EFFICACY STUDIES IN LIBERIA AND GHANA

The Need for the Studies:

Because malaria represents the most prominent and vexing health issue 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. For this reason, several rounds of efficacy testing for the patches was undertaken in different locales in West Africa and with different populations.

Study Design:

An everyday "real life" test of the efficacy of the patches as a mosquito-avoidant was evolved that compared the amount of mosquito biting experienced: 1) by subjects using the patches for protection; and 2) by subjects not using the patches for protection. For both ethical and logistical reasons it was decided to use "pre-treatment" and "post-treatment" measures with the same subjects rather than employ experimental (using patches) and control (not using patches) groups. Subjects using the patches 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 design 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 in West Africa, subjects had a realistic and omni-present 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 data-collection instrument developed was a structured, objective self-reporting form. It consisted of a two-part questionnaire, the first part 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 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-intense 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 remain alert to the amount of mosquito biting that they experienced. At the conclusion of the week using 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:

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.

An inspection was made of the distribution of the responses for both of the items in each study and standard deviations computed for those studies for which statistical analysis was applied (Valley View University and the Liberian Refugee Camp).

Findings: 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 reduction in the mean

frequency of biting experienced by subjects after using the patches. Pre-treatment means fell at or slightly above 4.0 on the rating scale ("More"), while post-treatment means fell 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 heavily clustered at or next to the high end of the scale (high frequency of biting) while the post-treatment responses were heavily clustered at or close to 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 rating scale. A brief explanation accompanies each study's chart. Due to the unique conditions under which the study was conducted in the Liberian Refugee Camp and their possible impact on the results for that study, a more comprehensive discussion is provided with that study's chart.

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, a one-tailed *t*-test for unpaired data was applied. Under the assumption that the variances for the pretests and posttests were not equal Welsh's correction was applied. Although the data were not dispersed in a "normal" (Gaussian) pattern it was believed that *Student's t* could be applied with the Welsh correction with little likelihood of a Type I (α) error.

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:

The visibly large pre vs. post-treatment mean differences (representing reduced frequency of biting after using the patches) were shown to be extremely significant. These results were consistent across both of the studies subjected to statistical analysis.

Although the *n*'s in each of the studies were small (≤ 30) and the distributions skewed, the extremely significant differences ($p < .0001$) 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 means in each of these studies would likely prove significant.

Discussion:

A criticism of self-report studies (pre and post-treatment) is the "placebo effect", whereby subjects believe that they experience changes because they were subjected to a treatment (whether or not that treatment did, in fact, engender any real changes). In this study the placebo effect was not believed to have been an issue in subjects' response patterns: being bitten by a mosquito is a vivid, tangible event. There are no subjective degrees of being bitten: each 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 vivid enough as to not being masked by their having received a treatment.

The selection of a design and instrument that were "field friendly"; i.e., easy to implement and adaptable to varied settings proved very helpful, especially in managing the data collection in the Liberian Refugee Camp.

Although the distributions of the responses in both studies were heavily skewed and the variances for the pre and post-treatment measures in the Valley View University study were significantly different, the application of Welsh's correction and the extremely high level of significance of the differences between the pretest and posttest means in both studies vindicated the application of parametric statistical analysis.

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 follow-up study at the Noguchi Memorial Institute should provide additional important insights in the efficacy of a product that shows so much promise in the ongoing fight against the largest and most pernicious health problem in Africa.