Malaria Prophylaxis Initiative (MPI)

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A NEW METHODOLOGY FOR PREVENTION (PROPHYLAXIS) OF MALARIA AND OTHER VECTOR-BORNE DISEASES©

"Wherever the art of medicine is respected,
there is also respect for humanity"
Hippocrates 400 BC

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TERMS USED

Arthropod: Any of a phylum of invertebrate animals comprising those with segmented bodies and jointed limbs (e.g., insects).

Dengue: A worldwide flu-like viral disease (*filoviridae* family RNA virus) spread by the bite of an infected *Aedes* mosquito. Unlike the mosquitoes that transmit malaria, *Aedes* bite during the day. Dengue is common in Africa and is one of the most common viral diseases spread to humans by mosquitoes. All types of dengue virus are re-emerging worldwide and causing larger and more frequent epidemics. Hemorrhagic fever is a severe, often fatal complication of dengue, particularly amongst children and young adults. There is no specific treatment for dengue. Prevention rests solely on avoiding mosquito bites.

Co-Infection: The condition of simultaneously being Infected with two diseases which generally share a common etiology, e.g., drug users who are co-infected with HIV and HCV (Hepatitis C Virus). The opportunistic infection potential existing between malaria and HIV also makes persons suffering with either of these diseases more susceptible to becoming infected with the other (co-infected). Further, HIV-infected persons who contract malaria are more likely to develop a more severe form of the disease. This suggests that malaria prophylaxis might be considered as a part of a comprehensive HIV prevention and treatment program.

Filariasis/Lymphatic Filariasis: The US Centers for Disease Control and Prevention states that lymphatic filariasis affects an estimated 120 million persons in tropical areas of the world, including sub-Sahara Africa. This disease is transmitted by infected mosquitoes which spread the infection from person to person (in similar fashion to the transmission of malaria). All persons who are exposed to mosquitoes may become infected. No vaccine is available, nor has effective drug prevention been documented. Like malaria and dengue fever, protection is achieved by avoiding mosquito bites.

IRS: Indoor Residual Spraying. A widely-employed methodology for protecting against mosquitoes. Its limitations have to do with the extraordinary resistance and adaptability of mosquitoes and other arthropods to insecticides, requiring regular change-off of the chemicals used. Traditionally, DDT has been used but has experienced disfavor as it had been banned for use in the US and the EC for decades due to both short-term and long-term toxicity concerns. The pyrethroid family of chemicals has seen recent acceptance in this role although it too requires change-off after a period of time due to the aforementioned adaptability of the arthropods it is intended to defeat. The issue of toxicity requires protective gear for the persons engaged in the spraying along with a careful training program and highly-regulated application methodology.

ITN's: Insecticide Treated Nets. A generic expression for bednets treated with insecticide to increase their efficacy and permit a more open weave. This more open weave helps alleviate the heat build-up in sleeping area which has contributed to the low usage of nets by recipients.

LLIN's: Long-Lasting Insecticide Treated Nets. A more current terms for bednets relating a newer generation of nets with greater longevity due to the use of stronger fibres and an improved pre-assembly impregnation methodology for the insecticide into the fibres permitting a longer effective life. The bane of all bednets is the repeated washing required due to typically dusty conditions in most of Sub-Sahara Africa. The LLIN's all utilize one of the pyrethroid family of insecticides. However, in Benin, Nigeria and Thailand, resistance to pyrethroid insecticide has been reported in *Anopheles gambiae* and *Anopheles minimus*, the two *anopheline* species representing the major vectors of malaria in these regions.

Malaria: An infectious disease… caused by a parasitic protozoan of the genus *Plasmodium* in red blood cells, which is transmitted to humans by the bite of an infected female *anopheles* mosquito.

Microbe: A microorganism which causes disease.

Microorganism: A living being too tiny to be seen by the unaided eye (e.g., a bacterium).

Morbidity: The number of cases of a particular disease reported within a particular society within a specific period of time.

NAFDAC: National Agency for Food & Drug Administration and Control of the Republic of Nigeria. This is the Federal agency tasked with testing and regulating the acceptance of all drugs, chemicals and active agents proposed for use and/or sale in the Republic of Nigeria.

Olfactory: Referring to the sense of smell. Mosquitoes and other biting arthropods largely utilize their keen olfactory sense rather than their poor eyesight to locate and target their "prey". Careful investigation to the present suggests that mosquitoes are attracted to the carbon dioxide (and to a lesser degree lactic acid) expelled in breath and perspiration. The range at which mosquitoes can detect a person using their highly-tuned olfactory sense is a surprising 36 meters.

Opportunistic Infection: An infection caused by pathogens (bacterial, viral, fungal or protozoan) that usually do not cause disease in a healthy host. Opportunistic infection is a product of *immunodeficiency*: a compromised immune system weakened by disease presenting an "opportunity" for the pathogen to infect. An opportunistic infection process between HIV/AIDS and malaria renders HIV/AIDS-infected persons more prone to severe malaria and malaria-infected persons more vulnerable to HIV infection.

Parasite(s): An animal living in or on another organism, usually to its harm. There are several species of malaria parasites: *Plasmodium vivax, ovale, malariae and falciparum.* They have proved amazingly resistant to the wide variety of drugs that have been deployed against them.

Patches: *TPI* transdermal mosquito-repellant patches. The *TPI* patches employ a safe, non-toxic active agent – B-1 thiamin – and may be used safely with young children as well as adults. These patches have been approved by government regulatory agencies in several West African nations as well as by the drug regulatory body of the EC. They also enjoy widespread usage in the US and the Caribbean. Their use in Sub-Sahara Africa is to protect against mosquitoes and other biting arthropods that transmit disease, especially malaria. The patches intervene in the ability of the biting arthropods to use their sharp olfactory senses to detect their targets. It is important to note that since most biting arthropods utilize the same (olfactory) methodology for locating their human "targets" the patches are useful in protecting against other vector-borne diseases such as dengue fever (and hemorrhagic fever as a product of dengue fever), filariasis and river blindness. In the US, the patches serve to protect against Lyme Disease ticks and mosquitoes bearing the West Nile Virus and viral meningitis.

Prophylaxis: A measure (or measures) designed to prevent the spread of disease.

Protozoan: Any of a phylum or sub-kingdom of lower invertebrate animals that are not divided into cells or are considered as made up of a single cell.

River Blindness: *Onchocerciasis* or river blindness is a parasitic disease transmitted from one person to another through the bite of a blackfly (*Simulum*). It is a thin parasitic worm that can live for up to 14 years in the human body. It is the world's second leading infectious cause of blindness. It is endemic (but not exclusively) to West Africa.

TPI: TPI International, Ltd. The manufacturer of the mosquito-repellant patches, among other products. TPI is an American firm which pioneered the development of non-drug healthcare products using the highly-effective transdermal route of administration more than twenty years ago.

Transdermal: Refers to a widely-used route of administration for drugs and other active agents that are introduced into the bloodstream through the skin. The medication or active agent is incorporated into an impregnated patch and is released into the system in carefully regulated fashion over an extended period of time. This has become a desirable method for administering medications and other active agents as it avoids injections, pill-taking regimens and the effects of introducing active agents into the digestive system. Its limitations have to do with the size of the molecules of the intended active agents: if the molecule is too large (high molecular weight) the agent will not pass though the skin (e.g., insulin) and cannot be introduced into the system in this fashion. The *TPI* mosquito-repellant patches utilize this highly successful route of administration, offering a uniquely long (36 hour) efficacy period.

Vector: an organism that transmits infection by conveying pathogens from one host to another. In the case of malaria in Sub-Sahara Africa this is the *anopheles gambiae* mosquito; for dengue fever, the *Aedes* mosquito and for river blindness the blackfly (*Simulum*).

A Foreword from Dr. Kenneth Kaunda

As Founder Chairman of the Kenneth Kaunda Children of Africa Foundation, an organization I established to fight against…HIV/AIDS in Africa, I am seized with a lot of challenges that need concentrated efforts of various stakeholders to help mitigate the impact they pose.

I am distressed to have recently discovered a most unfortunate connection between HIV/AIDS and the even greater killer of young children, malaria. Children who are infected with either of these diseases are more prone to become infected with the other. This is called "opportunistic infection" and is as dreadful to contemplate as it is to be experienced by these innocents. We are duty-bound to do everything in our power to protect our precious African children from disease, especially these two rapacious killers.

It has further come to my attention that there is a new and innovative methodology for protecting our children from malaria – it is a simple little patch that keeps mosquitoes at bay and it is safe even for very young children. It is designed to protect children no matter where they are or whatever they are doing. It also protects against the insects that transmit dengue fever, the hemorrhagic fever that results from dengue fever, filariasis and river blindness.

It behooves us to give this new approach our kind attention in pursuit of acquiring an important new weapon in our fight against these dreaded killers of our children.

Your brother,

Kenneth D. Kaunda, Dr. GCEZ
First President of the Republic of Zambia

PROLOGUE:
Adding To The Mix

Probably at no time in history has malaria been so prominently at the forefront of world consciousness. In defiance of the triumphant march of medicine and science in many important areas, this pernicious disease has mushroomed to nearly unmanageable proportions in many venues and has surprisingly arisen in venues where it had never been seen before. According to some estimates, over half of the population of Sub-Sahara Africa may be transporting one or more of the four malaria protozoans in their blood – although many of them never exhibit symptoms associated with the disease.[1] If the estimates about the number of malaria parasite "carriers" is accurate there is an almost limitless resource pool of "attractive" parasite-infected blood [2] for the *anopheles gambiae* mosquito to draw from to infect previously-untainted victims.

In response, health organizations throughout the world are in high gear attempting to "stem the tide" of this insect-borne epidemic including undertaking extensive research to find an effective, affordable and safe anti-malaria vaccine. However, in the best case, this will be some time in coming and in the interim the two most prominent weapons deployed against malaria are insecticide treated nets (ITN's/LLIN's) and interior insecticide spraying (IRS).

In both instances, there are heartening results in terms of reduction of the incidence of the disease and children's deaths. However, both of these resources working in concert cannot account for protecting more than a minority of the vulnerable population from infection.

A New Methodology

It is typical of human nature to be skeptical about new and different ways of doing things. This makes it difficult for a new methodology to gain acceptance in the face of long-held reliance on existing methodologies*, especially if they demonstrate benefit. This is the hurdle that the mosquito-avoidant patches must overcome even though they have shown their ability to provide the full time "go anywhere/do anything" protection against mosquito-biting that is so clearly needed.

Many adults and children, accustomed to applying mosquito-repellant lotions to cover every square centimeter of exposed skin have difficulty accepting the fact that a small (less than five cm. square) patch can protect the entire body. Consistent with this, children in a Ghanaian secondary school – observing that a classmate wearing a patch seemed invulnerable to mosquito attacks – were convinced that he was being protected by a form of voodoo.

Old habits die hard. Nevertheless, the mosquito-avoidant patches were designed and produced based on solid science and employing an effective and well-documented route of administration.

It would be remiss not to mention other prevalent and sometimes deadly vector-borne diseases, specifically dengue fever (and consequent hemorrhagic fever), lymphatic filariasis and river blindness. In all of these cases, the disease is transmitted by arthropod vectors that utilize the same (olfactory-driven) target-seeking mechanism that the patches were designed to thwart.

As a result, please consider that there can be a "better mousetrap" to add to the mix in battling the world's deadliest killer and the other dreaded vector-borne diseases.

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[1]Host resistance is a recognized phenomenon although the reason(s) underlying this may not be well understood.

[2]Children who harbor gametocytes (the stage transmissible to mosquitoes) of the parasite *Plasmodium falciparum* attract about twice as many mosquitoes as children who do not harbor these gametocytes. Lacroix R, Mukabana WR, Gouagna LC, Koella JC (2005) *Malaria Infection Increases Attractiveness of Humans to Mosquitoes*. PLoS Biol 3(9): e298.

*see Appendix III re: bednets and insecticide spraying; also see "The Search for An Ideal Mosquito Avoidant."

INTRODUCING A NEW METHODOLOGY

*In the 1990's Residents of Asembo Bay (in Western Kenya) were bitten 60-300 times a year by a malaria-carrying mosquito**

*National Center for Infectious Diseases, Division of Parasitic Diseases, Centers for Disease Control and Prevention, April 11, 2007
Photo taken in Tanzania. Published online by IHDRC, University of Brighton, Mayfield House, Falmer, BN1 9PH, United Kingdom

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HIV/AIDS AND MALARIA

Early on in the twenty first century, Africa faces grave problems that are unique in their intensity and extensiveness. Political instability, despotism, genocide, human trafficking, poverty, hunger and disease top the list. The western Sudan region of Darfur immediately comes to mind but is by no means unique. Sadly, the marshaling of resources from around the world seems to have produced – at best –marginal results.

In terms of disease, malaria and HIV/AIDS clearly top the list. The spread of these two diseases appears to be out-of-control in Sub-Sahara Africa and other impacted regions And, unfortunately, there is a malevolent tie-in between them. According to the African Medical and Research Foundation (AMREF) website newsletter, May 10, 2007, an opportunistic infection process between HIV/AIDS and malaria renders HIV/AIDS-infected persons more prone to severe malaria and malaria-infected persons more vulnerable to HIV infection, yielding a potentially large volume of co-infected persons. This has its unfortunate parallel in the large number of co-infected HIV/HCV (Hepatitis C virus) sufferers. Equally frustrating, both the HIV and malaria microbes are fast-reproducing which gives them an uncanny ability to develop resistance to medications.

For more than two years, *MPI* has been working with a new technology for combating malaria and other vector-borne diseases, field testing it in West Africa and acquiring governmental approvals in several nations. Based on these experiences, we are proposing the inclusion of this practical and effective approach in the battle against the number one killer of children and adults in Sub-Sahara Africa and other mosquito-endemic regions. Moreover, the mutual disease susceptibility existing between malaria and HIV/AIDS suggests that malaria prophylaxis could be an important component of programs for prevention, control and amelioration of HIV/AIDS.

Within the same broad category of vectors that transmit malaria are the arthropods that transport dengue fever and consequent hemorrhagic fever, lymphatic filariasis and river blindness. The same methodology that has been employed against the malaria-bearing vectors may also be utilized against the vectors that transmit these diseases.

With this in mind, please take a careful look at our initiative for combating these sources of human misery.

A NEW APPROACH TO AN OLD PROBLEM

Worse Than You Imagined

Although malaria is a worldwide dilemma afflicting as many as 500 million persons per year, 90% of those afflicted live in Sub-Sahara Africa[1]. In Africa, *3,500 people die from malaria every day, most of whom are children.* Shockingly, it is estimated that *a child dies from malaria every 30 seconds* in this region and it is the leading cause of death of children there. This disease kills more than one million children each year in Africa alone. *In regions where the disease is hyperendemic 40% of toddlers may die of acute malaria*.

Unfortunately, most African children do not receive treatment save for unregulated herbal remedies. Although the Ministry of Health in Ghana has approved a significant number of herbal medicines, on a local level most of the herbal treatments utilized are more a product of folk culture than science. The estimated annual cost to Africa for malaria is approximately $12 billion. In addition, people infected with HIV/AIDS are more prone to severe malaria, and malaria infection can contribute to an increased incidence of HIV virus.[2]

Sometimes, the attempted solution becomes the problem. The *inappropriate use of anti-malarial medications* is one of the highest contributors to the increasing morbidity. Recently, health researchers, working from Togo but gathering data from Senegal eastward and southward have observed the *emergence of drug-resistant strains of malaria* in West Africa.*

In attempting to combat hunger, urban agriculture projects have been initiated in West Africa. Unfortunately, these appear to be breeding-grounds for the *anopheles* (malaria-bearing) mosquito. At the pilot project in Kumasi, Ghana, researchers have noted higher biting rates at night in areas of urban agriculture. The evaluation of these programs is under careful investigation by entomologists in both Kumasi and Accra.

Attempted Solutions

The most historical and visible approach to the problem is the use of insecticide-treated bed nets, which have demonstrated efficacy but require a careful installation and cannot protect children when they are not in bed (very often the case) or when they leave their beds at night. To compound the problem, the Noguchi Memorial Institute for Medical Research in Ghana[3] indicates that mosquitoes appear to adapt to the nets: “their [the mosquitoes’] behavioral changes in biting patterns in response to insecticide treated nets (ITNs) continue to present a great challenge against control efforts.”

The large-scale use of insecticides has been questioned due to their potential human and environmental toxicity issues and – surprisingly – the ease with which insects Develop resistance to them.* As reported earlier, studies have shown the *anopheles* mosquito’s uncanny ability to develop resistance to the most widely-used insecticides for interior residential spraying and impregnating bednets (see Appendix III).

Topical mosquito repellants [avoidants] can be effective but have definite limitations. Their efficacy period is generally in the three to eight hour range. Due to toxicity concerns, it is strongly recommended that they are not reapplied often (or at all), leaving adults unprotected a large portion of the day.

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* In the early 1960’s only 10% of the world’s population was at risk of contracting malaria. This rose to 40% as mosquitoes developed resistance to pesticides and malaria parasites developed resistance to treatment drugs. Malaria is now spreading to areas previously free of the disease. Sources: The Malaria Control Programme, World Health Organization, *Third World Network Features, Health Canada* and The Centers for Disease Control and Prevention (US).

Because topical agents must not come into contact with the eyes, mouth or open wounds and are toxic if swallowed, they are risky for use with children; moreover, their concentration level (dosage) is highly critical for children. In addition, every square centimeter of exposed body surface must be treated to afford full protection. Topical sprays and lotions also lose their effectiveness due to perspiration, exposure to rain, bathing, swimming or rub-off from contact.

As there are several species of malaria parasites (*Plasmodium vivax, ovale, malariae and falciparum*), it should be observed that *no single drug* is capable of protecting against all of them. Multi-compound drugs that protect against all of these species are available but are expensive. Moreover, anti-malarial medications are also under-produced relative to need, often exhibit deleterious side effects and are dosage-critical for children. Many of these medications *cannot be tolerated by children* even in substantially reduced dosages. In households where written instructions may not be understood, dosage-critical medications for children may be dangerous.

A Viable New Approach

The mosquito-avoidant patch represents a viable, affordable and individualized approach to the problem. The patches contain no dangerous or toxic substances, are safe for children and are not dosage-sensitive. They attack the root cause of malaria infestation -- the bite of the *Anopheles* mosquito -- by generating a body action that keeps the mosquito away from the person using the patch.

The active agent is B-1 thiamin which has no toxicity issues and is not dosage-critical for either children or adults. The transdermal route of administration offers a controlled, sustained release of the active agent, allowing continuous 36 hour protection. They are not subject to falling off or loss of potency due to perspiration, exposure to rain, bathing or swimming.

The mosquito-avoidant patches are widely marketed in the US and the European Community. They have been approved by the Ghana Food & Drugs Board, the National Agency for Food & Drug Administration and Control (NAFDAC) in Nigeria and the Ministry of Health in the Côte d'Ivoire after extensive review and testing.

Over the past two years, on-the-ground efficacy testing in a variety of settings in West Africa has produced consistently positive results and the testing process remains ongoing.

In sum, the transdermal mosquito-avoidant patches appear to offer the full-time "go anywhere, do anything" protection that will help African children and adults avoid the deadly bite of the *anopheles* mosquito and intervene the cycle of infection and death that has prevailed for so long.

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[1] Compared to 31 million people who are infected with HIV in Sub-Sahara Africa. Sources: (1) UNAIDS 2006 Report on the Global AIDS Epidemic; (2) Until There's A Cure Foundation [HIV/AIDS], © 2004. 2006

[2] African Medical and Research Foundation (AMREF), online newsletter, May 10, 2007 update

[3] *Evaluation of the Efficacy of Impregnated Thiamine-Based Formula Adhesive Tape Against Mosquito Bites in Malaria-Endemic Areas*. Preliminary report by the Department of Parasitology of the Noguchi Memorial Institute for Medical Research, Legon, Ghana, September, 2006.

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THE MOSQUITO-AVOIDANT PATCHES

"The test of the morality of a nation is what it does for its children."
Dietrich Bonhoeffer, Theologian

Although malaria is the number one killer of children worldwide (exceeding HIV), there are limited means for protecting them. Traditional anti-malaria methodologies exhibit efficacy but have not made the hoped-for impact. Approaching the problem from a different vantagepoint, we have introduced a new type of malaria prophylaxis – the mosquito avoidant patch – as a practical, inexpensive and efficacious way of preventing children and adults from being bitten by parasite-bearing mosquitoes. The patches are easy to use, offer continuous 36 hour efficacy and are safe for use even with very young children. The active agent is vitamin B1-thiamin. The action of the patches is surprisingly simple.

Like other biting insects, the *anopheles* mosquito (which transmits malaria parasites) relies on olfactory cues (smell) to detect its human targets. The specific smell they key into is the carbon dioxide (and lactic acid) expelled in breath and perspiration. To intervene this process, the patches introduce B-1 thiamin into the system via a transdermal (through the skin) route of administration. Within a short time the B-1 passes through the system and is excreted through the sweat glands. This becomes a continuous process. The smell of the unmetabolized B-1 on the skin surface masks the odor of the carbon dioxide in the breath and perspiration and makes the person "invisible" to mosquitoes and other biting insects. It is analogous to stealth technology for military aircraft (being invisible to enemy radar). In addition, the odor of B-1 thiamin is repugnant to biting insects. As a result, the patches offer a disarmingly simple, safe, inexpensive yet effective means of shielding children from being bitten wherever they go and whatever they are doing. The patches' insect-repellant action is similar to the well-known DEET-based topical applications; however they offer a significantly longer efficacy period (36 hours vs. 8 hours), greater ease of application, freedom from toxicity concerns and no loss of potency due to perspiration, rain, bathing or swimming.

In the US, the patches are used to protect against mosquitoes bearing the West Nile Virus and viral meningitis[1] as well as Lyme disease ticks. They are also marketed extensively in Europe. The respected Noguchi Memorial Institute for Medical Research[2] undertook an initial field study of the B-1 thiamin patches with follow-up studies underway shortly. Other efficacy studies conducted in "real life" settings in Ghana and Liberia have yielded consistently positive results.

The patches have been licensed by the Ghana Food & Drugs Board, the National Agency for Food & Drug Administration and Control (NAFDAC) in Nigeria and the Ministry of Health of the Côte d'Ivoire. They have been recommended by the Ghana Schools Health Education Programme for use in that nation's schools.

We are strongly interested in working closely with concerned humanitarian and philanthropic organizations to implement a malaria prophylaxis campaign utilizing this "new technology" approach in concert with traditional methodologies.

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[1] Humans are incidentally infected by arboviruses; the arboviruses that cause viral meningitis are transmitted to humans by arthropod vectors (including mosquitoes, ticks, sand flies, and midges).

[2] A joint-venture research undertaking between the Japanese government and the University of Ghana. The Institute is distinguished in parasitology and tropical diseases.

COMPASSION CORPS PROJECT



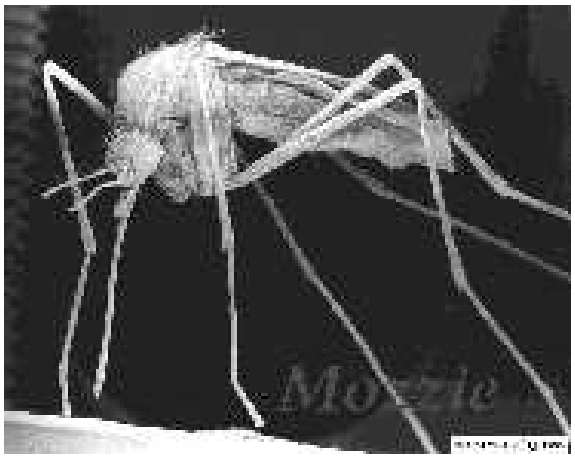

These photos were taken in January, 2008 in a village near Timbuktu, Mali where Pastor Moha runs a school for the local children ("Elijah House"). Pastor Moha lost a child to malaria shortly before these photos were taken and has a keen interest in protecting the children from malaria.

The Compassion Corps is a faith-based organization from Philadelphia, USA. whose mission is to provide basic hygiene and medical needs to villagers who are presently not receiving medical care. The Compassion Corps solicits contributions of basic medical supplies (bandages, sutures, alcohol, antibiotic medications, etc.) in the US. They conduct similar programs in Liberia, Senegal and Morocco.

When the Compassion Corps learned about the TPI Mosquito Repellant Patches they acquired a small amount of funds to purchase the patches and the manufacturer supplemented their purchase with additional patches as a donation. Compassion Corps volunteers used the TPI patches with the children in this village with very positive results.

One of the photos features Pastor Moha holding a sheet of the Mosquito Repellant Patches in the process of applying them on the children. Other photos show the patches being applied to the children, both by Pastor Moha and Compassion Corps volunteers from the US. The patches are placed on the children's backs, between their shoulder blades to prevent the children from picking at them and causing them to fall off.

EXAMINING THE NEW METHODOLOGY



The mosquito has been characterized as the most dangerous animal on earth. One out of every 17 people on the planet will die from a mosquito-borne disease.[1]

[1] Mark S. Fradin MD. *Mosquitoes and Mosquito Repellents: A Clinician's Guide*. Annals of Internal Medicine 1998; Vol. 128; Issue 11: pp 931-940 [1].

THE SEARCH FOR AN IDEAL MOSQUITO-AVOIDANT

"Ultimately, the best cure for malaria is not to get bitten."
History Channel (US) Documentary, July 26, 2007

The World Health Organization advocates protection against mosquito bites as the first line of defence against malaria. David N Durrheim**,** Peter A Leggat. *Prophylaxis against malaria*. BMJ 1999;318:1139 (24 April).

The difficult part has been finding the means for achieving that protection. Numerous authors argue that there has been an over-emphasis on insecticides as an insect avoidant noting that various species of mosquitoes in several locales have developed resistance to the widely-used insecticides. They also address the human toxicity and environmental concerns linked to insecticides:

> The researchers hope that these kinds of discoveries will eventually suggest new and effective ways to keep mosquitoes from preying on people that will be less poisonous than the insecticide and repellent sprays now in common use. For example, a compound might be found that reduces the mosquitoes' response to human odors. Laurence J. Zwiebel *et a*l, *Proceedings of the National Academy of Sciences* online Nov. 27, 2006.

As a result many authors endorse alternative methods of "vector" control. They argue that the potential opportunities inherent in the use of attractants [or repellants] in the control of the mosquito vector have not been fully utilized and that the search for the ideal insect repellant to the present has been disappointing:

> Use of personal protection measures may have been compromised by widely publicised reports of encephalopathic reactions in children associated with the most widely used insect repellant, diethyltoluamide (DEET), and the nonchalance of many travellers. David N Durrheim**,** Peter A Leggat. *Prophylaxis against malaria*. BMJ 1999;318:1139 (24 April)

> Insect repellents must cover *all* exposed skin; mosquitoes will attack just a few centimeters beyond the area coated with repellent. Swimming, sweating, and hot weather require frequent reapplication. J Scott*. Mosquitoes Bite*. Journal Watch Emergency Medicine. August 1, 1998

> …the search for the perfect topical insect repellent continues. This ideal agent would repel multiple species of biting arthropods, remain effective for at least 8 hours, cause no irritation to the skin or mucous membranes, cause no systemic toxicity, be resistant to abrasion and rub-off, and be greaseless and odorless. No available insect repellent meets all of these criteria. To be effective, a repellent must show an optimal degree of volatility, making it possible for an effective repellent vapor concentration to be maintained at the skin surface without evaporating so quickly that it loses its effectiveness. Abrasion from clothing, evaporation and absorption from the skin surface, wash-off from sweat or rain, higher temperatures, or a windy environment all decrease repellent effectiveness [17, 34-37]. The repellents currently available must be applied to all exposed areas of skin; unprotected skin a few centimeters away from a treated area can be attacked by hungry mosquitoes [33, 35]. Mark S. Fradin MD. *Mosquitoes and Mosquito Repellents: A Clinician's Guide*. Annals of Internal Medicine 1998; Vol 128; Issue 11: pp 931-940.

The B-1 thiamin-based transdermal patches address these issues:

- They are greaseless and odorless. Application is easy.
- They are resistant to abrasion and rub off and will not wash off the skin as a result of sweat, rain, bathing or even swimming.
- Their uniquely long (36 hour) efficacy period permits protection all day and night without re-application.
- They have no toxicity or dosage-sensitive issues.
- There is no problem maintaining B-1 vapor concentration at the skin as the B-1 supply is continually being replenished from the stores in the patch.
- They are effective against multiple species of mosquitoes and other biting arthropods.

The repellant methodology employed by the patches responds directly to Dr. Zwiebel's call for an approach "that reduces the mosquitoes' response to human odors".

The freedom of the patches and their active agent from any toxicity or dosage-sensitive issues addresses the central concern expressed by all of the authors about insect repellant toxicity and neurotoxicity.

In response to the issues raised by Dr. Scott, the patches will not wash off the skin as a result of sweat, rain, bathing or even swimming.

In response to the numerous issues raised by Dr. Fradin in his summary paragraph, the patches are effective against multiple species of mosquitoes and other biting arthropods. They exhibit a uniquely long (36 hour) efficacy period, permitting round-the clock protection without re-application. They are resistant to abrasion and rub off, wash off from sweat and rain and are greaseless and odorless. Application is easy. Further, there is no difficulty maintaining B-1 vapor concentration at the skin as it is continuously replenished from the stores in the patch.

Clearly, the concerns expressed about topical applications and sprays do not apply to the patches. However, eliminating negatives alone does not establish viability. In addition to avoiding the problems endemic to applications and sprays, the patches have demonstrated their ability to protect users against biting in a series of efficacy studies in mosquito-rich environments in West Africa. In accomplishing these things, the patches appear to have met the requirements set forth by the various authors for an ideal mosquito-avoidant.

B-1 THIAMIN PATCHES AS AN INSECT REPELLANT AND ANTI-MALARIAL PROPHYLAXIS:
A Physician's Commentary

Following discussions with parties involved in an anti-malaria program in West Africa, I investigated B-1 thiamin serving as an insect avoidant (repellant) in the form of a transdermal patch. These patches are being used as a prophylaxis against vector-borne diseases (malaria, dengue fever, hemorrhagic fever, lymphatic filariasis and river blindness) in afflicted areas by protecting people from the bite of the *anopheles* mosquito, the *Aedes* mosquito and the blackfly.

It is accepted that biting insects use olfactory receptors as a primary means of locating their "prey". It follows that disrupting the olfactory signaling process deprives them of their ability to do this. This is the methodology employed by B-1 thiamin as an insect repellant and is similar in concept (but not action) to the widely-used topical insect repellants such as DEET (see *Appendix I: Selected Documentation: Olfactory Cues.*.). An important distinction is that the thiamin B-1 patch is completely non-toxic when used as directed.

The first step in disrupting the signaling process is delivering the agent into the blood stream. Delivery of B-1 thiamin into the blood stream utilizes the established transdermal mechanism and is facilitated by the small size of the B-1 molecule. This route of administration allows for a well-regulated, sustained delivery of the agent.

The method by which B-1 thiamin disrupts the olfactory signaling process is easily understood. Unmetabolized B-1 in the system is excreted at the skin surface as a volatile gas capable of overwhelming the odor of the naturally-emitted olfactory cues (carbon dioxide and lactic acid) needed by biting insects to locate their targets. This is more thoroughly discussed in *"Explanation of the Action and Efficacy of B-1 Thiamin Transdermal Patches as an Insect Repellant".*

A brief history of the use of B-1 thiamin as an insect-repellant provides the context from which the patches evolved (*Appendix II: History of B-1 Thiamin As An Insect Repellant*).

In science it is not uncommon to discover new and non-traditional applications for familiar substances and technologies. For example, there are a number of pharmaceuticals that have been found to be therapeutically helpful in treating conditions other than those for which they were developed. In addition, we see the use of vitamin D, a known treatment for osteoporosis, showing good research in the prevention of many cancers. From this vantagepoint, it is interesting to examine B-1 thiamin serving a function that is very different from its accustomed role in health and nutrition.

Respectfully submitted,

Robert J. Zieve, MD, Director
PineTree Clinic for Comprehensive Medicine
Prescott, AZ

EXPLANATION OF THE ACTION AND EFFICACY OF B-1 THIAMIN TRANSDERMAL PATCHES AS AN INSECT-REPELLANT

1. Transdermal Medications:

The skin has evolved to minimize entrance of noxious chemicals and UV radiation into the body. But from a pharmacological perspective, delivering drugs across the skin is an important goal. Transdermal delivery would avoid numerous problems with the oral route, including drastic pH changes, the deleterious presence of food and enzymes, variable transit times, pulse entry (rapidly fluctuating drug plasma concentrations), side effects and inadequate patient compliance, while also eschewing needle delivery and its associated inconvenience and even patient phobia. (*Journal of Nature Biotechnology* 22, 165-167 [2004]).

Impregnated polymers (transdermal patches) can safely store and deliver controlled amounts of medication across the epidermis for systemic distribution.

Transdermal medications have been in clinical use for many years. Some of the products that have been medicated in this fashion include: nitroglycerin, estradiol, clonidine, fentanyl, nicotine and scopolamine. (Deputy for Acquisition and Advanced Development, USAMRMC). Recently, the FDA has approved the use of transdermal patches to deliver medications for treating Parkinson's Disease, Alzheimer's Disease, depression, menopause and osteoporosis. In an article written for the general public, "Top Health Breakthroughs" in *Parade* magazine, December 9, 2007, under the heading of *A Better Way to Take Medicines*:, Dr. Isadore Rosenfeld profiles the increasing use of transdermal patches in medicine:

> "More medications are being delivered topically via the skin rather than by mouth or injection. This includes male and female hormone supplements and weekly birth-control medications, as well as treatment for Alzheimer's disease, early Parkinson's disease, depression, attention-deficit/hyperactivity disorder in children (ADHD) and post-shingles pain. These patches have the advantage of not causing gastric irritation and they're less likely to affect the liver."

An important advantage of transdermal patches is ease of compliance. It is generally accepted in the medical community that the less frequently a drug is dosed, the higher patient compliance will be. Because of its sustained release capability, a single patch can be used in place of several repeated doses of oral medications, leading to better compliance. In fact, it may be said that transdermal administration combines the relative ease of oral medication with many of the advantages of IV (intravenous) administration (see above).

Another advantage of transdermal patches is that a lower total dose of the medication is required and that the patches maintain an even level of medicine within the blood.

However, many substances are not amenable to the transdermal route of administration. The substance to be transmitted in this fashion must be composed of small enough molecules (low molecular weight) that it can be absorbed across the skin. There is a limited number of drugs and chemicals that are candidates for such delivery because *few molecules yield skin permeability coefficients sufficiently high to develop clinically active plasma levels***.** An example of a molecule that is not capable of being medicated in this fashion is insulin. Clearly, the transdermal route of administration would be preferable to injection; however, the insulin molecules are simply too large to be absorbed across the skin. By comparison, thiamin hydrochloride (B-1 thiamin) molecules are of sufficiently low molecular weight to be medicated across the skin.

In sum, transdermal medication offers a readily accepted, non-toxic, carefully regulated dosing system that eliminates the need for multiple dosings over a sustained period.

For a small number of persons who are allergic to adhesive, patches may cause skin irritation.

2. Toxicity of Thiamin

Upper limits for B-1 thiamin ingestion have not been set because there are no known toxic effects from the consumption of thiamine in food or through long-term oral supplementation (up to 200 mg/day).

Emergency medicine toxicology texts state that in supplement doses of 50-500 mg this vitamin is generally non-toxic. The patches contain ≥100 mg. of B-1 thiamin which is released in uniform, gradual fashion over a period exceeding 24 hours, insuring that dosages at any time fall well below the published potential toxicity level.

Thiamin toxicity is extremely rare, and requires doses far greater than that delivered by the patches.

Poison control medical source books do not even contain a listing for specific treatment for thiamine toxicity. It is generally the *fat soluble vitamins*, such as A, D, E, and K, as well as Vitamin B3 that require specific antidotes or treatments. (Mark Rosenbloom, MD, MBA, FACEP, Adjunct Associate Professor of Medicine, Emergency Medicine, Feinberg School of Medicine at Northwestern University).

3. B-1 Thiamin Transdermal Patches

Thiamin is a is a water-soluble vitamin needed to process carbohydrates, fat, and protein. Vitamin B1 is nontoxic, even in very high amounts.

B-1 thiamin has sufficiently small molecules to be transmitted across the skin. Some other vitamins are given safely through the transdermal route, such as B12.

It is well established that excess B-1 thiamin, like all other water-soluble vitamins, is excreted and flushed from the body by perspiration and urination. It is the excretion of unmetabolized B-1 thiamine through perspiration as a volatile gas that overwhelms the olfactory receptors of mosquitoes hence impairing their ability to locate their prey.

Over a period of years, the Australians were reported to have used both tablets and liquid B1-thiamin for repelling biting insects. However, unlike the oral form which is often passed through the body too quickly, the impregnated polymer patch allows for uniform, sustained transmission of its B-1 thiamin stores, delivering up to 36 hours of medication.

The Action of B-1 Thiamin Patches

The action of the B-1 thiamin-based insect-repellant patches is based on biting insects' use of olfactory cues as their primary means of locating their human targets. This is widely documented in the literature. Current approaches to deterring mosquitoes involve "cloaking" the required olfactory cues to prevent the insect from identifying its target. The two principal olfactory stimuli used for targeting by biting insects are the carbon dioxide and – to a lesser degree – lactic acids expelled as volatile gases through human breath and perspiration ("host attractants"). The action of the patches is to introduce a safe, non-toxic agent into the system that will be expelled through the sweat glands as a volatile gas which will present an odor capable of overwhelming ("cloaking") the odor of the carbon dioxide and also the lactic acid. This interrupts the olfactory signaling needed by the biting insect to detect its "target".

B-1 thiamin is the ideal agent to accomplish this: (1) Thiamin hydrochloride molecules are sufficiently low in molecular weight (small enough) to be medicated transdermally; i.e., to pass through the skin unimpaired and into the bloodstream; (2) Thiamin B-1 introduced in excess of the system's nutritional needs (≈ 1.2 mg./day) is expelled through the sweat glands and urine.

Because thiamin B-1 is water soluble but not fat soluble it is able to pass through the system unmetabolized and into the sweat glands, thus reaching the skin surface as thiamin B-1 where it becomes a volatile gas; (3) Thiamin B-1 has an odor that – although largely undetectable to humans – is strong and repugnant to biting insects and is capable of "overwhelming" the odor of the carbon dioxide and lactic acid normally expelled by humans as described above; and (4) Thiamin B-1 is non-toxic in doses far exceeding that required to accomplish the "cloaking".

The insect-avoidant action of B-1 thiamin is therefore similar to that of the widely-used topically-applied insect repellant DEET (N, N-Diethyl-Meta-Toulamide) in a specific way. Both agents interrupt the olfactory signaling needed by biting insects to detect their targets by "cloaking" the odor of carbon dioxide and lactic acid with a substitute – repugnant – odor. However, there are large differences in action, efficacy and risk between the two repellants.

Topically-applied repellants must show an optimal level of volatility, making it possible for an effective repellent vapor concentration to be maintained at the skin surface without evaporating so quickly that they lose their effectiveness (short efficacy period). However, with the patches, the long-term sustained release of the active agent into the system ensures a continuous replenishment of B-1 as a volatile gas at the skin surface, eliminating this concern.

The recommended adult concentration for DEET is 30%, which balances efficacy period and toxicity avoidance. Although the literature varies on this issue it appears that the maximum safe efficacy period for this agent is approximately eight hours; however, it is not recommended to apply a second coating of the agent in the same day to achieve an extended coverage period.

The sustained release patches have an efficacy period of 36 hours. Data to the present indicate that continuous use of the patches produces a surplus of B-1 in the system so that by week's end it is possible to continue receiving coverage 24 hours or more after the expected "life" of the last patch. This permits four patches to supply sufficient B-1 for a full week's coverage.

4. Secondary Nutritional Benefits of B-1 Thiamin Supplement

Our bodies use dietary thiamin as a cofactor in energy metabolism. B-1 thiamin combines with phosphate to form the coenzyme *thiamine pyrophosphate* (TPP*)*, which is essential in reactions that produce energy from glucose or that convert glucose to fat for storage in the tissues.

Every cell of the body requires B1 thiamin to form the fuel the body runs on – *adenosine triphosphate* (ATP). Nerve cells require vitamin B1 in order to function normally. However, thiamin deficiency is rampant in many parts of the world, including areas of Africa. An article in the *American Journal of Clinical Nutrition*, 1979 Jan;32(1):99-104., found biochemical deficiency of thiamin in young Ghanaian children. The article states that this evidence of widespread biochemical thiamin deficiency is indicative of an at-risk population among young children for clinical thiamin deficiency.

A study from 2001 in the *American Journal of Clinical Nutrition* states that reports of a high incidence of thiamin deficiency during pregnancy and lactation were previously reported in India, Malaysia, and Ghana, where, in some cases, the consumption of foods rich in thiaminases was also implicated.

5. Summary

Thiamin-based transdermal patches are an extraordinarily simple, effective, non toxic and inexpensive way to protect against being bitten by mosquitoes and insects that are vectors for malaria and other disease pathogens. It is not a treatment for those who have malaria, dengue fever, consequent hemorrhagic fever, lymphatic filariasis or river blindness, but it is an important investment in prevention against these diseases. The use of this uncomplicated prophylaxis is far less expensive than treating these diseases through hospitalization or other costly therapies.

FIGURE EXCERPTED FROM THE PRELIMINARY REPORT BY THE DEPARTMENT OF PARASITOLOGY OF THE NOGUCHI MEMORIAL INSTITUTE FOR MEDICAL RESEARCH:

"Evaluation of the Efficacy of Impregnated Thiamine-Based Formula Adhesive Tape Against Mosquito Bites in Malaria-Endemic Areas"

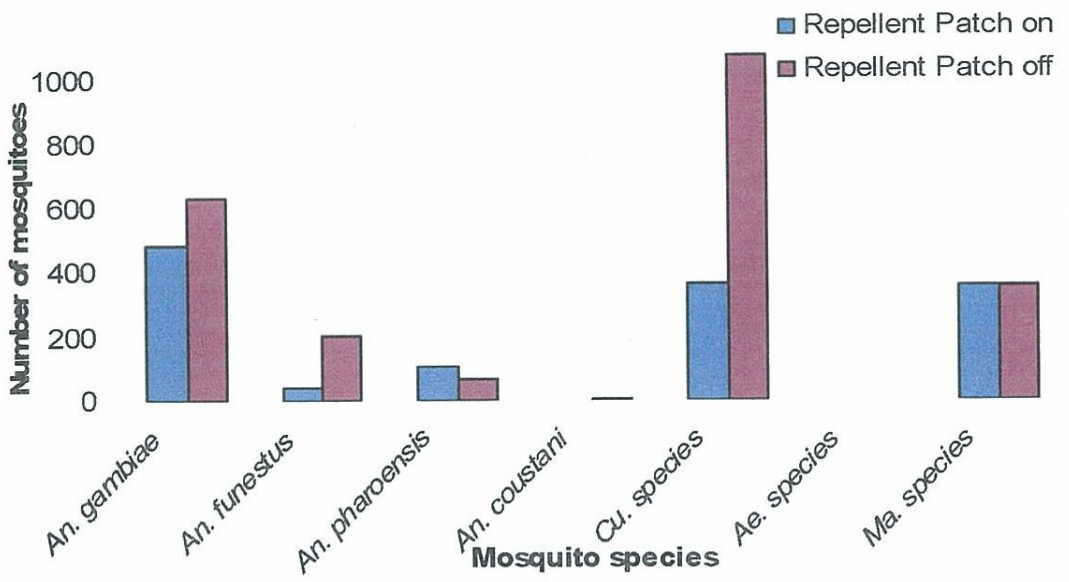


Figure 4: Species distribution of outdoor mosquito collections off persons with and without the repellent

The findings from this study revealed a nearly 2:1 ratio between the number of mosquitoes collected by the collectors wearing patches and the number collected by those not wearing the patches (2,353 collected *without* the patch vs. 1,361 collected *with* the patch). As there were errors in the field implementation protocols, NMIMR is undertaking a new round of field trials throughout the country using revised protocols. It is anticipated that this could yield heightened differences between the "*with patches*" and "*without patches*" groups.

EFFICACY STUDIES IN LIBERIA AND GHANA

The Need for the Studies:

Because malaria is the most prominent and vexing health problem in Africa, it is clear that a product which promises breakthrough protection against the bite of the *anopheles* mosquito demands serious on-the-ground testing in "real life" situations. In its report dealing with the mosquito-avoidant patches, the highly-regarded Noguchi Memorial Institute for Medical Research observes:

> "…species *Anopheles gambiae* and *An. funestus* that transmit malaria… also transmit the parasite that causes lymphatic filariasis. It was thought that if the repellence of the adhesive patch could be demonstrated in the field its value would not be restricted to malaria but also against other mosquito vector-diseases of medical importance, e.g., haemorrhagic fevers, etc. in the tropics".

In the same report, the Institute further asserts:

> "…novel vector control tools are required to compliment existing measures for synergy to subsequently reduce the disease burden."

A review of the action and history of B-1 thiamin as an insect repellant coupled with the commercial success of the B-1 transdermal patches in the USA, Europe and the Caribbean suggests the potential for these patches to become the "new technology" mosquito-avoidant ("novel vector control tools") alluded to in the Noguchi report and a leading anti-malarial prophylaxis. The need for a test of their ability to perform in this capacity is evident. To address this need, a cluster of efficacy studies for the patches was initiated in different locations in West Africa with diverse subject populations.

Study Design:

The focus of the studies was to create an everyday, "real life" test of the efficacy of the TPI B-1 patches as a mosquito-avoidant. Accordingly, the studies were conducted in diverse settings in two West African countries with the stipulation that the design and implementation remain constant in all locations. On-the-ground realities influenced the design. To acquire the maximum amount of information without creating prohibitive logistical burdens a "pre-treatment"/ "post-treatment" design was selected using a single group of subjects in each setting. This design compared the frequency of biting experienced by subjects before using the patches vs. the frequency of biting experienced by these subjects once they had initiated the use of the patches. Subjects went about their everyday lives in the usual places with no changes.

Lacking practical objective or third party means for quantifying the frequency of biting (e.g., consistent observation or recording of subjects), a structured, non-anecdotal self-reporting design was selected. This permitted relatively uncomplicated implementation in the field and prompt feedback. Since mosquitoes are a persistent everyday problem and rank high in the awareness of everyone living in West Africa, subjects had a realistic experiential basis on which to report their mosquito-biting experiences.

To address the issue of the generalizability of the findings the study was replicated in various locales with different populations to determine whether or not a clear and consistent pattern of results emerged. Accordingly, studies were conducted with six diverse and geographically dispersed groups: two in Ghana and four in Liberia. These groups exhibited a wide diversity in subjects' ages and environments: young adults in a university setting in Accra, Ghana, residents of a Liberian refugee camp in Ghana, adults and children in schools and clinics in the Salvation Army program in Monrovia, Liberia, adult church members and school children and teachers in two different settings in Monrovia and adult staff members in a leading newspaper in Monrovia.

Additional studies are ongoing in another newspaper in Monrovia and in a large outdoor industrial program in Ghana.

Instrumentation:

The instrument developed for acquiring the data was a structured, objective self-reporting form. It consisted of a two-part questionnaire, the first part to be completed by subjects before their use of the patches and the second part after their use of the patches. In the first part, subjects were asked to rate the frequency with which they were bitten by mosquitoes in normal, everyday life using no anti-mosquito prevention (pre-treatment) and in the second part they were asked to rate the frequency with which they were bitten by mosquitoes after they had begun or completed usage of the mosquito-repellant patches (post-treatment).

For each of the items, subjects were instructed to respond by selecting one of the discrete options along a five-point rating scale. The rating scales for both pre and post-treatment items were identical. The options ranged from no biting on the low end ('None") to a high frequency of biting on the high end ("A Lot").

Item number one asked subjects to identify the amount (frequency) of mosquito biting that they experienced *before* receiving the patches. They were given five options: "None", "Very Little", "Some", "More" and "A Lot". The least possible frequency of biting ("None") was given a value of 1 on the rating scale, the next point ("Very Little") a value of 2 and upward to the greatest possible frequency of biting ("A Lot") which was given a value of 5 on the rating scale. Hence, the lower the number, the less amount of biting experienced; the higher the number the greater amount of biting experienced.

Item number two asked subjects to identify the amount of biting that they experienced *once they had begun or completed using the patches* using the same rating scale, ranging from the least amount ("None", value of 1) to the greatest amount ("A Lot", value of 5).

Procedure:

Subjects were volunteer participants living and working in typical West African mosquito-endemic environments. They were asked to rate the frequency of biting that they experienced in everyday life prior to using the patches.

The subjects then received a one-week's supply of four TPI mosquito-avoidant patches, each containing ≥ 100 mg. of B-1 thiamin in controlled release (transdermal) form and the standard instructions for use. They were asked to follow the instructions and pay close attention to the amount of mosquito biting that they experienced. At the conclusion of the week during which they were wearing the patches, they were asked to record the frequency of mosquito biting that they experienced while using the patches, using the same rating scale as the pretest measure.

Treatment of the Data:

(a) Measures of Central Tendency and Variability:

In each study, the responses from all subjects to the "*before*" item were pooled and a mean computed. This represented the baseline, pre-treatment mean for that study. The lower the number, the less biting experienced. Similarly, the responses from all subjects in each study to the "*during or after*" item were pooled and a mean computed. This represented the post-treatment mean for that study. The lower the number, the less biting experienced.

The distributions of the responses for both the pre and post-treatment items In each study were inspected and plotted. For those studies in which statistical analysis was applied (Valley View University and the Liberian Refugee Camp) standard deviations were computed.

(b) Statistical Analysis:

The data from the Valley View University and the Liberian Refugee Camp studies were subjected to parametric statistical analysis. As a direction for the results was predicted (lower posttest means), a one-tailed *t*-test for unpaired data was utilized. Under the assumption that the variances for the pretests and posttests were not equal, Welsh's correction was applied. Hence, even if the data were not dispersed in a "normal" (Gaussian) pattern it was believed that *Student's t* could be applied using the Welsh correction with little likelihood of a Type I (α) error.

Findings:

(a) Central Tendency and Variability:

Subjects' response patterns were nearly identical across all of the studies. Comparison of the pre-treatment and post-treatment means revealed a highly-visible post treatment reduction in mean frequency of biting. Pre-treatment means clustered at or slightly above 4.0 on the rating scale ("More"), while post-treatment means clustered between 1.5 and 1.77 (between the lowest and second lowest points on the rating scale). There was also consistency among the studies in the distribution of the responses. In all cases, the pre and post-treatment response patterns were heavily skewed in opposite directions. The pre-treatment responses were negatively skewed; i.e., heavily clustered at the high end of the scale (high frequency of biting), while the post-treatment responses were positively skewed; i.e., heavily clustered at the low end of the scale (low frequency of biting). The means and standard deviations for the Valley View University and Liberian Refugee Camp studies are presented below:

Table I:
Pretest and Posttest Means and Standard Deviations
Valley View University Study

Pretest Mean: 4.000	Pretest Standard Deviation: 1.114
Posttest Mean: 1.667	Posttest Standard Deviation: 0.758

Table II:
Pretest and Posttest Means and Standard Deviations
Liberian Refugee Camp Study

Pretest Mean: 4.563	Pretest Standard Deviation: 0.512
Posttest Mean: 2.188	Posttest Standard Deviation: 0.403

Three-dimensional bar graphs for each study displaying both the pre and post treatment means follow. Each study's bar graph is followed by a chart displaying the rating scales for the two questionnaire items and indicating the mean response for each item by a large "X" on that scale. A brief interpretation accompanies each chart. Due to the unique conditions under which the Liberian Refugee Camp study was conducted and the possible impact of these conditions on the outcome of that study, a more detailed interpretation was provided .

(b) Statistical Analysis:

In both of the studies subjected to statistical analysis, the differences between the pre and post-treatment means in the predicted direction – lower post treatment frequency of biting – were "extremely significant" ($p < .0001$).

In the Valley View University study, the difference between the means of the pre and post treatment measures was statistically significant ($t = 9.483$ with 51 df) in the predicted direction

(less biting post-treatment) at a extremely high level of confidence ($p < .0001$; "extremely significant").

In the Liberian Refugee Camp study, the difference between the means of the pre and post treatment measures was statistically significant ($t = 14.572$ with 30 df) in the predicted direction (less biting post-treatment) at a extremely high level of confidence ($p < .0001$; "extremely significant").

Interpretation of the Findings:

Although the *n*'s in the studies were small (≤ 30) and the distributions skewed, the extremely significant ($p < .0001$) differences between the pre and post-treatment means vindicated the application of statistical analysis.

Because of the uniformity of the response patterns across all of the studies and the extremely significant differences between the pre and post-treatment means in the two studies subjected to statistical analysis it was decided not to subject the remaining four studies to statistical analysis while nevertheless maintaining an assumption that the difference between the pretest and posttest measures in each of these studies was significant.

Discussion:

A criticism of self-report designs (pre and post-treatment) is the "placebo effect", whereby subjects believe that they experience changes in terms of the dependant variable because they were subjected to a treatment (whether or not that treatment did, in fact, engender any real changes). In the present studies the placebo effect was not believed to have been operational in skewing subjects' response patterns: being bitten by a mosquito is an observable, tangible event. There are no subjective degrees of being bitten: a mosquito bite is a digital, not analogue, experience (one is either bitten or is not bitten). Hence, although subjects received an anti-mosquito treatment, the reality of being bitten is perceived to be prominent enough that it would not have been masked by treatment-engendered expectations.

The selection of a design and instrument that were "field friendly"; i.e., easy to implement in varied and demanding settings, proved important in acquiring the needed data. This was especially true in the Liberian Refugee Camp study.

In the Liberian Refugee Camp study, the range between the "before" and "after" means was nearly identical to those exhibited in the other field studies and was statistically significant at the same (high) level as in the Valley View study ($p < .0001$). However, in comparison to the other studies, the means of both the "before" and "after" measures were elevated i.e., the frequency of biting – both "before" and "after" – was higher. This is believed to reflect several issues unique to the refugee camp.

Sanitary conditions in the camp were poor and maintaining even basic hygienic practices appeared difficult. There was marginal shelter for the refugees and an abundance of standing water, which served as breeding grounds for mosquitoes. Malaria was rampant. Due to the scarcity of proper shelter and refugee immobility, the subjects in this study provided a veritable "food supply" for mosquitoes. In addition, several participants reported sharing their patches with family members, reducing or even negating their efficacy. (NB: product design and efficacy is based on one person using all four of the patches provided in uninterrupted sequence for one week).

A provisional conclusion that may be drawn from this study is that even under what were likely "worst scenario" conditions and an undefined amount of usage contrary to their intended/designed application, the patches exhibited efficacy. There were persistent requests from study participants for additional patches.

The consistency of the results from setting to setting is compelling. The closely-matched results from diverse study populations in widely different settings and geographic areas show a persistent pattern of post-treatment reduction in biting that is difficult to explain other than in cause-and-effect terms. The anticipated follow-up study at the Noguchi Memorial Institute should provide important additional insights into the efficacy of a product that shows so much promise in the ongoing fight against the largest and most pernicious health problem in Africa.

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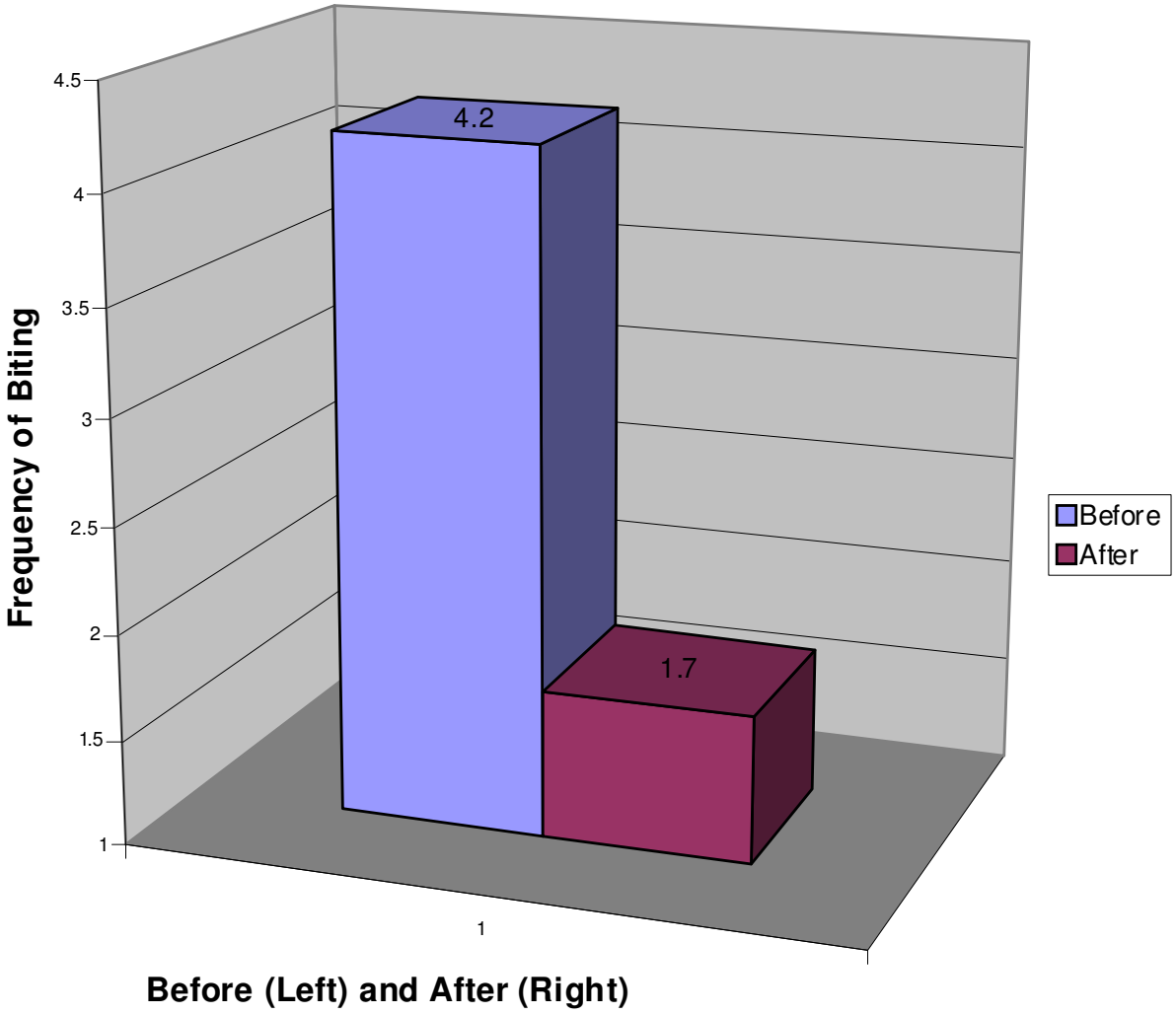
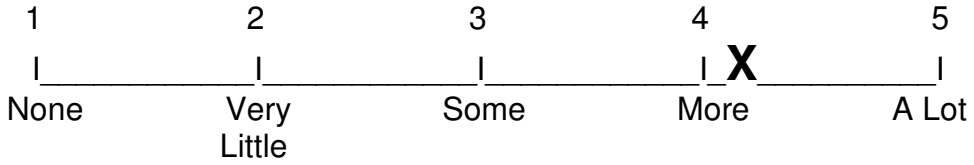
SALVATION ARMY - MONROVIA



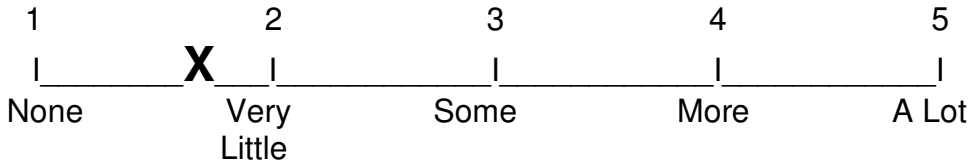
COMPARISON OF MEAN FREQUENCY OF MOSQUITO BITING:
BEFORE USING PATCHES AND DURING/AFTER USING PATCHES

Study: Salvation Army, Monrovia, Liberia

1. *Before* using patches:



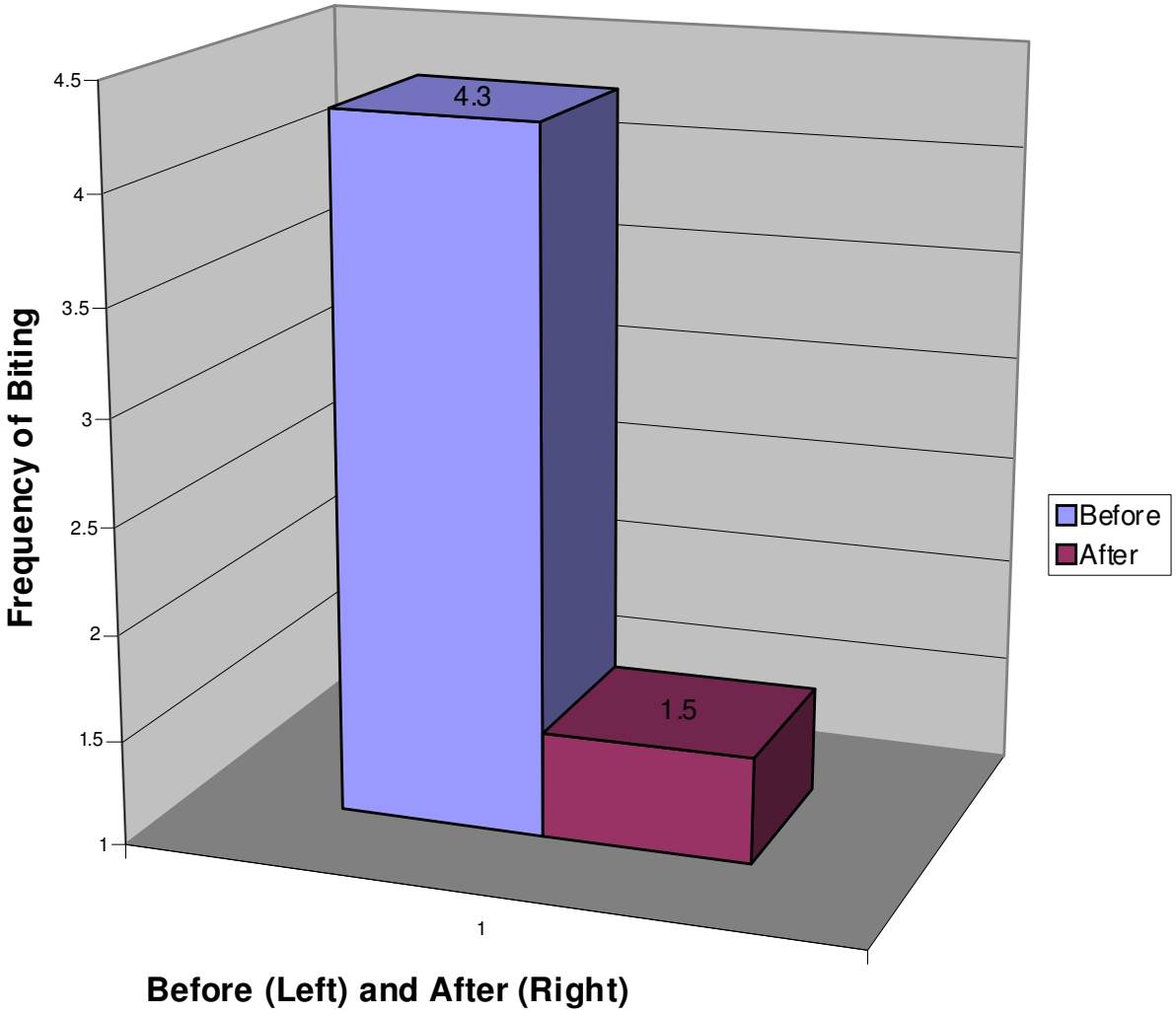
2. *During or after* using patches:



EXPLANATION:

Before using the patches, participants in this study reported being bitten – on average – on the high end of the scale, above "More". After applying the patches, they reported being bitten – on the average –on the low end of the scale, between "None" and "Very Little", slightly closer to "Very Little".

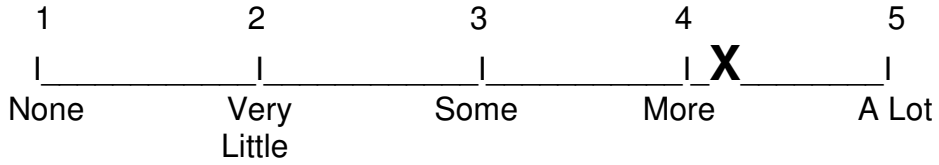
ROCK_CHURCH INTERNATIONAL - MONROVIA



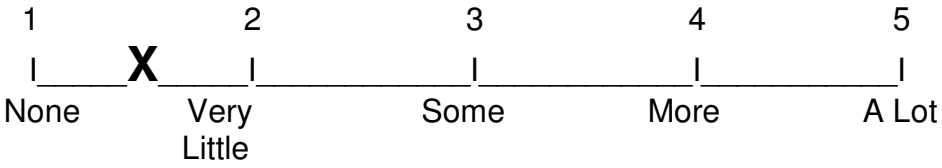
COMPARISON OF MEAN FREQUENCY OF MOSQUITO BITING:
BEFORE USING PATCHES AND DURING/AFTER USING PATCHES

Study: Rock Church International, Monrovia, Liberia

1. *Before* using patches:



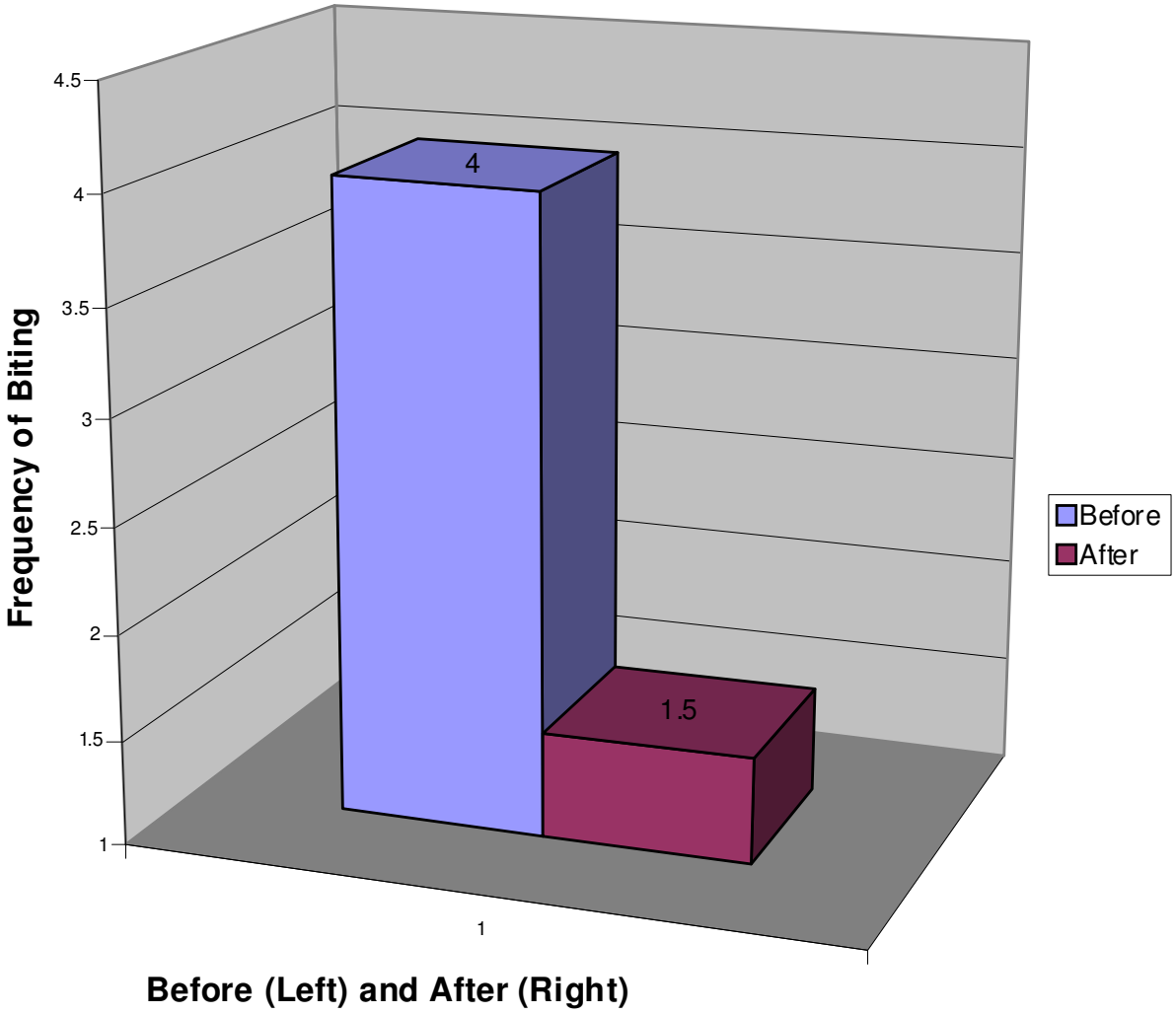
2. *During or after* using patches:



EXPLANATION:

Before using the patches, participants in this study reported being bitten – on average – on the high end of the scale, above "More". After applying the patches, they reported being bitten – on the average –on the low end of the scale, between "None" and "Very Little".

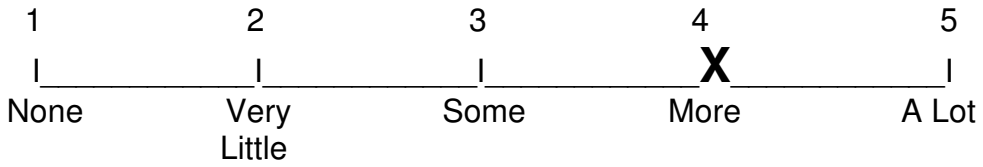
UMC - MONROVIA



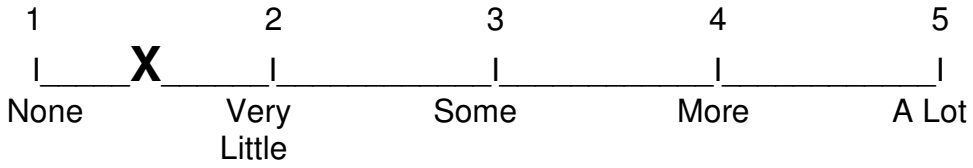
COMPARISON OF MEAN FREQUENCY OF MOSQUITO BITING:
BEFORE USING PATCHES AND DURING/AFTER USING PATCHES

Study: United Methodist Church, Monrovia, Liberia

1. *Before* using patches:

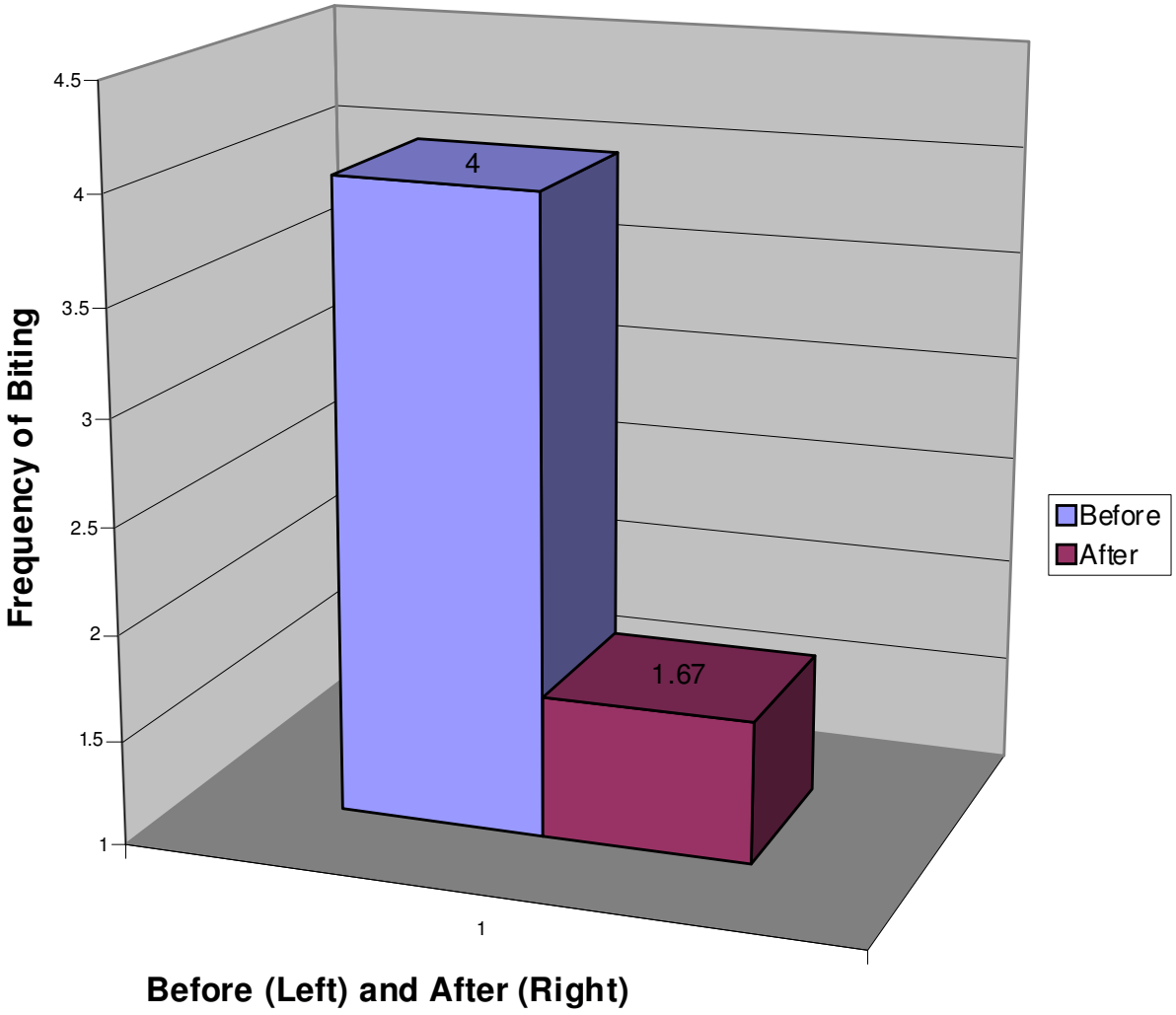


2. *During or after* using patches:



EXPLANATION:

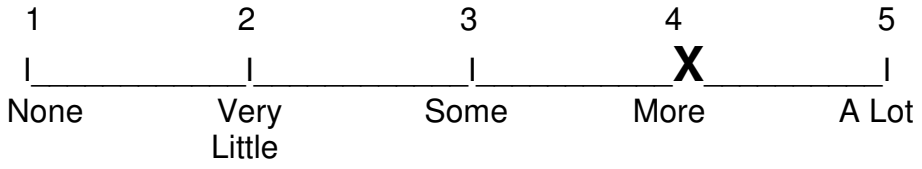
Before using the patches, participants in this study reported being bitten – on average – on the high end of the scale, slightly above "More". After applying the patches, they reported being bitten – on the average –on the low end of the scale, between "None" and "Very Little".


4.5
4
3.5
3
2.5
2
1.5
1
Frequency of Biting
4
1.67
1
Before
After
Before (Left) and After (Right)

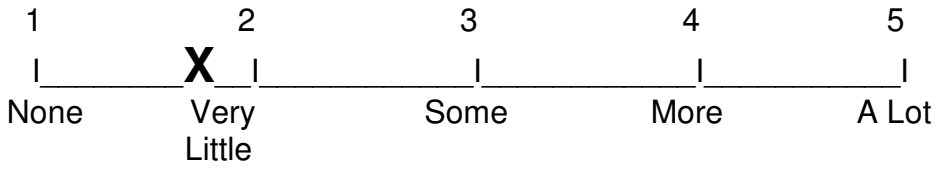
COMPARISON OF MEAN FREQUENCY OF MOSQUITO BITING:
BEFORE USING PATCHES AND DURING/AFTER USING PATCHES

Study: Valley View University, Accra, Ghana

1. *Before* using patches:



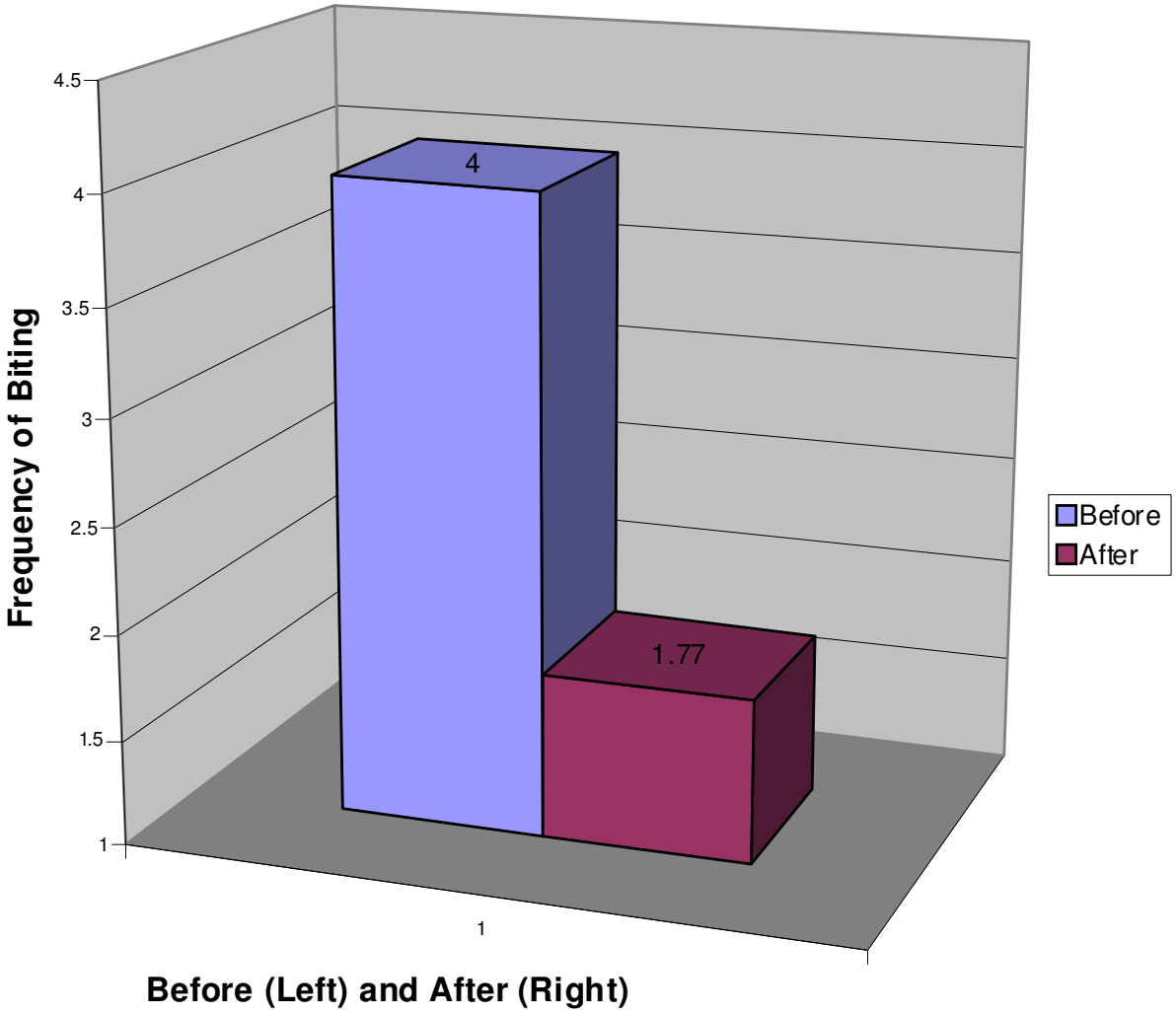
2. *During or after* using patches:



EXPLANATION:

Before using the patches, participants in this study reported being bitten – on average – on the high end of the scale, slightly above "More". After applying the patches, they reported being bitten – on the average –on the low end of the scale, between "None" and "Very Little", closer to "Very Little".

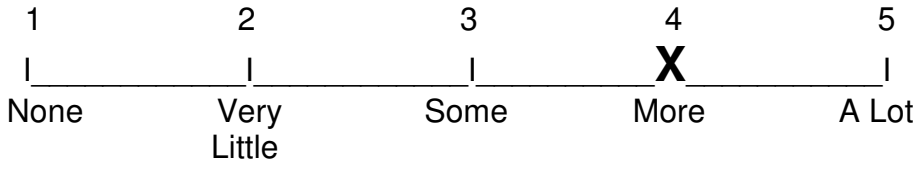
PLAIN TRUTH NEWSPAPER - MONROVIA



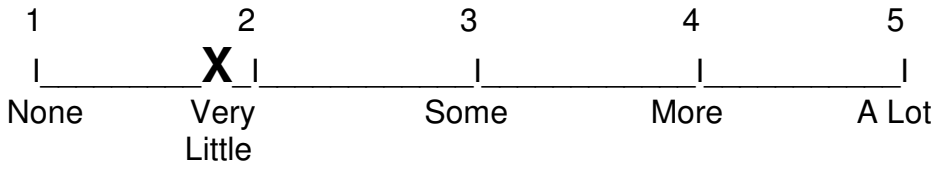
COMPARISON OF MEAN FREQUENCY OF MOSQUITO BITING:
BEFORE USING PATCHES AND DURING/AFTER USING PATCHES

Study: The Plain Truth (Newspaper), Monrovia, Liberia

1. *Before* using patches:



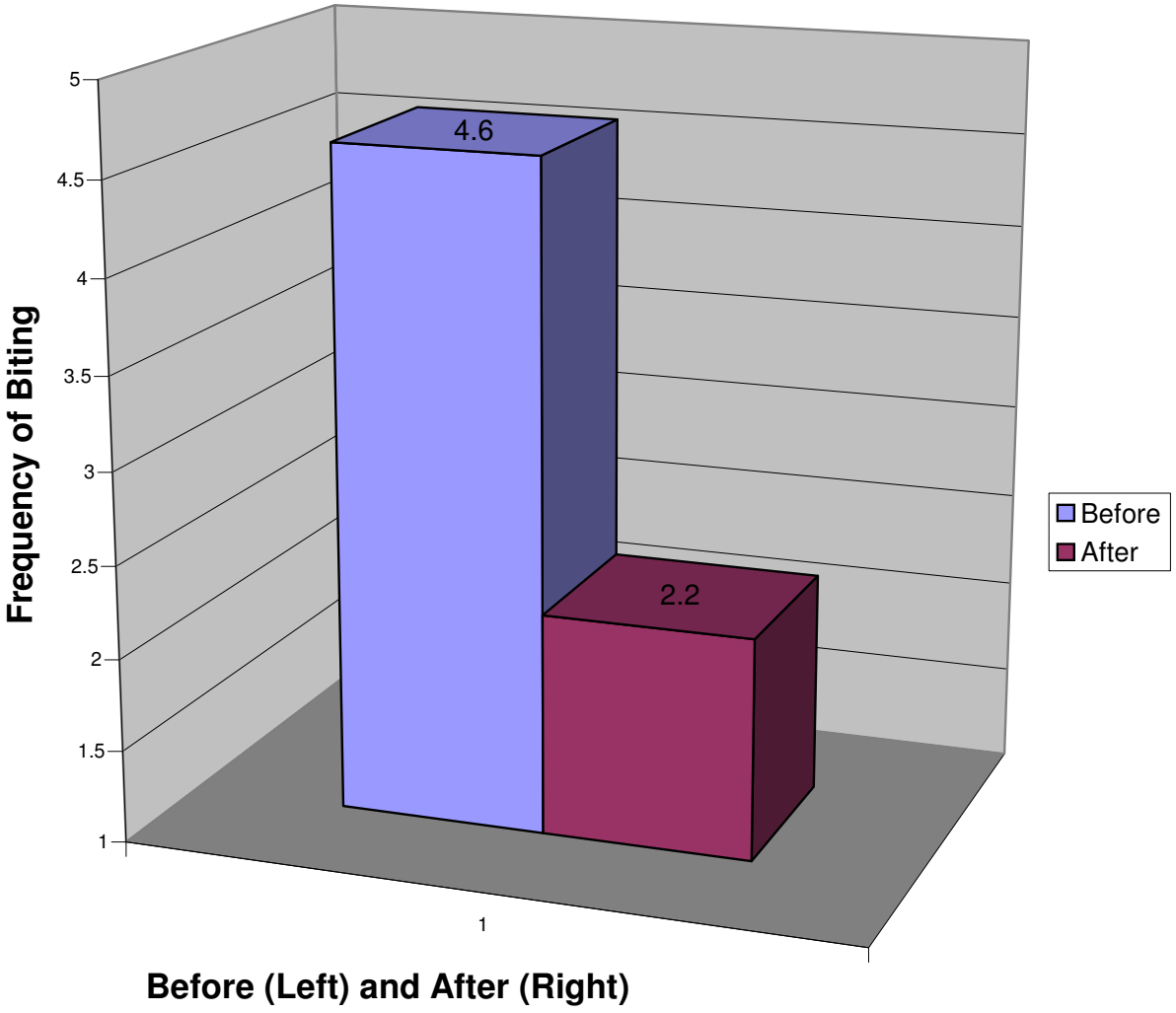
2. *During or after* using patches:



EXPLANATION:

Before using the patches, participants in this study reported being bitten – on average – on the high end of the scale, at "More". After applying the patches, they reported being bitten – on the average –on the low end of the scale, between "None" and "Very Little", closer to "Very Little".

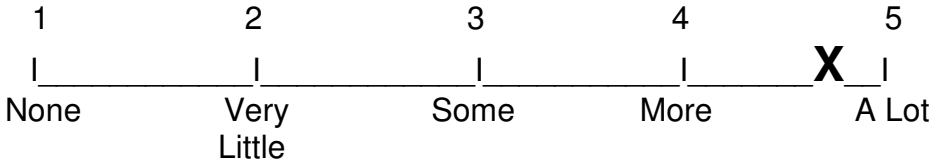
LIBERIAN REFUGEE CAMP ACCRA, GHANA



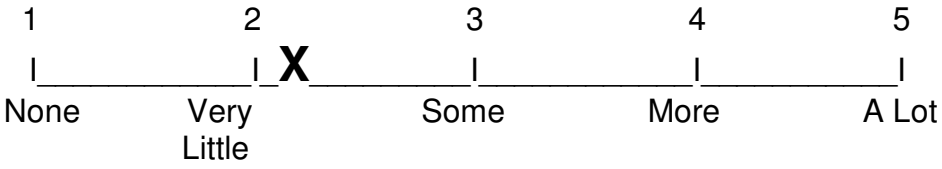
COMPARISON OF MEAN FREQUENCY OF MOSQUITO BITING:
BEFORE USING PATCHES AND DURING/AFTER USING PATCHES

Study: Liberian Refugee Camp, Accra, Ghana

1. *Before* using patches:



2. *During or after* using patches:



EXPLANATION:

Before using the patches, participants in this study reported being bitten – on average – on the high end of the scale, close to the maximum -- "A Lot". After applying the patches, they reported being bitten – on average – on the low end of the scale, slightly above "Very Little". average – on the low end of the scale, slightly above "Very Little".

The range between the "before" and "after" means is nearly identical to those exhibited in the other field studies. However, in the present case, it is evident that both of these measures are elevated in comparison to the other studies; i.e., the frequency of biting -- both "before" and "after" -- is higher. This is believed to reflect several phenomena unique to the refugee camp setting and is reviewed in further detail in the Discussion section.

POSTLOGUE

An Inclusive Approach to Combating Malaria

In the fight against malaria, the B-1 thiamin mosquito-avoidant patches have been proposed as a "new technology" for protecting children and adults against the bite of the *anopheles* mosquito. They are unique in their long (36 hour) efficacy period and their comprehensive "go-anywhere/do anything" umbrella of protection that is especially important for active children. They are also safe for young children.

While awaiting a breakthrough in scientific research that will yield a safe, economical and long-term vaccine against malaria on a large scale, this dread disease remains a constant threat and reasonable people in affected areas should adopt all appropriate measures to combat it. Unfortunately it is very easy to think in "either/or" terms – choosing one approach over another – even when there are clear advantages to employing all potentially viable resources.

With this in mind, MPI is committed to an inclusive approach to combating malaria and other vector-borne diseases. Children and adults using the patches are encouraged to adopt other appropriate measures against these diseases such as clearing land and eliminating standing water, teaching and encouraging sanitation and implementing personal hygiene measures. In addition, insecticide-treated nets (bednets) are inexpensive and are becoming more widely available. Although their scope of protection has limitations their use a prevention measure is strongly recommended. Pesticide spraying inside homes has shown efficacy, although it is necessary to "change off" from one pesticide to another periodically to avoid mosquito resistance from developing. In deference to toxicity concerns, caution in usage must be observed. However, popular insect-avoidant measures such as repellant lotions and sprays, smoking coils and other such devices become redundant when using the patches. Parents are advised that care should be exercised in dispensing medications to children. Several of the adult anti-malaria drugs (when available) – particularly compound drugs that protect against all four malaria protozoans – cannot be tolerated by children even in reduced dosages.

The battle against malaria and the other vector-borne diseases that plague Sub-Sahara Africa is a complex and difficult one and all practical and realistic weapons should be employed to combat them. In this battle the patches can provide the safe, day-by-day comprehensive coverage that forms the nucleus of a prevention program which incorporates the other measures recommended above.

Cost

The patches see widespread usage in the US, Europe and the Caribbean largely as a recreation-related item (vacationers, campers, fishermen, hikers, picnickers, etc.) as well as sporadic seasonal use protecting against biting insects. In these markets, their use is occasional rather than continuous and they are priced accordingly. However, in Africa they serve as a necessary health item: their use is continuous and their cost must be matched to usage and economic realities. The annual cost for protecting a child (even in small quantity purchases) is far less than a single hospital visit and for adults the patches are far less expensive than the widely-prescribed drug *Malarone*.

Bednets and Treatment Kits

MPI works closely with manufacturers of long-lasting insecticide treated nets (ITN's/ LLIN's) approved by the World Health Organization (WHO) to provide bednets in all sizes and colors. In addition, net treatment kits -- primarily used to convert untreated nets into ITN's but also used to re-treat older ITN's – are available economically. Insecticide treatment permits nets to be made with a more open weave which makes them lighter and, importantly, less of a "heat trap" for the sleeping environment. This should hopefully engender better user compliance.

Summing It Up:

As discussed earlier, medical researchers, receiving generous grants from foundations, NGO's and philanthropic organizations around the world are "pulling out the stops" in the race to find an effective, safe, child-friendly and economical anti-malaria vaccine. Unfortunately, they are facing the same task that their predecessors faced over the decades (this is a very old battle): that the four malaria protozoans are what are called "fast-reproducing microbes", which gives them the ability to "adapt" to new medications very quickly. By the time you have read this explanation the protozoans that were "newborns" in the first sentence likely have grandchildren. In addition to the difficult scientific challenge, bringing a new, apparently viable vaccine to market involves substantial testing followed by regulatory approvals, followed by the funding process, manufacturing, packaging, shipping, distributing, etc. And, hopefully, most of the vaccine reaches its target population rather than the black market.

All of this means – in a practical sense – that concerned parties cannot afford to accept the *status quo* while waiting for the "ultimate cure" to come along to save lives. Everything that can be done to defeat malaria must be done. And it is universally agreed that the best way to accomplish this is by prophylaxis – disease prevention through keeping children and adults from being bitten by the *anopheles* mosquito.

It is also clear that depriving the *anopheles* mosquito and other disease-bearing vectors of their blood supply has the potential for making a dramatic impact on the spread of malaria and the other vector-borne diseases discussed earlier. This is accomplished by keeping mosquitoes and other arthropod vectors away from their intended victims. Easy to say, difficult to do. The mosquito and insect-avoidant patches, used in concert with the other measures recommended above, are positioned to play a special role in accomplishing this.

“I pray God look with favor upon your journey and deliver you safe back.”

Geoffrey de la Tour-Landry, 1371

APPENDIX I

Selected Documentation:

OLFACTORY CUES ARE THE PRIMARY MEANS
THROUGH WHICH BITING INSECTS FIND HOSTS

There are numerous and often redundant references in the literature to biting insects using olfactory cues as their primary means of "targeting" their prey. The citations below provide a sampling of representative commentary on this topic.

1. "Mosquitoes are attracted to people by skin odors and carbon dioxide from breath. The active ingredients in repellents make the person unattractive for feeding."
U.S. Department of Health & Human Services, Centers for Disease Control and Prevention.

2. "The mosquito is the most dangerous animal on the planet. It relies on its sense of smell to find the source of its blood meals." Laurence J. Zwiebel. *Exploration*. The online research journal of Vanderbilt University. November 26, 2001.

3. "The specific smell that attracts these insects is the carbon dioxide (and lactic acid) expelled in breath and perspiration." CDC National Center for Infectious Diseases, Division of Vector-Borne Infectious Diseases. Online Newsletter.

4 "The factors involved in attracting mosquitoes to a host are complex and are not fully understood [6-11]. Mosquitoes use visual, thermal, and olfactory stimuli to locate a host. Of these, olfactory cues are probably most important.

Carbon dioxide and lactic acid are the two best-studied mosquito attractants. Carbon dioxide, released mainly from breath but also from skin, serves as a long-range airborne attractant and can be detected by mosquitoes at distances of up to 36 meters [3, 13-15]. Lactic acid, in combination with carbon dioxide, is also an attractant. Mosquitoes have chemoreceptors on their antennae that are stimulated by lactic acid, important for in-flight orientation….

DEET is believed to work by blocking insect receptors (notably those which detect carbon dioxide and lactic at acid long ranges) which are used to locate hosts." Mark S. Fradin MD Mosquitoes and Mosquito Repellents: A Clinician's Guide. *Annals of Internal Medicine*, 1 June, 1998; Vol 128; Issue 11: pp 931-940.

5. "There is a plethora of evidence to suggest that host seeking in mosquitoes is mediated by info chemicals emanating from the host. Info chemicals are synonymous with semiochemicals. Mosquitoes have evolved a wide range of host-oriented responses. As Gibson & Torr (1999) reported, 'carbon dioxide appears to be universally attractive to mosquitoes, and is probably the most understood of the volatile host cues' (p. 2)." Abstracted from: *Mosquito Host Attractants*. A scholarly paper by Jason Pike.

6 Abstract: Olfactory cues play an important role in the attraction of major disease vectors towards their host. A.O. Oduolaa & O.O. Aweb. *Behavioural biting preference of Culex quinquefasciatus in human host in Lagos Nigeria.* Jnl Vector Borne Diseases 43, March 2006, pp. 16–20

APPENDIX II

THE HISTORY OF B-1 THIAMIN AS AN INSECT REPELLANT

The earliest reference to the use of B-1 thiamin as insect repellant apparently traces to Australia approximately 50 years ago. The data are anecdotal and describe that the route of administration was oral with daily dosage varying between 25 to 100 mg. Since that time, additional anecdotal data reflect the use of B-1 thiamin in this capacity in various parts of the world. In 1958, the first scientific article dealing with the use of B-1 thiamin as an insect repellant appeared in a learned journal in Switzerland:

> *Insect repellant properties of vitamin B1*.] [Article in German] Schweiz Med Wochenschr. 1958 Jun 28;88(26):634-5. RAHM U.MeSH Terms Insects* PMID: 13568728 [PubMed - OLDMEDLINE for Pre1966].

Since that time, additional anecdotal reports in a similar vein continued to appear. The route of administration apparently remained oral, dosages remained within the same range and there was no systematic attempt to promote B-1 thiamin as an insect repellent in any commercial way. Reportage remained anecdotal until mention of the insect-repellant quality of B-1 thiamin appeared in 1969 in a US medical journal along with a brief explanation of its action:

> "Some studies suggest that taking thiamine (vitamin B1) 25 mg to 50 mg three times per day is effective in reducing mosquito bites. This safe vitamin apparently produces a skin odor that is not detectable by humans, but is disagreeable to pregnant mosquitoes." (*Pediatric Clinics of North America*, 16:191, 1969).

Apparently, the use of B-1 thiamin as an insect-repellant continued on the part of individuals who had heard of this application for the vitamin. However, there was no systematic attempt to organize the body of anecdotal reports bearing on the efficacy of B-1 utilized in this manner until 1995 when a brief reporting appeared in *Handbook of Dietary Supplements*: "Some individuals appear to find thiamin effective as an insect repellant (1)." Pamela Mason. *Handbook of Dietary Supplements*. Blackwell Science, 1995.

Although there appeared to be a solid constituency of people who used B-1 thiamin as an insect repellant and were pleased to share their success in doing so on the internet, there appeared little interest on the part of the major pharmaceutical companies to develop or market B-1 thiamin as a prophylaxis against malaria. Hence, there were none of the efficacy studies that typically attend such large-scale commercial efforts. Further mention of the action of B-1 thiamin as an insect repellant did not appear in the literature until 2006 in the newsletter of the American Academy of Anti-Aging Medicine which stated that vitamin B-1 helps repel insects and mosquitoes.

Various internet services focusing on travel to parts of the world where vector-borne diseases are prevalent (e.g., Africa), invariably address the issue of mosquito-avoidance and discuss numerous methodologies for accomplishing that. Most of them include at least a brief discussion of B-1 thiamin as an insect-avoidant agent. Two typical entries follow.

The International Travel Healthline Supplemental Health Recommendations states:

> "Vitamin B-1 (thiamine) is often an effective insect repellant for some people (the smell can repel biting insects). Take one Vitamin B-1 (100 milligrams) tablet by mouth each morning and evening …."

This is echoed by an on-line travel advisory service for students, International Service Learning. In their on-line document *Getting Ready to Go to Tanzania; Health Issues* they state:

> ""As an optional prophylaxis for mosquito control, you can take 100 mg of Vitamin B-1 (Thiamin) daily to give your skin a mosquito repulsive 'flavor'."

A recent New Zealand Dermatological Society internet posting (DermNet) states:

> "Thiamin (vitamin B1) can be used as a systemic insect repellant (the skin has a characteristic smell)." Extracted from: Textbook of Dermatology. Eds.: Rook, A., Wilkinson, D.S., Ebling, F.J.B., Champion, R.H., Burton, J.L. Fourth Edition. Blackwell Scientific Publications

For some time, German pharmacies have been vending ampoules containing liquid B-1 thiamin for topical application use. Its purpose is to create a skin surface odor that will repel biting insects.

The difficulty with orally-administered B-1 as an insect repellant is the length of the efficacy period, typically four hours. This means that for full-time coverage consistent re-dosing would be necessary, an obviously impractical regimen. Topical applications likewise have short efficacy period and require re-administration with similar practicality issues, as well as vulnerability to "wash off" from rain, bathing or swimming or rub-off as a product of contact or friction. This left a potentially-viable active agent – B-1 thiamin – in search of a more practical route of administration.

In 2003, a US company with extensive experience producing impregnated polymer (transdermal) patches for healthcare applications, developed a B-1-based, sustained-release patch as an insect repellant and has successfully marketed it domestically and internationally. Their distributor in the UK was granted European Community registration for the patches as an insect-repellant and is actively marketing the product throughout the European Community.

The highly-respected Noguchi Memorial Institute for Medical Research in Legon, Ghana conducted an initial study of the B-1 thiamin patches in a mosquito-intense environment with follow-up studies to follow. Other efficacy studies conducted in diverse settings in Ghana and Liberia have yielded positive results. After extensive review and testing, the Ghana Food & Drugs Board, the National Agency for Food & Drug Administration and Control (NAFDAC) in Nigeria and the Ministry of Health of the Côte d'Ivoire have all approved the TPI B-1 thiamin mosquito patches for unrestricted distribution and in Ghana the Schools Health Education Programme has recommended them for use in the schools there.

A program based on including the B-1 patches as a prophylactic measure in the battle against malaria – *the West African Malarial Prophylaxis Initiative* – was initiated in Ghana, Liberia, Nigeria and Côte d'Ivoire. It expanded to other African nations as well as nations on other continents which faced large-scale vector-borne disease problems and its name was revised to the *Malaria Prophylaxis Initiative (MPI)*. The program undertakes to protect children and adults against the bite of the *anopheles* mosquito and other disease-bearing vectors through large-scale use of the B-1 thiamin patches in disease prevention programs. Because the vectors responsible for the spread of dengue fever, hemorrhagic fever, filariasis and river blindness utilize the same mechanism for locating their victims as the *anopheles* mosquito, the B-1 transdermal patches are expected to play a similar role as a prophylaxis in combating these diseases.

APPENDIX III

INSECTICIDE SPRAYING AND BEDNETS

Insecticide spraying

Insecticide spraying is employed in large-scale outdoor aerial spraying projects, but increasingly in interior spraying of the walls of huts and houses. Spraying programs have shown a short-term reduction in the incidence of malaria. However, one of the widely used insecticides, DDT, has been prohibited in the US and the European Community for the past thirty five years due to toxicity issues. More importantly, mosquitoes have shown the ability to develop a surprisingly robust resistance to most pesticides in a relatively short period of time. Studies in India have conclusively demonstrated strong mosquito resistance to DDT. Many health organizations perceive that the most widely used form of spraying – household interior residual spraying (IRS) – represents an acceptable balance between effectiveness and toxicity risks. Because both the US and European Community prohibit domestic use of DDT, many developing nations that suffer from malaria are reluctant to use DDT for fear (largely unjustified) of losing aid support from these sources. However, the increasing use of the pyrethroid family of insecticides has served to offset these concerns. At any rate, cost-effectiveness studies suggest that insecticide-treated nets may exhibit a cost/reward advantage over insecticide spraying.

ITN's/LLIN's (bednets)

Bednets have been used for generations in tropical regions to avoid the discomfort of continuous insect intrusion, even before science was aware that the mosquito is a disease-bearing insect. In recent years, the pyrethroid insecticides – permethrine, deltametrhrin and alphacypermethrin – have been approved by the World Health Organization for the impregnation of bednets to enhance their effectiveness. Unfortunately, in Benin, Nigeria and Thailand, resistance to pyrethroid insecticide has been reported in *Anopheles gambiae* and *Anopheles minimus*, the two *anopheline* species representing the major vectors of malaria in these regions. This is considered a major setback to vector control using bednets.

Bednets are relatively inexpensive. In venues where they have been used, there has been a gratifying reduction in the incidence of malaria. However, by themselves, they cannot provide the needed full-time protection against malaria. To be set up properly bednets require beds. In many African huts and homes there are no beds – family members sleep on mats or on the floor. If several family members are using a bed, rigging a bednet so that everyone is protected may require a small engineering task, as any exposed body part becomes a target. Anyone leaving the bed during the night also becomes a target for mosquitoes. Bednets make the sleeping area beneath them noticeably warmer and this additional discomfort discourages many people from using them. It is disappointing that the user compliance rate (actual usage) for bednets that have been distributed free by humanitarian organizations and governmental agencies is only about 30%. Moreover, neither adults or children can lead their lives under bednets, even during the high risk evening hours. Thus, although the consistent use of bednets has been shown to reduce the incidence of malaria, by themselves they cannot provide the comprehensive, full-time, "go anywhere/do anything" protection that children and adults need to avoid the deadly bite of the *anopheles* mosquito.

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The Noguchi Memorial Institute for Medical Research is a semi-autonomous Ins
University of Ghana established in 1979; and a constituent member of the Colle
Health Sciences, University of Ghana. The Institute was built and donated to th
Ghana by the Japanese Government. It's history cannot be told without making
of Dr. Hideyo Noguchi, a Japanese scientist who died in Ghana in 1928 while re
into yellow fever.

The Institute is a biomedical research facility and conducts research mainly into
communicable diseases and nutrition. It is made up of nine Academic Departme
has several facilities. The facilities are also used for training both undergraduat
postgraduates from tertiary institutions in the country and abroad. It has strong
the Ministry of Health and provides high end laboratory support to public health
programmes of the Ministry. The Institute also provides training in laboratory m
technicians of the Ministry of Health.

Principal Research Areas

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- Onchocerciasis
- Filariasis
- Diarrhoeal Diseases
- Buruli ulcer
- Tuberculosis
- HIV/AIDS
- Sexually Transmitted Disease
- Food Security
- Micronutrients
- Parasite Immunopathology
- Viral Haemorrhagic Fevers
- EPI Diseases
- Sickle Cell Disease

Key Facilities

- General Laboratories
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- Animals Experimentation
- Conference Hall
- Clinical Research Facility
- Electron Microscope
- Mercury Analyser
- Liquid Nitrogen Plant
- Staff Canteen
- Sample Collection & Stor Facility
- Research project office b
- Administrative Block for W
- Health Support Centre

- Plant Medicine
- Antioxidants
- Environmental Pollution
- Infant and Maternal Mortality
- Molecular Biology

Contact director@noguchi.mimcom.net with comments or questions regardi
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