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The use of malaria nosodes to reduce malaria prevalence in vulnerable communities*

This pilot study was designed to assess the effectiveness of malaria nosodes as a homeopathic prophylaxis. The primary goal was to reduce malaria parasitic density among residents in a low-income community in Freetown, Sierra Leone. In 2006, 731 participants were recruited and tested for malaria and after receipt of their test results, healthy subjects were enrolled in a double-blind, randomized study. The implementation of the clinical study was then carried out in four phases. About half of the subjects (54%) were assigned to a homeopathic group and during the beginning of each phase (every 4 months), they were administered 5 granules of malaria nosode D200. The remaining 45% of the participants were in the control group and they received 5 placebo granules per phase. Within a year, the malaria parasitic load decreased significantly among all residents. However, the overall efficacy of the homeopathic therapy could not be confirmed after the second phase of the study. Despite this setback, the results of this study generated information regarding the malaria-risk profiles and treatment seeking behaviors of residents in the community. The results also provided valuable insights and meaningful strategies for developing full scale intervention programs in vulnerable communities.

Introduction

Malaria is a mosquito-borne parasitic disease, and each year, about 40% of the world's population is at risk of infection. Despite the latest global intervention efforts, the disease is still the main cause of morbidity and mortality in developing countries. The region that is most affected is Sub-Saharan Africa where approximately 400 million people suffer from malaria symptoms each year, and about 20-50% of these cases result in hospitalization. Although there are several species of malaria parasites in the region, the most virulent and the most common cause of infection is *Plasmodium falciparum* which is transmitted by the female Anopheles mosquito. Many studies have shown that pregnant women and children are the most vulnerable with high levels of maternal anemia, perinatal mortality, low birth weight and developmental disorders among the children (Samba, 2004, Guyatt, Snow, 2001; Holding, Kitsao-Wekulo, 2004).

The quest for new preventive measures and treatment for malaria continues on several fronts. Efforts are underway to develop and test the effectiveness of new drugs and vaccines aimed at reducing the disease burden in endemic communities. Unfortunately, these strategies so far have focused primarily on conventional drug treatments that even when proven effective, may not be readily affordable for most of Africa's residents in the high risk regions. Further, for those in endemic areas, the intake of these drugs over an extended period may result in undesirable side effects. Table 1 (below) shows a comparison of the commonly used drug therapies; it illustrates the cost of treatment per malaria episode,

and possible side effects of these drugs. Chloroquine is one of the cheapest drugs available but it is no longer effective for falciparum parasites.

| Drug | Cost per treatment (Euro) | Effectiveness | Possible side effects |
|---------------------------------------|----------------------------------|----------------------|-------------------------------------|
| Resochin (Chloroquine) | 2 | poor | Hearing problems |
| Pyrimethamin + sulfadoxine (Fansidar) | 5 | poor | Allergic reactions |
| Mefloquine / Lariam | 52 | high | Congestive heart failure, psychosis |
| Atovaquone + proguanil (Malarone) | 52 | Limited data | Abdominal discomfort |

Table 1: Comparison of commonly used treatment therapies for malaria

The purpose of this study was to investigate the use of homeopathic therapies as alternate, safe, and affordable remedies for reducing the burden of the disease in endemic communities. Prior to the study, few evidence-based studies had been conducted to assess the efficacy of homeopathic or alternative therapies for the treatment of malaria in Africa (Van Erp, Brands 1996; Wilcox, 1999, Müller et al, 2001; Wilcox, Bodeker, 2004). One such study by Van Erp and Brands (1996) investigated the efficacy of homeopathic treatments on 75 malaria patients and they were able to demonstrate a clinical improvement in 90.7% of subjects. In a later study, the authors concluded that homeopathy has an effect that is comparably better than chloroquine, the commonly used drug at the time of their research.

Our study was designed to assess the efficacy of homeopathic nosodes as a malaria prophylaxis. This was accomplished by administering the therapy to a large sample of participants, and over an extended time period (one year). The use of the homeopathic globules in this study was mainly aimed at the prevention of *P. falciparum* malaria, which as noted earlier is the most fatal form of the disease. Another reason for pursuing this study was that if proven to be effective, the malaria nosode would be available to residents at a relatively low cost, compared to the aforementioned conventional drug therapies. A bottle of Tropica nosode contains 2000 globules (10g) and would cost only about € 35. This amount would be sufficient to treat about 135 adults annually.

Research Design and Methods:

Study area and population

The study took place from June 2006 and July 2007, in Kroo Bay, a low-income community in Freetown, Sierra Leone. Kroo Bay was chosen because of the considerably high risk for malaria, high rates of poverty and lack of affordable health care. The community is located in the

northwest corner of Freetown, on the seafront next to brackish waters that feed into the Atlantic. Kroo Bay, a slum settlement at the time of the study had approximately 12 000 inhabitants. The risk of infectious diseases such as malaria has been high in this community due to unsanitary conditions, overcrowding and poor housing structures. Although the residents are vulnerable throughout the year, the main transmission period for malaria usually begins in June and ends in January.

Design

The double-blind randomized controlled trial was divided into four phases. The first phase was implemented in June 2006, following approval of the project by the Ethics Committee. After a series of organizational meetings, public awareness and mobilization campaigns, a community meeting was held in the Kroo Bay Health Center (KBHC) to discuss the project objectives. Thereafter, participants were recruited over a period of three weeks. Eligible subjects were those deemed to be healthy, 18 years old, and residents living within 10 km of the KBHC. As mandated by the Ethics Committee, each subject was given a consent form and was enrolled only after signing the form.

Questionnaires were handed out to enrollees to evaluate their personal health history, previous malaria diagnoses malaria, use of mosquito nets and previous treatment regimens. Under the supervision of a medical doctor, nurses at the KBHC conducted physical examinations and recorded the weight, height and other anthropometric measures of the enrollees. Thereafter, laboratory technicians proceeded with a blood draw of each subject using the finger-prick method. All blood samples were sent to the laboratory for malaria diagnosis. Approximately 10% of the slides were randomly selected and sent to an independent laboratory for cross-validation.

Study participants returned to the health center in the following week to get their blood test result and notification of treatment, if any. Those who tested positive people with a high parasitic load with clinical symptoms (high fever) were treated promptly with Quinine and paracetamol, the State recommended treatment.

For the clinical study, subjects with no substantially underlying diseases, normal body temperature, and low parasitic load were randomly divided into two subgroups. The first group was given inactive placebo globules and the second given Tropicana nosodes. Individuals assigned to both groups received five globules each, with these globules similar in taste and appearance. No food intake was allowed at least 30 minutes before or after taking the globules. All participants were advised to report any subsequent malaria symptoms (including high fever) to the nurses of the KBHC. Subjects were also assigned a program identification card and told to return after four months for their second prophylactic treatment. During the course of each phase, our staff of four community health

workers visited the area regularly and compiled a weekly health report.

After four months, the second phase of the study was executed using similar procedures: blood test draws, physical exams, and placebo or homeopathic globules were re-administered to participants in the respective categories. The same procedures were repeated after 4 months in Phase III. In the fourth phase, in addition to repeating the procedures in phases I, II and III, a final questionnaire was administered to assess each patient's health status, and treatment seeking behaviors. The data compiled over the entire study period including location, blood test results, medical history and demographic characteristics of patients were later used to assess the treatment-seeking behaviors and effectiveness of the therapy. Statistical analysis was done using the Statistical Program for Social Sciences Version 14.0 (SPSS, Inc., Chicago, IL). The methods included the calculation of odds ratios with corresponding confidence intervals to assess the risk and incidence of malaria among the different treatment categories. Also relevant was the analysis of the parasitic burden measured among all participants, and by treatment category.

Results

Participant Profile

As noted earlier, 731 people initially registered in Phase I after signing the consent form and completing the baseline questionnaire. Based on this information, the average age of the participants was 38.6 years, of which approximately 73% were women and 27% men. The mean height was 137.16 cm and the mean weight of 61kg. The average length of stay in the community was 18.5 years. The literacy rate was very low: more than half of the residents had no formal education, about 11% only an elementary education, 25% secondary education, 6% had a technical or vocational training, and less than 0.5% had a college degree. A review of employment status showed that only a third (34%) was employed mostly as petty traders selling household items, fruits and vegetables in the local markets.

Of the original 731 registrants, only 534 were formally enrolled in the clinical study. The others either did not satisfy the criteria as specified in the study guidelines, or did not show up for their follow-up visit to pick up their test results. Table 2 shows the distribution of all eligible entries displayed across the two treatment groups. These are based on the randomization in the baseline period and the treatment during the subsequent phases of the study.

| Eligible persons | Baseline Phase I | Follow-up Phase II | Follow-up Phase III | Follow-up Phase IV |
|------------------|------------------|--------------------|---------------------|--------------------|
| Homeopathic | 54% | 57% | 55% | 55% |
| Placebo | 45% | 40% | 43% | 43% |

Table 2: Distribution of all persons eligible for participation across the treatment groups in Phase I, II, III & IV

Overall, both groups were well represented across the phases with approximately 55% of participants in the homeopathic group and 45% in the control group. An average attrition rate of approximately 15.6% was recorded. This dropout rate was predictable and acceptable for many reasons. In the later phases of the study participants were considered unsuitable if they i) had serious health conditions including clinical malaria symptoms that ruled out the use of prophylaxis; ii) were pregnant with the births likely to occur during the duration of the project, and iii) if they could not be reached due to a change of residence, or simply stopped participating in the study due to personal reasons.

Malaria symptoms and Types of treatment therapies sought by the residents

In Phase I, residents were asked about the frequency of previous cases of malaria and where they sought treatment. On average, the number of self-reported incidents of malaria was 3.24 per year. Though high, this number was deemed to be fairly representative of Kroo Bay, which as noted earlier is a malarious area with significantly higher risks than other parts of the city. A frequency distribution showed that about 8% could not comment on malaria episodes during the past year. Nearly 52% reported an annual frequency of 1 to 3 cases of malaria and nearly 40% reported about 4 incidents. Since the questionnaires was based on self-reported incidents and possibly self-diagnosis of the illness during the years, this information could not be fully confirmed.

The survey in Phase 1 also showed that 24% of those with malaria were likely to seek treatment at the state hospital, 30% at local pharmacies and 19% went to itinerant drug vendors. The latter were often likely to be illegal drug peddlers selling a diverse range of medications to residents to treat a host of diseases. Perhaps most worrisome in this baseline survey was that 57% of the respondents indicated that they had previously self-treated with chloroquine, despite the documented resistance of *Plasmodium falciparum* to this medication. Only about 10% of the respondents indicated that they had been administered Quinine, the government recommended therapy; further some noted that taking Quinine had caused some allergic reactions. Overall, the preliminary results from this first phase reaffirmed the need for developing affordable, reliable and effective (sustainable) antimalarials to improve the health care among all members in this high risk community.

Phase I: Malaria morbidity (incidence) in the baseline period

As mentioned earlier, the laboratory tests were performed to diagnose malaria from patient blood films, and if detected to estimate the parasitic density. For 68% of the patients, the malaria test was negative, and parasites could not be detected in blood. Approximately 29.9% had a positive test result with an average parasitic density of 401/ul. About eight clinical cases of malaria were also identified (1.5% of the blood

samples). These individuals were immediately treated with Quinine and paracetamol, and asked to return in subsequent weeks for further treatment at the KBHC. Individuals with negative test results or low parasite density were divided into two groups.

Phase II: Malaria morbidity analysis by treatment groups

To analyze the relationship between treatment type (Phase I) and results of the blood test (Phase II), the Fisher's exact test method was applied. When reviewing the results by treatment groups, 96.3% of the individuals taking the homeopathic globules tested negative - compared with 86.7% in the placebo group. Another way of looking at this is that among the subjects who tested positive during phase 2, 13.3% were in the placebo group and only 3.7% were in the homeopathic group. These results were statistically significant ($p < 0.001$), and though the effect size was low (18%), the findings showed a favorable relationship between treatment type and malaria results in Phase 2. When checking the estimated risks, the odds ratio was 3.622 (95% CI, 1.64 to 7.96) for persons in the placebo group. One can conclude that in Phase 2, participants in the placebo group had at least three times higher probability of being tested positive relative to subjects in the homeopathic group.

Phase III: Malaria morbidity analysis by treatment groups

In Phase III, the health data showed that 82.5% were negative and 17.5% positive for malaria. During this period, no clinical case was identified. In the patients who tested positive for malaria parasites, the average parasitic load was 98.82/ul which was significantly lower than the preceding phases. However, further analysis of the data across the treatment groups showed that the disease risk among subjects in both the placebo and homeopathic groups was equal. Approximately 82% of patients in the homeopathy group tested negative for malaria parasites, and similarly 80% of those in the placebo group were negative. The results were confirmed using the Fisher's exact test method ($p = 0.421$). The odds ratio for persons was 1.1 (95% CI 0.66-1.82) in the placebo group, compared with those from the homeopathy group, implying that the risk of malaria was virtually identical for both groups.

Phase IV: Malaria morbidity analysis by treatment groups

In Phase IV, 91.1% of the patients tested negative and 7.9% tested positive for malaria. The medical tests identified three patients with clinical symptoms of malaria. The average parasitic density observed during this period was 86/ul, the lowest value observed throughout the study. To assess the risk of malaria, the Fisher's exact test method was used here as well and no statistical differences were observed between the treatment groups ($p = 0.816$). Among those receiving the homeopathic treatment 92.1% tested negative, versus 93.3% for those in the placebo

group. These results were consistent with the results of phase III. The odds ratio was 1.014 in Phase IV (95% CI 0.948-1.084). These statistical results revealed that the malaria parasitic density had decreased overall during the study, and at this latter stage there were no protective advantages among participants of the homeopathic group when compared with the control group.

Comprehensive risk analysis in all phases

The information collected in all four phases of the pilot study information was entered into a database for comprehensive analysis of the malaria burden among residents over a one year period. This analysis was based on the blood test results compiled during all four phases based on the parasitic density of *P. falciparum*. For the analysis, the focus was on only the subjects with complete test results recorded across all four phases. For example, those who participated in initial phases of the study and later dropped out for various reasons were excluded in the analysis. This reduced the sample size of this broad-based analysis to 184 persons. Of these, 45% were in the control group and the remaining 55% were in the homeopathic group. A comparison of the parasitic density across these participants with complete records confirmed the trend of malaria prevalence levels throughout the study. The results showed a significant reduction in the mean parasite density for malaria in patients who had participated in all four phases. As shown in Table 3, the average density in this subset of patients was 76/ul in Phase I, 23.1/ul in Phase 2, 18.5/ul in Phase III, and IV in the phase 7.7/ul.

PHASES

| PHASES | Mean value | STD. Error | 95% confidence interval | |
|----------|------------|------------|-------------------------|-------------|
| | | | Upper limit | Lower limit |
| 1 | 76.335 | 19.790 | 37.309 | 115.402 |
| 2 | 23.099 | 6.786 | 9.710 | 36.488 |
| 3 | 18.508 | 3.432 | 11.737 | 25.279 |
| 4 | 7.740 | 2.143 | 3.511 | 11.969 |

Table 3: Mean parasite density among eligible participants in all phases

This temporal trend was representative of the larger sample size in the individual phases. A test of the mean differences between the phases confirmed the reduction of the parasitic density between the pre-intervention phase (phase 1) and the post-intervention phase (phase IV) with t value of 4.125 ($p < 0.0001$). The overall analysis of the mean parasite density by treatment groups also showed some significant differences, but these were not as dramatic as the results at each stage. As shown in Table 4, the overall mean parasite density for the homeopathic group was statistically lower (24.77/ul) than the results in the placebo group (38.1/ul). A comparison of all four phases showed that the differences observed, especially in the first and second phases were considerable. However, the benefits of homeopathic group were no longer

apparent in the fourth phase.

PHASES

| Treatment | Mean value | STD. Error | 95% confidence interval | |
|-------------|------------|------------|-------------------------|-------------|
| | | | Upper limit | Lower limit |
| Placebo | 38.079 | 7.773 | 22.743 | 53.415 |
| Homeopathic | 24.772 | 6.969 | 11.022 | 38.523 |

Table 4: Mean parasite density by treatment type among participants in all phases

Finally, an analysis of variance (MANOVA) using the repeated measures design was done in order to establish the total variability of the mean parasite density during the study period. The method used in the study was based on the key factors and type of treatment (placebo or homeopathy). The results of the repeated MANOVA confirmed a significant reduction of the mean total parasitic density across the four phases of the study. However, during the latter phase of the pilot study, the type of treatment did not contribute significantly to the observed variability of the mean parasite density.

Final thoughts and future directions

In the search for an affordable and safe treatment regimen for malaria in endemic communities, we explored the use of Tropica nosode (a homeopathic prophylaxis) as a possible option for residents. The malaria prevalence rate at the beginning of the study was approximately 29.9%, which was fairly consistent with previous malaria risk profiles generated for the region. During phase II of the pilot study, the results were promising with the chances that Tropica nosode might significantly lower the risk of malaria infection. However, these protective benefits were not sustained in the third and fourth phases. Rather, in the latter phases the malaria risk levels were found to be comparatively similar in both treatment categories. The failure to fully establish the efficacy of the homeopathic globules in these subsequent phases may have also been due to additional factors, notably the operational challenges encountered during the course of the study. For example, due to the large sample size of this study, there were some challenges with the turnaround time in reading blood films and related quality control in the laboratory that might have influenced the microscopic interpretation of some of the blood films. These issues were promptly addressed in the study including sending 10% of the slides the cross validation with an independent lab. However, the corrective steps may not have been adequate particularly in light of the large sample size of the study population. In future investigations, we hope to utilize rapid diagnostic kits to detect the presence of parasitemia after which the positive slides would be sent to the labs to evaluate the

parasitic density. Doing so will improve the turnaround time for test results and allow technicians to interpret the positive slides with even better accuracy. Another challenge in this study was associated with the low literacy rates among the participants coupled with the behavioral practices that may have affected patient compliance particularly during Phase II, which coincided with the religious holiday month of Ramadan. The planning of future projects will require a more careful consideration of the religious calendars to avoid potential conflicts. Overall, despite these challenges, there were some promising results from this study, specifically the community-wide reduction in the incidence of malaria and the overall decline in parasitic density among the participants. Public awareness and mobilization campaigns against malaria may have heightened community awareness of the disease prompting greater use of testing for the disease and use of preventive measures. One could also make the case that the notable decreases in the mean density of malarial parasites among residents in both groups were probably due to our efforts to promote greater awareness among residents about malaria, and the team's efforts to provide malarial health services for an entire study, which lasted for a whole year. Further, following the clinical intervention, all of the self-reported measures among the subjects confirmed significantly higher levels of positive health, as reported among the participants particularly among those in the homeopathic group. The declines in parasitic levels observed among all participants, regardless of treatment group may also have been due to the real effects of the homeopathic pellets in reducing the burden of the disease, thus lowering the overall risks of disease transmission within the entire community. Specifically, participants in the control group may have benefited from the secondary effects of the homeopathic prophylaxis resulting in a community-wide reduction in the disease burden. These trends, along with the effects of seasonality, are certainly worthy of further investigation. A replication of the study will help validate the research findings and establish the long term benefits of using Tropica nosodes in reducing the burden of malaria within endemic communities.

In conclusion, future efforts to reduce the burden of malaria in endemic communities must entail a mix of affordable and sustainable strategies such as those utilized in this pilot study. Intervention programs must integrate community awareness campaigns with a combination of conventional treatment therapies such as the state recommended therapies, plus the use of Tropica nosode as a homeopathic prophylaxis. Collectively, these complementary approaches are likely to yield meaningful results that are evident at the community-wide level.

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