

**Evaluating Malaria Interventions in Africa:
A Review and Assessment of Recent Research**

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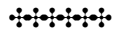
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Evaluating Malaria Interventions in Africa: A Review and Assessment of Recent Research

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Summary

This paper reviews the literature of malaria intervention studies in Africa over the last ten years, and specifically assesses the state of the art of evaluation of those interventions. Five primary types of malaria intervention studies were found: (1) vector control evaluation studies, (2) vaccine trial evaluation studies, (3) case management evaluation studies (includes chemoprophylaxis and malaria treatment trials), (4) diagnostic evaluation studies (trials of new quick and easy methods of diagnosing malaria) and, (5) cost-effectiveness evaluation studies. Methodological criteria used to identify the evaluation studies included outcomes measured at the community level, use of a rigorous design – experimental, quasi-experimental or pre/post intervention evaluation, and a minimum sample size of 100. The bulk of the literature (ten studies) focused on vector control evaluation studies. In addition, three vaccine trial evaluation studies, three case management evaluation studies, three diagnostic evaluation studies and three cost-effectiveness studies are included. There are several studies that did not stand up to the methodological criteria, but that we considered important from a methodological point of view and were included in our discussion.

This review presents four major findings. First, the usefulness of existing studies is limited by their methodological shortcomings, particularly by the lack of standardized indicators. Second, due to the lack of standardized outcome indicators, between-study comparisons are extremely limited which essentially affects everything we can do in terms of evaluating malaria programs or interventions. Third, there is a paucity of evaluation studies on the (possible) synergistic effect of using more than one type of intervention to combat malaria. Fourth, due to the nature of malaria transmission, which can vary seasonally and spatially, it is difficult to generalize study results to other areas and years.

In terms of the evaluation designs used, the randomized controlled clinical trial (RCT) is clearly the preferred gold standard in malaria intervention studies. However, because of the nature of malaria transmission and disease, and because of the lack of standard indicators, the majority of results from the studies have severely limited generalizability.

Given the human and financial toll malaria is taking on societies throughout the world, continued research on ways to prevent and treat malaria is essential. In order for health professionals to be able to implement effective, large-scale programs to control malaria, at the national or sub-national level, more systematic evaluation protocols are needed. These evaluations should focus on essential program elements using standardized indicators in a wide variety of locations.

Abbreviations

ITBN	Insecticide-treated bed-net
Non-ITBN	Non-insecticide-treated bed-net
PCV	Packed cell volume
EIR	Entomological inoculation rate
PS	Pyrimethamine-sulphadoxine (Fansidar®)
RCT	Randomized controlled clinical trial
IEC	Information, Education and Communication

Introduction

According to the most recent data, 40% (2,400 million) of the world population in over 90 countries is affected by malaria. In any given year, nearly 10% of the global population will suffer a case of malaria (Malaria International, 1998). There are 300 - 500 million clinical cases of malaria worldwide each year with the majority occurring in sub-Saharan Africa (WHO, 1998). Malaria has been estimated to cause 9% of all disease in Africa (Nchinda, 1998). According to recent data, there are 1.5 – 2.7 million deaths due to malaria each year, the bulk of which occur in sub-Saharan Africa where an estimated 360 million people live in areas of stable, endemic *Plasmodium falciparum* transmission (Snow et al., 1999a). The sheer scale of the malaria burden in sub-Saharan Africa results from the broad distribution and coexistence of several contributing factors: (1) climatic conditions which are ideal for malaria transmission, (2) highly efficient *Anopheles gambiae sensu lato* and *Anopheles funestus* vectors, (3) a parasite population composed overwhelmingly of *P. falciparum*, by far the most virulent human malaria species, and (4) poverty and lack of healthcare infrastructures (Craig et al., 1999; Beier et al., 1999; Snow et al., 1999a). The result is widespread *P. falciparum* transmission at intensities, expressed as its entomological inoculation rate (EIR). The EIR, which is the product of the vector biting rate times the proportion of mosquitoes infected with sporozoite-stage malaria parasites, sometimes exceeds 1,000 infective bites per year in populations lacking the resources to prevent or treat the disease (Craig et al., 1999; Beier et al., 1999; Snow et al., 1999a; Killeen et al., 1999b). Finally, the direct and indirect cost of malaria rose to \$13 billion in 1997 with Africa taking the brunt of the burden, while spending on research, prevention and control worldwide probably amounts to no more than \$2 billion (WHO, 1998).

Factors that are actively contributing to the resurgence of malaria include (1) rapid spread of resistance of malaria parasites to chloroquine and other quinolines, (2) frequent armed conflicts and civil unrest forcing large populations to settle in difficult conditions, often times in areas of high malaria transmission, (3) migration of non-immune populations from areas of low malaria transmission to areas of high malaria transmissions, (4) vector abundance and transmission potential caused by climatological changes as well as water development projects including dams and irrigation, (5) adverse socioeconomic factors leading to reduced health budgets, (6) high birth rates leading to a rapid increase in susceptible populations under 5 years of age, and (7) the development of both physiological and behavioral traits in vector populations which undermine vector control efforts, particularly insecticide use (Nchinda, 1998; WHO, 1998).

In 1999, WHO (and partners) established the “Roll Back Malaria” campaign, which has sought to renew efforts to combat the disease. One of the main objectives of this effort will be to encourage the investments necessary to develop effective interventions to alleviate the burden of malaria. As more

money is spent on national efforts to combat malaria, there will be an increasing need to establish effective means of evaluating the effectiveness of these programs. The purpose of this paper is to assess the current state of evaluation of malaria interventions.¹ The paper falls into several sections. The next two sections describe the epidemiology of malaria (for the reader for whom this is a new area), and the current view of evaluation methodology for international public health programs. After a short description of our methods and the criteria used to select the studies, the central section of the paper includes a detailed presentation of the results of our discussions and readings. A discussion section concludes with nine recommendations.

Demography and Epidemiology of Malaria

Over a century has elapsed since mosquitoes were identified as the vectors of *P. falciparum* parasite (Ross, 1911), yet the demographic parameters of malaria and the epidemiology of the disease remain somewhat controversial fields. In terms of the demographic impact of malaria we know that malaria certainly influences the mortality and morbidity of populations (though the extent remains controversial and highly dependent on quality of data used to build the classic indicators of direct and indirect cause of death and illness). Malaria is also probably influential in migration patterns, though this aspect has rarely received much attention (e.g., Bilsborrow, 1981). The reverse direction of effect – the influence of migration on the disease – is beginning to attract considerable attention as the infection rates from malaria increase in previously low endemic areas such as highlands or arid lands. Malaria's influence on fertility is also relatively unstudied, though doubtless important in terms of the interactions (biological and social) between fertility, fecundity and outcomes of pregnancy. Malaria infection and particularly malarial anemia is an obvious area of focus for reproductive health programs.

Aspects of malaria epidemiology that remain subject to considerable debate include the relationship between exposure and clinical outcome (Beier et al., 1999; Molineaux, 1996; Molineaux, 1997; Lengeler et al., 1998; Lengeler et al., 1997; Snow et al., 1999a; Greenwood, 1997), the nature of malaria pathology and protective immunity (Rogier et al., 1999; Greenwood, 1997; Gupta et al., 1999; Smith et al., 1999), and the mechanisms by which both parasites and vectors adapt to intervention measures and how best to implement malaria control (Greenwood, 1997; Lines, 1996; Snow et al., 1999b; Lengeler and Snow,

¹ The distinction between “intervention” and “program” is important. In general terms an “intervention” is a potential program but it is commonly regarded as still in an experimental or test stage. We might expect higher levels of standards to be maintained when evaluating interventions, for example, than programs. Our emphasis in this paper focuses on scientific interventions. This is partly to assess the state-of-the-art evaluation tools and indicators, but it is also because there are virtually no published reports of malaria programs (vis. national or even subnational programs) that have been evaluated.

1996). Many aspects of these important issues have yet to be satisfactorily resolved, making the design and evaluation of malaria control programs a notoriously difficult task (Greenwood, 1997; Lengeler and Snow, 1996; Lengeler et al., 1998).

What is apparent is that malaria morbidity and mortality increase with transmission intensity and that effective vector control will always reduce all-cause mortality (Lengeler et al., 1998; Lengeler et al., 1997; Molineaux, 1997; Beier et al., 1999). In essence, a decline in the Entomological Inoculation Rate (EIR) always leads to a positive response in terms of morbidity in human populations (Beier et al., 1999).² Although, in malaria-endemic Africa, EIR values greater than one infective bite per year are sufficient to maintain high prevalence of blood-stage parasites in the human population, even if clinical symptoms are not manifest, particularly in children. In areas of such high transmission and stable prevalence, a distinction must be made between a symptomatic, clinical case of malaria and an infection because most of these are chronic and asymptomatic (Trape and Rogier, 1996; Greenwood, 1997; Alles et al., 1998; Gupta et al., 1999; Smith et al., 1999).

The disease burden caused by malaria, its age distribution and spectrum of clinical manifestations are complex functions of transmission intensity (Trape and Rogier, 1996; Greenwood, 1997; Alles et al., 1998; Gupta et al., 1999). First, the overall mortality burden of malaria does not increase linearly with transmission intensity so the impact of vector control measures such as bed nets, in terms of their capacity to protect individuals, appears to decrease with increasing EIR (Lengeler et al., 1998). Second, the clinical manifestation of malaria and its distribution among children of different ages varies with transmission intensity and seasonally. High intensity, perennial transmission tends to cause intense morbidity and mortality in the earliest years of life primarily manifested as anemia; whereas more modest, seasonal transmission results in the slow acquisition of protective immunity with greater risk of cerebral forms extending into later childhood and adulthood (Trape and Rogier, 1996; Greenwood, 1997; Alles et al., 1998; Gupta et al., 1999). Thirdly, the disease burden resulting from malaria transmission is difficult to quantify. Malaria-specific mortality often grossly underestimates the disease burden caused by malaria, particularly at high transmission intensities (Molineaux, 1997; Snow et al., 1999a). This is because asymptomatic malaria infections often exacerbate the effects of other pathogens, which are ultimately diagnosed as the cause of death (Molineaux, 1997; Snow et al., 1999a). This is further examined in the discussion section, following an analysis of current evaluation methods in this field.

² EIR is the product of the vector biting rate times the proportion of mosquitoes infected with sporozoite-stage malaria parasites.

Why Evaluate?

The science of evaluation has received considerable attention recently. This has been driven by the current climate of budgetary constraints in many international, donor-funded programs. But it also comes from impatience with poor results from several decades of experimentation with different program designs, organizational changes, and philosophical developments in the sphere of international public health and development.

Evaluation has been defined as the application of social science and epidemiological methods and procedures to judge and improve the ways in which social policies, interventions and programs are conducted, from the earliest stages of defining and designing programs through their implementation (Rossi and Freeman, 1993, Bertrand et al., 1996). Thus, driven by the need to demonstrate relative success (and cost) of one program over another, in a world of competing and declining resources, efforts by the public health research community have focused on four main areas: developing appropriate, standardized indicators, defining populations of interest, expanding or adapting appropriate evaluation research designs to capture the impact of programs on the populations of interest, and enhancing existing or developing better methods of data collection and analysis.

Evaluation of public health interventions or programs (family planning, diarrhea prevention, or any other major problem effecting a community) includes both program monitoring and impact assessment. Monitoring refers to how well the program is carried out at different organizational levels and at what cost, and it tracks change over time in terms of resources used, production and use of services. Impact assessment measures the extent to which changes in actual outcome indicators can be attributed to the program intervention. This is an important distinction since impact evaluation requires a far more rigorous design to measure *cause and effect*, than monitoring, but it also usually requires more resources over shorter periods of time. Ethical and logistical issues have obliged the research community to expand the portfolio of designs to include more quasi-experimental designs, and more methods of analysis that cope with the phenomenon of endogeneity which is classically reflected by the “targeted program,” (Angeles et al., 1995; Gertler and Molyneaux 1994).

Given the fact that malaria is a community or population level problem, it is appropriate to evaluate programs to combat this problem at a higher aggregate level. As with any wide scale problem, such as family planning, this requires certain properties within a study that enable generalization beyond the immediate study group. It also requires standard measurement of the main outcomes and efforts on behalf of the research community to make the results of research as understandable to as wide an

audience as possible. These have been the central foci of those leading the evaluation efforts in the population community in the past few decades. Preliminary work on infectious disease in general, and malaria in particular, suggests that evaluation of malaria interventions, at a population level (so that it is highly relevant and accessible for policymakers and health professionals), has been largely absent. While advances in evaluation methodology for reproductive health programs have reached into many areas of international public health, including diarrheal intervention research, acute respiratory infections and food supply programs (Buckner et al, 1995), evaluation of infectious diseases (their indicators, designs and the training necessary to implement them) have not, beyond STDs, received the same attention.

The aim of the paper, therefore, is to review published research on malaria intervention in Africa over the past ten years, and to arrive at some conclusions as to the state of how those interventions are being evaluated. The same criteria that have been applied in other large scale intervention and evaluation studies are used here: namely, identification of existing indicators of important outcomes, evaluation or research design used, including any sampling scheme, methods of data collection and analysis applied to each relevant intervention against malaria. This paper is not a comprehensive meta-analysis of all malaria intervention research in Africa, especially since it only goes back 10 years. But much malaria control research presents a complicated problem for the person wishing to do meta analyses, and that is the lack of standardization within the practice of evaluating malaria. Thus, the paper is intended to be a guide to the state-of-the-art in *evaluating malaria interventions*. It asks “where are we now?”, and proposes some next steps to improving and expanding the portfolio of how malaria interventions are currently evaluated.

Methodology

Library databases were used to identify evaluation studies of malaria interventions. MEDLINE was the primary database used in the search. The initial search resulted in over 300 documents on malaria from 1988 to 1999. The search was limited to articles in English and pertaining to humans. Key words in the search included malaria, Africa, community-based interventions, vector control, transmission, interventions, behavior change, cost-effectiveness, effectiveness, efficacy, evaluation, impact, indicators, program impact, program evaluation, and study design. A database of the articles was created using a spreadsheet to allow easy filtering and sorting. Categories included unique number, author, topic of study, year, source, type of paper, country and outcome indicator. Once this primary database of articles was created, it was reviewed to identify the studies meeting the criteria for selection. From 300 studies first identified in the literature search, 19 studies that met the criteria for inclusion were analyzed in depth.

Criteria for selecting research studies

Several criteria were used to identify the studies to be included in the review. Although malaria affects people throughout the world, much of the resources currently allocated to malaria research goes to sub-Saharan Africa due to the severity of the problem in this region. Therefore, this review focuses on studies carried out in Africa. Studies needed to meet a minimum standard of methodological rigor, defined as an experimental or quasi-experimental design, with a pre/post test design. In addition, a minimum sample size of 100 was required. Studies that met these qualifications were reviewed and abstracted for type of intervention, study methodology, outcome measures and findings. These studies were also categorized into five groups: vector control studies, vaccine trial studies, case management studies, diagnosis studies and cost-effectiveness studies.

Results

Most literature on malaria interventions is based on descriptive studies. These studies were primarily concerned with gathering demographic and epidemiological malaria data from the populations of interest. The intention of this paper however is to review only the literature that evaluates the effectiveness of an intervention and therefore descriptive studies have not been included.

The intervention measures commonly applied in malaria control programs can be categorized as being either preventative or curative, depending on whether they attempt to reduce transmission of malaria infection to humans or interfere with the pathogenic proliferation of the parasite within the human host (Killeen et al., 1999b). The best-established methods of control remain those which directly target the vector, including larval habitat reduction, insecticide-treated bed-nets (ITBN), domestic spraying with insecticides, and personal protection with physical barriers or repellents. Other forms of prevention that might be classified here are “future” vaccines against malaria and knockout gametocytes. Curative measures are currently limited to chemotherapy and chemoprophylaxis with antimalarial drugs. Although malaria transmission is cyclical and human to mosquito transmission is an important determinant of the level of infection in a population, available evidence indicates that widespread chemotherapy or chemoprophylaxis with front-line antimalarial drugs is unlikely to reduce malaria transmission intensity (Buckling et al., 1997;Hogh et al., 1998).

Prompt diagnosis and effective curative treatment are currently central to any malaria control program. Regardless of the transmission intensity, the availability of basic outpatient and inpatient health services have a dramatic impact on malaria mortality and alleviate some of the other consequences of morbidity

(Snow et al., 1999a). One of the other advantages of developing curative interventions is that they are readily implemented as a part of conventional health infrastructures (Greenwood, 1997; Alles et al., 1998).

Our review of the general trends in malaria interventions suggests that the projects fall into four categories, leading the evaluations to follow the same groupings with an additional category for cost-effectiveness evaluations. (1) *Vector Controls*: most of the research falls under this first main category which includes evaluations of ITBNs, insecticide-treated curtains, and DDT house spraying interventions. (2) *Vaccine Trials*: includes evaluations of the new SPf66 vaccine. (3) *Case Management*: includes evaluations of anti-malarial drug studies (prophylaxis and treatment). (4) *Diagnostic Studies*: evaluations of studies on the development of quick and reliable means of diagnosing malaria in the community. (5) *Cost-effectiveness*: analysis of the cost of interventions at a community level.

1. Vector control evaluation studies

Ten vector control studies have been done in Africa that met the criteria for this review (see Table 1 and Figure 1). Figure 1 lists the studies for easier referencing, while Table 1 presents a detailed comparison across the studies of research designs, measurements and outcomes or results. All but one of these studies (10) attempted to evaluate the effectiveness of ITBNs. Study 10 attempted to measure the effectiveness of insecticide-treated curtains vs. no curtains. In addition to ITBNs, studies 2 and 4 also attempted to measure the effectiveness of insecticide-treated curtains.

Figure 1: Vector control studies (from Table 1)

1.	<i>Snow et al.</i> ,	1988;	<i>Gambia</i>	(1987)
2.	<i>Sexton et al.</i> ,	1990;	<i>Western Kenya</i>	(1988)
3.	<i>Alonso et al.</i> ,	1991;	<i>Gambia</i>	(1989)
4.	<i>Beach et al.</i> ,	1993;	<i>Western Kenya</i>	(1990-1991)
5.	<i>Jaenson et al.</i> ,	1994;	<i>Guinea Bissau</i>	(1990-1991)
6.	<i>Premji et al.</i> ,	1995;	<i>Tanzania</i>	(1992-1993)
7.	<i>Nevill et al.</i> ,	1996;	<i>Coastal Kenya</i>	(1993-1995)
8.	<i>Binka et al.</i> ,	1996;	<i>Ghana</i>	(1993-1995)
9.	<i>Snow et al.</i> ,	1997;	<i>Coastal Kenya</i>	(1994-1995)
10.	<i>Habluetzel et al.</i> ;	1997;	<i>Burkina Faso</i>	(1994-1996)

1a. Methodologies of the vector control studies

All the studies included in this review used a similar longitudinal design, with a minimum of at least one pre- and post-test measurement observed. All of the studies began by gathering epidemiological data on

the subjects. If they had malaria (with clinical symptoms) they were treated and brought to baseline before the intervention was implemented (only study 3 did not attempt to bring all participants to this base-line level). If the individual did not recover after treatment, they were usually excluded from the study. This served two purposes: first, control and treatment subjects were more comparable, and second, a base line was established for better analysis with respect to pre- and post- intervention time points within treatment and control subjects.

As illustrated in Table 1, six of the studies used a pre/post experimental design with at least one control group (1,2 and 7-10). Villages in these studies were randomly assigned to serve as either an experimental or control group. The remaining four studies used a pre/post quasi-experimental design with a control (3-5 and 6). Villages or households in these studies were not assigned randomly to the experimental or control groups for logistical convenience. Some critics regard this lack of randomization of the communities as a major weakness of the design of these studies, but the authors have frequently argued that this did not cause any significant selection bias in their results (for detailed discussions of various aspects of the design and results of the bed-net studies see Bermejo et al., 1992, Choi et al., 1995; Lengeler et al., 1996, Kirkwood et al., 1997, and Lengeler et al., 1998).

All of the studies used permethrin as the insecticide to impregnate the nets and/or curtains. Study 1 used a double-blind design with respect to bed-net impregnation while study 5 used a single-blind design. The remaining studies did not use a blind design approach for impregnating the bed-nets. It is arguable that a true double-blind procedure cannot be obtained due to the fact that the reduction in insect nuisance is likely to be so substantial that neither the study population nor the field staff can remain unaware of which communities or individuals have the treated nets (Bermejo et al., 1992).

There is a debate as to whether the effectiveness of a vector control study can be conducted at an individual level. As more people in a community become infected with malaria parasites, there is a greater risk for others in their community to become infected. Thus, individuals and households are often viewed as dependent units of a community, and analysis should therefore be based on differences at the community level (Bermejo et al., 1992). Only study 2 used analyses at less than a community level by attempting to measure changes in indicators at the household level.

As shown in Table 1, eight of the ten studies used children or infants as the target populations (1, 3, 4 and 6-10). There are several reasons for children to be targeted. Firstly, children in endemic areas are more severely affected by malaria than adults (adults have multiple chronic infections but concomitant

protective immunity against severe forms of the disease). Secondly, due to the high prevalence and severity of symptoms of malaria in children, changes in indicators would be much easier to assess enabling the use of smaller sample sizes.

There were two main distinctions between the studies with respect to the types of controls used. Studies 1, 3 and 5 assessed the effectiveness of ITBNs by comparing them to a control of non-ITBNs. In addition, study 3 attempted to assess the effectiveness of Maloprim used as a chemoprophylaxis compared to the use of no chemoprophylaxis. This was done by randomly assigning either Maloprim (treatment) or a placebo (control) to individuals in the treatment communities only. The remaining studies compared ITBNs and/or insecticide-treated curtains to a control of no nets or no curtains respectively. This type of control was used to assess the effectiveness of sleeping under a ITBN or having insecticide-treated curtains compared to the use of no net or no curtains.

1b. Results of the vector control studies

All of the studies showed the use of a vector control procedure (ITBNs or insecticide-treated curtains) to be effective in alleviating malaria burden (Table 1). There were many different methods used by the researchers to assess effectiveness, which led to several limitations.

The outcome indicators listed on the right hand column in Table 1 show the number and range of different indicators used by the researchers to assess the effectiveness of the vector control programs. In total, *nine* different outcome indicators were used between the ten studies. The outcome indicators fell into three main categories: morbidity due to malaria (incidence and/or prevalence), nutritional status, and mortality (both all-cause and malaria-specific). Studies 1, 2, 4-6 and 7 used malaria morbidity in the evaluations (1, 2, 4 and 7 used incidence; 5 and 6 used prevalence). Study 9 used nutritional status to assess effectiveness. In addition to malaria morbidity, studies 1 and 6 also used nutritional status. Studies 3, 7, 8 and 10 used mortality to assess effectiveness (3 and 8 used all-cause and malaria-specific; 7 and 10 used all-cause only). As mentioned, study 7 also used morbidity in addition to mortality as an outcome indicator. Not only were very different indicators used between the studies, but the indicators themselves were measured differently. This lack of consistency both within and between studies points to several important limitations in the evaluation methodology.

Although none of the studies' main objectives were to assess changes in entomological indicators, four of the studies (1, 2, 4 and 5) assessed the effectiveness of the vector control intervention on reducing the numbers of mosquitoes found in the area, though very different approaches to measuring mosquito

density were used in the studies. Mosquito collection took place in the evening or early morning within houses selected at random from both experiment and control communities. Varying methods of mosquito collection were used such as knockdown catches, exit traps, adhesive ceiling mats and aspirators. Study 1 used observed mosquito density only, without assessing the proportion of collected mosquitoes infected with malaria sporozoites. The remaining studies used an enzyme-linked immunosorbent assay (ELISA) to identify the proportion of infected mosquitoes. A consistent conclusion was that the use of ITBNs appeared to significantly reduce mosquito densities in all locations.

All of the studies that attempted to measure changes in malaria prevalence and/or incidence used at least one form of the following indicators: parasitaemia (the density of malaria parasites present in the study subject's blood), spleen rate or fever/chills. The lack of standardization led each study to define a case of malaria using different criteria.

Clinical observation measures

Typically, researchers made a distinction between an observed case of malaria and a clinical case of malaria. An observed case of malaria was usually defined as any fever or chills. Fever was used as an indicator of malaria prevalence and incidence in studies 1, 4, 5 and 6, when combined with the study's pre-allocated measure of parasitaemia (see below). Studies 1, 2, 5 and 6 defined fever simply by observation or report. Only study 4 classified a fever as greater than 37.5° C. Of the studies that used fever as an indicator, all but study 2 went on to use additional indicators to measure malaria prevalence and/or incidence. Study 2 based its results solely on the differences of observed fevers and chills between the treatment group and the control group. In this case, any observed fever/chills was assumed to mean that there was a malaria infection present. Study 7 used hospital admissions due to severe malaria symptoms to define cases of malaria.

Biological measurement through microscopy

The use of thick film slides for diagnosing a malaria infection is considered the 'gold standard' and was used in determining malaria incidence and/or prevalence in studies 1, 4, 5 and 6. Clinical malaria was generally defined as having a level of parasitaemia in the blood greater than 5,000 per μl , while *any* parasitaemia found in a blood sample was classified as merely an infection. Studies 1 and 6 used this type of distinction. Study 5 used any microscopically observed infection to define a case, without distinguishing infections on the basis of parasite density, such as having greater than 5,000 per μl . Study 4 used only clinical cases of malaria as an indicator of malaria incidence, but clinical malaria in this case was defined as a parasitaemia level in the blood greater than 2,500 per μl .

Studies 1, 6 and 9 used changes in hematological or developmental status as a means of assessing effectiveness. Both studies 1 and 6 used packed cell volume as an indicator of hematological status. Study 1 used any observed changes in packed cell volume (PCV) to measure changes in nutritional status. In Study 6, the researchers defined nutritional status with the presence of anemia, either any (PCV < 33%) or severe (PCV < 20%). Study 9 used weight for age and mid-upper arm circumference to assess developmental status.

Mortality

Studies 3, 7, 8 and 10 attempted to measure the effectiveness of either ITBNs or insecticide-treated curtains by differences in mortality between treatment and control groups at post-intervention. As seen in Table 1, all of these studies found all-cause mortality rates to be significantly reduced among children in the treatment groups compared to controls. The researchers in studies 3 and 8 also attempted to measure malaria-specific mortality rates by using a post-mortem verbal autopsy. No significant differences in malaria-specific mortality were found between treatment and control groups in either of these studies (Table 1).

All ten of the studies compared differences in indicators between treatment and control groups at the same points in time to assess the effectiveness of the intervention. Measurements of morbidity and nutrition were typically done during or just after the high-transmission seasons. Studies that attempted to measure mortality (all-cause and malaria-specific) generally gathered mortality data at least one year prior to and after the studies in order to identify trends. In addition, studies 5 and 6 used historical controls to measure changes in indicators within groups (treatment and control). This was done by establishing an epidemiological baseline during the high transmission season of year 1 (pre-intervention) and comparing this with epidemiological data during the high transmission season the following year (post-intervention). This type of methodology has limitations due to the fact that malaria transmission can vary from year to year. Because of this annual variation, contemporary controls should always be used in combination with historical controls (Bermejo et al., 1992).

2. Vaccine trial evaluation studies

Three studies done in Africa that evaluated vaccine trials and met the criteria for selection have been included in this review. Table 2 provides a summary of these studies including author, study design, indicators and results. All three studies that attempted to measure the effectiveness of the SPf66 vaccine

were conducted during the same years (1993-1994) and followed virtually identical methodologies. While the first study found a significant reduction in risk of clinical malaria in the treatment group, the remaining two studies found no significant differences between treatment and control groups.

Alonso and colleagues' study in Tanzania (1994) was the first in Africa to assess the effectiveness of the SPf66 vaccine. The study followed an experimental design conducted within a high malaria transmission community, randomly assigning children under five to receive either the vaccine or a placebo. The children were first screened for parasitaemia, and, if necessary, cleared by treatment with pyrimethamine/sulfadoxine [(PS) (brand name Fansidar®)] before being given the vaccine or placebo. The vaccine/placebo was given in three doses and children were monitored for one year. The study assessed differences in mortality and morbidity (in this case measured using incidence of clinical malaria) between the treatment and control groups. Passive case detection was used for obtaining mortality data and hospital records and verbal autopsies were used in establishing cause of death. Incidence of infection was defined by new cases of clinical malaria with fever $> 37.5^{\circ}\text{C}$ and a parasite density in the blood $> 2,000/$

1. Of the 586 children who participated in the study, six died from malaria. Five of the six children who died received the placebo. Results also suggested that the vaccine reduces the risk of malaria in children by 31%. These results are consistent with the results obtained from earlier studies done in Latin America (Alonso et al., 1994).

The second study (D'Alessandro et al., 1995) included was conducted in the Gambia from 1993 to 1994 and followed a similar basic methodology to assess morbidity and mortality as described above, with the following exceptions. First, unlike the Tanzania study, infants (6-11 months) were used as the study subjects in place of children (1-5 years). Second, in assessing morbidity, a more liberal definition of clinical malaria was used (fever $> 37.5^{\circ}\text{C}$ or a parasite density in the blood $> 6,000/$ 1). This study found conflicting results to those obtained in Tanzania by Alonso et al. (1994) (i.e., no significant differences were found in malaria-related mortality or morbidity between the infants who received the SPf66 vaccine and those who received the placebo).

The third study (Acosta et al., 1999) included was conducted in Tanzania from 1993 to 1994. Again, it followed an identical methodology as the two studies mentioned above with the following differences: First, this study only attempted to measure the effectiveness of the SPf66 on malaria-related morbidity and not mortality; and second, a clinical case of malaria was defined as a fever of at least 37.5°C and parasitaemia of any amount found in the blood. This study also used infants (6-11 months), not children, and it ultimately found conflicting results to those obtained in Tanzania by Alonso et al. (1994). No

significant differences were found in malaria-related morbidity between the infants who received the SPf66 vaccine and those who received the placebo.

This group of studies of vaccines against malaria well illustrates the lack of standardization in the field of malaria research and raises several key questions. Should clinical malaria be defined as a fever *and* parasitaemia or as fever *or* parasitaemia? If parasitaemia is used, at what threshold best represents a clinical case (i.e., 5,000/ l or 6,000/ l)? And additionally, which study group (infants or children) should be used and when? It would appear that answers to these questions are not straight-forward, and various research teams appear to use different methods for selecting which indicators they will use.

3. Case management evaluation studies

There has been an abundance of research conducted over the years in Africa on the efficacy and safety of drug treatments for malaria. Three specific case management studies have been included in this review that met the study design criteria. Table 3 provides a summary of these studies including author, study design, indicators and results. In addition, four studies that did not meet the inclusion criteria are briefly discussed.

The first study included in the review evaluated the effectiveness of Fansidar® compared to chloroquine with respect to parasite resistance. A quasi-experimental design was used. Chloroquine was used as a control treatment due to the *P. falciparum* parasite's known resistance to it. A placebo was not used. Resistance to treatment was measured using a scale similar to one established by WHO, where minimal resistance is classified as RI, somewhat resistant as RII, and highly resistant as RIII. The results of the study indicated that parasites are much less resistant to Fansidar® than to chloroquine (Bloland et al., 1993).

The second study included was a randomized trial of three treatments (chloroquine, amodiaquine and PS) conducted in the Gambia in 1994 (Müller et al., 1996). The authors measured the effects of each of these drugs on children aged 6 months to 10 years who were suffering from non-complicated *P. falciparum* malaria (defined as a fever > 37.5 °C and/or history of high fever over the past 2 days). Three hundred children were randomly assigned to one of the three treatment groups. They were reviewed for the first three days and at day 7 and 28 for malaria symptoms, parasitaemia and PCV.

It was found that during the first three days of treatment significantly more children treated with PS returned to the hospital with malaria symptoms. On day 7 it was found that significantly more children

treated with chloroquine were parasitaemic than in either the amodiaquine or PS groups. On day 28 overall parasitaemic failure (individuals with parasitaemia in blood) was significantly lower in the PS group than either of the other two. PCV also increased significantly less in the children of both the chloroquine and amodiaquine groups than in the PS group. It was concluded from these results that PS acts more slowly than chloroquine and amodiaquine in controlling the clinical features of malaria (Müller et al., 1996).

The third study included in this review was a randomized control trial conducted in the Gambia in 1995 that assessed the effectiveness of two regimens of drug treatments, Fansidar® + chloroquine or Fansidar® alone. This trial followed a very similar methodology to the Müller et al. (1996) study design but with only two treatment groups. It attempted to measure the effects of the two treatments on children aged 1-10 years old suffering from uncomplicated *P. falciparum* malaria. Four hundred and five children were randomly assigned to one of two treatment groups. They were reviewed during the first three days, and at day 7 and 28 for malaria symptoms, parasitaemia and PCV.

It was found that during the first three days after treatment significantly more children who received Fansidar® alone, compared to those who received both Fansidar and chloroquine, returned to the clinic with malaria symptoms. At day 7 there was no significant difference in the parasitaemic failure rates (malaria symptoms plus any parasitaemia or no symptoms plus parasitaemia $> 5,000/ l$) between the two treatment groups. At day 28 the results were the same with no significant differences in parasitaemic failure rates found between the two treatment groups. As well, no significant differences were found between the two groups with respect to PCVs. It was concluded that Fansidar® plus chloroquine is a more effective treatment for malaria symptoms than Fansidar® alone although there appears to be no significant effect on PCV or parasite cure rate (Bojang et al., 1998).

Three additional studies were identified that evaluated the effectiveness of different types of case management interventions but did not meet the study design criteria. These studies assumed that the drugs used in the trials were effective treatments for malaria. They compared the effectiveness of one treatment to another (or the same treatment under different condition) but lacked a true control or a pre/post test study design. Two studies attempted to determine the comparative effectiveness of regimens of chloroquine or mefloquine (used as treatment and /or chemoprophylaxis) on maternal and child health in rural Malawi. These studies used a multitude of outcome indicators in the evaluation. Results were mixed depending on the outcome indicator (Steketee et al., 1996). The third study was also conducted in Malawi. It attempted to assess the effectiveness of different iron therapy regimens during treatment of

malaria with PS in children. The results indicated that there was no significant difference in hemoglobin levels between the groups receiving different iron therapy regimens. However, the results did indicate that iron therapy may inhibit the action of PS (Nwanyanwu et al., 1996).

An additional study evaluated the effectiveness of interventions to increase chloroquine (used as a chemoprophylaxis) compliance among pregnant women in Malawi. The interventions included new health education messages, distribution of sugarcoated chloroquine tablets (to improve taste), and a combination of both strategies. The study showed that improving the product was the most important factor in increasing compliance, and that changing the health education message can also have an impact on compliance (Helitzer-Allen et al., 1994).

Many of the same methodological limitations that were pointed out for the vector control studies exist for the case management studies including a lack of standardized indicators and nonrandom assignment of treatment and control subjects. An additional limitation is the lack of a true control in some of the studies. This is most likely due to ethical concerns over non-treatment groups.

4. Diagnostic evaluation studies

Although diagnostic evaluation studies should not be regarded as intervention studies, they are closely linked to how the scientific community measures the outcomes to their studies, and as such we decided they merited inclusion. Three diagnostic studies that met the study criteria have been included in this review, and all three evaluated the effectiveness of new rapid “dipstick” methods for diagnosing malaria. “Dipstick” refers to kits that do not require laboratory conditions, and need only minimal training of qualified staff (non-medical), making the methods quicker and compatible with fieldwork or diagnosis in smaller health units than the traditional microscopy test. It should be noted that the microscopy method (using a microscope to actually count malaria parasites found in the blood) is still considered the gold standard for diagnosing clinical cases of malaria, though as noted above, the level of parasite densities that are held to be *significant* is left to the discretion of the researcher.

All the studies evaluated the sensitivity, specificity and positive and negative predictive values of the new methods. All used traditional microscopy tests performed on the same blood samples by health professionals as a standard for comparison. As well, all three studies used blood samples taken from patients at health clinics who showed symptoms of malaria.

The first two studies were carried out in Uganda in 1996 and 1999. The first evaluated the effectiveness of two new histidine-rich protein 2 (HRP2) diagnostic methods, ICT Malaria P.f.TM and *Parasight*TM -F. In addition to the HRP2's ease and quickness, results showed that these tests worked just as well as microscopy tests. It should be noted that at the time of the study, the ICT Malaria P.f.TM test was 50% more expensive than the *Parasight*TM -F test (Kilian et al., 1997). The second study also evaluated the *Parasight*TM -F method. It concluded that in certain situations *Parasight*TM -F can serve as a viable alternative to microscopy, especially in rural and poorly staffed diagnostic facilities in endemic areas, where case management plays a vital role in malaria control programs (Kilian et al., 1999).

The third study was conducted in the Gambia in 1996. It assessed the effectiveness of another dipstick method, OptiMAL[®], which uses parasite lactate dehydrogenase for diagnosing malaria. Results showed that this method was a reliable means of diagnosing malaria, and researchers concluded that this method can be used in areas where microscopy is not available and for urgent malaria diagnosis at night and weekends, when routine laboratories are closed (Cooke et al., 1999).

The results of these studies are promising. Costs permitting, these new, quick and easy-to-use diagnostic methods could be used in the field at times when the traditional microscopy method is not available. This would be advantageous for several reasons. First, only individuals suffering from a true case of malaria would receive expensive anti-malaria treatments, thus reducing the cost of unnecessary treatment. And secondly, if used in malaria intervention evaluations, more standardized and equally accurate outcome indicators could be established for measuring prevalence.

5. Cost-effectiveness studies

Three studies done in Africa that evaluated cost-effectiveness of malaria interventions have been included in this review. Each study evaluated the cost-effectiveness of very different approaches to malaria treatments and/or interventions. In addition to these studies, an article was identified that reviews the cost-effectiveness research done thus far on the use of ITBNs (Mills, 1998).

The first study compared the cost-effectiveness of two different interventions: ITBNs and the SPf66 vaccine (Graves, 1998). A decision tree model was used in the analysis, which relied on data from the Gambian bed-net studies. Morbidity and mortality averted were used as outcome indicators. It was found that the SPf66 vaccine would be a much more cost-effective malaria intervention than ITBNs. The SPf66 vaccine was calculated to have averted 743 deaths at a cost of \$252.00 each while ITBNs were calculated to have averted 1,537 deaths at a cost of \$711.00 each. The SPf66 vaccine was calculated to have averted

50,502 malaria attacks at a cost of \$3.71 each while ITBNs were calculated to have averted 69,415 malaria attacks at a cost of \$15.75 each. There were several limitations to the study including the fact that no attempt was made to incorporate economies of scale and no benefit was assumed for partially immunized children (Graves, 1998).

The second study assessed the cost-savings of microscopy-based versus presumptive diagnosis of malaria (Jonkman et al., 1995). The study took place at a hospital in Malawi in 1993. Treatment costs were measured in three separate weeks during the rainy season. In weeks I and II, uncomplicated *P. falciparum* malaria cases were treated with antimalarial drugs after presumptive diagnosis. In week III, antimalarial drugs were restricted to patients with parasitaemia found through microscopy-based diagnosis. The proportion of antimalarial prescriptions to overall prescriptions dispensed fell dramatically in the third week. The study estimated the hospital could save \$14,000 annually by using microscopy-based diagnoses of malaria prior to chemotherapy (Jonkman et al., 1995).

The third study assessed the cost-effectiveness of three separate communication interventions that were intended to increase compliance to the malaria chemoprophylaxis program provided by the Ministry of Health in Malawi (Helitzer-Allen et al., 1993). This program used chloroquine as the chemoprophylaxis. The three interventions were (1) distribution of chloroquine and a new health education message, (2) distribution of non-bitter tasting coated chloroquine and the original health education method, and (3) distribution of non-bitter tasting coated chloroquine and a new health education message. The cost-effectiveness analysis demonstrated that the three interventions are each more cost-effective than the current malaria chemoprophylaxis program, if the measure of effectiveness is compliance (Helitzer-Allen et al., 1993).

There are several limitations to these cost-effectiveness evaluations. First, there is a lack of standardization in methodological approaches between cost-effectiveness studies. For example, neither the “cost” nor the “effectiveness” aspects of the ratio are measured consistently between studies as we have seen above, so it is impossible to draw general conclusions. Second, it needs to be better recognized that cost-effectiveness ratios are specific to a particular project and location, and that single point estimates of cost-effectiveness are likely to be very misleading when used as a general guide. Third, with respect to ITBN studies, further exploration is needed of the value of willingness-to-pay studies as a guide to setting prices (Mills, 1998).

Discussion

This review points to four major findings. First, the usefulness of existing studies is limited by their methodological shortcomings, particularly by the lack of standardized indicators. This is of particular concern when attempting to measure malaria incidence and prevalence. This appears to be a problem not only in the choice of indicators used for measuring outcomes, but also how those indicators are measured. Second, due to the lack of standardized outcome indicators, between study comparisons are virtually impossible. Third, there is a paucity of evaluation studies on the synergistic effect of using more than one type of intervention to combat malaria. -- This despite the evidence that many Africans are using several methods of protection against malaria at once, and evidence that all foreign travelers to malarial endemic areas are advised to use multiple forms of malaria prevention (see the travel advisory pages of CDC and WHO). Fourth, due to the nature of malaria transmission that varies from year to year and village to village, it is difficult to generalize study results to other areas and years. This last point is a major challenge to methodologists, and probably accounts for the paucity of studies that have attempted very broad scale assessments of malaria interventions.

Defining a case of malaria?

How researchers define and/or diagnose a case of malaria is essential in assessing incidence as well as prevalence, both crucial indicators in measuring the effectiveness of a malaria intervention. Essentially there are two factors that define a case of malaria, presence of an illness and malaria parasites in the blood. The first component, illness, is normally depicted by the presence of clinical symptoms such as a severe headache, and a spiking fever with chills. The presence of malaria parasites in the blood is normally found by simple observation of a blood sample under a microscope. In the simplest or most straight-forward scenario, an individual would have both, clinical symptoms and malaria parasites in the blood. The matter becomes more complicated, however, when the issue of malaria parasite tolerance, or level of immunity, is considered. This is the situation where individuals living in areas of intense malaria transmission develop a tolerance to the parasite, enabling them to live without clinical symptoms but with levels of the parasite in their blood above zero. This is where the problem lies. What level of parasite density, in addition to clinical symptoms, is necessary to define a case of malaria? Should an individual with no clinical symptoms but with a high level of malaria parasite density be considered a case, since they are at the least a “potential” case of malaria? Should an individual suffering from severe clinical symptoms but who only has a minimal level of parasites be considered a case? Clearly the context of the situation must be considered when determining a case of malaria. But this has led to researchers using different criteria in defining a case. Many malariologists and experienced scientists in the field use a subjective view as to the prevailing malaria transmission situation, and select their outcome indicators

from there. An example of this would be when a researcher assumes that transmission of malaria must be high if there is high prevalence of malaria in that area. This might lead the researcher to use a higher parasite density ($> 5,000/\mu\text{l}$) as the primary definition of malaria (due to the assumption that people in high transmission areas are able to tolerate higher parasite densities without showing clinical malaria symptoms). Yet, this could in turn lead to an under estimate of infection, and a bias in the results of the study, since even low levels of EIR may produce high prevalence data (Beier et al, 1999). We offer that this problem of the relationship between prevalence and transmission and the definition of malaria for evaluation purposes needs attention before the science of evaluating malaria interventions can move forward.

Evaluating vector control interventions

The literature suggests that ITBNs have the potential to be an effective strategy in reducing mortality and perhaps morbidity due to malaria. For an ITBN program to be effective, it must be implemented at the community level, which is logistically, economically and socially challenging. Much can be learned from the studies done thus far on the effectiveness of vector controls.

Although all the studies in this review showed that vector control is effective, several limitations should be considered. First, between study comparisons are extremely limited due to the lack of standardized indicators. Therefore, the results of vector control evaluations must be assessed independently for each study. Second, each vector control intervention study targeted a specific location. The intensity of malaria parasite transmission in these locations can be expressed in terms of EIR. Because malaria transmission intensity in Africa is highly variable with annual EIRs ranging from <1 to $>1,000$ infected bite per person per year, the local area EIR should be kept in mind when attempting to evaluate the effectiveness of a community-based vector control intervention (Beier et al., 1999).

Furthermore, human malarias are transmitted exclusively from human to human via *Anopheles* mosquito vectors. This means that malaria is very much a community level problem, because controlling transmission in any subset of a community inevitably will effect transmission to other members of the community in the immediate vicinity (Woolhouse et al., 1997). The best example of this is the observation that bed-nets, especially ITBNs, can reduce the malaria burden of unprotected individuals over considerable distances (Binka et al., 1998) and can reduce the community level transmission intensity by about ten-fold (Killeen et al., 1999a). This is because such measures reduce the lifetime malaria transmission potential of individual vectors by shortening their lifespan and/or diverting them to feeding on non-human hosts. In this respect, the evaluation of programs to control malaria, or any other

vector-borne disease with exclusively human reservoirs, deserve special attention and appropriate analysis. We therefore argue that the definition of community effectiveness as the simple product of individual effectiveness and coverage (Lengeler and Snow, 1996) is probably inappropriate for malaria control programs. We suggest that comparisons of protected and unprotected individuals within the same community will underestimate the impact of malaria transmission control.

As more resources are used for evaluating ITBN programs, many key methodological problems need to be addressed. A summary of the limitations of bed-net research is described below (Bermejo et al., 1992). This list of limits is also relevant for the most part to other malaria intervention studies.

- (1) *Health indicators.* Again, the most striking limitation is the lack of standardization. While the incidence of clinical malaria is the most commonly used indicator, neither the definition of a clinical attack of malaria nor methods of case detection are standardized across the studies.
- (2) *Bed-net usage.* There has been a failure to record whether the bed-nets were actually used. Future trials must take into account that the use of bed-nets and curtains is seasonal and age dependent.
- (3) *Randomization.* In many studies, the interventions are not introduced randomly. Thus, their results are possibly biased. Randomization is especially desirable when variables such as child mortality are being measured, as it is very difficult to control for all the possible confounding variables.
- (4) *Controls.* Malaria transmission varies from year to year and from village to village. Because of this annual variation, the use of historical controls should not be used. Indeed, more use of control groups would frequently enhance the interventions we have compared.
- (5) *Sample size.* When assessing the potential of community-wide distribution of ITBNs for malaria control, each individual or household is not an independent unit. The sampling unit must be the community or village and analysis should be based on the differences between them including the spatial aspect where villages are separated by sufficient distance to be beyond the normal flight range of the mosquitoes common to the area.
- (6) *Comparisons with other available measures.* There has been very little research comparing residual insecticide house spraying to ITBNs, and this despite the fact that many local governments and malaria control units with ministries of health are still using residual insecticide methods to control acute situations or malaria epidemics.

Recommendations

As the resurgence of malaria, as well as other infectious diseases, continues to take its toll on individuals and communities around the world, policymakers will need to make informed program-level decisions.

This will require more reliable, accurate and diverse community-based data. In addition, the evaluation methodologies (designs employed and indicators and analysis plans used) need urgent, interdisciplinary attention. The following recommendations should be considered in the next steps to advancing evaluation methodologies used in malaria interventions.

- (1) An attempt should be made as soon as possible to develop and test standardized outcome indicators. Indicators of morbidity from malaria (or “potential malaria”) are probably the most urgently needed. They are needed both for use within the studies so that as little subjective information on the context of malaria is introduced as possible, and for comparative evaluation across studies. But programs at the national or sub-national level also need guidance in which indicator best suits their need in terms of evaluating and monitoring different types of programs. After this challenge has been met, the all cause vs. malaria specific cause of death debate should be tackled. But this cannot be done until a standard morbidity indicator is agreed upon. The usual indicator of transmission intensity, the EIR, has a generally accepted definition, but the method of data collection is far more problematic.
- (2) Because of the complications of measuring malaria at different transmission levels, with different immunological status prevalent in different age and gender groups, and across different locations, some guidelines should be developed to give researchers and health professionals a more accurate foundation on which to select their indicators.
- (3) We recommend assessing the feasibility of combining into a summary index, both malaria prevalence indicators and the EIR measures in order to develop a truly robust and comparative measure of malaria transmission. This effort will require considerable, and long term, cross-disciplinary training among epidemiologists, statisticians, medical geographers and entomologists.
- (4) Given the problems identified in the evaluation designs used for malaria intervention, we also recommend increased attention be paid to the quality and quantity of both control and experimental groups. To assess malaria control impact at a community level sufficient numbers of communities need to be enrolled in the protocol, and ideally the intervention randomized across the communities. This is, of course, logistically and financially challenging, but should nevertheless receive more attention than is indicated by this review.
- (5) More flexible uses of quasi-experiments might expand the portfolio of intervention designs currently in use. For example, lengthier longitudinal study designs might expand our knowledge of the

changing incidence of malaria in relation to specific interventions. This would be accomplished by observing several transmission seasons after the intervention has been implemented.

- (6) Further use of econometric analysis might enable researchers and evaluators to overcome some of the problems inherent in the variation of malaria intensity. This would require advanced statistical analysis such as the use of multi-level modeling. The benefits might be considerable, as seen in the recent studies of program impact of family planning and reproductive health programs have shown (eg Angeles, Mroz and Guilkey, 1996). The models could ideally include the capacity to control for a certain amount of unobserved factors causing endogeneity and a bias towards over or under estimating the impact of programs, (the targeting of malaria protection measures in a community, for example). Multi-level post hoc modeling might also enable the researchers to control for the heterogeneous nature of the spread of malaria transmission across communities.
- (7) Although single drug treatments have proven successful in treating clinical malaria, they do nothing to prevent the transmission of the parasite. For this reason, we recommend more resources be diverted to reducing malaria transmission through better implementation (and evaluation) of vector control programs, and through combination therapies (as in TB and HIV).
- (8) Another area that remains unclear is the impact of information, communication and education (IEC) campaigns, and other health education interventions, to encourage the proper use of vector controls, chemoprophylaxis, field diagnosis, and vaccines. This becomes increasingly important as evidence mounts that presenting people with the knowledge of the advantages of using ITBNs against malaria is insufficient to encourage or maintain use and re-use over the medium or long term (Snow et al, 1999). Evaluating IEC campaigns that are intended to prevent/reduce malaria transmission is going to require further adaptation of existing communication evaluation research at the community level.
- (9) Economic evaluation of malaria control efforts has been particularly weak. In our view this is mainly because of the difficulty in assessing all the aspects of the impacts of malaria on daily living, but it is clearly also compounded by poor or inconsistent indicator measurement. As new drugs and vaccines emerge, further cost-effectiveness evaluations must be conducted comparing them to ITBNs and other control initiatives

Table 1: Summary of Vector Control Studies

Ref #	Author, Date	Study design, Participants, Setting	Interventions/control	Outcome indicators	Results
1	Snow et al., 1988	<ul style="list-style-type: none"> ▪ <u>Pre/post, randomized experimental, (double-blind), 16 villages (7 intervention/ 9 control), 454 children (1-9 years),</u> ▪ Gambia (1987) 	<p>Intervention / treatment:</p> <ul style="list-style-type: none"> ▪ ITBN (permethrin) <p>Control:</p> <ul style="list-style-type: none"> ▪ Non-ITBN 	<p>Malaria incidence:</p> <ul style="list-style-type: none"> ▪ Parasitaemia/ clinical malaria (\square 5000/ l), ▪ Spleen rate, ▪ Fever <p>Nutritional status:</p> <ul style="list-style-type: none"> ▪ PCV 	<p><u>With respect to control:</u></p> <ul style="list-style-type: none"> ▪ <u>63% reduction in incident of fever in ITBN group</u> ▪ PCV: Significant increase in ITBN group, ▪ Parasitaemia: Significant decrease in ITBN group, ▪ Spleen rate: Significant decrease in ITBN group,
2	Sexton et al., 1990	<ul style="list-style-type: none"> ▪ Pre/post randomized experimental, ▪ 2 villages, 105 families, 478 people, ▪ Western Kenya (1988) 	<p>Intervention / treatment:</p> <ul style="list-style-type: none"> ▪ ITBN (permethrin) ▪ TC (permethrin) <p>Control:</p> <ul style="list-style-type: none"> ▪ No nets or curtains 	<p>Malaria incidence:</p> <ul style="list-style-type: none"> ▪ SMR with respect to observed fever/chills 	<p>With respect to control:</p> <ul style="list-style-type: none"> ▪ SMR: Significant reduction in ITBN/TC groups, ▪ SMR: Significantly less in TC than ITBN groups, ▪ Incidence: Significant reduction in ITBN/TC groups
3	Alonso et al., 1991	<ul style="list-style-type: none"> ▪ Pre/post, quasi-experimental, ▪ 73 villages- 17 intervention (PHC)/ 56 control (NPHC), (6mo – 4yrs), ▪ Gambia (1989) 	<p>Intervention / treatment:</p> <ul style="list-style-type: none"> ▪ ITBN (permethrin) ▪ Maloprim <p>Control:</p> <ul style="list-style-type: none"> ▪ Non-ITBN ▪ Placebo 	<p><u>Mortality:</u></p> <ul style="list-style-type: none"> ▪ <u>All-cause</u> ▪ <u>Malaria specific (post-mortem verbal autopsies)</u> 	<ul style="list-style-type: none"> ▪ <u>Villages with ITBN + Maloprim- 37% reduction of children (1-4) and 30% reduction in infants (<1) in all-cause mortality</u> ▪ <u>No significant change in malaria-specific mortality between treatment and control groups.</u> ▪ No significant change between (ITBN + Maloprim) and (ITBN + placebo)
4	Beach et al., 1993	<ul style="list-style-type: none"> ▪ Pre/post quasi-experimental, ▪ 6 villages, 2 ITBN/ 2 TC/ 2 control, (children < 6 yrs), ▪ Western Kenya (1990-1991) 	<p>Intervention / treatment:</p> <ul style="list-style-type: none"> ▪ ITBN (permethrin) ▪ TC (permethrin) <p>Control:</p> <ul style="list-style-type: none"> ▪ No nets or curtains 	<p>Malaria incidence:</p> <ul style="list-style-type: none"> ▪ Fever (> 37.5° C), ▪ <u>Parasitaemia (> 2500/mm³).</u> 	<p>With respect to control:</p> <ul style="list-style-type: none"> ▪ Significant reduction of incidence of parasitaemia in ITBN and TC group, ▪ Less but significant reduction of incidence of fever in ITBN and TC groups

Ref #	Author, Date	Study design, Participants, Setting	Interventions/control	Outcome indicators	Results
5	Jaenson et al., 1994	<ul style="list-style-type: none"> Pre/post quasi-experimental , (single-blind), 6 villages, 3 intervention/ 3 control: (pops: 87,49,187,86, 33,151), Guinea Bissau (1990-1991) 	<p>Intervention / treatment:</p> <ul style="list-style-type: none"> ITBN (permethrin) <p>Control:</p> <ul style="list-style-type: none"> Non-ITBN 	<p>Malaria prevalence:</p> <ul style="list-style-type: none"> Illness with fever (interviews) Plasmodium prevalence (malaria parasites found in blood) 	<p>Illness:</p> <ul style="list-style-type: none"> Treatment group- 2 of 3 villages Significant reduction, post-intervention, Control- No significant change pre/post intervention, <p>Plasmodium prevalence:</p> <ul style="list-style-type: none"> Treatment- all 3 villages significant reduction post-intervention, Control- No significant change pre/post intervention
6	Premji et al., 1995	<ul style="list-style-type: none"> Pre/post quasi-experimental, 13 villages, 4 groups: Group II- intervention (3 villages)/ Group IV- control (4 villages), (6-40 months), Tanzania (1992-1993) 	<p>Intervention / treatment:</p> <ul style="list-style-type: none"> ITBN (permethrin) <p>Control:</p> <ul style="list-style-type: none"> No nets 	<p>Malaria prevalence:</p> <ul style="list-style-type: none"> Parasitaemia (any & \geq 5000/ l) <p>Nutritional status:</p> <ul style="list-style-type: none"> Anemia: any (PCV <33%) & severe (PCV < 20%) 	<ul style="list-style-type: none"> Parasitaemia (\geq 5000/ l): Significant reduction in treatment group (pre to post intervention), No significant change in parasitaemia prevalence (any) in control group (pre to post intervention), <u>Significant reduction of RR of malaria in treatment group (pre to post intervention).</u> Treatment group saw a 54% reduction in anemia in relation to control
7	Nevill et al., 1996	<ul style="list-style-type: none"> Pre/post, randomized experimental, 56 zones, 1000 people each, 28 treatment and 28 control, (children 1-59 months old), Coastal Kenya (1993-1995) 	<p>Intervention / treatment:</p> <ul style="list-style-type: none"> ITBN (permethrin) <p>Control:</p> <ul style="list-style-type: none"> No nets 	<p>Mortality (all-cause)</p> <p>Morbidity</p> <ul style="list-style-type: none"> Hospital admission rates (intention-to-treat) 	<p>With respect to control:</p> <ul style="list-style-type: none"> 30% reduction in all-cause mortality in children 1-59 months, 44% reduction in hospital admissions for severe, life-threatening malaria
8	Binka et al., 1996	<ul style="list-style-type: none"> Pre/post, randomized experimental, 96 zones, 48 treatment and 48 control, (children 6-48 months), Ghana (1993-1995) 	<p>Intervention / treatment:</p> <ul style="list-style-type: none"> ITBN (permethrin) <p>Control:</p> <ul style="list-style-type: none"> No nets 	<p>Mortality</p> <ul style="list-style-type: none"> All-cause Malaria specific (postmortem verbal autopsy) 	<p>With respect to control:</p> <ul style="list-style-type: none"> 17% reduction in all-cause mortality in children (6-59 months), No significant change in malaria-specific mortality

Ref #	Author, Date	Study design, Participants, Setting	Interventions/control	Outcome indicators	Results
9	Snow et al., 1997	<ul style="list-style-type: none"> ▪ Pre/post, randomized experimental, ▪ Community of ~1000 people- 56 zones: 28 intervention zones (787 infants) and 28 control zones (692 infants), (Infants 1-11 mo), ▪ Coastal Kenya (1994-1995) 	<p>Intervention / treatment:</p> <ul style="list-style-type: none"> ▪ ITBN (permethrin) <p>Control:</p> <ul style="list-style-type: none"> ▪ No nets (< 6%) 	<p>Nutritional status:</p> <ul style="list-style-type: none"> ▪ Z-score- weight for age ▪ Z-score- MUAC, 	<p>With respect to control:</p> <ul style="list-style-type: none"> ▪ Significant increase in weight for age Z-score in ITBN group, ▪ <u>Significant increase in MUAC Z-score in ITBN group</u>
10	Hablutzel et al., 1997	<ul style="list-style-type: none"> ▪ Pre/post, randomized experimental, ▪ 158 villages, 78 treatment and 80 control (children 6-59 months), ▪ Burkina Faso (1994-1996) 	<p>Intervention / treatment:</p> <ul style="list-style-type: none"> ▪ TC (permethrin) <p>Control:</p> <ul style="list-style-type: none"> ▪ No curtains 	<p>Mortality (all-cause)</p>	<p>With respect to control:</p> <ul style="list-style-type: none"> ▪ Over all, 15% reduction in all-cause mortality in children 6-59 months (over 2 year period) <p><i>Note:</i> Year 1: Significant decrease of all-cause mortality; Year 2: no significant change of all-cause mortality</p>

Notes

*Significance is defined at $\alpha = .05$

ITBN Insecticide-treated bed-nets

TC Insecticide-treated curtains

SMR: Standardized morbidity/mortality ratio

PHC / NPHC: With health clinic/ no health clinic

RR: Risk ratio

MUAC: Mid-upper arm circumference

PCV Packed cell volume

Table 2: Summary of Vaccine Trial Evaluation Studies

Ref #	Author, Date	Study design, Participants, Setting	Interventions/control	Outcome indicators	Results
1	Alonso et al., 1994	<ul style="list-style-type: none"> ▪ Pre/post, randomized experimental (double-blind), ▪ 1 village, 586 children, 274 treatment and 312 placebo (1-5 years), ▪ Tanzania (1993-1994) 	<p>Intervention / treatment:</p> <ul style="list-style-type: none"> ▪ SPf66 vaccine x 3 <p>Control:</p> <ul style="list-style-type: none"> ▪ Placebo 	<p>Mortality:</p> <ul style="list-style-type: none"> ▪ Passive case detection <p>Morbidity (clinical malaria):</p> <ul style="list-style-type: none"> ▪ Clinical: fever > 37.5° C and parasite density > 20,000/ 1 	<p>Mortality:</p> <ul style="list-style-type: none"> ▪ Of 6 deaths due to malaria (1 vaccine, 5 placebo) <p>Malaria prevalence:</p> <ul style="list-style-type: none"> ▪ 31% significant risk reduction of clinical malaria among vaccinated children exposed to high transmission
2	D'Alessandro et al., 1995	<ul style="list-style-type: none"> ▪ Randomized experimental (double- blind), ▪ 547 infants, 316 treatment and 231 placebo, (6-11 months), ▪ Gambia (1993-1994) 	<p>Intervention / treatment:</p> <ul style="list-style-type: none"> ▪ SPf66 vaccine x 3 <p>Control:</p> <ul style="list-style-type: none"> ▪ Placebo (polio vaccine) 	<p>Mortality:</p> <ul style="list-style-type: none"> ▪ Passive case detection <p>Morbidity (clinical malaria):</p> <ul style="list-style-type: none"> ▪ Fever > 37.5° C or parasite density > 6,000/ 1 	<p>Mortality:</p> <ul style="list-style-type: none"> ▪ No significant change between treatment and placebo groups <p>Morbidity:</p> <ul style="list-style-type: none"> ▪ No significant change between treatment and placebo groups (3% reduction/ p=.81)
3	Acosta et al., 1999	<ul style="list-style-type: none"> ▪ Two arm, randomized experimental (double-blind) ▪ 1,207 infants, 604 treatment and 603 placebo (6-11 months) ▪ Tanzania (1993-1994) 	<p>Intervention / treatment:</p> <ul style="list-style-type: none"> ▪ SPf66 vaccine x 3 <p>Control:</p> <ul style="list-style-type: none"> ▪ Placebo 	<p>Morbidity (clinical malaria):</p> <ul style="list-style-type: none"> ▪ Fever > 37.5° C and any parasite density found in blood 	<p>Morbidity:</p> <ul style="list-style-type: none"> ▪ No significant change between treatment and placebo groups (2% reduction/ p=.84)

Notes

*Significance is defined at $\alpha = .05$ unless otherwise noted

Table 3: Summary of Case Management Evaluation Studies

Ref #	Author, Date	Study design, Participants, Setting	Interventions/control	Outcome indicators	Results
1	Bioland et al., 1993	<ul style="list-style-type: none"> Pre/post quasi-experimental, 2 villages, 226 children (>5 years), Kenya & Malawi (1990) 	<p><u>Intervention / treatment:</u></p> <ul style="list-style-type: none"> Pyrimethamine/sulphadoxine (Fansidar®) <p>Control:</p> <ul style="list-style-type: none"> Chloroquine 	<p>Parasite resistance:</p> <ul style="list-style-type: none"> RI, RII, & RIII (RI least resistant/ RIII most resistant) 	<ul style="list-style-type: none"> Parasites found to be much less resistant to PS than chloroquine
2	Müller et al., 1996	<ul style="list-style-type: none"> Randomized experimental with 3 treatment groups, 300 children (6m-10years with malaria); 100 per treatment group, Gambia (1994) 	<p>Treatment 1 (Tx1):</p> <ul style="list-style-type: none"> Chloroquine <p>Treatment 2 (Tx2):</p> <ul style="list-style-type: none"> Amodiaquine <p><u>Treatment 3 (Tx3):</u></p> <ul style="list-style-type: none"> Pyrimethamine/sulphadoxine (Fansidar®) 	<p>Morbidity: days 3, 7 & 28</p> <ul style="list-style-type: none"> PCV Parasitaemia in blood Malaria symptoms requiring hospitalization 	<p>Day 3:</p> <ul style="list-style-type: none"> Significantly more children from Tx3 returned to hospital for malaria symptoms than Tx1 and Tx2 <p>Day 7:</p> <ul style="list-style-type: none"> Significantly more were parasitaemic in Tx1 compared to Tx2 & Tx3 <p>Day 28:</p> <ul style="list-style-type: none"> Significant reduction of parasitaemic failure: Tx1 > Tx2 > Tx3 PCV increased Significantly less in Tx1 than Tx3 with no significant change between Tx1 & Tx2
3	Bojang et al., 1998	<ul style="list-style-type: none"> Randomized experimental, 405 children (1-10 years with malaria); 203 TX1 (PS only) and 202 TX2 (PS + Chloroquine), Gambia (1995) 	<p>Treatment 1 (Tx1):</p> <ul style="list-style-type: none"> Pyrimethamine/sulphadoxine (Fansidar®) alone <p>Treatment 2 (Tx2):</p> <ul style="list-style-type: none"> Pyrimethamine/sulphadoxine + chloroquine 	<p>Morbidity: days 3, 7 & 28</p> <ul style="list-style-type: none"> PCV Parasitaemia in blood (any and > 6,000/ l) Malaria symptoms requiring hospitalization Fever 	<p>Day 3:</p> <ul style="list-style-type: none"> Significantly more children from Tx1 than Tx2 returned to hospital for malaria symptoms <p>Day 7:</p> <ul style="list-style-type: none"> No significant difference of parasitaemic failure rate between Tx1 and Tx2 <p>Day 28:</p> <ul style="list-style-type: none"> No significant difference of parasitaemic failure rate or PCV between Tx1 and Tx2

Notes

*Significance is defined at = .05

PS Pyrimethamine/sulphadoxine (Fansidar®)

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