why under one mortality is often lower than 1-5yrs, in this context]. In the same vein, mathematical models have postulated that the most effective control/curative method is that of "boosting acquired immunity and minimising immunity loss" [Shonkwiler, 36]. Immunity is clearly a valuable ally in the fight against malaria in areas where consistent access to anti-malarials cannot be assured. Interventions that compromise the early acquisition of immunity may merely shift the age distributed mortality curve to the right. The death of an adult wage earner is far more devastating to the future of a family than the death of a child [Wisner, 37]. Note also that while those with Premunition will develop malaria at slower rate than non-immunes, and while the duration and severity of their symptoms will be lessened, they are also more likely to fall victim to Drug Resistant malaria.

**Iatrogenic Consequences** - Radical or clinical cure? Given this understanding about premunition, it behooves us to ask 'Do certain kinds of treatment erase premunition and diminish immunity?' Radical cure for *P. vivax* requires the deliberate use of primaquine as a hypnozoiticide to attack dormant parasites sequestered in the liver, but *P. falciparum* does not have a latent liver stage and the new artemisinin derivative+combinations are also gametocytocidal so radical cure can be effected with no additional drugs. Since premunition is largely predicated on the presence of the parasite, the immuno-epidemiological consequences of rapid and comprehensive parasite clearance in an individual that is likely to be rapidly re-infected needs to be considered (especially if he/she cannot be assured consistent access to anti-malarials).

Unfortunately, there have been few studies on this issue since [Pringle & Avery-Jones 1966]. The following case study, though highly speculative, illustrates the possible consequences:

"In May 1996, a cohort of 197 volunteers aged 18-55 years were randomly recruited for malaria incidence studies in the Kassena-Nankana District of northern Ghana, radically cured, and their clinical status followed for 20 weeks through the peak malaria transmission season. A further 202 adults were sampled and followed up in the same way one year later without being treated. Following radical cures using chloroquine diphosphate (25mg/kg body weight over 48 hours) and Fansidar (sulphadoxine 500 mg + pyrimethamine 25 mg per tablet, Hoffman - La Roche), forty-nine percent (97/197) of volunteers in the treatment group developed clinical malaria in the 20 weeks, compared with 38% (77/202) in the group that were not treated, indicating that the tendency is for those without parasitaemia to have higher incidence of clinical episode. Clinical malaria in the treated group was associated with significantly more symptoms, although the parasitaemia densities on presentation were lower. It is postulated that the treatment group became sick at lower parasite densities as a result of a loss of parasite tolerance."

[Owusu 2001](#)

Further circumstantial evidence has since been gathered following a study of 536 children given radical cure with quinine, fansidar and primaquine, with researchers concluding cautiously, that "the elimination of chronic, relatively low-grade parasitemia may have established susceptibility to acute, relatively high-grade parasitemia." [Baird 2002](#).

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Radical Cure - In this context, it is important to understand two factors: 1) that artemisinin and its derivatives are the most potent and rapidly acting of the antimalarial drugs. They reduce the infecting malaria parasite biomass by roughly 10,000 - fold per asexual (2-day) life cycle, compared with 100-fold to 1000-fold for other antimalarials and 2) that "the non-specific immune response of unexposed individuals is less effective at clearing post treatment parasite residuum than the specific immune response of semi-immune individuals" [White 1997]. Parasite clearance will be assured amongst immunes. This may not always be a good thing. Parasite clearance is a cruel, albeit tantalizing, illusion in a place where people will be rapidly re-infected, and with no consistent access to anti-malarials. Being parasite clear in this context does not mean the patient is 'healthier', for the price for being parasite clear is not just a higher persistent risk of malaria but actually poorer health: Putting the body through gruelling, more frequent, episodes of malaria and malaria treatment, is debilitating. Surely, this quandary needs to be examined further?

Studies on mice models investigating the kinetics of malaria under premunition, demonstrate that radical cure does indeed prevent premunition [Ton 2002].

In the absence of a clear, conclusive proof that parasite clearance in humans does not substantially diminish or erase immunity, one should err on the side of caution in areas where premunition is worth conserving. Where consistent access to anti-malarials cannot be assured, such as in the midst of a long-simmering conflict involving mass displacements, strategies that conserve premunition should be considered and investigated.

In the focus Area - While premunition in hyperendemic areas of Africa and Papua New Guinea has been documented, understood and universally accepted, its occurrence in Asia was contested, until, a detailed three-year clinico-epidemiological study of a Burmese village confirmed premunition in the focus area.

"A longitudinal study was undertaken in Oo-Do, a malaria endemic village in Myanmar [Burma] in 1995-97. Only 2 species, Plasmodium falciparum and P. vivax, were detected, with the former predominating. Data from 116 subjects showed that all were infected at one time or another, over a period of 3 years, with a 38% reinfection rate after eradication of patent parasitaemia. The high rate of prevalence (90-100%) of parasite-specific antibodies in the indirect immunofluorescence antibody test and the presence of the primary vector (Anoph eles minimus) and 15 other species of Anopheles throughout the year indicated a high level of transmission. The spleen rate was 70% in 5-9 years old

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children and was inversely related with age. The incidence of parasitaemia was maximal (49%) in children aged 2-4 years, and then declined marginally with age. There was a significant difference ($P = 0.001$) between the asymptomatic and febrile parasitaemia levels. Also, malarial episodes occurred more frequently in children than in adults ($P = 0.001$). Taken together, all these facts indicated that the inhabitants of Oo-Do had progressively developed non-sterile partial protective immunity against $P$. falciparum malaria, or premunition. To our knowledge, this is the first detailed clinico-epidemiological study to document the occurrence of premunition in Myanmar." [Soe-Soe 2001$^{42}$]

Should Asymptomatic Individuals be Treated? Once acquired, a study of children aged between four and 14 showed that premunition appears to be density dependant, self-regulating at sub-clinical levels of around 1000 parasites/ml of blood, with different species and genotypes dominating at different times. Reducing or eliminating stable parasitemia in highly endemic regions provides an increased opportunity for other species to multiply when the constraint imposed by density-dependent regulation is removed resulting in increased sequential, debilitating infections and new opportunities for transmission [Bruce 2000$^{43}$]. This observation backs up Owuso and Baird cited above. Where consistent access to anti-malarials cannot be assured and where individuals are likely to be rapidly reinfected, it does not make sense to remove the benefits of premunition.

Can premunition be salvaged and should children be treated with radical cure? - Premunition may not be age/exposure dependent and erasure need not be permanent - Based on (1) epidemiological data that date back to the beginning of the 20th century, (2) data from the treatment of people with syphilis by deliberately infecting them with malaria parasites, and (3) data from their own studies of immigrant populations in Irian Jaya, Baird and colleagues have hypothesized that children might develop resistance to malaria at a slower rate than adults. According to this hypothesis, it is the constitutive differences in the immune responses between children and adults, rather than differential exposure to a sufficient number of protective antigenic variants, that explain the slow acquisition of protective immunity in children [Hviid 1998$^{44}$]. Understanding how rapidly immunity develops to severe malaria is essential, as severe malaria should be the

$^{44}$ Hviid, Lars (2000) Clinical disease, Immunity and Protection against Plasmodium falciparum malaria in Populations living in Endemic Areas Expert Reviews in Molecular Medicine
primary target of intervention strategies, and predicting the result of interventions that reduce host exposure will require consideration of these dynamics. Note that if a plant-based suppressive cure were to be used then the dilemma would be resolved.

**Why is Conserving Premunition Difficult?** - The biggest problem with attempting to conserve premunition lies in the risk of fostering drug resistance. The difference between conserving and erasing premunition lies in the difference between effecting a radical cure and a clinical cure. Radical cure erases all parasite residuals, clinical cure merely reduces the parasite load to the point where malaria symptoms are absent. There appears to be only one way in which clinical cures can be employed to conserve premunition without selecting for drug resistance; the use of plant based medicines. The second issue is transmission. In areas where vector control is possible and consistent access to antimalarials is assured there is no need to conserve premunition, on the contrary, one should be treating as many people as possible with radical cure so as reduce the number of hosts capable of transmitting malaria. This strategy naturally leads to a higher epidemic risk in a population cleared of immunity, but this risk is worthwhile IF most of the population lies within an area where integrated transmission control strategies are possible and the majority have consistent access to anti-malarials (see below). Clearly the population this paper addresses does not fall into this category.

**Thai Malarial Zone Classifications** - A1 Perennial transmission areas: 1.5 million people live in these areas. A2 Seasonal transmission: 2.3 million. B1 High risk areas: 11.4 million [Chareonviriyaphap 2000]. High risk areas are where integrated vector and transmission control strategies coupled with aggressive treatment has resulted in over 3 consecutive years of no LOCAL transmission. These areas are considered high risk because the environmental conditions have and continue to favour primary and/or secondary vectors ... but they have been temporarily "Rolled Back". In areas like this it is wise to treat as many with radical cure as possible in order to reduce the number of potential carriers. Even though total loss of community-wide immunity after 3 years makes these places very conducive to epidemics this risk is worthwhile because most of the population lies within an area where integrated transmission control strategies are possible and the majority have consistent access to anti-malarials.

Note also that plant-based remedies for immunes can provide clinical cures that do not result in complete parasite clearance thus allowing the population to better withstand mild bouts of malaria that will maintain immunity. Plant based medicines also solve access, shortage and time-to-treatment issues preventing the onset of severe and

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complicated malaria (mortality rates 15% in this area, according to SMRU - provided they get to a clinic)

**Conclusion:** Question strategies that attempt short-term treatment and transmission-control induced parasite clearance for populations who live in areas where consistent access to anti-malarials cannot be assured and where transmission control is not meaningfully possible. Focus on individual forest workers that may have acquired immunity, yet at high risk due to Population Movement and thus most likely to introduce new strains that confer no long term immuno-epidemiological benefit to the group.
4.6 Population Movement - Human migration is at the root of most malaria epidemics and severe malaria problems in South-east Asia [Singhanetra-Renard 199346].

The degree of genotype variance per kilometer is more pronounced in Forest Malaria which could explain why 'villagers in the focus area aged between 30-39 years, with frequent movement into the forest (despite presumed immunity) have the highest impact of malaria risk' [Butraporn47].

Agricultural Mobility - Agricultural practices such as swidden farming and logging in forested foothills expose populations to vectors that cannot be controlled. Furthermore, during the rainy season from June to October which is the growing season for hill rice farmers, when malaria transmission is at its highest, villagers usually sleep in field huts away from their houses in the village in order to control weeds, and keep away foraging animals. The relative risk of infection for people engaged in agricultural activity is estimated to be three times that of people living in residential villages. Although a higher biting density of vectors is generally evident at the village hut, the estimated inoculation rates in the two settings are similar [Samboon 199848].

Dry-Season Foraging - During the dry season, villagers enter the forests to seek roots, tubers, algae, mushrooms, reptiles, insects, crustaceans, fish, birds, and plants that can be eaten or sold. The poorer the access to markets, the greater the diversity of products that people need to grow or seek in the forest. In the rainy season, 53% of the women spent an hour or less gathering. In the cool season when agricultural demands are less, 64% of the women spent one to two hours gathering. In the hot season, however, availability factors more than other activities affect the amount of time spent obtaining wild food. The scarcity of nondomesticated food in the hot season results in the village women spending more time in this activity, and 31% spent two or more hours in gathering activities. [Moreno-Black49].

Day long journeys tend to be undertaken by adult men. Some activities, like frog-hunting, take place near small streams, while deer-hunters go on even longer forays, sleeping overnight in trees to avoid being shot at by each other.

49 Moreno-Black, Geraldine Cooking up Change: Transforming Diets in a Rural Thai Village - University of Oregon, Eugene, Oregon
Occupational Risk - Working in gem-mining pits, rubber tapping (once weekly during dry season, often between one and six am), firewood collecting, and logging,

Illegal Activities - Logging, smuggling and poaching often involve week-long stays in forests and encounters between infected and non-infected, non-immune groups [Singhanetra\textsuperscript{50}]. Opium planting season, in October, poses similar risks.

Military Displacement - Large scale forced displacements have and will continue to occur until the political situation in Burma is resolved. In the target population, from April to June 2002, over 5,000 people have been displaced, 6 villages burned, 6 schools destroyed, 5 churches burned, 15 villagers murdered including women and children as young as 2 years old, (12 in one massacre), 3 pastors captured, tortured for 5 days and still held captive-condition unknown, over 28 villages attacked, looted and forced to relocate and over 1,000 people now hiding in the jungle attempting to make it through Burma Army patrols into Thailand. Over 4,000 more would also attempt to flee but are too far from the border and too close under Burmese Army observation to escape. [Classified Document]

Cross-Border Movements - For military, political, cultural (Songkran), trade and economic reasons.

Conclusion: Malaria control measures (even) in the plains should utilize chemoprophylaxis and effective chemotherapy focusing on the people who travel into the forest [Myint 1991\textsuperscript{51}]. Impregnated nets are less relevant because some groups are continually on the move through the habitat of the vector. Insecticide treated blankets have been considered for forest workers - cost, utilization, access, disposal, and toxicity should be considered.

Locally available plant-based Repellents should be investigated.


\textsuperscript{51} Myint L & H Ye (1991) Study of the Malaria situation in Forested foothill and nearby plain areas of Myanmar. - Department of Medical Research, Yangon, Myanmar. - Southeast Asian J Trop Med Public Health 1991 Dec;22(4):509-14
4.7 Repellents – Low cost, easily available repellents are necessary for journeys outside the village to protect populations from new strains of malaria

Who needs them most - Forest workers exposed to new genotypes and thus more likely to introduce new strains that will not confer any long-term immunoepidemiological benefits to the community. Migrants and refugees in transit. Individuals with sub-therapeutic post-treatment drug residuals after treatment. Children older than 8 months, no longer protected by maternal antibodies. Pregnant women, especially primigravidae, during and up to three months postpartum. Individuals from adjacent communities where integrated vector control strategies have resulted in prolonged parasite clearance and hence loss of premunition. The cash-poor and those outside the cash-economy.

Who might be interested - The small minority of tourists and travelers who would like to support the local micro-economy. Those that object to the pollution caused by the manufacturing, packaging, advertising, transport and disposal of commercial products. Even smaller minority with allergic reactions to N,N diethylmethyldimethyltoluamide (DEET) formulations. Ethnobotanists.

Papaya Leaf Tea - A handful of young papaya leaves steeped in hot water, drunk twice a week, has been used as a prophylactic in numerous locations. Anecdotal evidence has been compiled of its use in Zimbabwe, Borneo, Sumatra, Ecuador, Irian Jaya, Brazil, Sulawesi, Malawi, [Berkelaar 2002]. A similar treatment, juice extracted from the crushed paste of a handful of young papaya leaves, was used by Ulrik Urban, during his detention in a Japanese concentration camp in Sumatra. [Personal Interview].

Neem, Margosa, Khomba Leaf Tea - Similar principle, extensively used in India. (see treatment section of this document for more details) Neem, Azadirachta indica, is a member of the Meliaceae (mahogany) family.

Mahogany seeds - Forest workers in Borneo take four to five mahogany seeds prior to spending extended periods of time in the forest. The seed casing is soft, so no preparation is required. Efficacy not formally proven other than the fact that this strategy has been employed over time across a variety of settings.

Lemon Grass - Fresh plants much more effective. Stalks better than leaves.

Burning Leaves to Release Volatile Essential Oils - Field studies to determine relative efficacy of the repellent action of vegetable, essential and chemical base oils against vector mosquitoes revealed that essential oils viz. Cymbopogan martinii martinii var. Sofia (palmarosa), Cymbopogan citratus (lemon grass) and Cymbopogan nardus

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52 Berkelaar, Dawn (ongoing) Papaya Leaf Tea as a Malaria Prophylactic? - compiled for ECHO (Educational Concerns for Hunger Organization; www.echonet.org)
(citronella) oils provided almost complete protection against Anopheles culicifacies and other anopheline species. [Ansari 1995].

Given that a 1% Neem oil - kerosene mix in lamps may provide economical personal protection [ICMR 1994], indicates that in areas where acquisition of either is not possible, burning neem leaves and / or mahogany leaves may be the next best option.

**Burning Cashew Nut Skins** - Remedy used by my own family in Sri Lanka.

**Receptivity** - Many villagers already use some of the above methods to protect against mosquito bites. The use of ground tobacco paste to protect against leaches is also well known and used.

**Conclusion:** Appropriate locally available repellents for Forest workers, backpack medics, etc should be further investigated, especially where Access is compromised.

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Sharma VP & MA Ansari (1994) Personal protection from mosquitoes (Diptera: Culicidae) by burning Neem Oil in Kerosene. Malaria Research Centre (ICMR), Delhi, India. J Med Entomol May;31(3):505-7 1994
4.8 Treatment Access – Without Consistent and Timely Access to Antimalarial Drugs, the Cost of Losing Protective Premunition becomes Significant

Cost, Time, Distance - The majority living in Border Forest areas are outside the cash economy or resource-poor, have little time available from subsistence farming and other occupations to travel seeking medical care and hence have infrequent access to antimalarial drugs.

Counterfeit Drugs - If and when drugs are obtained, it is usually in the form of a drug preparation commonly called "ya-chud". On average, a set of ya-chud for malaria infection consists of 3-5 drugs: antimalarial drugs together with others such as analgesic-antipyretics, steroids, anti-histamines, vitamins and antimicrobial agents (tetracycline). In 1992, the price of one ya-chud varied from 3-9 baht [Kamolratanakul55]. The probability that these preparations contain counterfeit drugs is very high. Of 104 shop-bought 'artesunate' samples from Cambodia, Laos, Myanmar (Burma), Thailand, and Vietnam, 38% did not contain artesunate [Newton 200156]. Field tests are confounded by the presence of detectable, but non-therapeutic quantities of artesunate in newer, more sophisticated counterfeit packaging complete with trademark holograms.

Drug Spoilage - With regards the frontline treatment of artemether and lumefantrine, (COARTEM®), stability tests show that the formulation is stable for 2 years at room temperatures of 25°C and below. The manufacturer recommends that it should not be stored above 30°C. [CDS/RBM 200257]. In the focus area, extremely high temperatures occur in March and April. The almost vertical position of the sun and the battle by the NE monsoon to retain itself just before the beginning of SW monsoon make it the hottest month of the year. The maximum temperature recorded in northwestern Thailand is 44.4°C at Uttaradit (63.3m above sea level) and 43.9°C at many stations at every altitude up to about 300m above sea level. Thus, very high maximum temperatures in April, say higher than 38°C, can be expected frequently and must be taken into consideration when drugs are being transported long distances by Backpack Health Workers.

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57 CDS/RBM (2002, 18 March) Review of Application for Inclusion of a Drug in the WHO Essential Drugs List - Fixed combination of artemether and lumefantrine (COARTEM®)
Military Impediments to Access - Access to public health services is primarily limited to urban areas. In rural and remote areas, services are provided on an outreach basis, perhaps once every four months or at best periodically. Several townships remain very difficult to access, such as Meh Set and Shadow townships where medicines for malaria and tuberculosis are unavailable [BERG 200058]. "They (villagers) cannot be reached easily by the KNU (Karen National Union) Health Department / KORD (Karen Office of Relief & Development) mobile teams as they are far from the border in the midst of DKBA-controlled territory. They are close to towns but have no money for medicines." [BERG 199859] In addition, the Burmese government has accused villagers of supplying medicines and batteries to the opposition KNU, as a result possession of either is now banned.

Drug Shortages - In one of the better known 'informal' cross border programs, around fifty percent of cases are currently going untreated due to drug shortages. [Classified communication]

Resistance - Even when drugs are available, the effective use of pharmaceutical anti-malarials is greatly compromised by wide-spread resistance to a number of formulations. The risk of resistance to new drugs is unknown, but assumed to be considerable simply because resistance to most other antimalarials has arisen faster along Thailand's borders than anywhere else on earth.

Experience from the Focus Area:

- Saw Thay Doh (M, 28), internally displaced villager from P— village, Shwegyin township (Interview #81, 3/00). "We don’t have medicine to treat the sick. There is no one coming to sell it here. We just stay in the jungle and treat them with bitter gourd leaves. Sometimes we eat boiled rice soup."
- Saw Mu Kaw (M, 23), internally displaced village head from x village, Dweh Loh township (Interview #145, 9/00) - The old people are cold and the young children cry because they have fever when they are sick and malarial. We can’t do anything because we have no medicine so some of them died. We don’t know how to get the medicine to heal them. We just go through this kind of thing day by day."

Necessity the Mother of Invention: Saw Po Hla (M, 43), KNU township official, Bu Tho Township Interview #219, 2/01 "In the case of malaria they use boiled Theh Ka Po [a small plant used as an herbal medicine] and drink it and they are cured. We don’t have medicine. We cannot come and buy medicine from this side (Thailand) because there

are a lot of problems on the way to come and bring (allopathic) medicine. They cannot go and buy (allopathic) medicine from the SPDC.” [above accounts from the Karen Human Rights Group Report 2001\textsuperscript{60}]

\textbf{Conclusion:} It is crucial that populations whose access to medical treatment is compromised, be encouraged to utilize affordable and appropriate solutions based on local resources. Furthermore, early intervention with local, plant-based Field Medicines may delay, if not halt, the onset of severe and complicated malaria.
**4.9 Field Medicine - Local Solutions** - *Early Intervention with local, plant-based Field Medicines may delay, if not halt, the onset of severe and complicated malaria.*

**Target Population** - The presence of different ethnic groups, displaced persons from different ecozones such as low-land farmers, urban dissidents and hill-tribe swidden farmers means that ethno-botanical knowledge is unevenly distributed across the target population. Furthermore, medical personnel educated under the allopathic model and misinformed about traditional practices inadvertently stigmatize plant-based interventions despite their obvious relevance to cash-poor populations with limited access to modern pharmaceuticals.

"For internally displaced women hiding in free-fire areas, there is simply no access to health care services. Women living in the jungle have no choice but to rely on their own knowledge of traditional medicines." [NCGUB Shadow Report 2001\(^{61}\)]

**Cultural Considerations and the Placebo Effect** - It should be noted that 'injection doctors' (*mor chiit yaa*), are a popular alternative to visiting clinics because injections are a highly valued means of taking pharmaceutical drugs because of their supposed efficacy in curing illness. Irrational and dangerous practices will continue to exist no matter what belief system is followed. The dangers of over-medication, and rampant self-medication using modern drugs is well documented across Asia.

**Experiences from the Focus Area**

- Po Naw (M, xx), internally displaced villager from S— village, Lu Thaw township (Interview #61, 3/01) "Some of the villagers went to get ‘kyaw pi’ [a type of leaf used to make herbal medicine] and some of them are healed. Some of the villagers who believe in animism treat the animist way and people are also healed."

- Saw Po Hla (M, 43), KNU township official, Bu Tho Township (Interview #219, 2/01) "No clinic and no medicine. They find plants like Na Paw Kyaw and they boil them to drink [as an herbal medicine]. The other medicines are Khoh Bay and Noh Bay [types of bark made into medicines]. In the case of malaria they use boiled Theh Ka Po [a small plant used as an herbal medicine] and drink it and they are cured. We don’t have medicine. We cannot come and buy medicine from this side [in Thailand] because there are a lot of problems on the way to come and bring medicine. They cannot go and buy medicine from the SPDC."

- Saw Maw Htoo (M, 31), internally displaced villager from D— village, Shwegyin township (Interview #71, 2/00) "We have a little medicine, but it is not enough. When we

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get sick, we take it. Mostly, when we get a fever or headache, we eat Nya Baw Saw, when our bodies have pain, we eat Blaw A'Mu, and when we get a cough, we eat Paw Pwaw. [These are herbal medicines made from plants and roots found in the forest.] Sometimes we are cured and sometimes not. Not only the children die from disease; the old people are also suffering from disease, and many have died in our area.” [All above reports from the Karen Human Rights Report 200163]

Local Ethnobotany - The hill tribes use a variety of plants to treat malaria [Anderson63]. Choices are dependant on plant availability and disease severity. There is very little consistency in usage between tribes, with a few notable exceptions: The Akha, Hmong and Lahu peoples are united in their use of Clerodendrum serratum roots, which they boil and drink.

- **Akha** - The Akha use Desmodium triquetrum, but its ancillary uses indicate it may be more of a tonic than a 'cure'.

- **Hmong** - The Hmong prepare infusions from Paederia wallichii, Psidium guajava (the leaves of which are mixed with that of Punica granatum), Saurauia roxburghii, Scoparia dulcis, and Viscum articulatum. They make poultices from Eryngium foetidum, Lonicera macrantha, Oroxylum indicum (particularly good for treating an enlarged spleen, as is Mussaenda pubescens), and Plumbago zeylanica. They are also know to pulverize the leaves of Euodia glomerata or Houttuynia cordata with eggs, steaming the concoction, and eating it.

- **Karen** - Karen treatments include: 1) boiling the bark of Alstonia scholaris, (no anti-protozoal activity detected in vitro. It is possible that reports of cures for malaria were made on the basis of temporary recovery from fever since it's alkaloids do have a depressant action on medullary centers - this action can bring down fever.) 2) stems and roots of Cleidion spiciflorum, and 3) the whole of Trichosanthes tricuspidata.

- **Lahu** - The Lahu drink infusions of Croton robustus bark, Helicteres elongata, Melastoma normale, Millingtonia hortensis, Polyalthia cerasoides and Trema cannabina. As most of these plants may have been chosen due to their 'bitter principle', we can regard them as containing alkaloids requiring further investigation.

- **Lisu** - The Lisu use the roots of Cassia occidentalis, Chloranthus elatior, and C. nervosus. Sambucus javanica plays a significant role in Lisu treatment: boiled infusions from the root of this plant are drunk to stop the fits and seizures caused by cerebral malaria.

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Receptivity - While hilltribe plant treatments are wildly inconsistent between tribes and even within them, (a factor of availability as well as culture and knowledge) the universal adaptation of certain practices indicates that efficacious treatments are well received. This receptivity extends even to introduced species such as *Eupatorium odoratum*, which is used as a blood coagulant, and *Aloe vera*, for burns.

Community Mobilization - Can people who have forgotten ancient practices re-incorporate plant-based medicines into primary health care? Can this ‘retraining’ work on a regional, state or national level? The case of Shodhini in India is illustrative. In 1987, several women's groups working in the field of health all over India came together to start the process of collecting information about herbs and recipes. This group, the Action Research on Alternative Medicine and Women's Health, with Rina Nissim as the convener, consisted of women from grassroot organisations like the Deccan Development Society (DDS), Action India, Aikya, SARTHI, Eklavya, Sadguru Water Development Foundation, Sabla Sangh and Vikalp; from support organisations like CHETNA; and from women's research and documentation organizations like Jagori and Anveshi. This field-based group was supported by a number of people all over India among whom mention must be made of Indira Balachandran, phytochemist at Arya Vaidyashala, Kottakal, Kerala; Shyama Narang, a gynecologist based in Bangalore; and Tanushree Gangopadhyaya an activist based in Ahmedabad.

I have named the long list of participants individually for this case to highlight how necessary collaboration and information sharing is for such a considered response.

Data collection covered nine states of India. In 18 months 600 remedies corresponding to 300 plants were collected. By 1990, the group began to clinically test the remedies in three field areas and train health workers in using these remedies in rural areas and urban slums. Soon the health workers were grinding and mixing plants for remedies. Dosages were expressed in local measurements such as a handful of dried leaves, or a stem one finger long. In the beginning herbal remedies were used for common complaints such as vaginal discharge, burning urination, anaemia, dietary problems and painful periods. By late-1991, Shodhini began trials for herbal remedies for uterine prolapse, excessive bleeding and complications in pregnancy and delivery. Presently, third or fourth generation ‘barefoot gynecologists’ are able to confidently diagnose and treat all sorts of common women’s ailments in Maharashtra, Gujarat, Rajasthan, Andhra Pradesh and Tamil Nadu. All of Shodhini's research is documented in "Touch Me, Touch Me Not" named after a common, yet frequently overlooked medicinal plant. "In contrast to the passive consumerism encouraged by modern medicine and the 'information-for-sale-to-be-jealously-guarded' attitude of modern medical practitioners,
self-help seeks to encourage autonomy through information sharing and control over resources [Gupta64].

Thai War-zone Experience - Critics claim that it is one thing to rekindle traditional plant based medicines in a stable community with relatively little displacement, it is quite another to do so in the midst of a long simmering conflict. But this is precisely when these initiatives have the best chance; when people are forced to use their initiative and imagination to make the best use of scarce resources. Dr Pennapha Subcharoen came to just these conclusions about traditional plant based medicines nearly two decades ago while director of the Wang Nam Yen Community Hospital in Prachin Buri on the Thai-Cambodian border. Dr Pennapha observed that it was the heavy cost of modern medicines on impoverished villagers that encouraged her to reduce their use: "Many of my patients had to spend the only money they had to hire vehicles to get to the hospital only to find that the medicines they needed were out of stock. I realised we had to be self-reliant. There was continuous fighting in the area bordering Cambodia and we had to do something to keep ourselves protected from shortages of drugs and medical supplies. Instead of waiting for medicine, patients suffering diarrhoea were often treated with guava leaves boiled in water with a pinch of salt. Banana leaves were used for patients with burns and other wounds." [Bhatiasevi 199965]. It would be wise to learn from such experiences. Dr Pennapha is currently director of the Institute of Traditional Thai Medicine,

Macro and Micro-Economic Benefits - Rosana Tositrakul, secretary general of the Thai Holistic Health Foundation, began in the early 80's by forming 'Traditional Medicine for Self Reliance', an NGO dedicated to reviving the knowledge of Thai traditional medicine as a means of empowering local communities. In 1990, the name was changed to Thai Holistic Health Foundation, 'ThaiHof', to reflect the expanded scope of the organization's efforts. Tositrakul went from village to village in the Kudchum district, in the central region of Thailand, collecting data on medicinal plants and learning about centuries-old herbal recipes. Initially she disseminated the information on photocopied pages. As the document grew from four to 16 pages, she switched to a magazine format and finally to publishing small booklets. Today the 40-title library has gone through more than 10 printings.

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65 Bhatiasevi, Aphaluck (1999) Traditional Medicine Advocate sees its use as only Natural, Bangkok Post February 1st 1999
In Thalaad, a village in Kudchum, Tositrakul joined forces with the abbot of the village temple, a group of traditional healers, and a doctor and nurse from the local hospital. Like Tositrakul, Abbot Phra Supajarawat believed that by alleviating their poverty and thus their low status, the rural poor's battered self-esteem would see an upswing. To his mind, environmental ecology was a tangible route for effecting this change, echoing as it did, the popular saying: "the forest is a supermarket for the villagers." The group set up a health center and herb garden in the temple compound in 1983. The villagers began visiting Wat Thalaad for herbal medicines and, empowered by their new sense of community, were soon planting their own herb gardens. By 1986, Kudchum villagers were spending 75 percent less a year on conventional medicines, down from approximately 12,000 baht per family to 3,000 baht. [Gampell 2000*]

4.9.1 Plant and Pill Profile - Artemisia annua and Artemisinin

Artemisinin is a complex compound that needs to be grown and harvested - Whether one uses the plant directly or as a commercial formulation, field cultivation and harvesting of Artemisia annua is the only viable method of 'producing' artemisinin, as synthesis of this complex molecule is both problematic and uneconomic. Artemisinin is a complex compound. It is not an alkaloid or an amine as the name suggests. It took X-ray crystallographic analyses to elucidate the unique structure of this plant metabolite. Look at the structure: C_{15}H_{28}O_{6}. Notice the five oxygen atoms? See Appendix 7.7 This sesquiterpene lactone endoperoxide has five oxygen atoms; two of them in a peroxide bridge system over a seven membered ring and two involved in a lactone ring structure. It is the peroxide bridge which is pertinent - biochemically, this classifies the compound as an 'oxidant' - and which links this compound to our own evolutionary response to the parasite in the form of GP6D deficiency, α-Thalassemia, and β-Thalassemia.

To understand how artemisinin works it is first important to understand that the malaria parasite survives by consuming hemoglobin in the host's red blood cells. The parasite does not metabolize the heme (Fe^{2+} iron) in the hemoglobin, instead, it stores the iron, in the form of a polymer called haemozoin inside a food vacuole. When artemisinin comes into contact with the iron in the hemozoin, the iron reacts with the endoperoxide bridge to create free radicals that destroy the parasite by alkylation of its proteins. The exact mechanism past this point vis a vis specific proteins is still unknown. Recent studies indicate that PfATP6 (which pumps calcium) may be the critical site of action. We don't actually know how it works.

The bottom line? Synthesis of this complex molecule is uneconomic as argued by Schmid & Hofheinz 1983 and Xu et al. 1986. If you want artemisinin, the best way to get it is to grow the plant. As a result, the technical literature on growing and harvesting high yielding plants is extensive. High yielding plant varieties have been developed for commercial cultivation at the Swiss Federal Research Station for Plant Production, Switzerland; MEDIPLANT (Centre de Recherches sur les Olantes Medicinales et Aromatiques), Switzerland; CPOBA-UNICAMP, Brazil [Magalhães 200?] ; CDRI-CIMAP, India; BIOTEC (National Centre for Genetic Engineering and Biotechnology), Thailand; Vietnam; Tanzania and Madagascar.

Yield Consistencies - Numerous factors determine yield including plant genetics, morphology, growing location, harvest time and local conditions such as soil quality,
ambient temperatures and humidity. The leaves of the herb (where 89% of the artemisinin is found, localized in the upper leaves) is usually collected when the plant is in full bloom, and preservation of the leaves is best achieved by shaded air-drying [Charles 1993], but it takes years of experience to judge how much of a given plant needs to be administered. Any ethical intervention should incorporate the few people who possess this knowledge base into rural public health programs as they have in China, Vietnam, Cuba, Korea and India. Micro-propagation of high-yielding varieties can overcome part of the problem.

Field Trials - One particular variety, Artemisia Annua A3, containing 0.63 - 0.70% artemisinin per dry weight has undergone successful field trials in the People's Democratic Republic of Congo. "Five malaria patients who were treated with A. annua tea showed a rapid disappearance of parasitaemia within two to four days. An additional trial with 48 malaria patients showed a disappearance of parasitaemia in 44 patients (92%) within four days. Both trials showed a marked improvement of symptoms. [Mueller 2000]. A3 is already growing successfully in many countries, including China, Cambodia, the Dem. Rep. Congo and Uganda, Sudan, South Africa and Tanzania.

Dosage - The typical dosage of Artemisia annua recommended to treat malaria is 20-40 grams of the dried herb per day in decoction. Much less than used by modern medical formulations of the isolated compound or its synthetic derivatives. As discussed earlier (in the Resistance section - 'The Original Combination Therapy'), this lends credence to the studies demonstrating 'other' active compounds in the herb.

Local possibilities - Thailand's National Centre for Genetic Engineering and Biotechnology (BIOTEC) has developed a variety of Artemisia annua which produces twice as much of the active compound artemisinin using micropropogation. Prior experiences with micropropogation technology by hilltribe groups indicate that commercial cultivation of Artemisia annua with 'standardised' yields may well be a viable option: When the Chiang Rai based Hill Areas Development Foundation required thousands of banana trees to reduce soil erosion as the first step towards reintroducing forest species in the Mae Chan and Mae Salong river basin watershed - local villagers were only able to produce 3,000 trees using the traditional method of separating banana pups from their mother trees. In response, the Centre developed and donated a low-cost

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micropropogation laboratory (around US$2,500) from which villagers are now producing over 20,000 banana trees a year [Ruff 2001].

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5 Discussion and Conclusions

The main ideas contained within this paper have been condensed overleaf into bullet points to assist the reader.

From the onset it must be understood that the evidence that has been collated herein can only be regarded as circumstantial. However, I believe sufficient material has been presented to argue the case that the use of plant based medicines as a means of mitigating access problems for remote resource-poor peoples, conserving protective premunition for those without consistent access to anti-malarial drugs and delaying the onset of drug resistance in the broader global struggle against malaria, merits further research.

Further research is called for due to the following shortfalls:

Conserving Premunition

Firstly, there are no documented investigations in English Medical literature that directly address the impact that radical-cure treatment regimes have on premunition, despite the obvious significance this research would have for remote populations without consistent and timely access to modern pharmaceuticals, living in areas where malaria is endemic. A recent study of premunition kinetics in mice models gives every indication that radical cure treatments may be doing more harm than good for these populations. The significance of this research is detailed in “Immunity / Premunition 4.5” sub-titled ‘Non sterilizing Immunity’

Delaying Drug Resistance

Secondly, there are no documented investigations in English Medical literature directly addressing the degree of efficacy that field formulations of Artemisia annua / Scutellaria sp have on malaria, despite the widespread employment of this plant combination over hundreds of years. In areas where drug resistance has consistently developed rapidly, it seems wise to employ alternate antimalarials in order to conserve the useful life of pharmaceutical drugs in the broader global struggle against malaria. The significance of this research is detailed in “Drug Resistance 4.4” sub-titled ‘The Original Combination Therapy’

Mitigating Access

Thirdly, there are no rigorously documented field investigations directly confirming or rejecting the direct use of plant anti-malarials as a means of addressing the malarial burden of resource poor peoples with limited access to modern pharmaceuticals. The significance of this research is detailed in “Access 4.8”

Until these questions have been addressed, we have to accept that we are simply not equipped to form informed opinions as to the value of field formulations of artemisia
annua. Furthermore, we need to reject the prevailing aversion to investigating traditional medicine as a viable programmatic option for what it is; uninformed and lazy prejudice. While it is understood that it is an indelible characteristic of the human condition to seek certainty, when this certainty is based on an incomplete understanding of the subject, an almost willful ignorance and a reluctance to question, we must be willing to declare and expose our ‘unknowing’.

In the meanwhile, the question still remains, 'Why are we CONTINUING to mislead resource-poor peoples away from freely available plant medicines (whose mechanisms of action we may as yet not be 'equipped' to understand), towards a reliance on unsustainable, expensive and often imported processed drugs. Remember, scientific exploration and discovery, even commercial exploitation and profit, need in no way be compromised by encouraging resource poor peoples who are outside the cash-economy anyway, to 'use what works' for themselves. To not acknowledge this is turpitude of the highest order. The irony needs to be understood: How do people who have used plants for hundreds if not thousands of years, the same people who introduced scientists to the bioactive compounds that form the very basis of the modern pharmaceutical industry, suddenly become viewed as ill-equipped to use them?

This paper merely seeks to open up the debate, to plant seeds of curiosity. Only by looking can we hope to see.
Overview of Main Arguments

Compromised Access
- Early treatment is crucial
- Resource poor people in this area are unlikely to receive timely, consistent access to treatment due to distance, displacement, shortages, drug spoilage, counterfeit anti-malarials, confiscation of drugs by military forces, and cost.
- Consistent Access to Treatment cannot be maintained Indefinitely

Loss of Immunity
- Where Sufficient Vector and Transmission Control is Not Possible (Forest Malaria + War Zone), People will get Repeated Infections
- Repeated Infections confer a non-sterilizing immunity that Reduces the Incidence, Severity and Duration of Illness. Since much of this immunity relies on the presence of parasite residuals, it is often called Premunition
  - The existence of Premunition has been established along the Thai-Burma border
  - Premunition is a valuable ally in the fight against malarial mortality where Sufficient Transmission Control is Not Possible and where Consistent Access to Treatment cannot be maintained Indefinitely.
- Protective Premunition levels are influenced by Transmission & Treatment
- Insufficient Reductions in Transmission result in delayed acquisition of premunition and subsequently Higher Overall Rates of Morbidity and Mortality if Consistent Access to Treatment cannot be maintained Indefinitely.
- Radical Cure Treatment eliminates parasite residuals thus diminishing naturally acquired premunition, resulting in Higher Overall Rates of Morbidity if Consistent Access to Treatment cannot be maintained Indefinitely.
- Pharmaceutical Clinical Cures that conserve Premunition cannot be employed without selecting for Drug Resistance

Increased Drug Resistance
- In areas where Transmission Control is possible, Integrated Strategies should be comprehensively implemented and drug treatment should be fast, comprehensive and aggressive. In all areas, it is crucial that the efficacy of intravenous, intra-muscular and suppository formulations of anti-malarial drugs be preserved for emergency treatment in situations where the patient is unable to ingest medicine orally. To that end, it is crucial that the effectiveness of pharmaceutical anti-malarials be maintained as long as possible.
- It is important to minimize the risks of Drug Resistance.
- Drug Resistance is a factor of the number of Unique Drug / Parasite Transactions
- Unique Drug / Parasite Interactions are greatest in areas of high transmission, providing more opportunities for Drug Resistance
- Drug Resistance has developed consistently faster along Thailand's forested borders than anywhere else in the world.

This paper assembles the evidence base for these assumptions and seeks to answer the question:
“Can Access Problems be Mitigated, Premunition be Conserved AND Drug Resistance Delayed in a Cost-effective and Sustainable manner?”
Glossary

**Anopheles:** Genus of mosquito comprising nearly numerous species that transmit malaria through the bite of its female.

**Bionomics:** The branch of biology concerned with the relations between organisms and their environment.

**Chemoprophylaxis:** Treatment involving the use of a drug to prevent infection/disease.

**Cerebral malaria:** Condition in which the brain is infected by the malaria parasite. Seizures are a common complication of cerebral malaria and are associated with an increased risk of death and neurological complications.

**Complicated (severe) malaria:** Malaria infection that is serious and life threatening, especially in children. Condition usually occurs as a result of delay in treating an uncomplicated attack of malaria, yet may develop very rapidly in children. Symptoms in children include coma, acute kidney failure, circulatory collapse and repeated convulsions. Adult symptoms include respiratory distress, severe anemia, generalized convulsions, and shock.

**Efficacy:** The extent to which an intervention achieves its intended effect under ideal circumstances.

**Endemic:** Continual, sometimes low-level presence of disease in a defined geographical area.

**Epidemic:** Occurrence of disease within a specific geographical area or population that is well in excess of the normal level, either within a specified geographical area or widespread among a population.

**Gametocyte:** Precursor of the sexual forms of the malaria parasite, which releases either male or female gametes within the stomach of the mosquito.

**Gametocyte carriage:** Carrying the infective form of the parasite in human blood.

**Parasitemia:** Circulation of parasites in the bloodstream.

**Plasmodium:** Genus of the parasite that causes malaria. The genus includes four species that infect humans: Plasmodium falciparum (causes the most serious form of the disease), Plasmodium vivax, Plasmodium malariae, and Plasmodium ovale.

**Premunition:** Premunition refers to a subset of immunity that is contingent upon the parasite being present. Premunition is thus a factor of the number of infective bites, with populations living in high transmission areas ironically experiencing lesser morbidity and mortality to those in low, seasonal transmission areas.

**Recrudescence:** Reappearance of disease in a host whose infection has been dormant/inactive. Malaria recrudescence (short term relapse or delayed) is due to the survival of malaria parasites in red blood cells.

**Uncomplicated (simple) malaria:** Malaria infection in which symptoms include fever, headaches, chills and sweats, muscular and abdominal pain, vomiting and diarrhea. Presentation is highly variable and mimics that of many other diseases. Without prompt and effective treatment, infection could lead to more serious, life threatening condition.

**Vector:** An organism, typically an insect, which transmits an infectious agent from one host to another.