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 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 TPI 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 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 it appeared that maintaining reasonable hygienic practices was nearly impossible. The refugees had marginal shelter and there was standing water in abundance, 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 other family members, reducing or even negating their efficacy in these instances (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 usage, the TPI patches exhibited efficacy. There were persistent requests from study participants for additional patches.

The consistency of the results from setting to setting in this group of studies 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.

NB: Charts and figures for this study available from MPI: info@defeatingmalaria.org