Economic Analysis of Malaria Control in Sub-Saharan Africa

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Executive Summary

Introduction

In 1998, the World Health Organization (WHO) identified malaria as a key priority, and announced the launch of the Roll Back Malaria campaign, which aims to bring about a significant reduction in the global malaria burden, with an initial emphasis on the high transmission areas of Africa. The new initiative has arisen out of a strong and growing political commitment to combat the disease, both in affected countries and the donor community. The aim of this report is to support this initiative through the synthesis and analysis of information on the cost-effectiveness and economic benefits of malaria control in sub-Saharan Africa (SSA). Whilst economic analysis is only one of many inputs into the decision-making process, it can provide policy-makers with important information on the interventions which represent the best value for money in Africa.

Chapter 1 describes the burden of disease due to malaria, and reviews existing literature which applies economic analysis to evaluate control interventions. In SSA, malaria is the single most important infectious disease in children, being responsible for the deaths of around one million children per year. The malaria health burden has an important morbidity as well as mortality component, with the severe forms of the disease (cerebral malaria and severe anaemia) the main reasons for hospital admissions of young children in malaria endemic areas. Millions more children and adults suffer mild uncomplicated clinical malaria each year. The epidemiology of malaria across SSA is far from homogeneous, with variations from intense perennial transmission, to highly seasonal low transmission, to sporadic transmission in areas normally malaria-free. Across this range of transmission intensity, there are associated age-specific patterns of malaria-related morbidity and mortality.

A review of economic evaluations of malaria control revealed many gaps and inadequacies in the literature. The number of analyses was very limited, and for some interventions there were no studies at all. Moreover, it was difficult to draw general conclusions because studies were related to specific geographical settings, and often drew their information from trials, which were not typical of operational situations. Comparison of the results was problematic because many of the studies used different methodologies and outcome measures, and did not include all the costs.

More studies are evidently needed that assess cost-effectiveness in operational settings for a variety of interventions. However, studies need time to undertake, but policy decisions on the allocation of resources to malaria control cannot be indefinitely delayed. A modelling approach was therefore used to provide a range of comparable estimates for the cost-effectiveness of the main prevention and treatment interventions in SSA, drawing on all available cost and effectiveness data.

Methods of Analysis

Details of the cost-effectiveness methodology used are provided in Chapter 2. The effectiveness of each intervention was modelled using a hypothetical population based on a model life table, and was calculated in terms of disability adjusted life years (DALYs) averted. The DALY is a measure of health outcome which incorporates both premature death and morbidity/disability,

and which facilitates comparison with other interventions that improve the quality of life, as well as with those that save lives. Estimates of DALYs averted were combined with information on costs to both governments and households to produce a likely range for the "cost per DALY averted" of each intervention. Results were produced for SSA, stratified by broad epidemiological zone where feasible, and by three economic zones stratified on the basis of per capita gross national product (GNP): very low income (under $315); middle income (between $315 and $1,000); and higher income (above $1,000). All costs were converted to 1995 US dollars.

Data on costs and effects were obtained through reviews of published and unpublished literature, and extensive consultation with experts working in both research and programme implementation. Effectiveness estimates were based on randomized controlled trials and meta-analyses where possible, and were adjusted by behavioural variables, such as compliance, to estimate operational effectiveness. Due to the high degree of uncertainty and variability surrounding many of the key parameters, probabilistic sensitivity analysis was used: cost and effectiveness input variables were entered as ranges, the model was estimated using a Monte Carlo simulation, and the cost-effectiveness ratios (CERs) were expressed in terms of likely ranges rather than point estimates.

The evaluation of CERs rests on a comparison with the cost-effectiveness of alternative uses of resources, which will depend on the specific context. As a broad guideline, an intervention was considered as "highly attractive" if the range for the cost per DALY averted fell entirely below $25, and "attractive" if it fell below $150. Estimates were also made of the total cost of implementing each intervention in a 'typical' low income country: data from Tanzania were used for illustrative purposes. This gives an indication of the affordability of each intervention.

The availability of data on the costs and effects of malaria control restricted the analyses to a sub-set of interventions to prevent malaria in childhood and pregnancy (Chapters 3 and 4 respectively) and to improve the case management of uncomplicated malaria (Chapter 5).

The Prevention of Malaria in Childhood

The following strategies were evaluated: insecticide treated nets (ITNs), residual spraying of houses, and chemoprophylaxis for children. The coverage of preventive interventions in SSA is currently very limited. Residual house spraying was advocated as the mainstay of the malaria eradication programmes during the 1950s and 1960s. Over time many countries have abandoned or curtailed their spraying programmes, although they are still widely active in parts of southern Africa. The treatment of mosquito nets with insecticide is a relatively new innovation. The efficacy of ITNs in reducing child mortality has recently been demonstrated in trials, but large-scale operational programmes remain rare. The provision of chemoprophylaxis to children represents an alternative to vector control in preventing malaria; it is not currently implemented in SSA, although large-scale programmes have been undertaken in several countries in the past.

A model of childhood malaria morbidity and mortality was used to explore the cost-effectiveness of preventive strategies in reducing morbidity and mortality in children under 5 years of age. The analysis was restricted to areas of moderate to high malaria transmission, as effectiveness data were not available from low transmission or epidemic areas.

Insecticide treated nets

The analysis of ITNs was based on the delivery mechanism used in the WHO Special Programme for Research and Training in Tropical Diseases (WHO/TDR) trials, where net treatment was done on a communal basis, with householders, community health workers and programme staff working together. Two possible scenarios were considered: first, where nets are distributed to households as part of the programme, and secondly where there is already a high degree of net ownership, and treatment is arranged for the existing nets. Estimates of the effectiveness of ITNs were drawn from the Cochrane meta-analysis of WHO/TDR trials conducted in SSA, adjusted using estimates of net retreatment rates in operational settings.

If net coverage was low and nets must be distributed as well as treated, the cost per DALY averted in a very low income country fell within the range of $19 to $85 and hence would be judged "attractive". The intervention would also be considered an "attractive" option in middle income countries (because the range fell under $150), but not in higher income countries. If net coverage in the community was already high and only treatment of nets was required, costs were significantly reduced. Under this scenario, the range for the CER in a very low income country decreased to between $4 and $10. Indeed, the intervention would be "attractive" for all income levels, and "highly attractive" in very low and middle income countries.

Residual spraying

Recent evidence on the health impact of residual spraying was not available, so it was necessary to rely on infant mortality reductions recorded during three controlled trials in the 1950s and 1960s. The effectiveness estimates were adjusted to account for non-compliance, and costs were calculated on the basis of one or two spraying rounds per year. With one round a year, the CER in very low income countries fell between $16 and $29, on the margin of "highly attractive" and "attractive", and for the other two economic strata, spraying would be considered an "attractive" option. If two rounds were required a year, the CER in each income group approximately doubled. Spraying would still be considered "attractive" in very low and middle income countries, but not in higher income countries (though given their higher income, they might well be prepared to pay in excess of the $150 per DALY averted cut-off point applied here).

Chemoprophylaxis for children

The analysis of chemoprophylaxis for children was based on a system of distribution of the antimalarial, Maloprim® by village health workers (VHWs). An estimate of the impact on child mortality was taken from a trial conducted in the Gambia, adjusted to account for compliance in operational settings. Costs were estimated for perennial transmission (12 months) and seasonal transmission (6 months), and were calculated for two scenarios. In the first scenario a network of VHWs was assumed already to exist, and in the second scenario it was assumed to be necessary to establish a VHW cadre to run the programme.

Where a network of VHWs already existed, the CER in very low income countries with perennial transmission fell between $3 and $12. The intervention would be considered "highly attractive" in very low and middle income countries, and "attractive" in the higher income strata. Even if it were necessary to set up a whole VHW programme just to implement this intervention, it would still be "attractive" in very low and middle income countries, with for example, a CER between $8 and $41 in very low income countries with perennial transmission.

Resistance and immunity

The cost-effectiveness of all of the interventions to prevent malaria in childhood could be adversely affected by the development of either insecticide or drug resistance. Insecticide resistance is not currently common in SSA, but could develop in response to widespread agricultural or public health use of insecticides. Resistance to certain drugs is already widespread, and there is concern that the provision of chemoprophylaxis could itself significantly increase the growth of resistance, which would have a detrimental effect on the cost-effectiveness of the intervention, and could also threaten the provision of effective case management. There is also concern that long-term use of preventive interventions in areas of high malaria transmission could reduce the rate at which immunity is acquired, increasing malaria morbidity and mortality in older age classes. This mortality "rebound" in later childhood may cancel out to some degree the mortality reduction achieved in the younger children.

Policy conclusions: cost-effectiveness of preventive measures

In summary, all of the interventions analysed that prevent childhood malaria are potentially attractive uses of resources. There is considerable overlap in the ranges for the CERs, so no one intervention can be identified as the most cost-effective in all situations.

Although the interventions are cost-effective, the financial costs of wide coverage are high, and affordability is likely to be a major barrier to widespread implementation. Unless nets are already widely used, or a strong network of VHWs is in place, achieving national coverage of the target group with any of the interventions is likely to increase the existing health sector budget by over 20%.

The Prevention of Malaria in Pregnancy

Evidence is growing that chemoprophylaxis or intermittent treatment of malaria in pregnancy has beneficial health effects. In 1986, WHO recommended that all pregnant women in malaria endemic areas receive regular prophylaxis, but this has rarely been accomplished effectively in practice. A model was developed to assess whether a drive to increase coverage was justified on the basis of cost-effectiveness. Two drug regimens were considered for primigravidae only: weekly chloroquine chemoprophylaxis; and two intermittent treatments with sulfadoxine pyrimethamine (SP). Whilst the impact on increasing birth weight of children born to primigravidae has been clearly shown in a meta-analysis, the sample sizes of the studies were too small to demonstrate a significant impact on neonatal mortality. The impact on mortality was therefore modelled, based on birth weight distributions and birth weight specific neonatal mortality rates. Estimates of effectiveness were adjusted for non-attendance at clinic and non-compliance with the prescribed regimen.

In the absence of parasite resistance, both drug regimens were clearly cost-effective. In very low income countries with SP the CER fell between $4 to $26, and for all economic strata with either drug, the CER fell clearly below $150. The intervention would therefore be considered an "attractive" option with either drug regimen. The chloroquine regimen was slightly less cost-effective than the SP regimen, because the latter was cheaper and was assumed to have higher compliance. The SP regimen continued to look "attractive" if coverage was extended to all gravidae, if three, rather than two treatments were provided; or if a share of antenatal care overheads were included in the costs.

Resistance
When drug resistance was allowed for, both regimens remained cost-effective up to high levels of resistance. In very low income countries, the intervention continued to look "attractive" up to 69% resistance if the chloroquine regimen were used, and up to 83% resistance if the SP regimen were used.

Policy conclusions: prevention of malaria in pregnancy
This intervention is highly cost-effective. The intervention is also relatively affordable for SSA governments, with an incremental cost equivalent to less than 1% of the existing health sector budget. However, these results are based on the addition of the intervention to an existing infrastructure of antenatal clinics. If antenatal care coverage is currently low, the incremental costs of providing the service through clinics would be significantly increased.

Improving the Case Management of Uncomplicated Malaria

WHO has argued that appropriate and timely case management should be seen as not only a key component of any malaria control programme, but also as a fundamental right of all populations affected by malaria. In reality, case management is often highly inadequate. Inappropriate drugs are prescribed, compliance with the recommended regimen is low, drugs are often ineffective due to resistance or poor quality, and patients with severe malaria are managed inappropriately.

Evaluation of interventions to improve case management is hampered by the lack of data on both costs and effectiveness, and the few studies that do consider such strategies generally do not include health outcomes. In order to analyse the interventions, a decision tree model was developed to translate changes in intermediate outcomes, such as compliance and drug efficacy, to final health outcomes. This model was used to assess the cost-effectiveness of interventions to improve the treatment of uncomplicated malaria, namely improving compliance, improving the availability of second and third line drugs, changing the first line drug for treatment, and the use of combination therapies. The results are presented for the two broad strata of low and high transmission. Cost-effectiveness was analysed using both gross costs (incremental costs of intervention only), and net costs (incorporating potential cost-savings to estimate the overall impact on the total cost of the treatment episode).

Improving compliance
An intervention to improve compliance was evaluated, including training of providers, health education for patients and care-takers, and the pre-packaging of chloroquine in plastic bags. This was highly cost-effective: for a very low income country with high transmission the CER was under $25 at any level of drug resistance below 77%. In low transmission areas the CER range fell under $25 up to 24% resistance, and under $150 up to 87% resistance. Results were very similar for middle and high income countries.

Improving the availability of second and third line drugs
It is generally recommended that a clear hierarchy of drugs should be available for the treatment of uncomplicated malaria, so that patients experiencing treatment failure with the first line drug can be prescribed an alternative. However in reality, access to second and third line drugs at peripheral facilities is often very poor. Analysis using the case management model showed that moving from a situation where only chloroquine could be prescribed to one where second and third line drugs were available was potentially highly cost-effective. In a very low income country, the CER range was under $25 at any level of chloroquine resistance greater than 6% in

low transmission areas, and at any level of resistance with high transmission. Moreover, in high transmission areas the intervention would lead to net cost-savings at any level of resistance above 40% in very low income countries, 22% in middle income countries, and 3% in high income countries.

Changing the first line drug for treatment

For decades, chloroquine has been the official first line drug for the treatment of uncomplicated malaria in nearly all African countries, but resistance is now widespread and increasing. A key issue facing African policy-makers is the question of when to change to a new first line drug. If the decision were considered with given levels of drug resistance, a switch from chloroquine to SP as the first line drug would appear highly cost-effective. However, this ignores the central concern that resistance to the replacement first line drug will rapidly increase once it is widely adopted, reducing the effectiveness of the new regimen. A dynamic framework, which incorporates the growth of resistance over time, is essential to evaluate the complex trade-offs between higher drug costs, immediate reductions in morbidity and mortality and reductions in the associated cost of treatment, and potential increases in resistance to replacement drugs, which could lead to higher morbidity and mortality in the future. The case management model, extended to cover a 10-year time period, was used as an analytical tool to help structure the problem, explicitly explore the trade-offs involved, and identify key parameters that have a significant influence on the results.

If the growth of drug resistance is ignored, an immediate change of first line drug appears highly cost-effective, whatever the level of chloroquine (CQ) resistance. By contrast, using a dynamic framework leads to strikingly different conclusions. With a starting CQ resistance of 20%, there should be a delay of several years before a switch is implemented, which would inevitably lead to higher rates of mortality in the short to medium term. The analysis showed that the appropriate time to change drugs is highly dependent on both empirical factors, such as the level and growth rates of resistance, and subjective factors relating to the preferences and priorities of policy-makers, and their attitudes to risk. The collection and dissemination of relevant information on this issue should be a key priority, and constructive advice should be provided to policy-makers to help them to weigh up the complicated trade-offs involved.

The use of combination therapies

The extended model was also used to evaluate the potential cost-effectiveness of combination therapies. It is argued that prescribing an additional drug, such as artemisinin, with the first line drug will reduce the growth rate of drug resistance. The cost-effectiveness of this strategy depends on the impact on the resistance growth rate. The limited analysis possible with the available data indicated that in very low income countries with high transmission, the CER range would be under $25 if the growth rate of SP resistance was reduced by at least 58%, and under $150 if the reduction was greater than 47%.

Diagnostic tests

The introduction of diagnostic tests was also assessed, but as the impact on health outcomes is not clear-cut, the analysis was restricted to an evaluation of net costs. In very low and middle countries, the range for the gross cost per test with microscopy was clearly lower than for the dipstick test, but in higher income countries there was some overlap in the ranges. The potential cost savings from using microscopy or antigen detection dipsticks rather than clinical diagnosis were assessed by comparing the incremental cost per test with the savings in drugs prescribed. Despite the low positive predictive values found for clinical diagnosis, the use of additional

diagnostic technology is unlikely to be cost-saving in SSA because the current range of first line antimalarials are relatively inexpensive drugs. If one of the more expensive antimalarials, such as mefloquine, became the first line drug, both microscopy and dipsticks would be clearly cost-saving in low transmission areas, where the accuracy of clinical diagnosis is likely to be lowest. For very low and middle income countries microscopy would also be cost-saving under high transmission, but the results are ambiguous for higher income countries, and for all countries with dipsticks.

Policy conclusions: improving case management of uncomplicated malaria
It is clear that many interventions to improve case management are potentially extremely good value for money but information is relatively poor, making it difficult to draw firm conclusions. This caveat particularly applies to the measures to improve compliance and the accessibility of second and third line drugs; results for both are extremely promising but need to be interpreted with some caution, as the data on the costs and effects of these interventions are so limited. Further analysis of the interventions considered here should incorporate consideration of potential trade-offs between the two objectives of making prompt, effective treatment as accessible as possible, and controlling drug use to reduce the growth rate of resistance.

Data on the costs and effects of improving the treatment of severe malaria proved inadequate to explore cost-effectiveness, except for a preliminary analysis of the cost-effectiveness of the introduction of artesunate suppositories. This intervention could be highly cost-effective, and it is plausible that this could also be the case for other interventions to improve the treatment of severe cases. More research is urgently needed in this area.

Both improving compliance and increasing the accessibility of second and third line drugs are relatively low cost interventions, representing well under 1% of the existing government health care budget in a very low income country. Switching from chloroquine to SP as the first line drug would also require only a small increase in the government health budget, of approximately 0.2% per year. However, the costs of switching to mefloquine, as a potential replacement for SP, would be much more substantial, requiring an increase of approximately 18%. The introduction of combination therapy was estimated to require a 5% annual increase in the current health care budget, and the net cost of using dipsticks for every suspected malaria outpatient case would require an increase of around 8%.

The Economic Impact of Malaria

Literature was reviewed on the economic burden of malaria, and the potential economic benefits to be derived from improved control (Chapter 6). Evidence indicates that malaria was a major economic burden for the households studied, which spent each month between $0.23 and $15 on malaria prevention methods, and between $1.79 and $25 on treatment. However, these data are inadequate to permit generalization beyond the original settings. Most studies have been done in urban areas, and thus are unlikely to represent expenditure in rural areas. In addition they report expenditure in a specific time period (usually a month), which cannot be extrapolated to an annual figure without better information on the seasonal distribution of malaria and cash availability.

No attempts have been made to estimate overall public expenditure on malaria prevention and treatment, but the numbers of patients seeking care for suspected malaria and data on unit costs of treatment suggest that the total cost is likely to be substantial. Around 20% to 40% of

outpatient visits in SSA are for “fever”, and suspected malaria among inpatients ranges from between 0.5% to 50% of admissions. An outpatient visit costs in the region of $0.96 in Malawi; inpatient treatment for severe malaria costs $35 per admission in a typical Kenyan district hospital and absorbed 9% of hospital inpatient recurrent costs.

In addition to these direct costs, malaria also has an economic impact through its effect on physical work capacity and labour productivity; land use; and child school attendance, school performance and cognitive development. However, studies on these issues have been fraught with methodological difficulties. There has been a general failure to take into account several important factors, including the specific nature of the malaria disease burden, the particular characteristics of the local economy, the coping strategies of households, and the effect of malaria on the production possibilities and incentives of households. There has also been a remarkable lack of attention paid to the relative incidence of malaria by socio-economic group, and especially its impact on the poorest. Systematic studies of the potential benefits of malaria control, disaggregated by region and population group, are required both to publicize and justify a major malaria control effort, and to inform the design and targeting of control interventions.

Policy Implications

Chapter 7 reflects on the economic evidence available to underpin Roll Back Malaria, and identifies key knowledge gaps and research priorities. The main cost-effectiveness results are summarized in Figure 1 for a very low income country with high transmission. The central message from this analysis is that all the malaria control interventions evaluated would be considered an attractive use of resources: in very low and middle income countries, the CER range clearly falls below $150 in each case. This was not the case for all interventions in higher income countries, but it is plausible that higher ability to pay for health care would mean that a higher CER cut-off was appropriate in these countries.

Cost-effectiveness depends on a range of factors specific to each intervention, but certain common influences can be identified, such as the length of the transmission season, the price of key commodities (such as nets and drugs), behavioural factors (such as compliance with drug regimens and retreatment rates for nets), and the degree of drug or insecticide resistance.

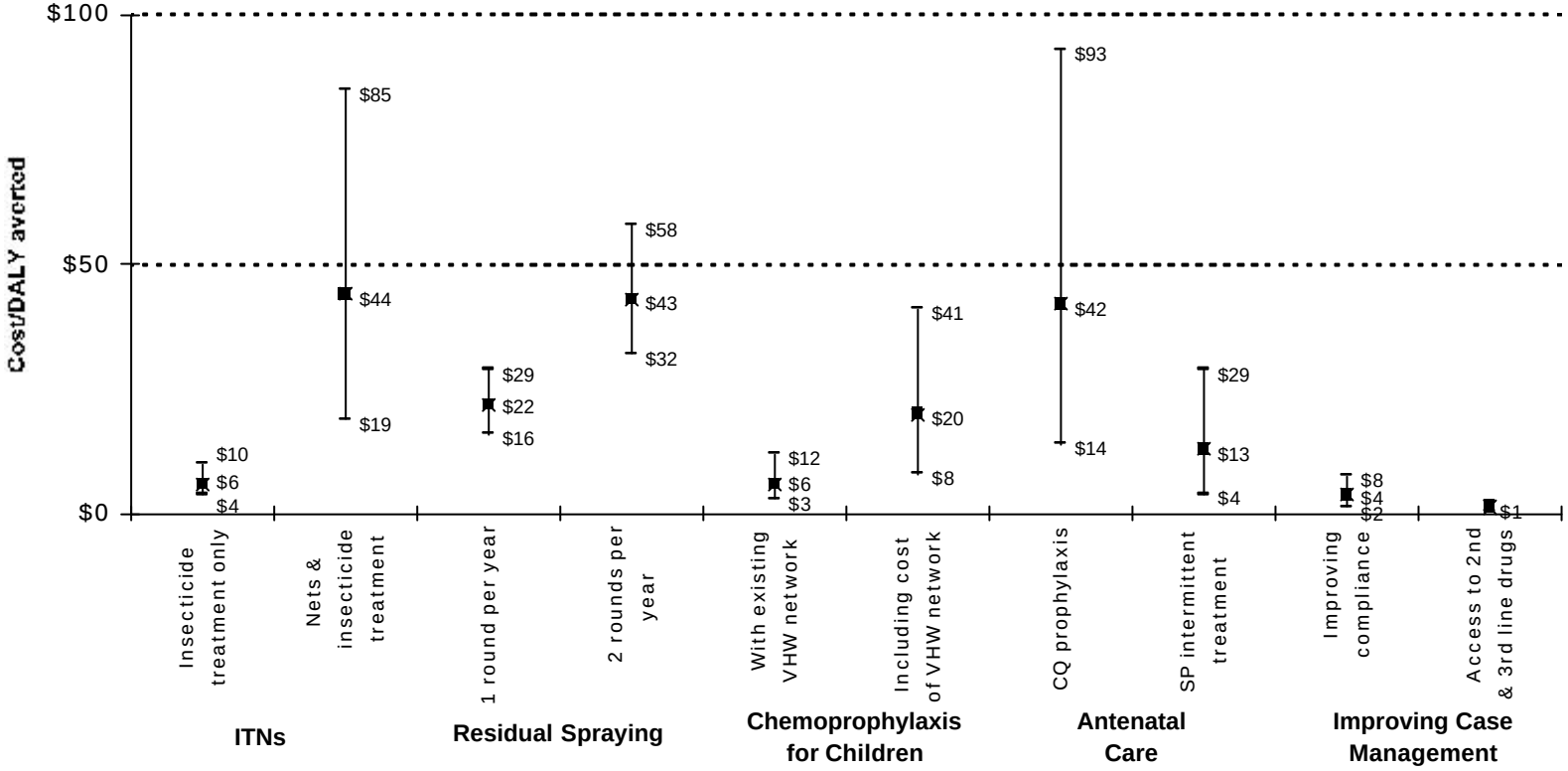
The level of existing infrastructure significantly affects incremental costs, and therefore cost-effectiveness, for ITNs, chemoprophylaxis for children, and prevention in pregnancy. This raises the crucial issue of a potential conflict between efficiency and equity. According to these results it would be more cost-effective to direct resources to areas where, for example, there is good antenatal care (ANC) coverage, a network of VHWs exists, or net utilization is already high. However, if resource allocation were based on this analysis, it would be likely that the better-off regions and households would benefit most. Those potentially excluded would be the poorer, more remote regions which are currently underserved, and households without nets, or with poor access to health services. It is therefore essential that information on the cost-effectiveness of interventions is always considered in conjunction with information on the characteristics of those benefiting. Where additional costs are required to reach those in greatest need, it is appropriate that benefits accruing to those groups be given greater weight.

Information on the total and per capita costs of packages of measures are summarised in Table 1. Depending on the choice of interventions, the cost per capita of malaria control packages was estimated to range between $0.03 and $2.06. If net usage is currently low, and no network of

VHWs already exists, high coverage with a package including effective prevention in childhood cannot be achieved for less than $0.81 per capita. In the face of many pressing priorities and limited resources, this is unlikely to be affordable to low income countries through locally generated funds alone. It is therefore likely that a prominent donor role in financing will be required.

Key knowledge gaps which severely hampered the estimation of cost-effectiveness were identified as the impact of a number of key interventions on health outcomes, costs of these interventions, and information on the development and impact of drug and insecticide resistance. The following recommendations are made for further research on the economics of malaria: analysis of the economic benefits of malaria control, disaggregated by region and population group; the collection of better information on the costs of interventions; operational research on the effectiveness, efficiency and equity of different delivery strategies; the development of a common cost-effectiveness methodology, which is broadly accepted and well disseminated; analysis of the actual and potential roles of the public and private sectors in malaria control; and empirical and methodological work on the adaptation of generalized cost-effectiveness estimates for use by country level policy-makers. The achievement of these recommendations on the scale needed will require considerable African capacity building in the fields of both economics and epidemiology.

Figure 1. Cost-effectiveness in a very low income country with high transmission: mean and 90% range for the cost/DALY averted (1995 US dollars)



Notes

ITNs: one treatment of deltamethrin a year, no insecticide resistance
Residual spraying: lambda-cyhalothrin, no insecticide resistance
Chemoprophylaxis for children: Maloprim®, perennial transmission, no resistance to Maloprim
Antenatal: primigravidae only, 50% CQ RII/RIII resistance, 10% SP RII/RIII resistance
Case management: gross costs, CQ as first line drug with 30% clinical failure

Table 1. Gross average annual cost implications of packages of malaria control measures in Tanzania (high transmission, very low income country) (1995 US dollars)

Package 1	
Antenatal intermittent treatment (primigravidae only, ANC	$0.2m
services exist)	$0.5m
Intervention to improve compliance	$0.3m
Improving the accessibility of 2nd and 3rd line drugs	
	$1.0m
Total cost	$0.03
Cost per capita	1%
Cost as percentage of existing health sector budget	
Package 2	
Net treatment (deltamethrin, one treatment per year)	$3.1m
Antenatal intermittent treatment (primigravidae only, ANC	$0.2m
services exist)	$0.5m
Intervention to improve compliance	$0.3m
Improving the accessibility of 2nd and 3rd line drugs	
	$4.1m
Total cost	$0.14
Cost per capita	4%
Cost as percentage of existing health sector budget	
Package 3	
Net distribution and treatment (deltamethrin, one treatment per	$22.7m
year)	$0.2m
Antenatal intermittent treatment (primigravidae only, ANC	$0.5m
services exist)	$0.3m
Intervention to improve compliance	
Improving the accessibility of 2nd and 3rd line drugs	$23.7m
	$0.81
Total cost	25%
Cost per capita	
Cost as percentage of existing health sector budget	
Package 4	
Residual spraying (lambda-cyhalothrin, 2 rounds a year)	$51.2m
Antenatal intermittent treatment (all pregnant women, ANC	$0.6m
services exist)	$0.5m
Intervention to improve compliance	$0.3m
Improving the accessibility of 2nd and 3rd line drugs	$7.6m
Confirmed diagnosis for every suspected case	
	$60.2m
Total cost	$2.06
Cost per capita	64%
Cost as percentage of existing health sector budget	

Source: Tables 3.12, 4.5 and 5.7

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Acronyms and abbreviations

ACR	Adequate clinical response rate
a.i.	Active ingredient
ANC	Antenatal care
AQ	Amodiaquine
ART	Artemisinin
CBA	Cost-benefit analysis
CEA	Cost-effectiveness analysis
CER	Cost-effectiveness ratio
CI	Confidence interval
CIF	Cost, insurance and freight
CQ	Chloroquine
CUA	Cost-utility analysis
DA	Death averted
DALY	Disability adjusted life year
DDP	Delivered duty paid
DHS	Demographic Health Survey
DYLG	Discounted year of life gained
EC	Emulsifiable concentrate
EPI	Expanded Programme on Immunization
FOB	Free on board
FTEs	Full time equivalent staff
GBD	Global Burden of Disease
GDP	Gross domestic product
GNP	Gross national product
HC	Health centre
IDA	Iron deficiency anaemia
IEC	Information, education and communication
IMCI	Integrated Management of Childhood Illness
IMR	Infant mortality rate
IP	Inpatient
ITN	Insecticide treated net
LBW	Low birth weight
LSHTM	London School of Hygiene and Tropical Medicine
MOH	Ministry of Health
NGO	Non-governmental organization
NIBP	National Impregnated Bednet Programme
NNMR	Neonatal mortality rate
NS	Neurological sequelae
OP	Outpatient
OTC	Over-the-counter
p.a.	Per annum
QN	Quinine
RBM	Roll Back Malaria
s.d.	Standard deviation
SP	Sulfadoxine-pyrimethamine
SSA	Sub-Saharan Africa
TBA	Traditional birth attendant

TWSA	Time without specific activity
VHW	Village health worker
WHO	World Health Organization
WHO/TDR	WHO Special Programme for Research and Training in Tropical Diseases
WP	Wettable powder
WTP	Willingness to pay
YLDs	Years of life lived with disability
YLLs	Years of life lost

Chapter 1 – Introduction

1.1 The opportunity to address malaria in Africa

In 1998, malaria was identified by the new Director General of WHO as a priority project, with the announcement of Roll Back Malaria (RBM). The overall aim is to reduce significantly the global malaria burden, with an initial emphasis on the high transmission areas of Africa[1, 2].

The new initiative has arisen out of a strong and growing political commitment to combat the disease, both in affected countries and the donor community. Strong political support has come from the Organization of African Unity and the G8 countries[3]. The World Bank and WHO African Region are planning a major Africa Malaria Initiative, which is expected to spearhead RBM[4]. The research community has established the Multilateral Initiative on Malaria, a global collaborative effort to enhance malaria research in Africa[5]. New alliances between the public and private sectors have been established, such as the Medicines for Malaria Venture, which aims to improve the availability of effective antimalarials in poor countries[6].

The opportunity now exists for a renewed attack on malaria in sub-Saharan Africa. The identification of the most appropriate approach urgently requires information on many aspects of the disease and its control, including the epidemiological and economic nature of the burden, and the cost-effectiveness, affordability, feasibility and acceptability of prevention and treatment interventions. The aim of this report is to analyse and synthesise available information on the cost-effectiveness of malaria control, and to review knowledge on the costs of malaria and the benefits of control. Whilst economic analysis is only one of many inputs into the decision-making process, it can provide policy makers with important information for identifying the interventions that represent the best value for money in Africa.

This chapter begins with a summary of the size and nature of the malaria burden of disease in SSA, followed by a review of previous work on the economic evaluation of control. The review documents the gaps and inadequacies in the literature, and identifies the need for comparable estimates of the main prevention and treatment interventions. The chapter concludes by explaining the selection of interventions evaluated in this report.

1.2 The burden of disease

In SSA, malaria is the single most important infectious disease in children, being responsible for the deaths of about 1 million children per year or 25% of all childhood deaths. The malaria health burden has an important morbidity as well as mortality component, with the severe forms of the disease being the main reasons for hospital admissions of young children in malaria endemic areas. Millions more children and adults suffer mild uncomplicated clinical malaria each year.

Although malaria has a wider global distribution, around 90% of the estimated 300 to 500 million new clinical cases of malaria per year occur in SSA. Malaria mortality and severe forms of the disease throughout SSA are almost exclusively due to *Plasmodium falciparum* infection, with *P.*

vivax relatively uncommon, especially in West Africa. The mild form of malaria presents as a febrile illness associated with other nonspecific signs and symptoms. The fever may be periodic and interspersed with afebrile intervals. No clinical syndrome is entirely specific for malaria and diagnosis tends to be confirmed by the presence of the parasite in the peripheral blood. However, in endemic countries there are asymptomatic carriers of the parasite and parasitological diagnosis does not, therefore, necessarily indicate that malaria is the cause of the presenting disease[7]. Malaria may also contribute to the severity of other childhood diseases and repeated infections can be a cause of chronic anaemia in children. The major complications of untreated *P. falciparum* malaria are cerebral malaria and severe anaemia. Cerebral malaria in children may be an important cause of neurological impairment in SSA[8].

Repeated exposure to malaria parasites gives rise to a protective immune response. The risk of developing severe malaria is almost exclusively confined to those who are not immune. In highly endemic areas this is limited to young children, and immigrants and travellers from non-endemic areas. In areas of low endemicity the whole population, including adults, may suffer from severe malaria. The relative frequency and epidemiological profile of the severe forms of malaria vary with transmission intensity. In areas of high perennial transmission the majority of severe malaria hospital admissions tend to be severe anaemia in very young children below the age of 3 years with relatively few cases of cerebral malaria. On moving to areas of lower transmission, cerebral malaria in later childhood (mean age of around 4 years) has been shown to be relatively more important than severe anaemia[9].

Pregnant women are more easily infected because the placenta is a preferential site for parasite development and possibly because natural immunity is depressed during pregnancy. *P. falciparum* malaria in pregnancy may lead to death, anaemia, hypoglycaemia and other complications in the mother as well as abortion, premature delivery and low birth weight. The risks are greatest for women during their first pregnancy[10].

Anopheles mosquitoes are the vector of malaria, with the most important species members of the *An. gambiae* complex (in particular *An. gambiae sensu stricto* and *An. arabiensis*), which are widely distributed throughout SSA. Ecological determinants of the relative abundance of the vector influence the pattern of malaria transmission seen in a given region.

The levels of malaria transmission intensity across much of SSA are generally accepted to exceed those from any other setting worldwide. However, the epidemiology of malaria across SSA is far from homogeneous, with variations from intense perennial transmission, to highly seasonal low transmission, to sporadic transmission in areas normally malaria-free. Across this range of transmission intensity, there are associated age-specific patterns of malaria-related morbidity and mortality.

Various classification systems have been used to describe malaria, none of which fully captures the epidemiological spectrum of the disease displayed in SSA. A simple but useful dichotomous system differentiates between stable (endemic) and unstable (epidemic) malaria. Stability is taken to imply transmission from year-to-year, albeit with the possibility of wide seasonal variations in transmission intensity and disease incidence. Depending on climatic conditions, seasonal transmission may vary from a few months to more than 6 months per year.

Malaria transmission in SSA tends to be characterized as intense, stable, perennial transmission of *P. falciparum*[11]. Under such intense transmission, individuals will experience their first infection in early childhood, and the highest rates of clinical disease and malaria mortality tend to be concentrated in children less than 5 years of age. With each subsequent exposure to malaria parasites, surviving children acquire an increasing degree of protective immunity, thereby decreasing the duration and severity of clinical malaria and lowering the risk of severe complications and death.

In parts of SSA, particularly highland areas, malaria transmission is unstable, meaning the disease occurs sporadically as an epidemic in areas generally free of the infection[12]. In such situations, all ages of the population may be at risk of clinical disease, as the degree of functional immunity tends to be limited in those adults exposed to the malaria parasites in previous epidemics.

It is important to understand the pattern of malaria transmission in order to assess the relative disease burden due to malaria, to allow for the appropriate design of control strategies and to predict the effectiveness of such interventions. The relationship between transmission intensity, control efforts and health outcomes is complex and not fully understood. Mathematical models of the transmission dynamics of malaria provide useful frameworks to allow the relative impact of different control strategies on transmission intensity to be assessed[13, 14]. However, a major shortcoming of these existing mathematical models is that human age-specific mortality is not an output. The current debate over the long-term implications for child mortality of reducing malaria transmission rates through the use of ITNs[15, 16] highlights the need to develop a robust theoretical framework linking transmission dynamics and malaria mortality rates.

1.3 Literature review of economic evaluations of malaria control in Africa

Studies to be reviewed were selected from on-line databases, and discussions with people working in the field identified additional, unpublished, literature. Table 1.1 provides a summary of economic evaluations that use African data[a]. Fifteen cost-effectiveness analyses (CEAs) and one cost-benefit analysis (CBA) were identified. Only two of the studies were based on evaluations of ongoing programmes. Six used data collected during trials, which were costed prospectively or retrospectively. The remaining eight involved the use of models, which combined estimates of costs and effects from different sources of literature and expert opinion.

This review summarizes available cost-effectiveness results for malaria prevention and treatment interventions, and identifies gaps in the literature. All costs were converted to 1995 US$ to facilitate comparison.

1.3.1 Malaria prevention

[a] Two studies presenting only a cost "per person protected" were not included, as this was not considered a measure of effectiveness[17, 18].

Twelve evaluations provided information on the cost-effectiveness of preventive interventions, covering ITNs, residual spraying, chemoprophylaxis for children, and chemoprophylaxis or intermittent treatment for pregnant women. In addition, two studies estimated the potential cost-effectiveness of a hypothetical vaccine.

Insecticide treated nets

Three CEAs were conducted during controlled trials, in the Gambia[19] (called here Gambia 1), Ghana[20], and Kenya[21]. Another Gambian study[22] evaluated the National Impregnated Bed Net Programme (Gambia 2). The Gambia 1 cost data were also used to estimate cost-effectiveness in two modelling studies[23, 24]. Permethrin was the insecticide used to treat nets in all the studies. The cost per death averted (DA) and the cost per discounted year of life gained (DYLG) are shown in Table 1.2, which summarizes all CEA results for currently available interventions that use comparable outcome measures. The Gambia 2 study reported a *net* cost-effectiveness ratio, which incorporated savings in treatment and prevention expenditure and reduced production loss. To maintain consistency with the other studies, these results are quoted as *gross* ratios, excluding these cost-savings.

The gross cost per DA was $219 in Gambia 1 and $665 in Gambia 2, much lower than the ratios of $2,112 found in Ghana and $2,958 in Kenya. The main reason for the lower ratios in the Gambian studies was that the cost of the nets themselves was not included. In The Gambia, net coverage in the communities prior to the trial was already high, so the intervention involved net treatment only. By contrast in Ghana and Kenya, initial net coverage was low and the intervention costs included the cost of the nets as well. In addition, the trials in Ghana and Kenya involved two rounds of treatment per annum (p.a.), whereas in the situation of seasonal transmission in the Gambia only one round was required.

The variation between the two Gambian studies was mainly due to the greater effectiveness found in Gambia 1. The first trial recorded a reduction in all cause mortality of 42% (children aged under 5 years)[25], which was much greater than the reduction of 25% achieved in Gambia 2 (children aged 1 to 9 years)[26]. Comparing the two trials that involved distribution of nets and two treatments per year, the Ghana trial was more cost-effective than the trial in Kenya. This was partly due to higher costs for staff and the sensitization and awareness campaign in Kenya. In addition, although the percentage reduction in child mortality was higher in Kenya than in Ghana (33% for children aged 1 to 4 years in Kenya[27], compared with 17% for children aged 6 to 59 months in Ghana[28]), underlying mortality rates were higher in Ghana. As a result, a given percentage reduction in mortality averted a much greater absolute number of deaths in Ghana[29].

Evans *et al* (1997[23]) used the Gambia 1 cost data to estimate the cost per DYLG of providing both nets and insecticide. They assumed a reduction in all cause mortality of 25% for children aged 0 to 4 years, and explored the impact on cost-effectiveness of changing various key factors. The model estimates fell between $10 and $118 per DYLG. The results demonstrated the importance of the number of nets distributed per child and compliance in affecting cost-effectiveness. Increasing the number of nets per child, from 0.5 to 3, raised the cost per DYLG almost sixfold, from $20 to $118. Reducing compliance from 100% to 50% led to a doubling in the cost-effectiveness ratio. Another modelling study, by Graves (1998[24]) of net treatment, used an estimated reduction in all

cause mortality of 35%, and the government costs from Gambia 1. A cost per child death averted of $829 was found (cost of nets not included).

All of these studies considered one particular method of delivering ITNs: a government programme established to purchase insecticide and organize net retreatment, and where necessary distribute nets, with no charges for users who provided only limited amounts of labour and resources such as water and detergent. No CEAs have been undertaken on other delivery modes, such as the use of social marketing, the involvement of the private sector, or the individual treatment of nets at home.

Chemoprophylaxis for children

The Gambia 1 ITN CEA[19] also evaluated the cost-effectiveness of adding prophylaxis to a net treatment programme. The researchers found that the addition of prophylaxis did not reduce mortality further, so the cost per DA increased from $219 with net treatment alone to $300 with the combined intervention. However, there was a marked incremental reduction in morbidity, reducing the cost per case averted from $33 to $23.

The Gambia 1 cost data were also used to estimate the cost-effectiveness of chemoprophylaxis alone[30]. Effectiveness data were taken from a controlled trial in rural Gambia[31], which evaluated the provision to children aged 3 to 59 months of fortnightly Maloprim, distributed by village health workers. The cost per child DA was $167, leading the authors to conclude that prophylaxis appeared to be more cost-effective than net treatment in the Gambia, although they acknowledged that maintaining compliance might require much more substantial investment in other settings. They also noted that wide-scale prophylaxis was not generally recommended due to the dangers of accelerated drug resistance and impaired natural immunity.

Residual spraying

Two estimates are available of the cost-effectiveness of residual spraying. Data from a trial conducted in Garki, Nigeria[32] were used by Barlow & Grobar to estimate a cost per case prevented of $342[33]. This result is difficult to interpret because the costs covered both research and implementation activities, and also appear to have included some costs of the accompanying drug administration and larviciding.

Walsh & Warren (1979[34]) provide the only estimate of the cost per DA of residual spraying. A simple model was used to calculate average estimates for a rural area of SSA with twice yearly DDT spraying. They assumed reductions in crude death rates of 40% and infant mortality rates of 50%, based on trials in the 1950s and 1960s, and derived a cost per adult death averted of $584, and a cost per infant death averted of $1,402. The cost data used in these estimates were based on a WHO report[35] and covered adult mosquito *and* larval control in a "small area of economic importance". It is not possible to isolate the costs of spraying alone, and it is not evident that the average costs for an area of economic importance such as an agricultural development project would be appropriate to a typical sub-Saharan rural area. It is also not clear how these cost estimates were derived, nor whether they included capital as well as recurrent costs.

Neither study can therefore be considered as an accurate estimate of the cost-effectiveness of spraying. Moreover, DDT is now rarely used for residual spraying, but no studies with health outcomes are available on the cost-effectiveness of using the newer pyrethroid insecticides.

Chemoprophylaxis in pregnancy

Three studies used data from Malawi to investigate the cost-effectiveness of chemo-prophylaxis or intermittent treatment provided to pregnant women during antenatal care visits[b].

Heymann *et al* (1990[37]) modelled the cost-effectiveness of CQ chemoprophylaxis, based on a protective efficacy of 23% in preventing parasitaemia and 36% compliance, giving an actual protective efficacy of 8%. This was combined with drug cost data to give a cost per case prevented of $15, which the authors concluded "is an unacceptably high cost in much of Africa". However, they noted that if prophylaxis were restricted to women in their first and second pregnancies, the drug cost per case prevented would be reduced to less than $6.

Schultz *et al* (1995[38]) used a decision-analysis model to assess the relative cost-effectiveness of three antenatal drug regimens in reducing low birth weight. Again only drug costs were included. They found a cost per low birth weight case prevented of $10 for a regimen of two treatment doses of SP, compared with $67 for a regimen of initial SP treatment followed by weekly CQ prophylaxis, and $123 for initial CQ treatment followed by weekly CQ. The results were extrapolated to give an estimate of the cost per DA, by assuming that infant mortality was 128/1000 for babies of adequate weight, and 257/1000 for low birth weight babies. This gave a cost of $81 per infant DA for the two doses of SP, $522 for the SP treatment and CQ prophylaxis regimen, and $951 for the CQ treatment and prophylaxis option[39]. The regimen of intermittent SP treatment was found to be more cost-effective because it was cheaper than the CQ regimens, compliance was assumed to be higher, and there was less drug resistance to SP. Univariate and multivariate sensitivity analyses were used to demonstrate that the relative cost-effectiveness of the three regimens was not changed by varying CQ efficacy, SP efficacy, or CQ compliance within reasonable ranges.

Helitzer-Allen *et al* (1993[40]) evaluated the impact on cost-effectiveness of methods to improve compliance with antenatal prophylaxis. They found a cost per compliant woman of $2.15 with the original practice, which fell to $1.64 following the introduction of a new health education message, and to $1.55 if coated (non-bitter tasting) CQ tablets were used. Only the cost of drugs and new health education were included in the costings.

All of these studies represent minimum estimates of the cost-effectiveness ratio because the costings were partial, covering drug costs only in the studies by Heymann *et al* and Schultz *et al*, and drug and health education costs in the study by Helitzer-Allen *et al*. Only the study by Schultz *et al* uses a measure of health outcome (deaths averted), which allows comparison with other malaria control strategies.

[b] Another study is forthcoming on the cost-effectiveness of intermittent treatment when HIV prevalence is high [36].

Potential malaria vaccines

Two analyses have modelled the potential cost-effectiveness of a malaria vaccine. Graves (1998[24]) assumed that a vaccine could be given in three doses before the age of 6 months through the Expanded Programme on Immunization (EPI) and remain effective up to the age of 5 years, and would reduce all cause mortality by an estimated 20%. Costs were based on the estimates for delivering hepatitis-B vaccine in The Gambia, assuming a price per malaria vaccine of $1.17. The estimated cost per DA was $294. A similar analysis was reported by WHO (1996[41]), which found that the cost per DYLG by a vaccine ranged between $0.36 and $41 in a high transmission area and between $5 and $621 in a low transmission area, depending on the duration of protection, the price per child, and whether the strategy could be delivered within the existing EPI schedule.

Other prevention interventions

No CEAs were found of other interventions such as untreated nets, other methods of personal protection, environmental management, or the control of epidemics.

1.3.2 Malaria treatment

One CEA and one CBA were identified on the case management of uncomplicated malaria. Sudre *et al* (1992[42]) used probability-based decision tree analysis to investigate the cost-effectiveness of three alternative drugs for the treatment of children at primary health care facilities in a hyper or holoendemic area of SSA. They considered CQ, amodiaquine (AQ) and SP, using case fatality rates derived from a Delphi survey of 19 malaria experts. In the absence of drug resistance, the drug cost per DA was $1.70 with SP, $1.47 with CQ and $2.35 with AQ. The cost per DA with CQ rose from $1.49 in the "low resistance" scenario to $2.56 in the "high resistance" scenario. The analysis showed that more deaths were prevented per dollar spent on SP than for CQ as long as the level of RIII CQ resistance was greater than 14%. The authors concluded that SP would be the drug of choice even in the "no resistance" scenario if the value of a death prevented was more than $2.66. (AQ was the least cost-effective drug in all scenarios examined.) Only the costs of the first line drugs were included, and the possibility of increased resistance to SP once it was adopted was not considered.

Schapira *et al* (1993[43]) used a mathematical model to incorporate the growth of drug resistance by assuming that once a drug is introduced on a wide scale, treatment failure increases exponentially at a rate of 11% per annum. Assuming that the first line drug would initially be CQ, they estimated when it would be appropriate to switch to SP, and from there to mefloquine and finally halofantrine, in order to minimize total costs over a 27-year period. Each death was valued at $843 to represent the loss in lifetime production. Their study was therefore structured as a CBA rather than as a CEA. They concluded that it would be appropriate to shift to SP after 5 years, when the proportion of treatment failures with CQ was 42%, and then to use SP and mefloquine for 10 years each, and halofantrine for two years. The model makes an important contribution in attempting to incorporate some dynamic aspects of the real world situation. However, it did not allow for the possibility that there is variation in the rate of growth of resistance to different drugs, and the model was constrained so that all four drugs had to be used in the 27-year period for at least 1 year in the specified sequence, and that SP and mefloquine had to be used for an equal length of time.

No CEAs with full costings were found on the case management of uncomplicated malaria, and no evaluations of the case management of severe malaria were identified. Data were also absent on all treatment outside the formal health care system.

1.3.3 Package of interventions

Only one study was identified that evaluated a package of interventions[c]. Hedman *et al* (1979[44]) reviewed a malaria control programme in a mining town in Liberia, which included residual spraying, larviciding, chemoprophylaxis for workers, and treatment. They calculated a cost per capita of $10.42. This was extrapolated to give a cost per case prevented of $19, based on the difference in parasitaemia rates between the town covered by the programme and the surrounding uncovered villages[45].

1.3.4 Comparing the cost-effectiveness of interventions

Only evaluations that have used comparable outcome measures can be directly compared. Studies for currently available interventions that quote a cost per death or per DYLG are shown in Table 1.2.

For several reasons it is difficult to draw conclusions on relative cost-effectiveness from these results, these include:

- the costings for some of the studies are partial, for example including only drug costs
- the methodology used varied between studies, e.g. in the choice of discount rate, or the treatment of costs to the community
- the majority of studies are concentrated in a couple of countries (Gambia and Malawi), and it is difficult to assess the generalizability of the conclusions to other epidemiological and economic conditions
- many of the studies are based on trial settings, which may not be a good indication of cost-effectiveness in operational situations
- for many interventions there are no data at all.

More studies are evidently needed that assess cost-effectiveness in programme situations for a variety of interventions. However, studies take time to undertake, but policy decisions on the allocation of resources to malaria control cannot be indefinitely delayed. It was therefore decided that a modelling exercise should be undertaken, to provide a range of comparable estimates for the cost-effectiveness of the main prevention and treatment interventions, drawing on all available SSA cost and effectiveness data. Details of the cost-effectiveness methodology used are provided in Chapter 2.

[c] A CBA of a "projected 8-year control programme" in Sudan is reported in Barlow and Grobar (1986)[33], which valued benefits as the present value of output gains due to reduction in disability. The study was excluded from the review because it was not possible to assess its quality, nor identify the interventions included in the planned control programme.

1.4 Choice of interventions for evaluation

Table 1.3 summarizes the availability of data on the costs and health outcomes of prevention and treatment interventions in SSA. The scarcity of data is immediately apparent. Relatively good health outcome data are available only for ITNs and prophylaxis/intermittent treatment in pregnancy, which are the only two interventions for which meta-analyses have been conducted. There are a few studies on the effectiveness of residual spraying and prophylaxis for children, but no data on the health impact of environmental management, or personal protection methods such as coils and sprays. Full cost data are relatively poor or non-existent for all prevention strategies except ITNs. In view of the lack of data, the analysis of the cost-effectiveness of preventive interventions was restricted to ITNs, residual spraying, and chemoprophylaxis for children (Chapter 3), and chemoprophylaxis/intermittent treatment for pregnant woman (Chapter 4).

The situation is even more problematic for interventions to improve case management. The few studies that do consider such strategies generally do not include health outcomes, and information on the cost side is also very poor. In order to address some of the key issues, a model was developed to translate changes in intermediate outcomes, such as compliance and drug efficacy, to final health outcomes. This model was used to analyse a sub-set of the interventions to improve the treatment of uncomplicated malaria, namely improving compliance, improving the availability of second and third line drugs, changing the first line drug for treatment, and the use of combination therapies (Chapter 5). In addition the net costs of introducing new diagnostic techniques was also assessed.

To complete the picture of the full report, Chapter 6 reviews the evidence on the economic cost of malaria and the benefits of control, and Chapter 7 outlines the policy implications of the analysis and highlights knowledge gaps and research priorities.

Table 1.1. Summary of economic evaluations of malaria control in SSA

Reference, area studied and study year	Intervention(s) evaluated	Study type	Outcome measure used
Aikins *et al*, 1998[22] The Gambia, 1991-2	Insecticide treatment of bednets	Programme evaluation	Child death averted Case averted DYLG
Barlow & Grobar, 1986[33], based on Molineaux *et al*, 1980[32], Nigeria, 1970-6	Residual spraying (accompanied by mass drug administration and limited larviciding)	Controlled trial and incurred costs	Case prevented
Binka *et al*, 1997[20] Ghana, 1993-1995	Provision and insecticide treatment of bednets	Controlled trial costed prospectively	Child death averted DYLG
Evans *et al*, 1997[23] Africa (Gambia cost data), 1996	Provision and insecticide treatment of bednets	Model using hypothetical cohort of newborns	DYLG
Graves, 1998[24], The Gambia, 1990	Insecticide treatment of bednets and hypothetical vaccine	Model using hypothetical cohort of newborns	Child death averted Case averted
Hedman *et al*, 1979[44] Liberia, 1976	Package of measures including residual spraying, larviciding, chemoprophylaxis and treatment	Programme evaluation	Per capita, extended to per case prevented in Mills, 1991[45]
Helitzer-Allen *et al*, 1993[40] Malawi, 1988	Improving compliance with antenatal chemoprophylaxis	Controlled trial costed retrospectively	Compliant woman
Heymann *et al*, 1990[37] Malawi, 1988	Antenatal chemoprophylaxis	Model using estimates of costs, efficacy and compliance	Case prevented
Picard *et al*, 1992[30] The Gambia, 1988	Chemoprophylaxis for children	Controlled trial costed retrospectively	Child death averted
Picard *et al*, 1993[19] The Gambia, 1989-90	Insecticide treatment of bednets with and without chemoprophylaxis	Controlled trial costed prospectively	Child death averted Case averted DYLG
Schapira *et al*, 1993[43], Africa, model covers 1993 - 2020	Changing the first line drug for the treatment of children	Model of health service costs and costs in terms of deaths	Deaths averted are valued in financial terms, outcome is level of CQ resistance when first line therapy should be changed
Schultz *et al*, 1995 & 1996[38] [39] Malawi, 1992 costs	Antenatal intermittent treatment and chemoprophylaxis	Model using decision tree analysis	Low birth weight prevented Infant death averted
Some, 1998,[21]	Provision and insecticide	Controlled trial costed	Child death averted

Reference, area studied and study year	Intervention(s) evaluated	Study type	Outcome measure used
Kenya, 1993-1994	treatment of bednets	prospectively	
Sudre *et al*, 1992[42] Africa, 1991	Drug treatment for children	Model using decision tree analysis	Case cured Child death averted

Table 1.1. Summary of economic evaluations of malaria control in SSA (cont.)

Reference, area studied and study year	Intervention(s) evaluated	Study type	Outcome measure used
Walsh & Warren, 1979[34], SSA, 1978	Residual spraying	Simple model using estimates of costs and effects	Adult death averted Infant death averted
WHO, 1996[41], Africa, 1996	Hypothetical vaccine	Model using hypothetical cohort of newborns	DYLG

Table 1.2. CEA results for currently available interventions using comparable outcome measures (1995 US dollars) (sensitivity analysis results in brackets)

Reference	Area studied and study year	Intervention(s) evaluated	Cost per child death averted (DA)	Cost per discounted year of life gained (DYLG)	Notes
Prevention in Childhood					
Picard *et al*, 1993[19]	The Gambia, 1989-90	Insecticide treatment of bednets	$219 ($167-$243)	$9 ($9-$14)	Sensitivity analysis for cost per DA based on reducing price of insecticide, and reducing effectiveness by 10%. Sensitivity analysis for cost per DYLG based on increasing discount rate on YLG to 6% and reducing effectiveness by 10%.
		Insecticide treatment of bednets and chemoprophylaxis	$300 ($246-$333)	$13 ($13-$20)	
Aikins *et al*, 1998[22]	The Gambia, 1991-2	Insecticide treatment of bednets	Net costs $494 ($326-$805)	Net costs $21 ($14-$35)	Sensitivity analysis for net cost ratios based on reducing price of insecticide, halving treatment costs, and reducing number of cases seeking treatment.
			Gross costs $665	Gross costs $27	Gross CEA results adapted from net CEA results excluding savings in other government and household costs (no sensitivity analysis available).
Binka,*et al*, 1997[20]	Ghana, 1993-1995	Provision and insecticide treatment of bednets	$2112 ($992-$2289)	$77 ($37-$84)	Sensitivity analysis based on increasing discount rate on costs to 10%, reducing number of treatments to one per year, reducing the insecticide cost by 50%, and reducing the number of nets distributed.
Some, 1998[21]	Kenya, 1993-1994	Provision and insecticide treatment of bednets	$2958 ($2838-$3120)	-	Sensitivity analysis based on varying discount rate on costs from 3% to 10%.
Evans *et al*, 1997[23]	Africa (Gambia cost data), 1996	Provision and insecticide treatment of bednets	-	$10-118	Quoted variation based on varying compliance from 50%-100%, age group protected from 0-4 years to 1-4 years, number of nets per child from 0.5 to 3, price of net from $9 to $33, life expectancy at birth from 50 to 84 years, and including 10 days for morbidity per episode.
Picard *et al*, 1992[30]	The Gambia, 1988	Chemoprophylaxis for children	$167	-	No sensitivity analysis.

Table 1.2. CEA results for currently available interventions using comparable outcome measures (1995 US dollars) (sensitivity analysis results in brackets) (cont.)

Reference	Area studied and study year	Intervention(s) evaluated	Cost per child death averted (DA)	Cost per discounted year of life gained (DYLG)	Notes
Prevention in Pregnancy					
Schultz *et al*, 1995[39]	Malawi, 1992 costs	Antenatal treatment and chemoprophylaxis:		-	Only drug costs were included. Sensitivity analysis based on varying ANC attendance, compliance with both drugs, SP cost, number of weeks of CQ prophylaxis, SP efficacy.
		2 SP treatments	$81 ($79-$352)		
		1 SP treatment, weekly CQ prophylaxis	$522 ($212-$812)		
		1 CQ treatment, weekly CQ prophylaxis	$950 ($317-$951)		
Treatment					
Sudre *et al*, 1992[42]	Africa, 1991	Drug treatment for children:		-	Only drug costs were included. Sensitivity analysis based on varying probability of lethal and minor side-effects, probability of malaria infection, case fatality rate and compliance. No resistance scenario: No resistance to any drugs Low resistance scenario: CQ - RI 23%, RII 4%, RIII 0% AQ - RI 3% SP - no resistance High resistance scenario: CQ - RI & RII 57%, RIII 34% AQ - RI & RII 60%, RIII 7%
		CQ			
		No resistance scenario	$1.47 ($0.21-$3.36)		
		Low resistance scenario	$1.49 ($0.22-$3.36)		
		High resistance scenario	$2.56 ($0.31-$4.34)		
		AQ			
		No and low resistance scenarios	$2.35 ($0.34-$5.40)		
		High resistance scenario	$2.89 ($0.40-$5.67)		

Reference	Area studied and study year	Intervention(s) evaluated	Cost per child death averted (DA)	Cost per discounted year of life gained (DYLG)	Notes
					SP - no resistance
		SP	$1.70		
		All resistance scenarios	($0.25-$3.92)		

Table 1.3. Summary of available data on the cost and effects of malaria interventions in SSA

Intervention	Effectiveness data on health outcomes	Cost data
ITNs	***	***
Residual spraying	**	*
Chemoprophylaxis for children	*	*
Chemoprophylaxis or intermittent treatment in pregnancy	**	*
Environmental management	-	-
Personal protection	-	*
Control of epidemics	-	-
Change in the drug used for first line treatment	*	*
Strategies to increase compliance with therapy	-	*
Improvements in drug availability	-	-
Improvements in diagnosis	-	*
Improvements in drug quality	-	-
Introduction of treatment algorithms	-	-
Training of health care staff	-	-
The use of combination drug therapies	-	-
Improvements in referral practices	-	-
Improvements in the treatment of severe malaria	*	-

Key:
– nothing
* very limited (one or two studies)
** fair (several studies)
*** good (several studies from a variety of settings)

References

1. WHO. *Roll Back Malaria: A global partnership*. Geneva: WHO, 1998.
2. Nabarro DN, Tayler EM. The "Roll Back Malaria" Campaign. *Science* 1998; 280: 2067-2068.
3. Organisation of African Unity. Harare declaration on malaria prevention and control in the context of African economic recovery and development. Harare, Zimbabwe: Thirty-third Ordinary Session, 1997.
4. WHO/AFRO. *African initiative for malaria control in the 21st Century (draft)*. 1998.
5. WHO. Multilateral perspective on malaria begins to take shape. *TDR news* 1998; 55: 1&12.
6. Butler D. Malaria research deal seeks to make up for industry's retreat. *Nature* 1998; 395.
7. Greenwood BM, Bradley AK, Greenwood AM, et al. Mortality and morbidity from malaria among children in a rural area of The Gambia, West Africa. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1987; 81(3): 478-86.
8. Brewster DR, Kwiatkowski D, White NJ. Neurological sequelae of cerebral malaria in children. *Lancet* 1990; 336(8722): 1039-43.
9. Snow RW, Bastos de Azevedo I, Lowe BS, et al. Severe childhood malaria in two areas of markedly different falciparum transmission in East Africa. *Acta Tropica* 1994; 57(4): 289-300.
10. Steketee RW, Wirima JJ, Slutsker L, Heymann DL, Breman JG. The problem of malaria and malaria control in pregnancy in sub-Saharan Africa. *American Journal of Tropical Medicine and Hygiene* 1996; 55(1 Suppl): 2-7.
11. Alles HK, Mendis KN, Carter R. Malaria mortality rates in South Asia and in Africa: implications for malaria control. *Parasitology Today* 1998; 14: 369-375.
12. Some ES. Effects and control of highland malaria epidemic in Uasin Gishu district, Kenya. *East African Medical Journal* 1994; 71(1): 2-8.
13. Macdonald G. *The epidemiology and control of malaria*. Oxford: Oxford University Press, 1957.
14. Anderson RM, May RM. *Infectious diseases of humans. Dynamics and control. pp 392-422*. Oxford: Oxford University Press, 1992.
15. Snow RW, Omumbo JA, Lowe B, et al. Relation between severe malaria morbidity in children and level of Plasmodium falciparum transmission in Africa. *Lancet* 1997; 349(9066): 1650-4.
16. Coleman PG, Goodman CA, Mills A. Rebound mortality and the cost-effectiveness of malaria control: potential impact of increased mortality in late childhood following the introduction of insecticide treated nets. *Tropical Medicine and International Health*, 1999; 4: 175-86.
17. Nevill CG, Watkins WM, Carter JY, Munafu CG. Comparison of mosquito nets, proguanil hydrochloride, and placebo to prevent malaria. *British Medical Journal* 1988; 297(6645): 401-3.
18. El Gaddal AA, Haridi AAM, Hassan FT, Hussein H. Malaria control in the Gezira-Managil Irrigated Scheme of the Sudan. *Journal of Tropical Medicine and Hygiene* 1985; 88: 153-159.
19. Picard J, Aikins M, Alonso PL, Armstrong Schellenberg JR, Greenwood BM, Mills A. A malaria control trial using insecticide-treated bed nets and targeted chemoprophylaxis in a rural area of The Gambia, West Africa. 8. Cost-effectiveness of bed net impregnation alone or combined with chemoprophylaxis in preventing mortality and morbidity from malaria in Gambian children. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1993; 2: 53-7.
20. Binka FN, Mensah OA, Mills A. The cost-effectiveness of permethrin impregnated bednets in preventing child mortality in Kassena-Nankana district of Northern Ghana. *Health Policy* 1997; 41: 229-239.
21. Some ES. *Optimizing the community effectiveness of insecticide-impregnated bednets used for malaria control in coastal Kenya: Implications of perceptions, programme organization, compliance, and costs.* PhD Thesis, Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, University of London, 1999.
22. Aikins MK, Fox-Rushby J, D'Allessandro U, et al. The Gambian National Impregnated Bednet Programme: Consequences and net cost-effectiveness. *Social Science and Medicine* 1998; 46(2): 181-191.
23. Evans DB, Azene G, Kirigia J. Should governments subsidize the use of insecticide-impregnated mosquito nets in Africa? Implications of a cost-effectiveness analysis. *Health Policy and Planning* 1997; 12(2): 107-114.
24. Graves PM. Comparison of the cost-effectiveness of vaccines and insecticide impregnation of mosquito nets for the prevention of malaria. *Annals of Tropical Medicine and Parasitology* 1998; 92(4): 399-410.
25. Alonso PL, Lindsay SW, Armstrong JR, et al. The effect of insecticide-treated bed nets on mortality of Gambian children. *Lancet* 1991; 337(8756): 1499-502.
26. D'Alessandro U, Olaleye BO, McGuire W, et al. Mortality and morbidity from malaria in Gambian children after introduction of an impregnated bednet programme. *Lancet* 1995; 345(8948): 479-83.

27. Nevill CG, Some ES, Mung'ala VO, et al. Insecticide-treated bednets reduce mortality and severe morbidity from malaria among children on the Kenyan coast. *Tropical Medicine and International Health* 1996; 1(2): 139-46.
28. Binka FN, Kubaje A, Adjuik M, et al. Impact of permethrin impregnated bednets on child mortality in Kassena-Nankana district, Ghana: a randomized controlled trial. *Tropical Medicine and International Health* 1996; 1(2): 147-54.
29. Mills A. Operational research on the economics of insecticide-treated mosquito nets: lessons of experience. *Annals of Tropical Medicine and Parasitology* 1998; 92(4): 435-447.
30. Picard J, Mills A, Greenwood B. The cost-effectiveness of chemoprophylaxis with Maloprim Gambian children aged less than five years old. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1992; 86(6): 580-1.
31. Menon A, Snow RW, Byass P, Greenwood BM, Hayes RJ, N'Jie ABH. Sustained protection against mortality and morbidity from malaria in rural Gambian children by chemoprophylaxis given by village health workers. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1990; 84(6): 768-72.
32. Molineaux L, Gramiccia G. *The Garki Project: Research on the epidemiology and control of malaria in the Sudan Savanna of West Africa*. Geneva: WHO, 1980.
33. Barlow R, Grobar LM. *Cost and benefits of controlling parasitic diseases*. Population, Health and Nutrition Department, World Bank, 1986.
34. Walsh JA, Warren KS. Selective primary health care: an interim strategy for disease control in developing countries. *New England Journal of Medicine* 1979; 301(18): 967-74.
35. WHO. WHO Expert Committee on Malaria: sixteenth report. *World Health Organization Technical Report Series* 1974; 549: 1-89.
36. Wolfe EB, Steketee RW, Haddix AC, Parise ME. Cost-effectiveness of sulfadoxine-pyrimethamine for the prevention of low birth weight associated with placental malaria. Emory University and CDC, forthcoming:
37. Heymann DL, Steketee RW, Wirima JJ, McFarland DA, Khoromana CO, Campbell CC. Antenatal chloroquine chemoprophylaxis in Malawi: chloroquine resistance, compliance, protective efficacy and cost. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1990; 84(4): 496-8.
38. Schultz LJ, Steketee RW, Chitsulo L, Wirima JJ. Antimalarials during pregnancy: a cost-effectiveness analysis. *Bulletin of The World Health Organization* 1995; 73(2): 207-14.
39. Schultz LJ, Steketee RW, Chitsulo L, Macheso A, Kazembe P, Wirima JJ. Evaluation of maternal practices, efficacy, and cost-effectiveness of alternative antimalarial regimens for use in pregnancy: chloroquine and sulfadoxine-pyrimethamine. *American Journal of Tropical Medicine and Hygiene* 1996; 55(1 Suppl): 87-94.
40. Helitzer-Allen DL, McFarland DA, Wirima JJ, Macheso AP. Malaria chemoprophylaxis compliance in pregnant women: a cost-effectiveness analysis of alternative interventions. *Social Science and Medicine* 1993; 36(4): 403-7.
41. WHO. *Investing in Health Research and Development: Report of the Ad Hoc Committee on Health Research Relating to Future Intervention Options.* Geneva: TDR/Gen/96.1, 1996.
42. Sudre P, Breman JG, McFarland D, Koplan JP. Treatment of chloroquine-resistant malaria in African children: a cost-effectiveness analysis. *International Journal of Epidemiology* 1992; 21(1): 146-54.
43. Schapira A, Beales PF, Halloran ME. Malaria - Living With Drug-Resistance. *Parasitology Today* 1993; 9(5): 168-174.
44. Hedman P, Brohult J, Forslund J, Sirleaf V, Bengtsson E. A pocket of controlled malaria in a holoendemic region of West Africa. *Annals of Tropical Medicine and Parasitology* 1979; 73(4): 317-25.
45. Mills A. The economics of malaria control. In: Targett G, ed. *Waiting for the Vaccine*. Chichester: Wiley & Sons, 1991: 333-47.

Chapter 2 – Methods of Analysis

2.1 Economic evaluation

Economic evaluation requires a comparison of the costs and benefits of different interventions. Different types of economic evaluation can be categorized by their treatment of benefits[1]. In cost-effectiveness analysis (CEA), benefits are described as units of health outcome, such as cases prevented or deaths averted[a]. In cost-benefit analysis (CBA), benefits are expressed in financial terms, usually using either the human capital or the willingness-to-pay approach. Due to the significant theoretical and practical problems with both of these approaches for valuing health outcomes[2], in practice CBA is rarely used to assess health care interventions. This study has used CEA to derive ranges for the cost per DALY averted by malaria control interventions.

2.2 Use of models

A modelling approach was used to synthesize data from a wide range of sources on the costs and effects of each intervention. Through the use of a standardized methodology it was possible to compare the cost-effectiveness of different interventions, and to generalize results from country-specific studies to predict cost-effectiveness in other economic and epidemiological settings, and in operational, rather than trial, situations. In addition, cost-effectiveness could be predicted over time, for example, as resistance to antimalarial drugs or insecticides increases.

Concerns have been raised about the use of models in economic evaluation, especially where the degree of analyst discretion is high[3]. Whilst results are dependent on both the model design and the accuracy of the input estimates, models perform a useful role when empirical evidence is limited and uncertainty is high, but policy decisions are required. The models aimed to capture the key variables and relationships affecting cost-effectiveness, rather than describing all the details of a particular situation. Moreover the desire to make the models as realistic as possible had to be balanced by the need to ensure that the results remained comprehensible to the policy-makers for whom they were intended[4].

2.3 Stratification

Rather than estimating cost-effectiveness for a limited sample of specific countries, the analysis provides general results for SSA, stratified by epidemiological and economic zones where feasible and appropriate.

Information is available that broadly stratifies SSA by type of malaria transmission, but data are lacking on the effectiveness of interventions in different epidemiological zones. Trials of preventive

[a] When outcomes are quantified using measures such as the DALY that incorporate weightings for disability and morbidity states, the term cost-utility analysis (CUA) is sometimes applied.

interventions, such as ITNs and residual spraying, tend to be conducted only in areas of high and moderate transmission, and meta-analyses of results combine studies conducted under both perennial and seasonal conditions[5, 6]. Prediction of effectiveness in areas with lower transmission, different lengths of transmission season or epidemic malaria is far from straightforward. The relationship between malaria transmission, mortality and intervention efficacy is complex and not well understood, due to the lower levels of acquired immunity in populations experiencing lower transmission. All effectiveness results for preventive interventions were therefore reported only for the broad category of moderate to high transmission. For the analysis of interventions to improve case management, it was possible to use different parameters for high and low transmission, reflecting differences in the age distribution of presenting cases, the positive predictive value of clinical diagnosis, and the probability of developing severe malaria. The results for treatment interventions were therefore presented for the two broad strata of low and high transmission.

Although effectiveness estimates could not be adjusted for length of transmission season, annual cost estimates were adjusted, for example, for the number of spraying rounds or months of prophylaxis required per year. Two alternatives were taken: perennial transmission (12 months) and seasonal transmission (6 months).

Cost estimates were also stratified on the basis of country income level, which is expected to influence the cost of non-traded inputs such as salaries. Three economic strata were identified on the basis of per capita GNP (Table 2.1): very low income (under $315); middle income (between $315 and $1,000); and higher income (above $1,000). By far the majority of SSA countries have a per capita GNP of less than $1,000. A cut-off of $315 was used to divide these countries roughly equally into the very low and middle income strata. Those in the higher income category are mainly southern African or island states, not typical of SSA, and were therefore categorized as a separate stratum. The population for the higher income stratum was modelled using a life table with a higher life expectancy at birth to reflect the anticipated difference in age-specific mortality rates (see below).

2.4 Calculation of effectiveness

Estimates of reductions in morbidity and mortality were used to calculate the effectiveness of each intervention in terms of DALYs averted, following the methods used in the Global Burden of Disease (GBD)[7]. The DALY is a measure of health outcome that incorporates both premature death and morbidity/disability. The DALYs caused by a given disease consist of the years of life lost (YLLs) and the years of life lived with disability (YLDs). Deaths averted are converted to YLLs using the age-specific life expectancies from the appropriate life tables. A West African life table with a life expectancy at birth of 50 years was used for very low and middle income countries, and a General Pattern life table with a life expectancy at birth of 65 was used for higher income countries[8]. It could be argued to be inequitable to use a lower life expectancy in poorer countries, as this implies that fewer years of life will be gained for each death averted in those countries. However, it was considered that the estimates would mainly be used to compare interventions within a given country context, where a local life expectancy would be more relevant[9]. These estimates should not be used for comparing investment in a given intervention between countries at different stages of economic development. Although any reduction in mortality rates would lead to revised life

expectancies in the intervention population, all YLLs were calculated using the initial life expectancies in order to give the same valuation to a death at a given age both with and without the intervention.

YLDs were calculated based on the duration of disability/morbidity, and disability weights given to each condition. The weights ranged between 0 and 1, with 0 representing full health and 1 representing death. The weights for each malaria-related condition were taken from the GBD study[7], and were derived using the person trade-off method at an international meeting held in Geneva in 1995. Malaria episodes had a weight of 0.211 with an average duration of 0.01 years, and neurological sequelae were given a weighting of 0.473 if untreated and 0.436 if treated (assuming that 5% of cases were treated), with the average duration of both being 35.4 years. Anaemia was given a disability weighting of 0.012 (with no duration specified as anaemia was defined in terms of prevalence rather than incidence).

The YLLs and YLDs averted by an intervention were summed to give the DALYs averted. DALYs were discounted at a rate of 3%, to account for time preference and the risk premium. The discounting of health benefits, which gives a lower weight to health benefits that occur further into the future, has been criticized as inequitable[10] and has attracted considerable controversy and debate. Those readers concerned about discounting should note that effectiveness is assumed to occur only in the year of the intervention, so discounting has an impact only on the number of YLLs per death averted. As all the interventions are mainly concerned with reducing mortality in children under 5 years of age, discounting has very little impact on the relative cost-effectiveness of the interventions. Age weighting of DALYs was not incorporated, because no consensus on the use of age weights has yet emerged, and the impact of the age weighting function used in the GBD has been shown to be counter-intuitive[9, 11]. The inclusion of age weights would have little impact on the relative cost-effectiveness of malaria control interventions, as it would affect all interventions more or less equally.

Using a generic measure such as the DALY, rather than intermediate measures of benefits such as cases prevented or cases cured, allows for comparison of preventive and treatment interventions. Moreover, as DALYs incorporate both mortality and morbidity/disability, it is possible to make comparisons with other interventions that improve the quality of life, as well as with those that save lives. Whilst several limitations of DALYs have been identified in recent critiques (e.g. Anand & Hanson 1997, Evans & Hurley 1995, Ugalde & Jackson 1995, Barker & Green 1996, Paalman *et al.* 1998[2, 9, 10, 12, 13]), they do have several important advantages in this type of analysis, and their use facilitates comparison with the results of other recent cost-effectiveness studies in developing countries (see, for example, Jamison *et al.* 1993[14]).

Estimates for the effectiveness of interventions were drawn from the literature, and based on results from randomized controlled trials and meta-analyses where possible. They are thus much closer to efficacy than effectiveness, since results from trial situations reflect adequate resourcing and close monitoring, and are unlikely to be achievable in an operational setting[15]. It was therefore necessary to adjust trial efficacy data by behavioural variables such as compliance, or retreatment rates for ITNs, to get an estimate of operational effectiveness. A linear relationship was assumed between compliance and effectiveness, such that zero compliance resulted in zero effectiveness, and the level of compliance achieved in the trial resulted in the trial reductions in mortality and morbidity (solid line in Figure 2.1). The trial effectiveness results were then multiplied by the ratio of estimated

operational compliance to trial compliance to calculate effectiveness under a programme situation, i.e.

$$\text{Operational effectiveness} = \text{Trial effectiveness} \times \frac{\text{Operational compliance}}{\text{Trial compliance}}$$

It is possible that the relationship between compliance and effectiveness is not linear (see dotted lines in Figure 2.1): for example, some threshold coverage level may be needed before significant effects occur. In the absence of suitable data this possibility could not be allowed for.

2.5 Calculation of costs

The cost of each intervention was calculated using the ingredients approach, which involved building up an estimate of cost by considering the quantity and value of each resource used[16]. Capital costs were annualized using a discount rate of 3%, and estimates of useful life from the literature. Estimates for cost inputs were obtained through reviews of published and unpublished literature, programme budgets, price catalogues, and consultation with experts working in research and programme implementation. All costs were converted to 1995 US dollars, using the US dollar period average market exchange rate in the study year, and the US Consumer Price Index[17, 18].

The costing perspective included costs to both the provider and the community where appropriate. Incremental out-of pocket expenses for households were included. The indirect costs of the time taken by patients to seek care, and the lost productivity due to morbidity, were not included due to the major valuation and measurement problems involved. However, estimates were made of the market value of volunteer worker time, based on the estimated value of local labour, as in certain circumstances it could be necessary for the provider to pay for these resources. Where non-compliance would have reduced costs, such as failure to re-treat a mosquito net, the estimates were adjusted to take this into account.

The majority of inputs are traded internationally (e.g. drugs, insecticide) and therefore one price was used for all SSA countries. Costs for drugs commonly used in SSA were obtained from the International Drug Price Indicator Guide 1996[19], which provides data on the average, minimum and maximum price from a number of vendors who supply the public sector in developing countries. Transport, insurance and delivery were assumed to add an additional 25% to the drug price, and 25% of drugs were assumed to be wasted. Labour costs were assumed to vary by the per capita income level of each economic strata. Valuing staff time is complex, as it involves assumptions about both the type of staff involved and the full salary rates for these workers, both of which vary greatly across Africa, making generalization difficult. In addition, data on salary levels are extremely scarce. Estimates of costs of full time equivalent staff (FTEs) for several health service levels for Safe Motherhood interventions[20] were extrapolated to provide estimates for the three economic strata. These estimates covered the average annual salary cost, scaled up to include extra benefits and allowances, and averaged to reflect differences in both the level of salaries and composition of staff at each health service level. Estimates for health centre, hospital and programme management staff are shown in Table 2.2.

Incremental versus average costs

It is standard practice in economic evaluation to calculate the costs of adding the intervention to the existing infrastructure, conventionally termed incremental costs, since this is the analysis relevant to local decision makers[16]. With generalized estimates such as those presented here, incremental costings can be difficult to interpret: they are measured from a given starting point of existing infrastructure, but the current level of community, health service and general infrastructure (such as roads), varies between countries, so their incremental costs will differ. It is not possible to capture all possible variations, but where the costs of interventions vary substantially, depending on the existing infrastructure, cost-effectiveness was calculated for more than one starting point. The provision of chemoprophylaxis in pregnancy was considered first, including only incremental costs, and secondly including a share of antenatal care overheads. The cost-effectiveness of ITNs was considered in situations of both high and low initial net coverage, and the provision of chemoprophylaxis for children was considered both with and without an initial network of village health workers.

Gross costs versus net costs

Malaria control leads to savings in expenditure on prevention and treatment. In some cost-effectiveness analyses, these cost-offsets are subtracted from the gross cost of the intervention to give a net cost. The calculation of these cost-offsets is complex. Savings in prevention expenditure will depend on the original rationale for using the preventive method, and whether the new intervention eliminates this need. Moreover, the level of initial expenditure is likely to vary considerably, depending on income levels and cultural factors. Savings in treatment expenditure will depend on the proportion of fever cases treated, the proportion of fever cases actually caused by malaria, the quality and type of care provided, and the proportion of costs that are variable,[b] and will therefore be saved if utilization falls. Due to these uncertainties in estimating cost-offsets, only gross costs were considered for the preventive interventions. The model developed to analyse interventions to improve case management allowed the net impact of an intervention on the overall cost of the care-seeking episode to be estimated. For the case management interventions, cost-effectiveness was therefore calculated using both gross and net costs.

Scale

Average costs may vary with the scale of the project or programme. For example, if large initial capital investment is required, one might expect falling average costs as the programme expands, a phenomenon termed economies of scale. For the malaria control interventions considered, the majority of costs are variable and significant economies of scale are unlikely. It was therefore concluded that any variations due to scale would be captured in the ranges used for the cost input variables. There may be some exceptions: at very small scales, the costs of supervision and management could be relatively large, increasing the average cost; and at very high coverage rates, the costs of reaching the last few members of the target population could be extremely high, also increasing average costs.

2.6 Handling uncertainty

[b] Variable costs are those that vary in relation to the level of activity, as opposed to fixed costs, which remain the same.

There is considerable uncertainty over the values of many of the key cost and effectiveness variables, because true parameter values are not known and there is a high degree of regional variation. This type of uncertainty is commonly handled by using point estimates for each input variable, and then conducting a sensitivity analysis by varying these estimates to test the robustness of the conclusions of the analysis. This can take the form of a one-way sensitivity analysis, where one variable is varied at a time; multi-way sensitivity analysis, where several variables are varied together; or a max-min analysis, where all variables are given their extreme "optimistic" and "pessimistic" values to elicit a best and worst case scenario. One, two or three-way sensitivity analysis tends to underestimate variation in cost-effectiveness; varying a larger number of inputs becomes unwieldy and difficult to interpret; and max-min analysis gives unlikely extreme outcomes[21, 22]. Moreover, these methods do not provide any information on where the ratio is most likely to fall within the range provided.

To address these problems, probabilistic sensitivity analysis was used. This allows for multivariate uncertainty by assigning ranges rather than point estimates to model input variables[21-23]. The cost and effectiveness input variables were assumed to follow uniform, triangular or normal continuous probability distributions (Figure 2.2). If range information only was known for a variable, a uniform distribution was assigned along the range, to incorporate the maximum uncertainty in the true value. If available data showed a peaked distribution, a triangular distribution was used. Where data on the mean value and confidence intervals were available, for example from clinical trials, this information was used to construct a normal distribution.

The cost-effectiveness ratios (CERs) were estimated using a Monte Carlo simulation, in which input variables on both the cost and effectiveness side were varied within the ranges described. At each iteration, parameter values for each input variable were chosen at random from the defined probability distributions. The cost per person, DALYs averted per person and the CER were recorded as the outputs for each of the iterations, and the output variables were collated as probability distributions. The mean and range within which 90% of estimates fell were calculated (see Figure 2.3), and this was represented in summary form, as shown in Figure 2.4.

The simulations were run until all the output variables had reached convergence (defined as a percentage change in the output mean, standard deviation and percentiles of less than 1.5% after each 100 iterations[c]). The simulation assumed that all input parameters varied independently of each other, unless they were explicitly linked in the model.

This method of analysis cannot be compared with rigorous hypothesis testing. However, the representation of results as ranges rather than point estimates incorporated the variability and uncertainty surrounding many of the input variables, and allowed for relatively robust conclusions to be drawn from uncertain data inputs, even with large and complicated models[22].

2.6.1 Analysis of correlation between input and output variables

[c] In the case management model, the inclusion of cost-offsets meant that the net cost of the intervention was negative in certain circumstances, causing a discontinuity in the distribution of the CER. This meant that convergence for the ratio would not be achieved, so these simulations were run for a set number of 3,000 iterations.

The sensitivity of the CER to the values of the input variables was examined by calculating Spearman rank order correlation coefficients between each input variable and the output variable from the simulation results. The correlation coefficients indicated which input variables were most important in explaining the variation in the reported CERs, and whether the inputs were positively or negatively correlated with the CER.

2.7 Evaluation of cost-effectiveness results

The evaluation of CERs rests on a comparison with the cost-effectiveness of alternative uses of resources, which will depend on the specific context. However, a broad guide to which interventions count as "cost-effective" in low income countries[d] was provided by the Ad Hoc Committee on Health Research Relating to Future Intervention Options. They argued that anything costing less than $25 per DALY averted should be considered as "highly attractive", and that anything costing less than $150 per DALY averted should be considered "attractive"[24]. These guidelines were used to evaluate the CER results. It was assumed that if at least 95% of the iterations had a CER below a given threshold, one could be reasonably certain that the CER fell below this level. It should be noted that these thresholds are not appropriate in all situations. In particular in higher income countries, higher cut-offs may be appropriate since the ability to pay for health care interventions is higher.

Cost-effectiveness analysis can be used to identify interventions that represent good value for money per unit of output. However, highly cost-effective interventions can be extremely costly in financial terms. In order to shed further light on the policy implications of the cost-effectiveness analysis, the total and per capita costs of each intervention were estimated in the context of a very low income country, using data from Tanzania. To give an indication of affordability to government, the total cost of each intervention was expressed as a percentage of the current public sector health budget (including donor contributions).

[d] In this definition "low income" refers to countries with a per capita GNP of less than $765 in 1995.

Figure 2.1. Relationship between compliance and effectiveness, showing assumed linear relationship (——) and other possible relationships (- - - - -)

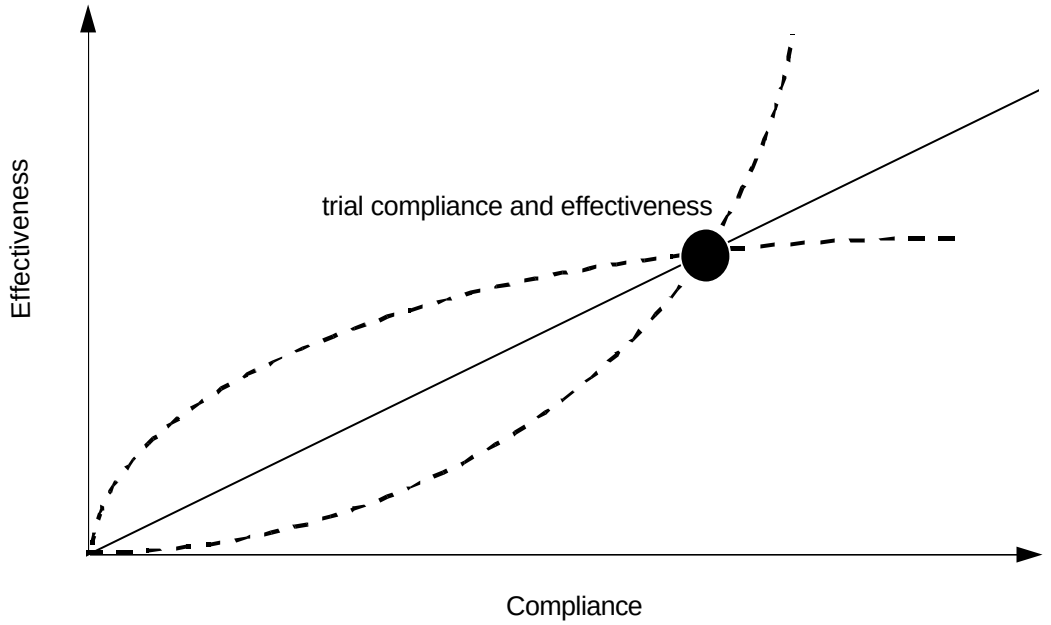


Figure 2.2. Probability distributions used for input variables in the Monte Carlo simulation

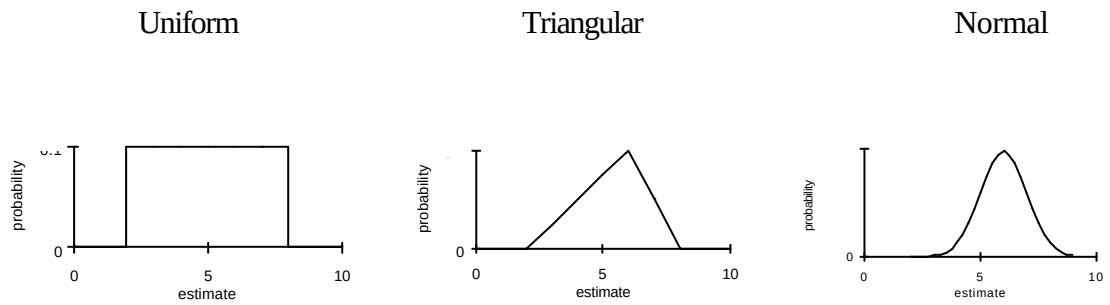


Figure 2.3. Probability distribution for CER from the Monte Carlo simulation

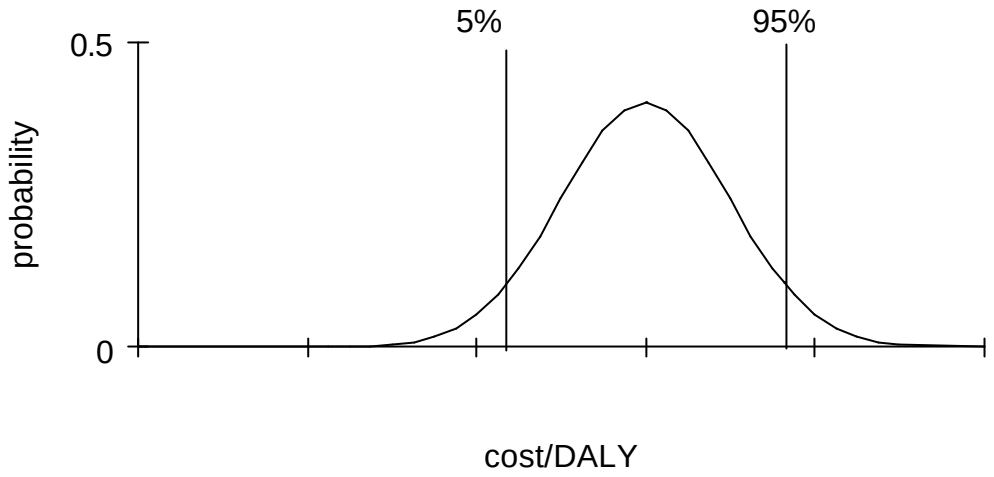


Figure 2.4. Summary presentation of mean and 90% range for CER

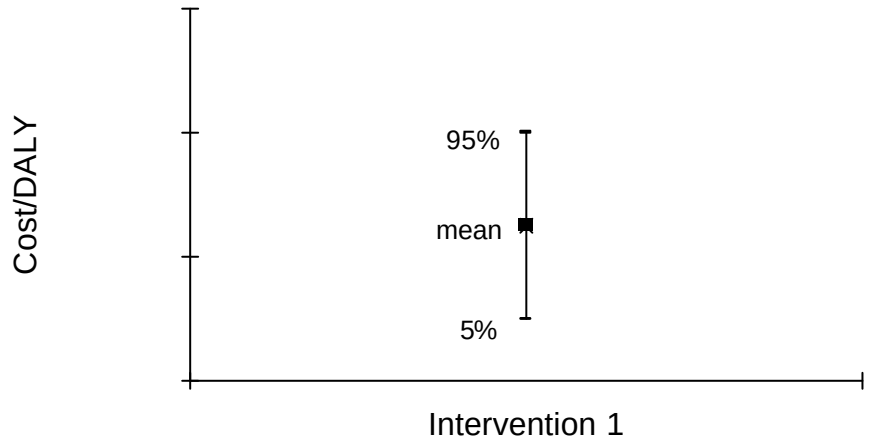


Table 2.1. Economic strata

Strata	GNP per capita in 1995	Countries in stratum
Very low income	Less than $315	Burkina Faso, Burundi, Chad, Democratic Republic of Congo, Eritrea, Ethiopia, Guinea Bissau, Kenya, Liberia, Madagascar, Malawi, Mali, Mozambique, Niger, Nigeria, Rwanda, Sierra Leone, Somalia, Sudan, Tanzania, Togo, Uganda
Middle income	$315 - $1,000	Angola, Benin, Cameroon, Cape Verde, Central African Republic, Comoros, Congo, Côte d'Ivoire, Djibouti, Equatorial Guinea, Gambia, Ghana, Guinea, Lesotho, Mauritania, Mayotte, Sao Tome and Principe, Senegal, Zambia, Zimbabwe
Higher income	More than $1,000	Botswana, Gabon, Mauritius, Namibia, South Africa, Seychelles

Source: GNP data taken from World Development Report, 1997.(25)

Table 2.2. Annual salary costs of full time equivalent staff (1995 US dollars)

Per capita income	Health centre	Hospital	Programme management[1]
Very low income	$2,275	$2,754	$3,691
Middle income	$2,993	$3,624	$4,856
Higher income	$8,603	$10,432	$13,963

Source: Extrapolated from Tinker & Koblinsky, 1992.(20)

[1] Programme management includes personnel involved in planning, administration, management and communications.

References

1. Drummond MF, O'Brien B, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes, Second Edition*. New York: Oxford Medical Publications, OUP, 1997.
2. Evans DB, Hurley SF. The application of economic evaluation techniques in the health sector: the state of the art. *Journal of International Development* 1995; 7(3): 503-524.
3. Buxton MJ, Drummond MF, Van Hout BA, et al. Modelling in economic evaluation: an unavoidable fact of life [editorial]. *Health Economics* 1997; 6(3): 217-27.
4. Sheldon TA. Problems of using modelling in the economic evaluation of health care. *Health Economics* 1996; 5(1): 1-11.
5. Gülmezoglu AM, Garner P. Malaria in pregnancy in endemic areas (Cochrane Review). In *The Cochrane Library*; Issue 3, 1998: Oxford, Update Software.
6. Lengeler C. Insecticide-treated bednets and curtains for malaria control (Cochrane Review). In *The Cochrane Library* Issue 3, 1998: Oxford, Update Software.
7. Murray CJL, Lopez AD. *The global burden of disease: A comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020*. Harvard School of Public Health (on behalf of WHO and the World Bank), distributed by Harvard University Press, 1996.
8. United Nations. *Model life tables for developing countries*. New York: 1982.
9. Paalman M, Bekedam H, Hawken L, Nyheim D. A critical review of priority setting in the health sector: the methodology of the 1993 World Development Report. *Health Policy and Planning* 1998; 13(1): 13-31.
10. Anand S, Hanson K. Disability adjusted life years: a critical review. *Journal of Health Economics* 1997; 16: 685-702.
11. Barendregt JJ, Bonneux L, Van der Maas PJ. DALYs: the age-weights on balance. *Bulletin of the World Health Organization* 1996; 74(4): 439-43.
12. Ugalde A, Jackson JT. The World Bank and international health policy: a critical review. *Journal of International Development* 1995; 7(3): 525-541.
13. Barker C, Green A. Opening the debate on DALYs. *Health Policy and Planning* 1996; 11(2): 179-183.
14. Jamison DT, Mosley WH, Measham AR, Bobadilla JL. *Disease control priorities in developing countries*. New York: Published for the World Bank by Oxford University Press, 1993.
15. Lengeler C, Snow RW. From Efficacy to Effectiveness - Insecticide-Treated Bednets in Africa. *Bulletin of The World Health Organization* 1996; 74(3): 325-332.
16. Phillips M, Mills A, Dye C. *Guidelines for cost-effectiveness analysis of vector control, PEEM Guidelines Series 3*. Geneva: WHO, 1993.
17. IMF. International Financial Statistics Yearbook. 1996: Washington DC.
18. IMF. International Financial Statistics. 1997; May: Washington, DC.
19. Management Sciences for Health. *International Drug Price Indicator Guide*. Boston: MSH, 1996.
20. Tinker A, Koblinsky MA. *Making motherhood safe*. Washington D.C.: The World Bank, 1992.
21. Manning WG, Fryback DG, Weinstein MC. Reflecting uncertainty in cost-effectiveness analysis. In: Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. *Cost Effectiveness in Health and Medicine*. New York: Oxford University Press, 1996: 247 - 275.
22. Critchfield GC, Willard KE, Connelly DP. Probabilistic sensitivity analysis methods for general decision models. *Computers and Biomedical Research* 1986; 19(3): 254-65.
23. Doubilet P, Begg CB, Weinstein MC, Braun P, McNeil BJ. Probabilistic sensitivity analysis using Monte Carlo simulation. A practical approach. *Medical Decision Making* 1985; 5(2): 157-77.
24. WHO. *Investing in Health Research and Development: Report of the Ad Hoc Committee on Health Research Relating to Future Intervention Options*. Geneva: TDR/Gen/96.1, 1996.
25. World Bank. *World Development Report 1997. The state in a changing world*. New York: Oxford University Press, 1997.

Chapter 3 – Prevention of Malaria in Childhood

3.1 Introduction

This chapter explores the cost-effectiveness of preventive strategies in reducing morbidity and mortality in children under 5 years of age through the use of a model of childhood malaria morbidity and mortality. The following strategies were evaluated: insecticide treated nets (ITNs), residual spraying of houses, and chemoprophylaxis for children.

Residual house spraying was first developed as an effective prevention tool during the Second World War, and subsequently was advocated as the mainstay of the malaria eradication programmes during the late 1950s and 1960s. However, over time many countries have abandoned or curtailed their spraying activities due to disillusionment over the failure to achieve the eradication goal, concerns over the safety and environmental impact of some insecticides, and administrative, managerial and financial constraints on implementation. Current WHO guidelines state that spraying "should never be an open-ended programme", but may be justified in certain circumstances, such as the control of epidemics, in areas of economic importance, in refugee camps and for the initial protection of non-immune settlers in development areas[1]. However residual spraying remains a major control activity in the southern African states of Botswana, Madagascar, Mauritius, Mozambique, Namibia, South Africa, Swaziland, Zambia and Zimbabwe, and is also practised in parts of Algeria, Angola, Tanzania, Uganda, Burundi, Rwanda, Ethiopia, Eritrea, Reunion and Comoros[2].

Over the last 15 years, ITNs have increasingly been advocated as an alternative method of preventing mosquito biting. Whilst mosquito nets have been used for centuries, and are common household items in some SSA countries, the treatment of nets with insecticide is a relatively new innovation, first tried in the 1930s[3]. The efficacy of ITNs for the control of malaria in children under 5 years of age has recently been demonstrated by several large-scale trials[4-7], which found reductions in all-cause mortality, ranging from 14% to 63%. However implementation of this intervention in SSA remains limited. Whilst many small-scale NGO projects have been established, only The Gambia runs a national programme for the treatment of nets.

The provision of chemoprophylaxis represents an alternative to vector control in preventing malaria. Whilst it is generally agreed that administration of prophylaxis to the whole population is not appropriate, targeted programmes have been advocated for vulnerable groups, such as non-immune travellers, pregnant women and children under 5 years of age. This strategy is not currently being implemented for children in SSA, although large-scale programmes have been undertaken in several countries in the past, such as Senegal, Ghana, Niger and Burkina Faso[8]. WHO no longer advocates widespread use of chemoprophylaxis due to problems of drug resistance and poor compliance[1].

A model is presented, and used to estimate the cost-effectiveness of each intervention in turn. The chapter concludes with a discussion of common themes of relevance to the interventions that concern their long-term effectiveness, and the feasibility and affordability of implementation.

3.2 A model of childhood malaria morbidity and mortality

The model uses standard life tables to describe the baseline populations[a] that have a stable age distribution and are growing at a constant rate of 2.6% per year, equal to the average SSA population growth rate between 1990 and 1995[9]. Assumptions were made about the rates of malaria-related morbidity and all-cause mortality in the baseline and intervention populations, and the mortality estimates were used to calculate the age distribution in each population, using standard demographic theory[10]. The deaths and morbidity/disability averted due to the intervention were calculated for each age class, and converted to YLLs and YLDs averted per child. The YLLs and YLDs averted in each age class were multiplied by the proportion of children in that age class, and summed together to give the DALYs averted per child in the target age group.

The target age group was defined as the age range over which effectiveness is assumed to be experienced. This was selected for each intervention on the basis of the results reported in the trials, and therefore varied from intervention to intervention. For ITNs, the target group was children aged 1 to 59 months, and for chemoprophylaxis, children aged 6 to 59 months. For residual spraying the target age group depended on the approach used for estimating effectiveness (see below). With Approach 1, which used estimates of the reduction in the infant mortality rate from controlled spraying trials, only children aged 0 to 11 months were included in the target group. With Approach 2, which used estimates of ITN effectiveness as a proxy for spraying effectiveness, the target group was children aged 1 to 59 months. With chemoprophylaxis only, the target group received the intervention, but with ITNs and residual spraying, coverage may be provided to other groups, although any health benefits they experienced were not included in the model.

As trials of preventive interventions tend to be conducted in areas of high/moderate transmission, the analysis can be considered relevant only for this epidemiological zone. Prediction of effectiveness in areas with lower transmission was not possible because the relationship between malaria transmission, mortality and intervention efficacy is complex and not well understood, due to the lower levels of acquired immunity in populations experiencing lower transmission. It was also not possible to differentiate between effectiveness in areas with different lengths of transmission season. However, annual cost estimates were adjusted, for example, for the number of spraying rounds or months of prophylaxis required per year, considering two alternatives, perennial transmission (12 months) and seasonal transmission (6 months).

Baseline levels of malaria associated morbidity were derived from a number of sources[11-14] (see Table 3.1). Without any intervention the annual incidence of clinical episodes of malaria per child aged 1 month to 4 years in a high transmission area was taken to be between 1 and 2.9. It was

[a] A West African life table with a life expectancy at birth of 50 years was used for very low and middle income countries, and a General Pattern life table with a life expectancy at birth of 65 was used for higher income countries, as described in Chapter 2.

assumed that between 3% and 7% of cases are severe, and that between 0.41 and 2.24% of severe cases result in neurological sequelae. The prevalence of malaria-associated anaemia was assumed to be 9%.

3.3 Insecticide treated nets

The analysis was based on the delivery mechanism used in the WHO/TDR trials, where net treatment was done on a communal basis, with householders, community health workers and programme staff working together. Two possible scenarios were considered: first, where nets are distributed to households as part of the programme (termed Nets and Insecticide Treatment), and secondly where there is already a high degree of net ownership, and treatment is arranged for the existing nets (Insecticide Treatment only). It was necessary to consider both scenarios as in some areas of Africa untreated nets are already widely used. For example, 58% of beds in rural Gambia had a net and in Brazzaville, Congo, 73% of households owned at least one net. However data from Sierra Leone, Burkina Faso and northern Ghana showed fewer than 10% of people using nets, and low rates were also found in Kenya, Tanzania and Malawi[15].

Bed nets are treated with a synthetic pyrethroid insecticide, which repels and kills mosquitoes and so inhibits their feeding on humans. Nets are washed immediately before treatment, allowed to dry and then soaked in a basin of insecticide diluted with water for a few seconds. They are then wrung out, and laid flat or hung up to dry. Whilst nets normally last for several years, the efficacy of the insecticide gradually wears off over time, so it is necessary to retreat the nets regularly. Two commonly used pyrethroids are considered in the model, permethrin and deltamethrin[b]. Deltamethrin is effective for about a year, so annual retreatments are adequate (assuming limited washing) but permethrin lasts only approximately 6 months[16], so more than one treatment is required per year if the transmission season is more than half a year.

The activities undertaken as part of the intervention are the training of staff and community health workers, a sensitization and awareness campaign to inform the community about the intervention, the procurement and transport of the insecticide and nets (where appropriate), and the initial treatment and subsequent retreatment of nets.

3.3.1 Effectiveness of ITNs

Estimates of the effectiveness of ITNs were drawn from the Cochrane meta-analysis of WHO/TDR trials conducted in SSA[17]. Children aged 1–59 months sleeping under ITNs experienced a significant reduction in all cause mortality of 19% (95% CI 14%–24%) and a reduction in clinical episodes of 46% (95% CI 41%–51%). The data on the reductions in mortality are based on the results of the meta-analysis for the five trials that included mortality as an outcome. The confidence intervals for the reductions in morbidity and mortality are slightly underestimated as they are not adjusted for group randomization. However, adjusting the confidence intervals would not change the significance of the effectiveness estimates (C. Lengeler, personal communication). The proportional

[b] Other suitable insecticides include lambdacyhalothrin, alpha-cypermethrin, cyfluthrin and etofenprox, but adequate price information was available only for permethrin and deltamethrin.

reductions in the incidence of severe malaria and the prevalence of malaria associated anaemia were set to equal the reduction in clinical episodes.

Effectiveness was assumed to be the same for the "Treatment and Nets" scenario and the "Insecticide Treatment only" scenario, and was assumed not to vary with the length of the transmission season, as in the meta-analysis all scenarios were combined[c]. The two insecticides considered were assumed to be of equal efficacy, although all the WHO/TDR trials used permethrin. The effectiveness of nets treated with deltamethrin and permethrin has never been directly compared in epidemiological terms, but the entomological evidence clearly suggests that deltamethrin is at least as effective as permethrin[18].

The effectiveness estimates were adjusted to account for non-compliance. A fully compliant child was defined as one whose net had recently been treated and who slept under the net. In practice, households may not re-treat their nets, and children may not sleep under them if they sleep outside in hot weather, the nets are used for other family members, or the nets are taken away, destroyed or sold. The average compliance of the WHO/TDR trials from which the effectiveness estimates were taken was 65%[4-7]. Retreatment rates under programme conditions are likely to be much lower than under trial conditions, and were given a range between 20% and 80%[19], while between 50% and 97% of children were assumed to use the net correctly[4-7]. These two estimates were multiplied together to calculate actual compliance. A linear relationship was assumed between compliance and effectiveness, such that zero compliance results in zero effectiveness, and 65% compliance results in the reductions in mortality and morbidity found in the meta-analysis. The effectiveness results from the meta-analysis were then multiplied by the ratio of actual compliance to trial compliance to estimate effectiveness under a programme situation. All effectiveness input parameters are listed in Table 3.2.

The DALYs averted per child aged 1 to 59 months by the intervention were on average 0.17 for very low and middle income countries and 0.05 for higher income countries. Fewer DALYs were averted per child in higher income countries because a life table was used with lower underlying mortality rates for children under 5 years. Mortality was by far the most important component of the DALYs. YLLs on average made up 98% of the DALYs averted by the intervention in the very low and middle income populations, and 92% in the higher income population.

3.3.2 Costs of ITNs

The cost per child for the purchase, distribution and annual treatment of ITNs was calculated using estimates of input parameters drawn from the economic evaluations that accompanied the WHO/TDR trials[20-23], supplemented by additional technical and economic data from other published and unpublished sources and expert consultation. The costing included the cost of the insecticide, staff, sensitization and awareness campaign, transport, other overheads, and community time.

[c] Contrary to what one might expect, the studies included in the meta-analysis found a higher protective efficacy in the "Treatment only" scenario than in the "Treatment and Nets" scenario (23% compared with 17%), but the number of trials of both type was small.

In scenario 1 (Nets and Insecticide Treatment) the cost of the nets was included, but in scenario 2 (Insecticide Treatment only) it was assumed that the nets did not constitute an incremental cost so they were excluded. All other costs were assumed to be the same for both scenarios, although in practice, some other costs, such as transport, may be lower in scenario 2, which does not require net distribution. Although the intervention is targeted at children under 5 years, it has been found in practice that it is necessary to provide ITNs to other household members as well, to ensure that the target group is covered[22]. Between 2 and 3.9 nets were therefore assumed to be distributed per child under 5 years[20, 22, 24, 25].

The range for the price of nets was obtained from the delivered, duty paid prices recorded in bed net trials for both locally made and imported nets (between $4 and $11.39)[20, 22, 24, 25]. Prices as high as $35 have been recorded for private sellers in Africa, but were not assumed to be representative of the prices obtainable for a large-scale programme. An annualized net cost was calculated on the basis of a useful life for a net of between 3 and 6 years[26].

The cost of the insecticide per net depends on the number of treatments per year, the cost per litre, the insecticide concentration, the dose used, the size of the net, the freight cost, and the wastage incurred. The average size of a double or family size net was assumed to be between 13 m and 18 m^2. More insecticide will be used than is indicated by the target dose for several reasons. During mixing some spillage is likely to occur, some insecticide will drip off nets while they are drying, and different fibres absorb different amounts of insecticide, making it hard to estimate the exact quantities needed when different types of nets are dipped together. Wastage due to these factors was estimated to be between 10% and 50% of insecticide used.

Minimum and maximum estimates for the cost per litre of deltamethrin and permethrin were taken from published sources and communication with recent purchasers, and were adjusted to cover freight costs. With deltamethrin the insecticide cost was based on one treatment a year in both seasonal and perennial transmission, but with permethrin the cost was based on one treatment a year for seasonal transmission, and two treatments a year for perennial transmission. Where more than one treatment is required per year, all non-net costs were doubled. This will slightly overestimate the additional cost as it should not be necessary to repeat all initial training and sensitisation.

Other costs, including the sensitisation and awareness campaign to explain and promote the intervention, transport, equipment and buildings, staff time, training and office supplies, were estimated by calculating the cost per net from the trials[20, 22, 24]. The costs of community time, staff, sensitisation and awareness campaigns, training and office supplies were assumed to vary by per capita GNP, so estimates were made for the three economic strata. In addition the community bears the costs of the detergent and water to wash and treat the nets, and provides much of the labour for dipping. Minimum and maximum estimates for each of these costs were incorporated. Variable costs were adjusted for the proportion of nets not retreated. Cost input parameters are listed in Table 3.2.

The cost per child depends on the insecticide used, the number of treatments required per year, the income level, and whether it is necessary to distribute nets as part of the intervention. The mean and 90% range for the cost per child under 5 is shown in Table 3.3 (adjusted for non-compliance). For "Nets and Insecticide Treatment" the mean cost per child ranged from $6.59 in very low income countries to $7.18 in higher income countries. The "Insecticide Treatment only" scenario was much

cheaper, with a cost of $1.12 in very low income countries, $1.18 in middle income and $1.70 in higher income countries[d]. For "Nets and Insecticide Treatment" the nets themselves made up the bulk of the cost, accounting for between 76% and 83%, insecticide accounting for 7%, and overheads (staff, sensitization and awareness campaign, transport, buildings and equipment etc.) the remainder. In the "Insecticide Treatment only" scenario, where nets are already owned by households and therefore not included in the cost, insecticide accounted for 43% and 41% in very low and middle income countries respectively, and 28% in higher income countries, the remainder being overheads. The costs to the community of their time and detergent for net washing were included in overheads and were relatively low (under $0.03 per child).

3.3.3 Cost-effectiveness of ITNs

Cost-effectiveness was calculated for each insecticide under seasonal and perennial transmission, for each income level, and both scenarios ("Nets and Insecticide Treatment" and "Insecticide Treatment only").

Considering first scenario 1, "Nets and Insecticide Treatment", the cost-effectiveness results for very low income countries for the two insecticides are shown in Figure 3.1. With one treatment per year using deltamethrin, the mean cost per DALY averted was $44, with the CER in 90% of the iterations falling between $19 and $85. With one treatment of permethrin per year there was a very slight increase in the CER to a mean of $45 (90% range of $19 to $86). As the effectiveness of the two insecticides was assumed to be the same, the difference is purely due to the slightly higher insecticide cost per net with permethrin (average of $0.53 compared with $0.38 with deltamethrin). As permethrin is effective for about 6 months, results are also shown for two treatments of permethrin per year, which increased the mean CER by $7, to $52 (90% range of $25 to $96). ITNs would therefore be considered an "attractive" option for very low income countries with either insecticide, as over 95% of the iterations had a cost per DALY averted below $150, but they could not be assumed to be "highly attractive" as the CER is not always below $25. The insecticide price data available indicate that deltamethrin is cheaper than permethrin, and therefore should be the insecticide of choice, especially in areas of perennial transmission where its longer effective duration is an advantage. However prices for insecticides are very variable, depending, for example, on the quantity ordered, the destination and the competitive conditions; so in practice, locally available prices would have to be considered. All other results are quoted for one treatment with deltamethrin per year (all results are summarized in Table 3.4).

Figure 3.2 shows the cost-effectiveness results for "Nets and Insecticide Treatment" with deltamethrin for the three income levels. There was no significant difference between the CER in very low and middle income countries, because effectiveness is assumed to be identical, and there was only a very slight increase in costs. However the CER was much higher in higher income countries with a mean of $177, and a 90% range from $79 to $334. This was partly attributable to higher salary and community time costs in higher income countries, but mainly due to the lower DALYs averted per child, as a result of the lower underlying mortality rates. In higher income

[d] With full compliance, the average cost per child would have been higher, for example, $8.06 for Nets and Treatment in a very low income country, compared with an adjusted figure of $6.59.

countries one cannot be certain that the "Nets and Insecticide Treatment" intervention is cost-effective at the $150 level.

Figure 3.3 shows the results for the second scenario, "Insecticide Treatment only". DALYs averted per child were assumed to be the same as with "Nets and Insecticide Treatment", but the cost per child was lower as the cost of the nets was not included. With this scenario, more than 95% of the iterations had a CER below $150 at all income levels and in very low and middle income countries the CER was clearly below $25.

In summary, if net coverage is low and nets must be distributed and treated, one can be reasonably sure that the intervention is an "attractive" option in very low and middle income countries, but not in higher income countries. If net coverage in the community is already high and only treatment of nets is required, the intervention is "attractive" for all income levels, and "highly attractive" in very low and middle income countries. The model considers health benefits only for children under 5 years. If benefits to other household members were also included, the CERs would be lower.

Rank order correlation coefficients were calculated to show the input variables which were most important in explaining the variation in the CER. For "Nets and Insecticide Treatment" the most important variables were the retreatment rate and the number of nets per child in the target group (negatively related to the CER), and the price per net (positively related). The number of nets treated per child was also important for "Insecticide Treatment only", together with the proportion of children using the net correctly and the reduction in mortality rate (both negatively related). The retreatment rate does not appear as an important variable in this scenario, because with "Insecticide Treatment only," both costs and effects vary with the retreatment rate, leaving the cost-effectiveness ratio relatively unchanged.

There are several reasons why the results may be over-optimistic. First, owners may wash their nets frequently, necessitating more regular retreatment even with long-lasting insecticides such as deltamethrin. For example, in The Gambia, it was most common to wash nets once in a 16-week period[27]. To illustrate the potential impact on cost-effectiveness, the cost per DALY averted with one or two treatments of deltamethrin per year is compared in Figure 3.4 ("Nets and Insecticide Treatment", very low income country). Using two treatments per year raised the mean cost per DALY averted from $44 to $50 and the upper end of the range from $85 to $93.

Costs per child may also vary with the scale of the programme. The importance of economies of scale for "Nets and Insecticide Treatment" is likely to be limited, because 80% to 90% of unit costs were made up of insecticide and nets, which would vary with the number of people covered (see Table 3.3). For "Insecticide Treatment only" overhead costs were more significant, but as the majority of these costs were also likely to be variable, scale is still unlikely to have an important influence on unit costs.

3.4 Residual spraying

Residual spraying involves the treating of all interior walls and ceilings using a handheld compression sprayer, and is effective against mosquitoes that favour indoor resting before or after feeding. The

delivery mechanism considered here is based on a government-run programme, where local temporary staff are hired and trained to spray all houses in their area. The intervention involves the training of staff, a sensitization and awareness campaign to inform the community, the procurement and transport of the insecticide, and the actual spraying of houses.

Four insecticides were considered: DDT, malathion, and two pyrethroids, deltamethrin and lambda-cyhalothrin. DDT was the most commonly used insecticide in the past, but in recent years, the use of organochlorines and organophosphates, such as DDT and malathion, has declined due to concerns about their environmental and safety impact, and the use of pyrethroids has increased[28, 29]. However, all of the insecticides assessed are still used to some degree in SSA[2].

3.4.1 Effectiveness of residual spraying

Evidence from controlled trials on the effectiveness of spraying on health outcomes is restricted to three studies that date from the 1950s and 1960s[30]. These studies provided results for the impact on infant mortality, but data were not provided for the impact on mortality of children over one year of age, or on morbidity.

Two approaches were used to estimate the effectiveness of spraying:

Approach 1: Infant mortality reduction from spraying trials
Estimates for reductions in the infant mortality rate (IMR) from the controlled trials in Pare Taveta (Tanzania), Kisumu (Kenya) and Garki (Nigeria) were used, ignoring effects on other age groups and reductions in episodes, anaemia and neurological sequelae. Reductions in the infant mortality ratem (IMR) of 41% were achieved in Kisumu, 51% in Pare Taveta and between 47% and 59% in Garki[30], so a range of between 41% and 59% was used in the model. Other trials which did not have a control arm also reported results within this range[31].

Approach 2: Assume effectiveness equivalent to ITNs
The only trial in SSA, which directly compared ITNs and residual spraying showed that there was no difference in the rate of reinfection after parasite clearance with spraying or ITNs[25]. It was therefore assumed that the results of the Cochrane review meta-analysis of ITN trials conducted in SSA[17] could be used to approximate the effects of spraying on morbidity and mortality. Children aged 1–59 months living in sprayed houses were assumed to experience a reduction in all cause mortality rates of 0.19 (95% CI 0.14–0.24) and a reduction in rates of clinical episodes, neurological sequelae and anaemia of 0.46 (95% CI 0.41–0.51).

The duration of residual effectiveness depends on the insecticide and dose used and the type of surface sprayed. It was assumed that on average one round of spraying would be required where transmission is seasonal, and two rounds where transmission is perennial. The four insecticides were assumed to be of equal effectiveness.

The effectiveness estimates were adjusted to account for non-compliance. Compliance implies that a household allows the team to spray their buildings fully. It was assumed that the studies which produced the effectiveness estimates experienced high levels of compliance of around 95%. However, in a contemporary operational setting people may object to the spraying of their houses

because of the inconvenience, the residue left on the walls, the smell, or fears about the health effects of inhaling the fumes. For example, householders in Namibia have refused entry to the spray teams[32], and in Zimbabwe, 21% of villagers refused to have some rooms in their homes sprayed[33]. Actual compliance with spraying was assumed to be between 70% and 95%. As with the modelling of ITN effectiveness, a linear relationship was assumed between compliance and effectiveness, such that zero compliance resulted in zero effectiveness, and 95% compliance resulted in reductions in mortality and morbidity found in the trials. The effectiveness results were multiplied by the ratio of actual compliance to trial compliance to estimate effectiveness under a programme situation. The same range for actual compliance was used for all of the insecticides considered, although it has been suggested that pyrethroids will be better accepted because, unlike DDT, they do not leave a visible deposit on walls. The effectiveness input variables are summarized in Table 3.5.

The DALYs averted per child depended on the approach used for calculating effectiveness. Using Approach 1 (reduction in IMR from spraying trials) on average 0.36 DALYs were averted per child aged 1 to 59 months in very low and middle income countries and 0.15 DALYs in higher income countries. Using Approach 2 (assuming equivalence to ITN reductions) effectiveness was slightly lower with an average 0.31 DALYs averted per child for very low and middle income countries and 0.08 DALYs for higher income countries. Fewer DALYs were averted per child in higher income countries due to the use of a life table with lower underlying mortality rates for children under 5 years. Effectiveness was greater with Approach 1, even though zero effectiveness was assumed for all children over 1 year of age, because the reduction in the IMR was so great and underlying mortality rates are highest in the under 1 age group.

3.4.2 Costs of residual spraying

A review of studies of the cost of spraying in SSA produced ranges for the cost per house sprayed of $3.71 to $8.93, and for the cost per capita of $0.24 to $6.70 (1995 US$)[25, 34-39]. However, these studies were either unclear about the costing methods employed or did not include all resources used, and are therefore difficult to compare or generalize. Moreover, the estimates were based on a variety of different insecticides, which vary greatly in price. It was therefore necessary to estimate spraying costs using the ingredients approach, based on cost data where available, and constructing estimates for other input variables from technical information on resources used and price information from catalogues and discussions with experts.

Cost estimates were made per house sprayed and included the costs of insecticide, staff, training, sensitization and awareness campaign, transport, other overheads, and equipment. The cost of the insecticide used depends on the cost per kilogramme or per litre, the insecticide concentration, the dose used, the surface area to be sprayed, and the wastage incurred. Even in a well run programme a certain amount of wastage will be normal due to spillage, mixture being unused at the end of a session, or overlapping in spraying. Wastage rates of between 10% and 50% of the target dose were assumed.

Minimum and maximum estimates for the cost per litre of DDT, malathion and deltamethrin were estimated from published sources and communication with recent purchasers. The price per litre for lambda-cyhalothrin was obtained by personal communications with the suppliers (G. White, personal communication). All insecticide costs were adjusted to cover freight. The mean costs of

insecticide per house were calculated (Table 3.6). The cheapest insecticide was DDT at $3.47 per house, and the most expensive, lambda-cyhalothrin at $4.52.

Staff costs depend on salary levels and the number of houses sprayed per day. It was assumed that local spraymen earn the daily rate for a relatively unskilled labourer, which was estimated at $3.83 to $5.18 per day for a very low income country, $4.68 to $6.33 in middle income countries and $14.03 to $18.98 in higher income countries. The number of houses sprayed per man-day will depend on the density of habitation, the size of the houses, and the insecticide used (if a less concentrated insecticide is used, more frequent mixing and filling of sprayers will be required). It was assumed that with a team of 5 workers, between 12 and 40 houses were sprayed per team per day. Training of sprayers was estimated to take between 4 and 10 days, at a cost of $10 per day. Training costs were not annualized as temporary workers would require training before each round. Costs were included for one supervisor for every three teams of sprayers, to coordinate activities, oversee the adherence to specified standards and the maintenance of equipment, and ensure that safety requirements were met.

Transport will be needed for the insecticide, equipment and personnel, and costs will vary depending on the density of habitation, the distance of the houses from the main depot, and the road quality. As transport costs depend on so many different factors, they are very hard to estimate using an ingredients approach. Instead, data were extrapolated from the transport costs for the ITN trials. An estimate was made of the proportion of ITN transport costs that were incurred in transporting insecticide, and the proportion incurred in transporting staff. The insecticide transport costs were scaled up to account for the greater quantity of insecticide used in spraying a house than in dipping a net. Costs for transport of personnel were assumed to be the same per person covered for spraying and ITNs. Differences in transport costs for different insecticides were not allowed for. Information from the ITN trials was also used to estimate costs for a sensitization and awareness campaign to inform and consult communities about the spraying. Households may incur time costs in preparing their houses (e.g. removing foodstuffs and cooking utensils), but these costs were not included because they are likely to be relatively minor, and are very difficult to measure and value.

The capital costs of the equipment involved (hand-operated compression sprayers, maintenance kits, equipment for weighing, packing and mixing the insecticides, and protective clothing) were annualized based on their expected useful lives.

The recurrent and annualized capital components were combined to calculate a cost per house sprayed per round, which was converted to a cost per child under 5 using an average household size of between 3.8 and 5.2, and the proportion of the population under 5. In areas of perennial transmission where two rounds of spraying take place per year, recurrent costs were doubled and capital costs adjusted to account for the higher number of houses sprayed and the more rapid depreciation of equipment. The costs of insecticide and sprayman time were adjusted for non-compliance, but all other costs were left unchanged. Cost input variables are shown in Table 3.5.

The cost per child depended on the number of spraying rounds required per year and the economic strata. The mean and 90% range for the cost per child under 5 using lambda-cyhalothrin are shown in Table 3.7 (adjusted for non-compliance). Costs were only marginally lower with other insecticides. With one round a year the mean cost per child ranged from $7.33 in very low income

countries to $7.56 in middle income countries and $12.50 in higher income countries. Two rounds per year increased costs to $14.65 in very low income countries, $15.12 in middle income and $25 in higher income countries[e]. Insecticide was the most significant cost, accounting for more than two-thirds of the cost in very low and middle income countries, and over half in higher income countries[f]. Staff costs accounted for 14%, 16% and 37% in very low, middle and higher income countries respectively, and overheads (training, transport and sensitization and awareness campaign) comprised about 16% of costs in very low and middle income, and 12% in higher income countries. Equipment was relatively insignificant, accounting for less than 1% at all income levels.

3.4.3 Cost-effectiveness of residual spraying

The cost-effectiveness of residual spraying was calculated using both approaches for estimating effectiveness, for each of the three income levels, with seasonal and perennial transmission. The simulations were halted after 1,100 iterations at which point all output variables had reached convergence.

Considering first Approach 1 (reduction in IMR from spraying trials), the cost-effectiveness results are shown in Figure 3.5 for very low income countries with seasonal transmission (one round a year), for the four insecticides. With lambda-cyhalothrin the mean cost per DALY averted was $22, with the CER in 90% of the iterations falling between $16 and $29 (all results are summarized in Table 3.8). As the effectiveness of the insecticides was assumed to be the same, the results for the other insecticides were very similar, with only slightly lower CERs, due to the marginally lower insecticide costs per house. As there was very little difference between the insecticides, and the modern pyrethroids are more likely to be used in future, all other results are presented only for lambda-cyhalothrin.

Results are shown in Figure 3.6 for the three economic strata. With one round per annum there was very little difference between the CERs in very low and middle income countries, because effectiveness was assumed to be identical and there was only a very slight increase in costs. However the CER was much higher in higher income countries with a mean of $86, and a 90% range from $60 to $120. This is partly attributable to higher labour costs in higher income countries, but mainly due to the lower DALYs averted per child as a result of the lower underlying mortality rates. With two rounds per annum, costs increased but effectiveness was assumed to stay the same, so all of the CERs approximately doubled, giving a mean of $43 in very low income, $45 in middle income and $172 in higher income countries.

The results were compared to the CER cut-offs of $25 and $150. With one round a year, spraying would be considered an "attractive" option for all income levels, as over 95% of the iterations had a cost per DALY averted below $150, but would not be considered "highly attractive" as the CER was not always below $25. If two rounds a year were required, spraying would still be considered attractive in very low and middle income countries, but not in higher income countries.

[e] Costs were adjusted for non-compliance; with full compliance the average cost per child would have been higher, for example, $8.56 for seasonal transmission in a very low income country.

[f] The cost of insecticide, equipment and overheads per house were not varied by economic strata, but the cost of these inputs per child is higher in higher income countries, because children under 5 make up a smaller proportion of the population in the life table used for the higher income stratum.

Results are presented in Figure 3.7 using Approach 2 for calculating effectiveness (assuming equivalent to ITN effectiveness). Costs per child were assumed to be the same as with Approach 1, but the DALYs averted per child are lower in Approach 2, so the CERs are higher. With this approach, the intervention remains attractive with either seasonal or perennial transmission in very low and middle income countries, but not in higher income countries for either transmission type.

Rank order correlation coefficients were calculated to show which input variables were most important in explaining the variation in the CER. With Approach 1 for a very low income country with seasonal transmission, the most significant input variables were the reduction in the IMR and the average household size, which were negatively related to the CER; and the sprayable surface area per household and wastage of insecticide, which were positively related. Household size was important because it affected the number of children assumed to be protected per house. Variations in the number of houses sprayed per team per day, the cost of internal transport, the salary of spraymen and the cost of external freight were also important.

The cost-effectiveness results should be interpreted with some caution because of the absence of up-to-date estimates of effectiveness in children under 5 years of age. The relationships between effectiveness and epidemiological parameters are not well understood, so considerable assumptions were made in extrapolating the results across regions with different transmission intensities and different lengths of transmission season.

The model was based on one round of spraying a year in areas of seasonal transmission, and two rounds a year in perennial transmission. Whether this is sufficient will depend on the actual length of the transmission season in seasonal areas and the type of insecticide used. DDT lasts for 6 months or more, but lambda-cyhalothrin lasts 3 to 6 months and malathion and deltamethrin only 2 to 3 months[29]. The duration of residual effectiveness will also be affected by the materials used in house construction, and behavioural factors, such as whether walls are regularly replastered.

3.5 Chemoprophylaxis for children

The intervention involves the provision to children of an antimalarial such as Maloprim®, chloroquine, pyrimethamine or chloroproguanil. Prophylaxis must be provided on a regular basis, so community-based volunteers such as VHWs are often involved in the distribution of drugs[40]. The analysis was based on the provision of prophylaxis on a fortnightly basis to children aged between 6 and 59 months. Carers bring children to the village health post at a pre-arranged time, and the VHW observes the child swallowing the pill. Defaulters are not followed up. The drug included in the model was Maloprim® (100 mg dapsone and 12.5 mg pyrimethamine), with a dose of a quarter tablet per 6-11 month year old, and a half tablet per 12-59 month year old[40]. The activities involved in the intervention are the training of VHWs and other health workers, community sensitization and the distribution of drugs.

3.5.1 Effectiveness of chemoprophylaxis for children

Several small-scale trials in SSA have shown that chemoprophylaxis can reduce episodes of fever and improve haemoglobin levels in children, but only one trial in rural Gambia was large enough to demonstrate a significant effect on child mortality[40, 41]. Estimates of effectiveness were based on the reductions in morbidity attributed to malaria and all cause mortality reported in this study. For children aged 6-59 months[g], the proportionate reduction in all cause mortality rates was 0.49 (95% CI 0.02–0.74) and the reduction in the incidence of clinical episodes was 0.73 (95% CI 0.25–0.90). It was assumed that the proportionate reduction in both the incidence of neurological sequelae following malaria infection and the prevalence of malaria associated anaemia was equal to the reduction in clinical episodes. The trial took place in an area of seasonal transmission. As no other studies were available it was assumed that the same annual reductions in morbidity and mortality would be achieved in areas of perennial transmission.

The effectiveness estimates were adjusted to account for non-compliance. Full compliance implies that the child visited the VHW at the correct time, and the correct regimen was provided and consumed. The average compliance from the Gambian trial was 72% in the study cohort of children from which the effectiveness estimates were taken. A linear relationship was assumed between compliance and effectiveness, such that zero compliance resulted in zero effectiveness, and 72% compliance resulted in reductions in mortality and morbidity found in the trial. Actual compliance under operational conditions is likely to be lower than under trial conditions, so the effectiveness results from the trial were multiplied by the ratio of actual compliance to trial compliance to estimate effectiveness under an operational setting. Actual compliance was assigned a range based on compliance rates reported in the literature. Allen *et al.* (1990)[42] evaluated the Gambian chemoprophylaxis programme over a 5-year period and found that compliance was lower in a programme situation, with an overall mean rate of 33.6%. In a similar programme in Kenya, which distributed chemoprophylaxis to pregnant women through VHWs, only 29% of women received prophylaxis[43]. However, MacCormack and Lwihula (1983)[44] found higher rates in their study of a prophylaxis programme for children in rural Tanzania, where community drug distribution led to the correct dosage being administered on 57% of occasions: overdosing was 15%, underdosing was 23%, but only 3% received no dose at all. The percentage receiving at least the minimum dose was 72%. The range of rates for actual compliance was set at between 29% and 72%. The effectiveness variables are summarized in Table 3.9.

On average 0.47 DALYs were averted per child aged 6 to 59 months in very low and middle income countries, and 0.09 DALYs in higher income countries.

3.5.2 Costs of chemoprophylaxis for children

The annual cost per child was calculated for the three economic strata. Drug costs were estimated using data on the price of Maloprim® from the British National Formulary 1997[45], allowing an additional 25% for freight and delivery, and 25% wastage. Estimates for all non-drug costs were taken from data provided by Picard *et al.* (1992)[46] from The Gambia, recalculated using a 3% discount rate for capital costs, and converted to 1995 prices. The cost estimates included initial training and sensitization, regular annual training and sensitization, delivery of the drugs, transport for

[g] In the Gambian trial, drugs were actually given to children aged 3-59 months, but the strategy subsequently adopted in the area targeted 6-59 month year olds,[40] so the latter age group was selected to represent actual practice.

the malaria control officer and the time of the VHWs (who would in fact work as volunteers, so a shadow price was put on their time, based on the marginal value of alternative agricultural work).

The cost estimates by Picard *et al.* were based on providing prophylaxis over a 20-week period. To enable these data to be generalized to settings with different lengths of transmission season, the costs were divided into fixed and variable components. The fixed components do not vary with the length of the transmission season (cost of initial and annual training of government employees and VHWs, and the sensitization and awareness campaign)[h]. The "variable" components (drugs, VHW time and transport) were estimated as a cost per month. Fixed and variable components were then combined to give an annual incremental cost per child for perennial transmission (12 months) and seasonal transmission (6 months).

The costs of drugs and transport were assumed to be constant across all income levels, but the costs of the initial and annual training of government employees and VHWs, the sensitisation and awareness campaign, supervision and the time of VHWs were assumed to vary by economic strata. The cost estimates come from The Gambia, which falls in the middle income bracket, so the data were extrapolated to estimate costs for very low and higher income countries. As the main source of cost variation between countries is staff remuneration, the costs for very low and higher income countries for these inputs were estimated using the ratios for salaries for the three economic strata. No costs were included for the time of villagers bringing children to the health post. These costs are difficult to measure and value, and were likely to be low as the VHWs would be located in the villages that they served. The costs of the drugs and VHW time were adjusted for non-compliance.

These incremental costs were based on the assumption that a network of VHWs, with basic training, already existed. However, in much of SSA this is not the case, and operating a programme for the community distribution of prophylaxis would require the establishment of a VHW cadre. The cost of this will vary, depending on the type and length of training, whether the VHWs are paid or voluntary, whether they are full or part time, the type of services they provide and the degree of support and supervision they are given. To obtain an estimate of the cost per child when the costs of establishing the cadre must be included, data on the annual cost of a VHW were taken from the literature. Estimates were available for Zambia and Swaziland[47]. The data for Zambia gave an annual recurrent cost per VHW, excluding drugs, of $591, and the Swaziland data gave a figure of $1,321 p.a. for a "low cost VHW" who would work part-time, and $2,891 for a full-time "high cost VHW" (again excluding drugs). The Zambia data were used for very low income countries, the Swaziland data for higher income countries, and an estimate for middle income countries was extrapolated from the very low income data, using the ratios for salaries for the economic strata. The cost per child aged 6-59 months was estimated by dividing the estimated annual VHW cost by the average number of people covered, multiplied by the proportion of the population in this age group. Estimates of population coverage per VHW from the literature ranged between 500 and 1,200[48, 49]. This cost was then added to the incremental cost of delivering prophylaxis per child, to give a total cost per child. This is a maximum estimate of the costs attributable to chemoprophylaxis delivery as, once established, the VHW would presumably undertake other activities as well.

[h] Supervision costs could not be separated from the "fixed" costs, and so were also treated as fixed, although in reality they would vary with the length of season.

The cost inputs used are shown in Table 3.9. Very few cost estimates were available so only three of the cost inputs were assigned distributions, the others being included as point estimates. The results therefore underestimate the actual degree of potential variation in the CER.

The mean incremental cost per child was $1.25 in seasonal transmission and $2.15 in perennial transmission (see Table 3.10). In middle income countries the mean incremental cost rose to $1.37 and $2.28 in seasonal and perennial transmission respectively, and in higher income countries to $2.29 and $3.27 respectively. Over 90% of incremental costs were made up of drugs and transport, with VHW time and fixed costs accounting for a small proportion of costs. The mean total cost per child was much higher at $5.86 for seasonal and $6.76 for perennial transmission in very low income countries, $7.43 and $8.34 in middle income countries, and $22.42 and $23.40 in higher income countries. The cost of running the VHW programme made up over two-thirds of the total cost.

3.5.3 Cost-effectiveness of chemoprophylaxis for children

Incremental and total cost-effectiveness were calculated for each of the three economic strata, under seasonal and perennial conditions. The simulation was halted after 2,800 iterations at which point all output variables had reached convergence.

The ranges for the CER for seasonal and perennial transmission are shown in Figure 3.8 for a very low income country (all results are summarized in Table 3.11.). Using incremental costs, the mean CER under seasonal transmission was $3, and 90% of the simulation results fell in the range of $2 to $7. Under perennial transmission the cost per DALY averted was slightly higher, with a mean CER in very low income countries of $6, and 90% of the estimates falling between $3 and $12. If prophylaxis was required for only 6 months a year, the CER was lower because the effects were assumed to be the same, but the variable costs were reduced. Results are also shown in Figure 3.8 using total costs. Including the annual costs of the VHW programme more than trebled the mean CER, increasing the range for the cost per DALY averted to between $7 and $36 for seasonal transmission, and between $8 and $41 for perennial transmission.

Figure 3.9 shows the incremental CER for the three different economic strata. There was no significant difference between the CERs for very low and middle income countries, but the CER was significantly higher in countries with higher per capita incomes, with a range of between $16 and $59 in seasonal transmission and between $23 and $85 in perennial transmission. This was partly attributable to higher costs in higher income countries, but mainly due to the lower DALYs averted per child. Similarly with total costs, Figure 3.10 shows that there was only a slight increase in the cost per DALY averted between very low and middle income countries, with an increase in the mean from $17 to $22 (seasonal) and from $20 to $24 (perennial). However the CER for higher income countries was much higher, with a mean of $315 in seasonal transmission (range $121 to $695), and a mean of $327 (range $129 to $723) in perennial transmission.

The model results show that where a cadre of VHWs already exists, the intervention would be considered “attractive” as 95% of the simulated CERs always fell under $150 in all economic strata, under seasonal or perennial transmission, and that for very low and middle income countries, it would be considered “highly attractive” as 95% of the CERs always fell under $25. If it were

necessary to set up a whole VHW programme just to implement this intervention (i.e. using total costs), one could no longer be sure that the intervention could be categorised as "highly attractive", as in no circumstances were 95% of the results using total costs under $25, and in higher income countries the intervention no longer appears "attractive" at the $150 cut-off. Maloprim® is a relatively expensive drug with a cost per prophylaxis dose of $0.07 for a child aged 1 to 4 years. The intervention would appear more cost-effective if a cheaper drug such as chloroquine could be used (equivalent cost per dose $0.02[50]).[i]

The effectiveness inputs were based on only one study, which was used as an estimate for the whole of SSA. The generalizability of the results is not known, especially as the relationship between effectiveness, length of transmission season and transmission intensity is not fully understood. Similarly there was only one study available on costs (Picard *et al*., 1992[46]), and these were adapted figures, derived from a trial of ITNs and chemoprophylaxis in The Gambia[20]. There was no way to judge whether these costs were representative for other settings, or if the extrapolations performed for other economic strata were appropriate. For example, the Gambian cost estimates were based on voluntary VHWs, but elsewhere in SSA true volunteer workers are rare and most programmes pay VHWs some sort of salary or provide perks, such as free health care services[47]. If a payment were required to give VHWs the incentive to participate, and it was greater than the marginal value of agricultural work used to value VHW time in the model, costs would increase.

3.6 Discussion of preventive interventions

Several common themes emerge as areas for concern with all three preventive interventions: the development of resistance to insecticides or drugs; the impact on the immune status of the population; the relationship between effectiveness and compliance; and the feasibility and affordability of implementation.

3.6.1 Resistance to drugs and insecticides

There have been reports of resistance to DDT in a wide range of SSA countries[51], but this does not necessarily imply that resistance has reached an operationally significant level. With the exception of the Gezira region of Sudan[37], widespread loss of vector susceptibility is not common. A worrying new development is the emergence of knock down resistance to pyrethroid insecticides in natural populations of *Anopheles* mosquitoes in Côte d'Ivoire and Burkina Faso[52, 53], where the insecticides are widely used in cotton production[54]. It is also possible that exposure to insecticide could lead to changes in mosquito behaviour, with for example a change in the period of peak biting to earlier in the day[8]. Pyrethroids are the only insecticides currently used for net treatment and are also increasingly used for spraying, so there is a threat that if widespread resistance develops, the interventions will gradually become less cost-effective over time.

The analysis was extended to estimate how the cost per DALY averted of ITNs and residual spraying would change as pyrethroid resistance develops. Resistance is defined here as the

[i] Rank order correlation coefficients were not calculated for this simulation: the results would be misleading due to the small number of input variables that could be given distributions.

proportion of vector biting that would not be prevented by appropriate use of the insecticide[j]. The relationship between resistance and effectiveness is difficult to predict. For example, even where an insecticide no longer has a killing effect on vectors, it may still have repellent power[8]. As a worst case scenario it was assumed that all vectors exhibiting resistance would not be prevented from biting, and that the relationship between effectiveness and resistance is linear. The rate of resistance was allowed to vary between 0 and 99%[k].

Figures 3.11 and 3.12 show CERs as a function of insecticide resistance for a very low income country with ITNs ("Nets and Insecticide Treatment", one treatment of deltamethrin per year) and spraying (Approach 1 to estimate effectiveness, one round with lambda-cyhalothrin per year). The results were used to calculate the threshold level of resistance at which the 90% CER range no longer fell below $150. This threshold resistance level was 43% for ITNs, and 82% for residual spraying. Whilst this analysis is highly speculative, as the impact of resistance on effectiveness is not well understood, it highlights the importance of monitoring resistance levels, and the need for investment in the development of alternative insecticides and more research on the factors affecting the evolution of resistance. In particular, the impact of the interventions themselves on vector susceptibility should be monitored: one reason for the absence of widespread insecticide resistance in SSA may be that large-scale spraying programmes have rarely been implemented.

With chemoprophylaxis, the concern is that resistance will develop to the drug used, which would obviously reduce the effectiveness of the programme. The relationship between the CER and the level of drug resistance is shown in Figures 3.13 and 3.14 using incremental costs and total costs respectively (very low income countries). Resistance was defined as one minus the adequate clinical response rate[55]. With incremental costs the CER range no longer fell below $25 at 53% resistance, or below $150 at 91% resistance. With total costs the equivalent threshold for $150 was 72% (i.e. one could never be certain that the CER was below $25).

Whilst the level of drug resistance influences cost-effectiveness, the implementation of the intervention could itself significantly encourage the development of resistance in the future, through an increase in drug pressure. This would in turn affect the cost-effectiveness of the intervention, and could also threaten effective case management. This negative externality is not captured in the CER, but may be extremely important if, for example, the intervention led to the loss of one of the few remaining affordable and effective antimalarials. However, no significant increase in resistance to Maloprim® was found after 5 years of regular administration in The Gambia[56].

In addition to affecting the efficacy of interventions, resistance to either drugs or insecticide is also likely to affect behaviour, as households will be less willing to participate if they perceive the intervention as ineffective. Resistance may therefore also reduce effectiveness through a decline in compliance.

3.6.2 Impact on the development of acquired immunity

[j] This is different from the operational criterion used by WHO of survival of more than 20% of mosquitoes at the currently known diagnostic concentrations[51].

[k] This implies that if resistance is 100% there will be zero effectiveness, although with ITNs, benefit may still be obtained from the physical barrier of the net.

Questions have been raised about the long-term epidemiological consequences for children who comply with preventive interventions in areas of high malaria transmission. It is possible that the rate at which immunity is acquired will be reduced, so that whilst malaria mortality falls over the younger ages relative to an unprotected population, there would be a relative increase in malaria mortality in the older age class[57-59]. This mortality "rebound" in later childhood may cancel out to some degree the mortality reduction achieved in the younger age classes, or at the extreme could even exceed it, depending on the actual relationship between transmission and mortality.

Empirical evidence on this phenomenon is not conclusive. The recent studies on ITN effectiveness involved at most a two-year follow-up period, so it was not possible to assess whether mortality/morbidity rebound occurred. No rebound was noted after two years of highly effective malaria control using residual spraying in Garki, Nigeria[60]. Following the use of prophylaxis some studies have found no evidence of impaired immunity[61, 62], but others suggest there may be some effects. Greenwood *et al.* (1995)[60] found a significantly higher incidence of clinical attacks in children who had received prophylaxis during the year after medication, although there was no increase in the risk of death. Menendez *et al.* (1997)[63] found that at the end of a chemoprophylaxis intervention in Tanzania, children who had received prophylaxis had higher rates of severe anaemia and malaria than non-prophylaxis groups, and concluded that the development of natural immunity was impaired. In view of the paucity of data on this issue, it is essential that long-term surveillance be included as a component of any preventive intervention to monitor potential effects on immunity, and that effective treatment services are also maintained. The potential implications of "rebound" mortality for the cost-effectiveness of ITNs are discussed in Box 1.

3.6.3 The relationship between compliance and effectiveness

The analysis incorporated the assumption that the relationship between compliance and the effectiveness of each intervention was linear. However, it is possible that the effectiveness of spraying or ITNs is due in part to mass killing of the mosquito population. It may therefore be necessary to reach some critical level of compliance before significant effects are observed. On the other hand, at high levels of compliance there may be some reductions in mortality and morbidity amongst non-compliers if children living in unsprayed houses or not sleeping under treated nets also receive fewer infectious bites per year. Effectiveness may therefore be expected to increase in a non-linear fashion, with disproportionately greater effects at higher

Box 1. Rebound mortality and ITNs

The model was extended to allow for a rebound in morbidity and mortality[64]. The rebound rate was defined as the percentage increase in morbidity and mortality compared with the no intervention situation, and was allowed to vary from 0% upwards. It was assumed that the rebound effect involved the same percentage increase in mortality, neurological sequelae, episodes and anaemia. Two scenarios were considered: first where reductions in morbidity and mortality were experienced by children aged 1 to 59 months and rebound mortality by children aged 5 to 9 years, and secondly where the reductions were experienced only by children aged 1 to 35 months and rebound was experienced by those aged 3 to 6 years. Baseline estimates of malaria morbidity and all cause mortality for children aged over 5 years are given in Table 3.1.

The rebound rate was calculated at which less than 95% of the iterations showed the intervention to be cost-effective at the $150 level (i.e. more than 5% of the iterations had negative effects, or positive effects but a CER of more than $150) and is shown in Figure 3.15 ("Nets and Insecticide Treatment", one treatment of deltamethrin per year, very low income country). As the rebound rate increases, the percentage of iterations giving a CER below $150 falls. With rebound occurring in children aged 5 to 9 years, above a 39% rebound rate one could no longer be reasonably certain that the CER was below the $150 cut-off. Changing the age range over which the rebound effect occurs had a significant effect on the relationship between cost-effectiveness and the rebound rate. Assuming that the reduction in morbidity and mortality occurred only in children aged 1 to 35 months, and that the rebound effect was experienced in the 3 to 6 year age group, substantially reduced the threshold rebound rate at which the intervention was no longer cost-effective, to 2.5%. These rates applied to the whole population. If there were no rebound amongst children who did not comply with the intervention, the increases in morbidity and mortality required to reach these thresholds amongst compliers would be much higher.

compliance levels. If the mass effect were, for example, more important with spraying than with ITNs, the relative effectiveness of spraying might be overestimated at low levels of compliance.

The spraying trials were accompanied by considerable decreases in vector density: for example, in Kisumu, *Anopheles Gambiae* were undetectable for 9 months, and in Pare Taveta, density fell by 80%[31]. Evidence of the existence of a mass effect with ITNs is inconclusive. Two studies in The Gambia failed to find any evidence of a mass effect[65, 66], but studies in Zaire and Tanzania found a significant reduction in mosquito density at village level[67, 68], and another Tanzanian trial found no significant difference between the reductions in mosquito density with spraying and ITNs[25].

3.6.4 Feasibility of implementation

The capacity to implement these interventions on a national scale may not be present in all SSA countries. The feasibility of running a national programme to distribute and treat nets is yet to be demonstrated, as at present no such programmes exist in SSA, and only one national treatment programme for existing nets is operating in The Gambia.

An effective spraying programme requires strong managerial capacity, especially as the timing of spraying relative to the transmission cycle is crucial. Both Zimbabwe and Namibia have reported

decreasing efficiency and effectiveness of spraying programmes due to constraints in planning, management and supervision[32].

The success of a chemoprophylaxis programme depends on the ability of VHWs to sustain the implementation of the intervention. Some studies have concluded that community-based health workers are a very effective channel for delivering prophylaxis. In The Gambia, volunteer VHWs were reported to administer prophylaxis conscientiously, and the reductions in morbidity and mortality were maintained over at least 3 to 4 years[40, 41]. Also in The Gambia, traditional birth attendants (TBAs) were found to be an effective and appropriate channel for providing antimalarial and iron prophylaxis to pregnant women[69, 70]. However, activity levels are low for all types of community health workers, and are especially low among part-time and volunteer workers, with high percentages desisting from any work at all after a time[47]. It is therefore unclear whether programmes in other settings would be able to sustain high coverage rates. Experience in western Kenya has shown that even in a well-supported community-based health programme, where VHWs delivered chemotherapy to pregnant women, the programme was able to reach only 29% of pregnant women[43]. The authors concluded that the programme was not effective in providing prophylaxis, and argued that asking VHWs to distribute the drugs was too difficult for many of them and may have overloaded them. Similarly, in a study on the use of VHWs for delivering malaria treatment in Zaire[48], the authors concluded that the programme was unlikely to be sustainable because of the non-comprehensiveness of the VHWs' care and their ambiguous position in the health care system.

3.6.5 Affordability

Another crucial consideration is affordability. The government budget required to implement the interventions on a nationwide scale for a very low income country such as Tanzania was estimated and is shown in Table 3.12. Net distribution and treatment would cost between $12 million and $38 million annually, representing between 12% and 40% of the existing government health care budget. Net ownership is currently low in Tanzania, so a programme concentrating solely on net treatment would not be appropriate, but for illustrative purposes an estimate was made of the burden of covering the incremental government costs. This would be between $1 million and $6 million per annum, or between 1.4% and 6% of the health budget.

Chemoprophylaxis for children would cost between $5 million and $8 million per annum where a VHW network already existed, representing between 5% and 9% of the existing budget. If a VHW programme had to be set up from scratch, the cost would be between $17 million and $29 million, or 18% to 31% of the existing budget.

Residual spraying has the highest costs of the three interventions. With one round per year the cost would be between $20 million and $36 million per annum, or 21% to 38% of the existing budget. With two rounds per year the cost would be between $40 million and $71 million per annum, or 43% to 76% of the budget.

These estimates demonstrate the influence of existing infrastructure on the incremental costs of the interventions. Unless either net ownership is already high or a network of VHWs already exists countrywide, a national prevention programme is likely to require an increase of more than a one-

fifth in the health sector budget, and could cost significantly more. This would involve a massive investment of scarce government resources and would not be affordable without substantial external assistance.

Government costs could be reduced by either improving the targeting of the interventions or introducing an element of cost-recovery. ITNs could be more narrowly targeted by restricting the distribution and treatment of nets to vulnerable groups, such as children under 5 and pregnant women. If distribution could be reduced to only one net per child, the total government cost per annum in a very low income country for "Nets and Insecticide Treatment" would fall to $7 million, representing 8% of the existing health sector budget. However, if the mass effect is important, restricting treated net use to a sub-set of households could reduce effectiveness in the target group.

The costs of spraying could be reduced by undertaking focal or targeted spraying rather than covering all areas, especially in regions with epidemic malaria. This would require an effective surveillance system, which could be costly, and the ability to respond quickly to news of an outbreak, which would require flexible organizational arrangements.

An alternative way to reduce the burden on the government budget would be to charge households for preventive services. There is concern that the price elasticity of demand for preventive interventions may be high, meaning that any increase in charges would substantially reduce utilization. With ITNs, households may be unwilling to pay for the insecticide component as its value is relatively difficult for them to perceive. At the start of the intervention in The Gambia, when insecticide was distributed free, about 80% of nets were retreated but when charges were introduced for the service, retreatment rates fell to less than 20% (though there is some evidence that after several years of charging, the retreatment rate is rising to around 35% to 40% when insecticide is available: J. Rowley, personal communication). With nets, the value of the commodity is easier to perceive, but the one-off capital nature of the purchase may be a barrier to affordability for households. Efforts are currently underway in several SSA countries (e.g. Tanzania, Malawi and Burkina Faso), to use social marketing to stimulate demand for nets and net retreatment. It remains to be seen whether households will have the willingness and ability to pay for ITNs, and there is also concern that the poorest will be excluded. Evidence at this stage is lacking on the costs of social marketing. Although a substantial share of costs would be borne by households, there is usually still a major element of government or donor subsidy for the promotional campaigns, development of brands, and often to cover a proportion of the net and treatment costs as well. It is likely that greater use of individual rather than community dipping of nets and the introduction of "dip-it-yourself" kits[71] would change the cost structure from that found in the trials, and overall costs could actually be higher. Work is urgently needed in this area to evaluate the impact of alternative distribution strategies on cost-effectiveness and affordability.

Cost-recovery has not been considered in the literature for spraying or chemoprophylaxis, presumably at least in part due to the anticipated negative impact on demand. Chemoprophylaxis does not have the added advantages of reducing nuisance biting, but it is more clearly identifiable with individual protection and the cost is much lower, making it more affordable. Nonetheless, it is generally assumed that preventive interventions targeted at children should not be charged for by the public sector[72]. With residual spraying, the mass effect has been considered potentially too important to consider excluding households that have not paid. In economic terms, the substantial

positive externalities from house spraying would result in sub-optimal service provision if households were asked to pay.

3.7 Summary and conclusions

All of the interventions for preventing malaria in childhood are potentially cost-effective in high transmission areas for very low and middle income countries. Evidence is not available for low transmission or epidemic areas. Results are shown in Figure 3.16 for all of the interventions in a very low income country with high transmission. Net treatment is highly cost-effective where net ownership is already high, but would still count as an attractive use of resources if nets were distributed. The mean CER for residual spraying is similar to that for "Nets and Insecticide Treatment" if two spraying rounds are required a year, but if only one round is required the mean CER is considerably lower, although there is considerable overlap in the ranges. Chemoprophylaxis for children appears a cost-effective intervention if a VHW network already exists, and still compares favourably with the other interventions, even if the costs of establishing a network are included. However, these results should be considered in the light of the potential reductions in acquired immunity, and the impact of insecticide and drug resistance. The possibility that chemoprophylaxis could increase the growth of drug resistance is especially serious, due to the potential negative externalities for case management and prevention in pregnancy.

Affordability is likely to be a major barrier to widespread implementation. Unless either nets are already widely used, or a strong network of VHWs is in place, achieving national coverage of the target group with any of the interventions would probably require an increase in the existing health sector budget of over 20%. Even if it were possible to generate these resources from external sources, significant operational problems would have to be tackled in implementation. The nature of these problems is different for the different interventions, and consideration should be given to local institutional strengths and weaknesses in deciding which intervention could be most effectively implemented. For example, if capacity exists to run an effective and well-timed spraying programme, it may be more cost-effective than an ITN intervention because compliance is likely to be higher. However, if the organizational and maintenance requirements of residual spraying are considered too arduous, a method such as ITNs, which relies more heavily on personal protection, could be more appropriate. The choice of an appropriate prevention strategy therefore, must take into account existing infrastructure, the financial resources available, the public acceptability of interventions, and local managerial capacity.

Figure 3.1. Cost-effectiveness of ITNs using deltamethrin versus permethrin: mean (¦) and 90% range for the CER in very low income country, for scenario 1 ("Nets and Insecticide Treatment"), using one treatment of deltamethrin p.a., one treatment of permethrin p.a., and two treatments of permethrin p.a. (1995 US dollars)

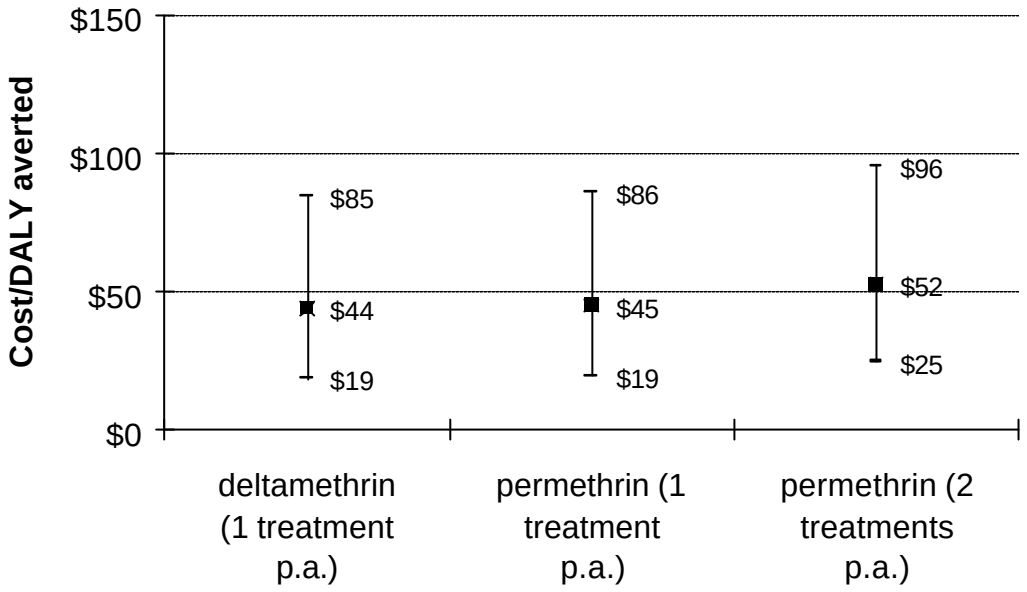


Figure 3.2. Cost-effectiveness of ITNs at different income levels for scenario 1 ("Nets and Insecticide Treatment"): mean (¦) and 90% range for the CER in very low, middle and higher income countries, using one treatment of deltamethrin p.a. (1995 US dollars)

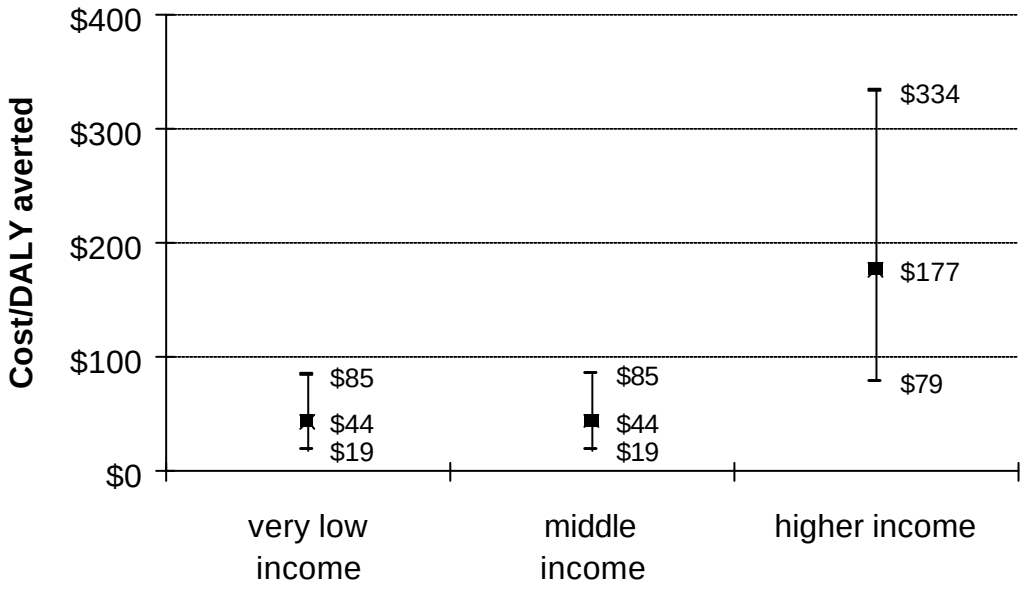


Figure 3.3. Cost-effectiveness of ITNs at different income levels for scenario 2 ("Insecticide Treatment only"): mean (¦) and 90% range for the CER in very low, middle and higher income countries, using one treatment of deltamethrin p.a. (1995 US dollars)

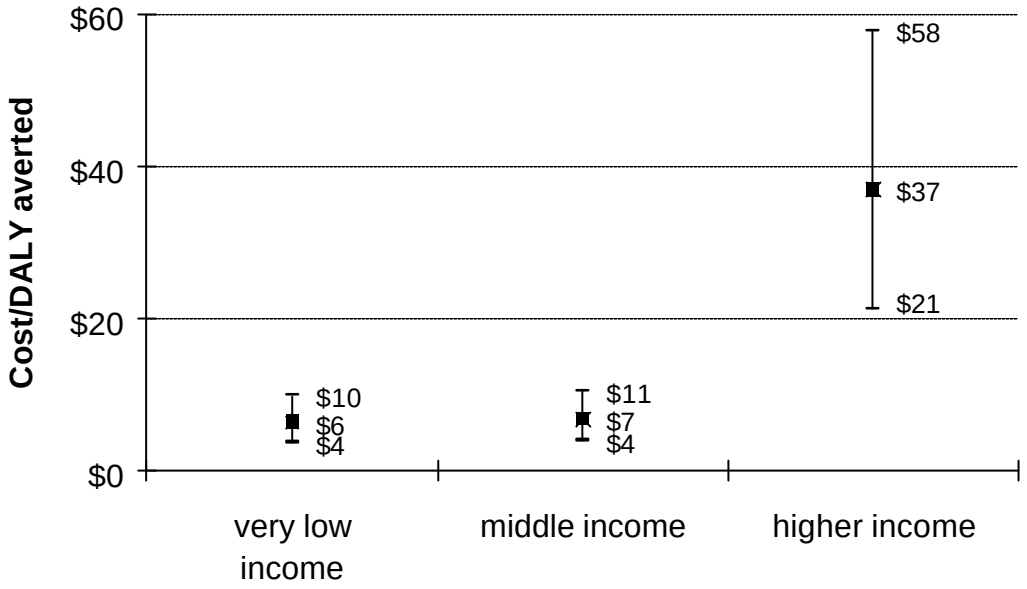


Figure 3.4. Comparison of the cost-effectiveness of ITNs with one or two treatments of deltamethrin p.a.: mean (¦) and 90% range for the CER in a very low income country, for scenario 1 ("Nets and Insecticide Treatment") (1995 US dollars)

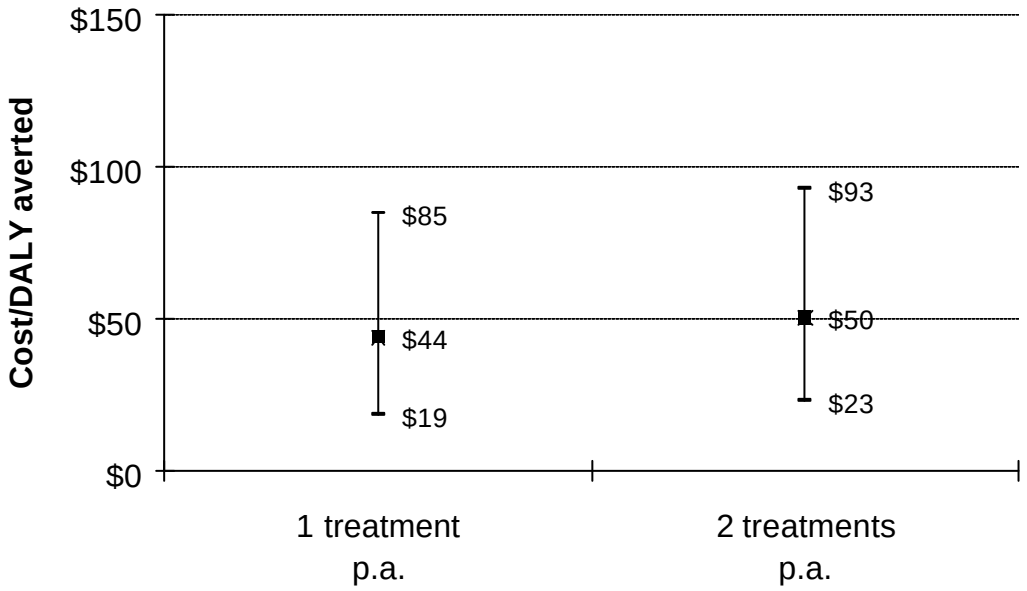


Figure 3.5. Cost-effectiveness of residual spraying with four different insecticides: mean (¦) and 90% range for the CER in a very low income country, with seasonal transmission, using Approach 1 to calculate effectiveness (1995 US dollars)

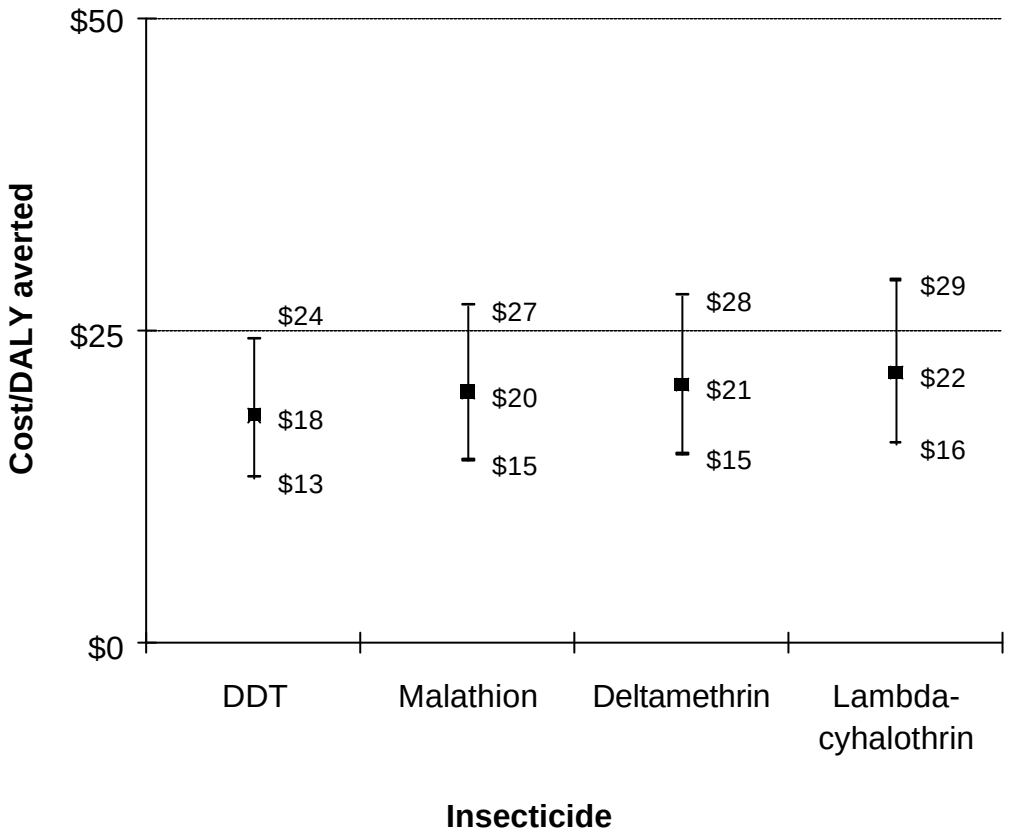


Figure 3.6. Cost-effectiveness of residual spraying for different economic strata: mean (¦) and 90% range for the CER for different economic strata, using lambda-cyhalothrin, and Approach 1 to calculate effectiveness (1995 US dollars)

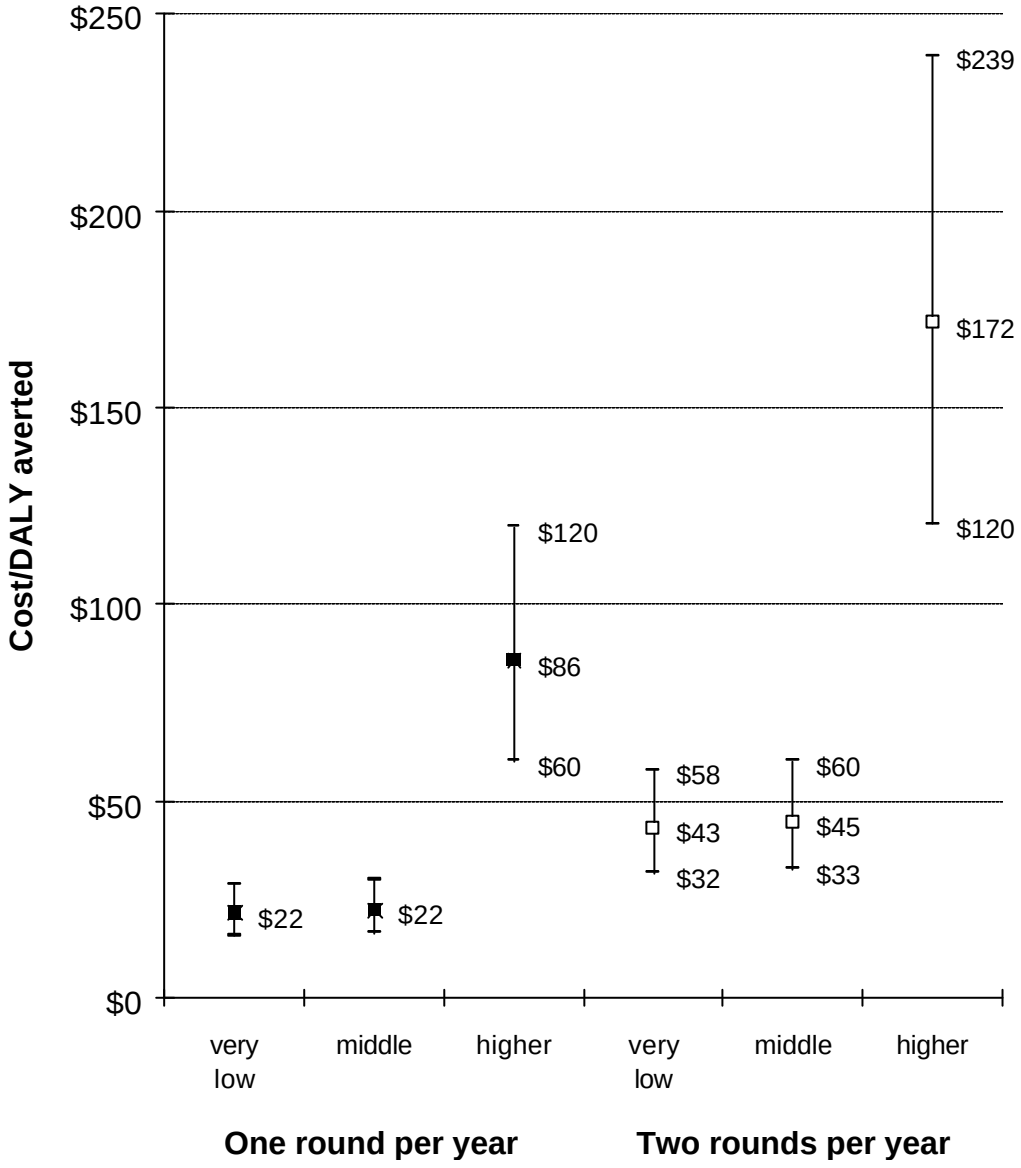


Figure 3.7. Cost-effectiveness of residual spraying using Approach 2 to calculate effectiveness: mean (¦) and 90% range for the CER for different economic strata, using lambda-cyhalothrin (1995 US dollars)

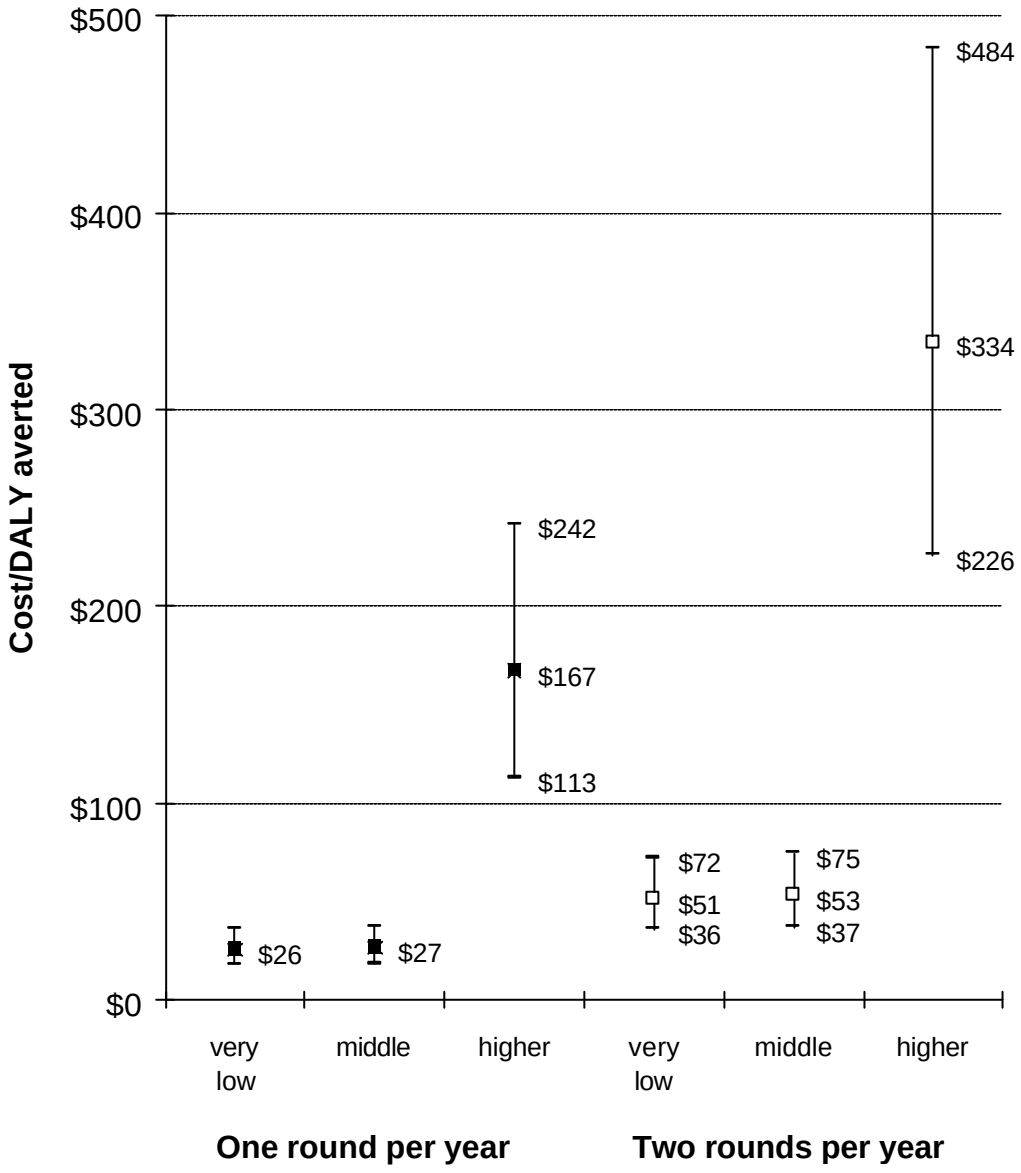


Figure 3.8. Cost-effectiveness of chemoprophylaxis for children: mean (¦) and 90% range for the CER in a very low income country, under seasonal and perennial transmission and using incremental and total costs (1995 US dollars)

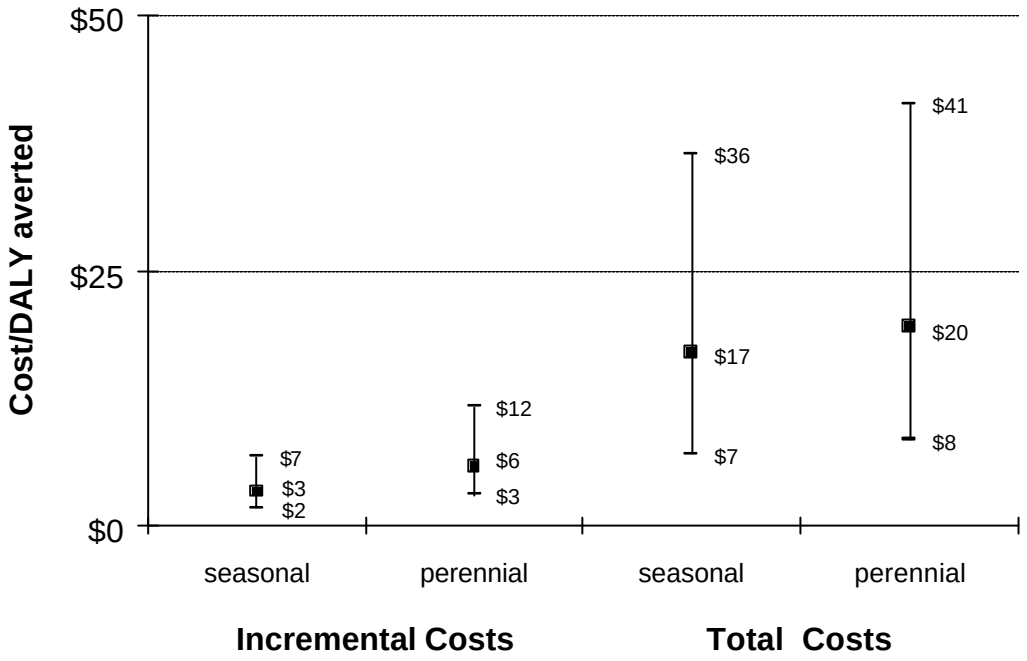


Figure 3.9. Cost-effectiveness of chemoprophylaxis for children for different economic strata: mean (¦) and 90% range for the CER under seasonal and perennial transmission and using incremental costs (1995 US dollars)

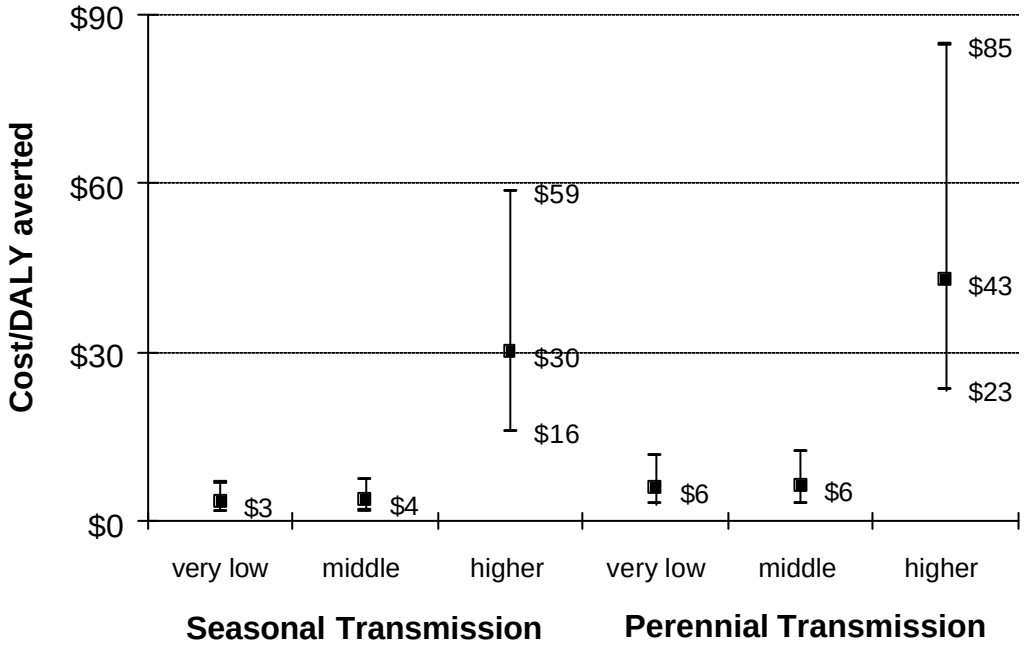


Figure 3.10. Cost-effectiveness of chemoprophylaxis for children using total costs: mean (¦) and 90% range for the CER under seasonal and perennial transmission for different economic strata (1995 US dollars)

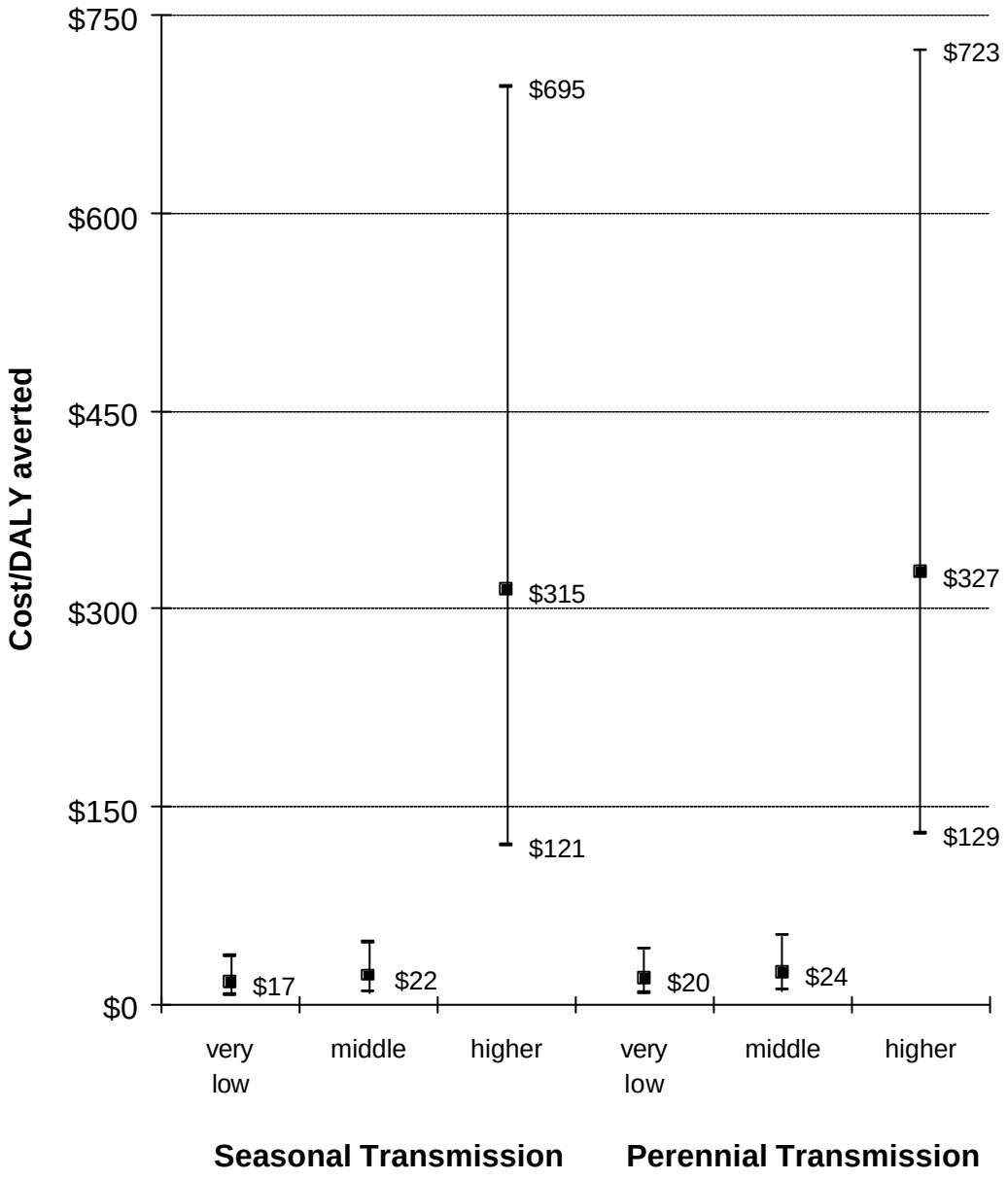


Figure 3.11. Cost per DALY averted by ITNs as a function of insecticide resistance in a very low income country, for scenario 1 ("Nets and Insecticide Treatment"), using one treatment of deltamethrin p.a., showing the mean CER (- - - -) and the 90% range (———) (1995 US dollars)

Figure 3.12. Cost per DALY averted by residual spraying as a function of insecticide resistance, in very low income country with seasonal transmission, using lambda-cyhalothrin, and Approach 1 to calculate effectiveness, showing the mean CER (- - - - -) and the 90% range (——) (1995 US dollars)

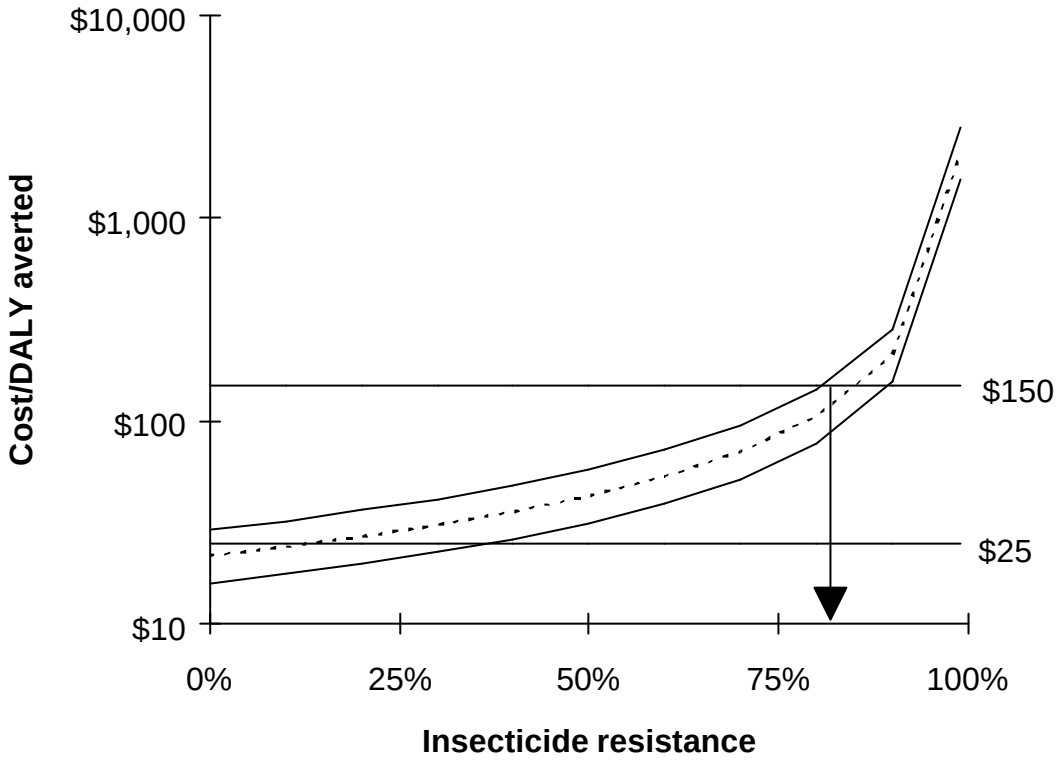


Figure 3.13. Incremental cost per DALY averted by chemoprophylaxis for children as a function of drug resistance, in a very low income country, with perennial transmission, showing the mean CER (- - - - -) and the 90% range (——) (1995 US dollars)

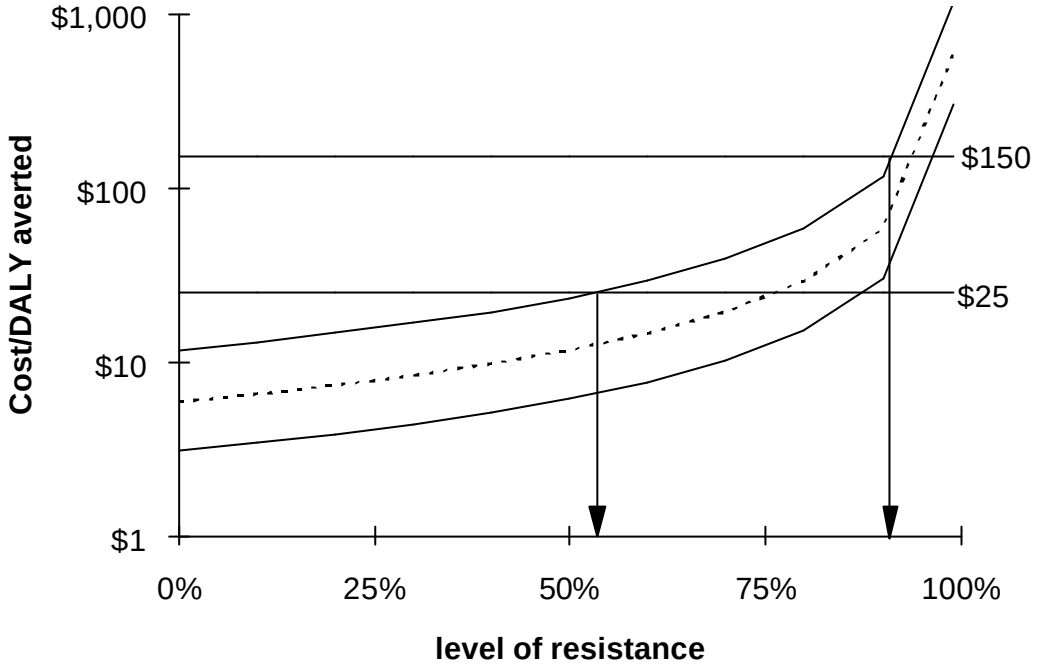


Figure 3.14. Incremental cost per DALY averted by chemoprophylaxis for children as a function of drug resistance, in a very low income country, with perennial transmission, showing the mean CER (- - - - -) and the 90% range (——) (1995 US dollars)

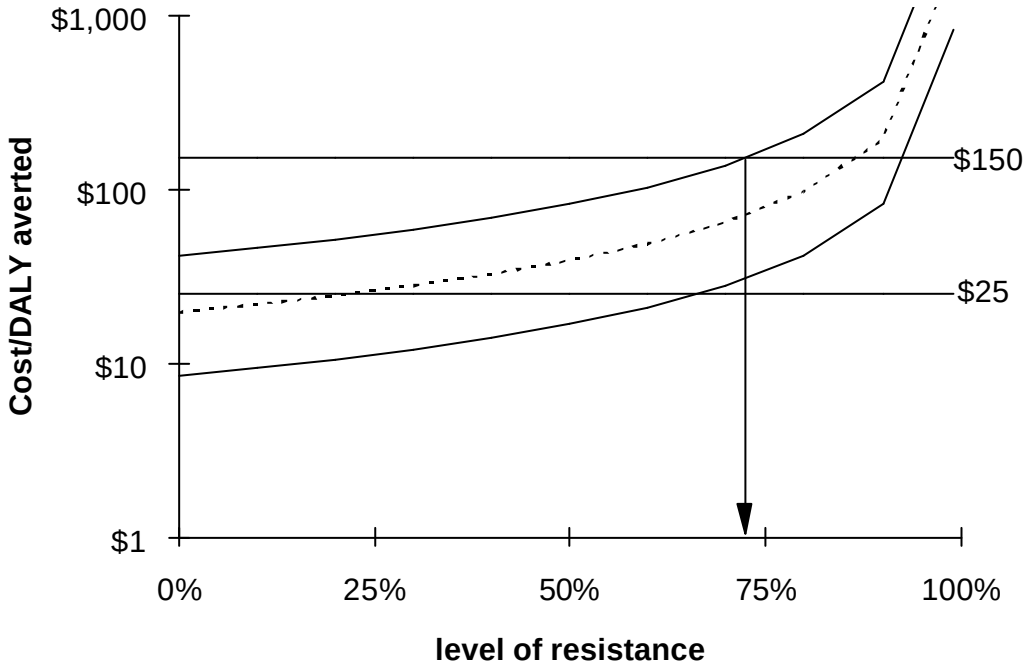


Figure 3.15. Percentage of iterations with a CER of less than $150 per DALY averted with the rebound effect in children aged 5 to 9 years and 3 to 6 years (very low income country, for "Nets and Insecticide Treatment", using one treatment of deltamethrin p.a.) (1995 US dollars)

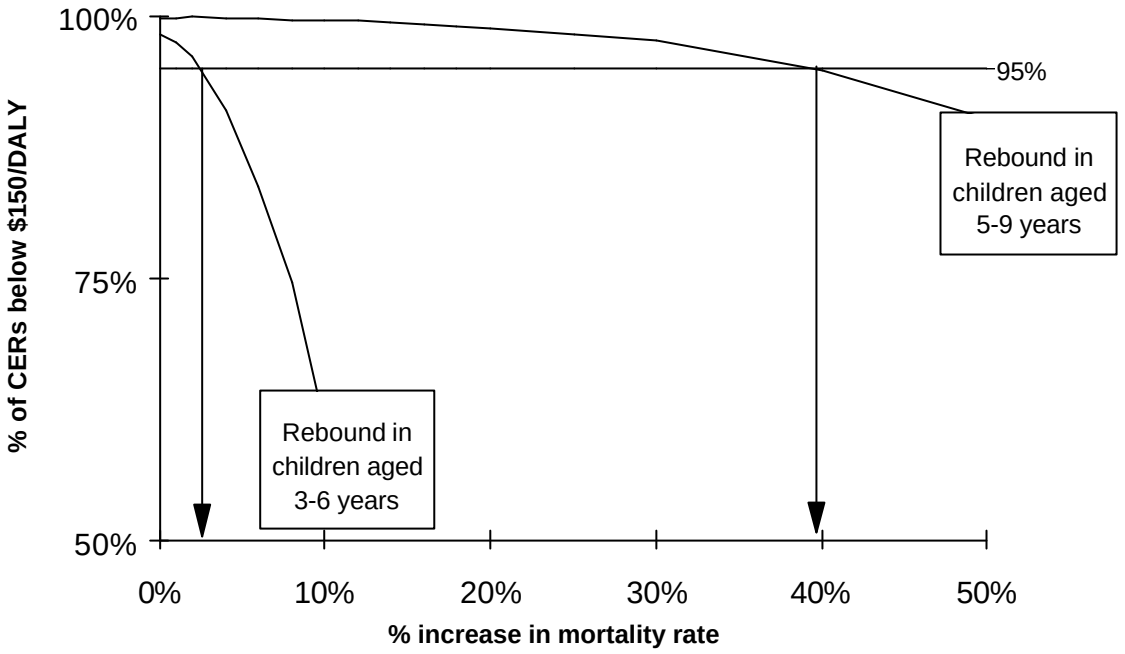
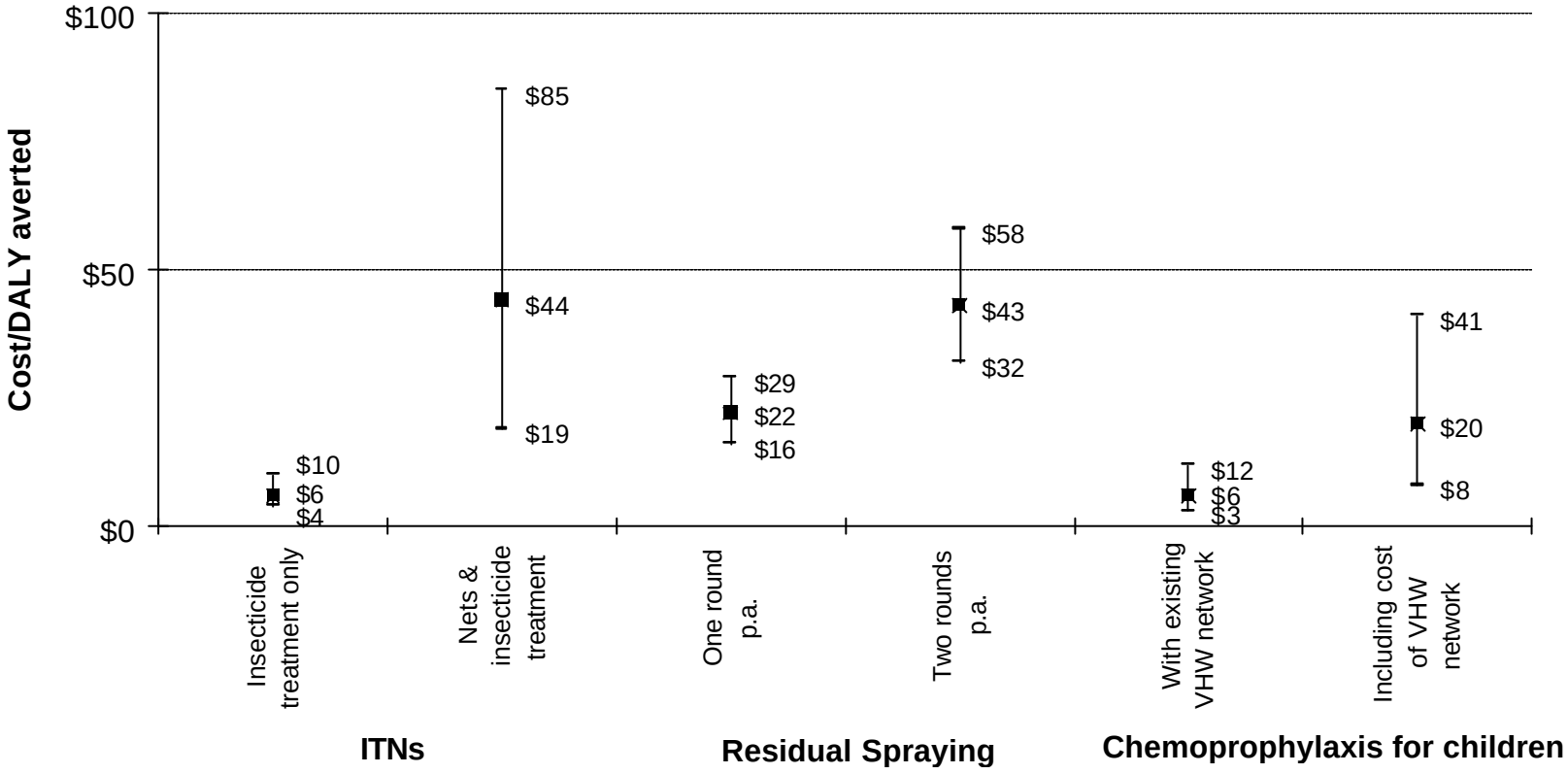


Figure 3.16. Comparison of the cost-effectiveness of preventive interventions in a very low income country: mean (¦) and 90% range for the CER (1995 US dollars)



Notes
ITNs: one treatment of deltamethrin a year, no insecticide resistance
Residual spraying: lambda-cyhalothrin, and Approach 1 to calculate effectiveness, no insecticide resistance
Chemoprophylaxis for children: Maloprim®, perennial transmission, no drug resistance

Table 3.1. Baseline estimates of malaria morbidity and mortality used in model of childhood malaria

Input variable	Probability distribution	Parameters	Source
Children under 5 years of age			
Annual incidence of clinical episodes of malaria per child	Triangular	mode = 1.5 min = 1.0 max = 2.9	Murray & Lopez 1996[12]; Nájera & Hempel 1996[11]; Greenwood *et al* 1987[13]
Percentage of episodes that are severe	Triangular	mode = 5% min = 3% max = 7%	Murray & Lopez 1996[73]; Nájera & Hempel 1996[11]; Greenwood *et al.* 1987[13]
Percentage of severe cases that result in neurological sequelae	Triangular	mode = 1.32% min = 0.41% max = 2.24%	Brewster *et al*. 1990[14]
Prevalence of malaria associated anaemia	Point estimate	9%	Murray & Lopez 1996[12]
Children over 5 years of age			
Annual incidence of clinical episodes of malaria per child	Triangular	mode = 0.55 min = 0.4 max = 1.1	Murray & Lopez 1996[12]; Nájera & Hempel 1996[11]; Greenwood *et al.* 1987[13]
Percentage of episodes that are severe	Triangular	mode = 1% min = 0.5% max = 1.5%	Murray & Lopez 1996[12]; Nájera & Hempel 1996[11]; Greenwood *et al.* 1987[13]
Percentage of severe cases that result in neurological sequelae	Triangular	mode = 0.5% min = 0.25% max = 0.75%	Murray & Lopez 1996[12]; Nájera & Hempel 1996[11]; Greenwood *et al.* 1987[13]
Prevalence of malaria associated anaemia	Point estimate	4%	Murray & Lopez 1996[12]

Table 3.2. Input variables used in the analysis of ITNs

Input variable	Probability distribution	Distribution arameters	Source
			All costs in 1995 US dollars
Effectiveness inputs			
Reduction in all cause mortality in children aged 1-59 months using ITNs	Normal	mean = 19% s.d. = 3%	Lengeler, 1998[17] C. Lengeler, personal communication
Reduction in malaria-related morbidity in children aged 1-59 months using ITNs	Normal	mean = 46% s.d. = 2.6%	Lengeler, 1998[17] C. Lengeler, personal communication
Retreatment rate	Triangular	mode = 30% min = 20% max = 80%	Chavasse *et al*., 1999[19]
Percentage of children sleeping under net	Triangular	mode = 0.72 min = 0.50 max = 0.97	Alonso *et al*., 1993, D'Alessandro *et al*., 1995, Binka *et al*., 1996, Nevill *et al*., 1996, Habluetzel *et al*., 1997[5-7, 74, 75]
Cost inputs			
Cost of net	Uniform	min = $4.00 max = $11.39	Imported and local nets used in trials [20, 22-25]
Useful life of net	Uniform	min = 3 years max = 6 years	Range given in Feilden, 1996[26]
Average size of net	Uniform	min = 13 m^2 max = 18 m^2	Feilden, 1996[26], J. Lines, personal communication
Nets distributed per child under 5 years	Uniform	min = 2 max = 3.91	Picard *et al*., 1993, Aikins *et al*., 1998, Binka *et al*., 1997, Curtis *et al*., 1998[20, 22, 24, 25]
Permethrin target dose	Uniform	min = 200 mg/m^2 max = 500 mg/m^2	Lines, 1996[16]
Deltamethrin target dose	Uniform	min = 10 mg/m^2 max = 25 mg/m^2	Lines, 1996[16]
Duration of permethrin effect	Point estimate	0.5 years	Lines, 1996[16]
Duration of deltamethrin effect	Point estimate	1 year	Lines, 1996[16]
Wastage (excess insecticide used compared with target dose)	Triangular	mode = 30% min = 10% max = 50%	G. White, D. Chavasse, M. Bhatia, J. Lines, personal communication, Curtis *et al*., 1998[25]
Cost of permethrin EC per kg active ingredient FOB	Uniform	min = $46.40/kg max = $63.00/kg	Acriviadis personal communication 1997, Zeneca personal communication to S. Meek, 1996, Feilden 1996[26], Zeneca personal communication to J. Lines, 1994

Table 3.2. Input variables used in the analysis of ITNs (cont.)

Input variable	Probability distribution	Distribution arameters	Source
			All costs in 1995 US dollars
Cost of deltamethrin EC per kg active ingredient FOB	Uniform	min = $684.40/kg max = $895.20/kg	Wery and Coosemans, 1993[36], P. Acriviadis personal communication 1997, and Mouchet, 1994[76].
External freight cost per tonne	Uniform	min = $651 max = $1560	Schofield, 1992[77]and G. White personal communication to C. Curtis, 1994
Cost of staff, sensitization & awareness campaign, office supplies and services per net			
very low income countries	Uniform	min = $0.07 max = $0.21	As for middle income but adjusted for lower income countries using estimated salary data from Tinker and Koblinsky, 1992 [78]
middle income countries		min = $0.09 max = $0.28	Aikins *et al*., 1998, Picard *et al*., 1993[20, 24]
higher income countries		min = $0.26 max = $0.80	As for middle income but adjusted for higher income countries using estimated salary data from Tinker and Koblinsky, 1992 [78]
Cost of community time per net	Uniform		
very low income countries		min = $0.02 max = $0.03	As for middle income but adjusted for lower income countries using estimated salary data from Tinker and Koblinsky, 1992 [78]
middle income countries		min = $0.02 max = $0.04	Aikins *et al*., 1998, Picard *et al*., 1993[20, 24]
higher income countries		min = $0.06 max = $0.11	As for middle income but adjusted for higher income countries using estimated salary data from Tinker and Koblinsky, 1992 [78]
Cost of transport per net	Uniform	min = $0.17 max = $0.33	Aikins *et al*., 1998, Picard *et al*., 1993[20, 24]
Cost of buildings and equipment per net	Uniform	min = $0.01 max = $0.04	Aikins *et al*., 1998, Binka *et al*., 1997[22, 24]
Cost of detergent per net	Uniform	min = $0.05 max = $0.07	Aikins *et al*., 1998[24], plus or minus 15%

Table 3.3. Breakdown of expected annual cost of ITNs per child under 5, using one treatment of deltamethrin p.a., adjusted for non-compliance (1995 US dollars)

Scenario		**Economic strata**		
		very low income	middle income	higher income
Nets and Insecticide	Net	$5.48 (83%)	$5.48 (82%)	$5.48 (76%)
Treatment	Insecticide	$0.48 (7%)	$0.48 (7%)	$0.48 (7%)
	Overheads	$0.63 (10%)	$0.70 (11%)	$1.22 (17%)
	Mean Cost	$6.59 (100%)	$6.66 (100%)	$7.18 (100%)
	90% range	$3.35 - $10.98	$3.39 - $11.05	$3.64 - $11.59
Insecticide	Net	0	0	0
Treatment only	Insecticide	$0.48 (43%)	$0.48 (41%)	$0.48 (28%)
	Overheads	$0.63 (57%)	$0.70 (59%)	$1.22 (72%)
	Mean Cost	$1.12 (100%)	$1.18 (100%)	$1.70 (100%)
	90% range	$0.37 - $1.70	$0.39 - $1.79	$0.51 - $2.59

Table 3.4. Cost-effectiveness of ITNs: mean CER and the range within which 90% of all CERs fell (1995 US dollars)

Scenario	Insecticide	Treatments per year	Economic strata	Mean CER	Range within which 90% of all CERs fell
Nets & Insecticide	Deltamethrin	1	very low	$44	$19 - $85
Treatment			middle	$44	$19 - $85
			higher	$177	$79 - $334
		2	very low	$50	$23 - $94
			middle	$51	$24 - $94
			higher	$214	$105 - $382
	Permethrin	1	very low	$45	$19 - $86
			middle	$45	$20 - $86
			higher	$181	$82 - $336
		2	very low	$52	$25 - $96
			middle	$53	$25 - $97
			higher	$222	$110 - $392
Insecticide	Deltamethrin	1	very low	$6	$4 - $10
Treatment only			middle	$7	$4 - $11
			higher	$37	$21 - $58
		2	very low	$13	$7 - $20
			middle	$14	$8 - $21
			higher	$74	$43 - $116
	Permethrin	1	very low	$12	$7 - $20
			middle	$13	$7 - $21
			higher	$60	$34 - $95
		2	very low	$15	$9 - $23
			middle	$16	$9 - $24
			higher	$82	$47 - $24

Table 3. 5. Input variables used in the analysis of residual spraying

Input variable	Probability Distribution	Distribution Parameters	Source All costs in 1995 US dollars
Effectiveness Approach 1: Infant mortality reduction from spraying trials			
Reduction in all cause mortality in children aged 0-11 months	Triangular	mode = 0.52 min = 0.41 max = 0.59	Molineaux, 1985[30]
Effectiveness Approach 2: Assume effectiveness equivalent to ITNs			
Reduction in all cause mortality in children aged 1-59 months	Normal	mean = 0.19 s.d. = 0.03	Lengeler 1998[17]
Reduction in malaria-related morbidity in children aged 1-59 months	Normal	mean = 0.46 s.d. = 0.026	Lengeler 1998[17]
Compliance	Triangular	mode = 0.825 min = 0.70 max = 0.95	Vundule *et al*. 1996[33], Attanayake, 1994[79]
Cost inputs			
Malathion and DDT target dose	Point estimate	2000 mg/m^2	Chavasse *et al*., 1997[29]
Deltamethrin target dose	Point estimate	20 mg/m^2	Chavasse *et al*., 1997[29]
Lambda-cyhalothrin target dose	Point estimate	25 mg/m^2	Chavasse *et al*., 1997[29]
Sprayable surface area per house	Uniform	min = 175m^2 max = 250m^2	Wery *et al*., 1993[36], Curtis *et al*. 1998[25], Attanayake, 1994[79], USAID[80]
Wastage (total insecticide used compared with target dose)	Uniform	min = 0.1 max = 0.5	USAID[80]
Cost of DDT WP per kg active ingredient FOB	Uniform	min = $4.67/kg max = $6.04/kg	Estimate using WHO, 1990[81] and Mouchet, 1991[76]
Cost of malathion EC per kg active ingredient FOB	Point estimate	$11.48/kg	Estimate using P. Acriviadis personal communication
Cost of deltamethrin EC per kg active ingredient FOB	Uniform	min = $684.40/kg max = $895.20/kg	Wery *et al*., 1993[36], P. Acriviadis personal communication., and Mouchet 1991[76]

Table 3. 5. Input variables used in the analysis of residual spraying (cont.)

Input variable	Probability Distribution	Distribution Parameters	Source All costs in 1995 US dollars
Cost of lambda-cyhalothrin EC per kg active ingredient FOB	Point estimate	$700/kg	G. White personal communication
External freight cost per tonne	Uniform	min = $651 max = $1560	Schofield, 1992[77] and G. White personal communication to C. Curtis, 1994
Cost per spraying pump	Uniform	min = $40 max = $120	Hudson price catalogue[82], Songane[34] (2 pumps per team)
Useful life of spraying pump	Point estimate	5 rounds	
Cost per maintenance kit	Uniform	min = $3 max = $10	Hudson price catalogue[82] (one kit between 3 teams)
Useful life of maintenance kit	Point estimate	2 rounds	
Cost per team of equipment for mixing insecticide	Uniform	min = $3 max = $4.95	Some, 1998[23], Phillips *et al*. 1991[83]
Useful life of mixing equipment	Point estimate	3 rounds	
Cost per team of equipment for measuring	Point estimate	$14.15	Phillips *et al.* 1991[83]
Useful life of measuring equipment	Point estimate	10 rounds	
Protective clothing per sprayman	Uniform	min = $16.08 max = $31.56	Bird (Zeneca) personal communication.Includes hats, visors, overalls, aprons, rubber boots, gloves and face masks
Useful life of protective clothing	Point estimate	4 years	
Sprayman salary cost per manday	Triangular		Estimate of daily wage rate for unskilled labourer (extrapolated from Tinker and Koblinsky[78], using half of health centre staff FTE, plus or minus 15%)
very low income		mean = $4.50 min = $3.83 max = $5.18	
middle income		mean = $5.50 min = $4.68 max = $6.33	
higher income		mean = $16.5 min = $14.03 max = $18.98	

Table 3. 5. Input variables used in the analysis of residual spraying (cont.)

Input variable	Probability Distribution	Distribution Parameters	Source All costs in 1995 US dollars
Men per team	Point estimate	5	M. Bhatia, personal communication
Houses sprayed per team per day	Uniform	min = 12 max = 40	Phillips *et al.* 1991[83], Curtis *et al*. 1998[25], USAID, Attanayake, 1994[79]
Number of days per spraying cycle	Uniform	min = 30 max = 60	USAID[80]
Supervisor salary cost per manday	Triangular		Estimate of daily wage rate for supervisory staff (extrapolated from Tinker and Koblinsky[78], using programme management staff FTE, plus or minus 15%)
very low income		mean = $14.00 min = $11.90 max = $16.10	
middle income		mean = $18.00 min = $15.30 max = $20.70	
higher income		mean = $53.00 min = $45.05 max = $60.95	
Number of teams per supervisor	Point estimate	3	
Training cost per day	Point estimate	10	
Number of days training per sprayman	Uniform	min = 4 max = 10	Phillips *et al.* 1991[83], J. Lines personal communication, Songane, 1997[34]
Transport cost per house	Uniform	min = $0.33 max = $0.98	Based on data from ITN trials scaled up to account for greater insecticide quantities for spraying[20, 24]
Sensitization & awareness campaign cost per person	Uniform	min = $0.020 max = $0.051	Estimated from costs in ITN trials[22, 24]
Average household size	Triangular	mode = 5.2 min = 3.8 max = 6.4	United Nations, 1997[84]

Table 3.6. Estimated insecticide cost per house sprayed for four insecticides using mean cost input variables (1995 US dollars)

	DDT	Malathion	Deltamethrin	Lambda-cyhalothrin
Target dose, mg/m^2	2000	2000	20	25
Sprayable surface per house, m^2	203.5	203.5	203.5	203.5
Target active ingredient per house, mg	407000	407000	4070	5087.5
% active ingredient	0.75	0.5	0.025	0.1
Target insecticide per house, mg	542667	814000	162800	50875
Wastage %	0.2	0.2	0.2	0.2
Total insecticide per house, mg	678333	1017500	203500	63593.75
Cost per kg or litre FOB	$4.02	$2.87	$19.75	$70
Cost insecticide per house	$2.72	$2.92	$4.02	$4.45
Freight cost per tonne	$1100	$1100	$1100	$1100
Freight cost per house	$0.75	$1.12	$0.22	$0.07
CIF cost of insecticide per house	$3.47	$4.05	$4.24	$4.52

Table 3.7. Breakdown of annual cost of residual spraying per child under 5, using lambda-cyhalothrin, adjusted for non-compliance (1995 US dollars)

Type of transmission		**Economic strata**		
		very low income	middle income	higher income
Seasonal	Insecticide	$5.03 (69%)	$5.03 (67%)	$6.27 (50%)
(One round p.a.)	Staff	$1.01 (14%)	$1.25 (17%)	$4.64 (37%)
	Equipment	$0.04 (0.6%)	$0.04 (0.6%)	$0.05 (0.4%)
	Overheads	$1.24 (17%)	$1.24 (16%)	$1.54 (12%)
	Mean Cost	$7.33 (100%)	$7.56 (100%)	$12.50 (100%)
	90% range	$5.76 - $10.18	$5.99 - $10.55	$9.12 - $17.57
Perennial	Insecticide	$10.07 (69%)	$10.07 (67%)	$12.53 (50%)
(Two rounds p.a.)	Staff	$2.02 (14%)	$2.50 (17%)	$9.28 (37%)
	Equipment	$0.08 (0.6%)	$0.08 (0.6%)	$0.10 (0.4%)
	Overheads	$2.48 (17%)	$2.48 (16%)	$3.08 (12%)
	Mean Cost	$14.65 (100%)	$15.12 (100%)	$25.00 (100%)
	90% range	$11.53 - $20.36	$11.92 - $21.09	$18.23 - $35.15

Table 3.8. Cost-effectiveness of residual spraying using lambda-cyhalothrin: mean CER and the range within which 90% of all CERs fell (1995 US dollars)

	Spraying rounds p.a.	Economic strata	Mean CER, $	Range within which 90% of all CERs fell
Effectiveness Approach 1: Infant mortality reduction from spraying trials				
	1	very low	$22	$16 - $29
		middle	$22	$16 - $30
		higher	$86	$60 - $120
	2	very low	$43	$32 - $58
		middle	$45	$33 - $60
		higher	$172	$120 - $239
Effectiveness Approach 2: Assume effectiveness equivalent to ITNs				
	1	very low	$26	$18 - $36
		middle	$27	$19 - $37
		higher	$167	$113 - $242
	2	very low	$51	$36 - $72
		middle	$53	$37 - $75
		higher	$334	$226 - $484

Table 3.9. Input variables used in the analysis of chemoprophylaxis for children

Input variable	Probability Distribution	Distribution Parameters	Source
			All costs in 1995 US dollars
Reduction in all cause mortality in children aged 6-59 months	Normal distribution truncated at 95% CI	mean = 49% CI 2% - 74%	Menon *et al*. 1990[40] (distribution truncated at upper and lower 95% CI to avoid extreme values which would lead to negative effectiveness, and bias estimates of the CER)
Reduction in malaria-related morbidity in children aged 6-59 months	Normal distribution truncated at 95% CI	mean = 73% CI 25% - 90%	Menon *et al*. 1990[40]
Actual Compliance	Uniform	min = 0.29 max = 0.72	Kaseje *et al*.[43], Allen *et al*., 1990[42]l, MacCormack and Lwihula, 1983[44]
Warehouse cost per tablet of Maloprim® (100mg dapsone and 12.5mg pyrimethamine)	Triangular	mean = $0.14 min = $0.12 max = $0.16	BNF, 1997[45], converted to 1995 prices, plus or minus 15%
Freight cost for drugs as a % of warehouse cost	Point estimate	25%	Foster 1991[85]
Wastage of drugs	Point estimate	25%	
Tablets per dose	Point estimate		
6-11 months		0.25	Menon *et al*., 1990[40]
12-59 months		0.5	
Doses per month	Point estimate	2.17	Assuming one dose a fortnight (Menon *et al*., 1990[40])
Annualised cost per child of initial training of staff and VHWs	Point estimate		
very low income countries		$0.10	Middle income estimate from Picard *et al*. 1992[46]Very low and higher income estimates as for middle income, but adjusted by ratio of salaries (using data adapted from Tinker and Koblinsky 1992[78])
middle income countries		$0.14	
higher income countries		$0.39	

Table 3.9. Input variables used in the analysis of chemoprophylaxis for children (cont.)

Input variable	Probability Distribution	Distribution Parameters	Source All costs in 1995 US dollars
Cost per child per month of staff, sensitization & awareness campaign, and supervision	Point estimate		
very low income countries		$0.24	Middle income estimate from Picard *et al.* 1992[46]. Very low and higher income estimates as for middle income, but adjusted by ratio of salaries (using data adapted from Tinker and Koblinsky 1992[78])
middle income countries		$0.32	
higher income countries		$0.90	
Cost of VHW time per child per month	Point estimate		
very low income countries		$0.01	Middle income estimate from Picard *et al.* 1992[46]. Very low and higher income estimates as for middle income, but adjusted by ratio of salaries (using data adapted from Tinker and Koblinsky 1992[78])
middle income countries		$0.01	
higher income countries		$0.03	
Transport cost per child per month	Point estimate	$0.19	Picard *et al*. 1992[46]
Cost of VHW per annum (excluding drugs)			
very low income countries	Point estimate	$591	Walt, 1990[47]
middle income countries	Point estimate	$778	As for very low income, but adjusted by ratio of salaries (using data adapted from Tinker and Koblinsky, 1992[78])
higher income countries	Uniform	min = $1321 max = $2891	Walt, 1990[47]
Number of people covered by VHW	Uniform	min = 500 max = 1200	Kaseje *et al*., 1987[49], Delacollette *et al*., 1996[48]

Table 3.10. Breakdown of expected annual cost of chemoprophylaxis per child adjusted for non-compliance (1995 US dollars)

Costing	Length of Transmission season		Economic strata		
			very low income	middle income	higher income
Incremental	Seasonal	Drugs	$0.67 (54%)	$0.67 (49%)	$0.67 (30%)
		VHW time	$0.03 (2%)	$0.04 (3%)	$0.10 (5%)
		Transport	$0.21 (17%)	$0.21 (15%)	$0.21 (9%)
		Other overheads[1]	$0.34 (28%)	$0.45 (33%)	$1.30 (57%)
		Mean cost	$1.25 (100%)	$1.37 (100%)	$2.29 (100%)
		90% range	$0.98 - $1.54	$1.09 - $1.66	$1.98 - $2.60
	Perennial	Drugs	$1.34 (62%)	$1.34 (59%)	$1.34 (41%)
		VHW time	$0.06 (3%)	$0.07 (3%)	$0.21 (6%)
		Transport	$0.41 (19%)	$0.41 (18%)	$0.41 (13%)
		Other overheads[1]	$0.34 (16%)	$0.45 (20%)	$1.30 (40%)
		Mean cost	$2.15 (100%)	$2.28 (100%)	$3.27 (100%)
		90% range	$1.61 - $2.73	$1.73 - $2.87	$2.67 - $3.91
Total	Seasonal	Drugs	$0.67 (12%)	$0.67 (9%)	$0.67 (3%)
		VHW time	$0.03 (1%)	$0.04 (1%)	$0.10 (1%)
		Transport	$0.21 (4%)	$0.21 (3%)	$0.21 (1%)
		Other overheads[1]	$0.34 (6%)	$0.45 (6%)	$1.30 (6%)
		VHW programme costs	$4.61 (78%)	$6.06 (82%)	$20.13 (82%)
		Mean cost	$5.86 (100%)	$7.43 (100%)	$22.42 (100%)
		90% range	$4.58 - $8.59	$5.77 - $11.01	$13.92 - $37.99
	Perennial	Drugs	$1.34 (20%)	$1.34 (16%)	$1.34 (6%)
		VHW time	$0.06 (1%)	$0.07 (1%)	$0.21 (1%)
		Transport	$0.41 (6%)	$0.41 (5%)	$0.41 (2%)
		Other overheads[1]	$0.34 (5%)	$0.45 (5%)	$1.30 (6%)
		VHW programme costs	$4.61 (68%)	$6.06 (73%)	$20.13 (86%)
		Mean cost	$6.76 (100%)	$8.34 (100%)	$23.40 (100%)
		90% range	$5.34 - $9.54	$6.58 - $11.96	$14.91 - $39.02

[1] "Other overheads" covers training, supervision, sensitization and awareness campaign.

Table 3.11. Cost-effectiveness of chemoprophylaxis for children: mean CER and the range within which 90% of all CERs fell (1995 US dollars)

Costing	Length of transmission season	Economic strata	Mean CER, $	Range within which 90% of all CERs fell
Incremental	Seasonal	very low	$3	$2 - $7
		middle	$4	$2 - $7
		higher	$30	$16 - $59
	Perennial	very low	$6	$3 - $12
		middle	$6	$3 - $12
		higher	$43	$23 - $85
Total	Seasonal	very low	$17	$7 - $36
		middle	$22	$9 - $47
		higher	$315	$121 - $695
	Perennial	very low	$20	$8 - $41
		middle	$24	$10 - $52
		higher	$327	$129 - $723

Table 3.12. Annual cost implications of full coverage of target population with prevention interventions in Tanzania (very low income country). Mean cost, and range (in brackets) within which 90% of cost estimates fell (1995 US dollars)

Intervention	Government cost p.a.	Cost as % Government health budget
ITNs (deltamethrin, one treatment per year)		
Nets and Insecticide Treatment	$22.7m ($11.6m - $37.8m)	24% (12% - 40%)
Insecticide Treatment only	$3.1m ($1.3m - $5.9m)	3% (1.4% - 6%)
Residual Spraying (lambda-cyhalothrin)		
Seasonal transmission (one round p.a.)	$25.6m ($20.1m - $35.6m)	27% (21% - 38%)
Perennial transmission (two rounds p.a.)	$51.2m ($40.3m - $71.2m)	55% (43% - 76%)
Chemoprophylaxis for children (Maloprim®, perennial transmission)		
Incremental costs only	$6.6m ($5.0m - $8.4m)	7% (5% - 9%)
Total costs (including cost of VHW programme)	$20.9m ($16.5m - $29.4m)	22% (18% - 31%)

Based on the following assumptions:

- Tanzania population of 29.2m[9]
- 70% of the Tanzanian population at high risk of malaria
- Proportion of the population in target group for each intervention calculated from model life table
- Government health budget per annum of $94m (including donor contributions)[86]
- Government cost for ITNs excludes cost of community time and detergent which are provided by households, and Government cost for chemoprophylaxis excludes cost of volunteer VHW time.
- No cost recovery

References

1. WHO. Implementation of the global malaria control strategy - Report of a WHO Study Group on the implementation of the global plan of action for malaria control 1993-2000. *WHO Technical Report Series 839* 1993.
2. WHO. Malaria Control - Country profiles, Second Meeting of Interested Parties on the Control of Tropical Diseases. Geneva: 1994.
3. Lindsay SW, Gibson ME. Bednets revisited - Old idea, new angle. *Parasitology Today* 1988; 4(10): 270-272.
4. Alonso PL, Lindsay SW, Schellenberg J, et al. A malaria control trial using insecticide-treated bed nets and targeted chemoprophylaxis in a rural area of the Gambia, West-Africa. 6. The impact of the interventions on mortality and morbidity from malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1993; 87(S2): 37-44.
5. D'Alessandro U, Olaleye BO, McGuire W, et al. Mortality and morbidity from malaria in Gambian children after introduction of an impregnated bednet programme. *Lancet* 1995; 345(8948): 479-83.
6. Binka FN, Kubaje A, Adjuik M, et al. Impact of permethrin impregnated bednets on child mortality in Kassena-Nankana district, Ghana: a randomized controlled trial. *Tropical Medicine and International Health* 1996; 1(2): 147-54.
7. Nevill CG, Some ES, Mung'ala VO, et al. Insecticide-treated bednets reduce mortality and severe morbidity from malaria among children on the Kenyan coast. *Tropical Medicine and International Health* 1996; 1(2): 139-46.
8. Greenwood BM. Bednets and mortality from malaria - Paper for the WHO Expert Committee on Malaria. London School of Hygiene and Tropical Medicine, 1998.
9. World Bank. *World Development Report 1997. The state in a changing world.* New York: Oxford University Press, 1997.
10. Caughley G. *The analysis of vertebrate populations.* John Wiley & Sons Ltd, Chichester 1977.
11. Nájera JA, Hempel J. *The burden of malaria*. WHO CTD/MAL/96.10, 1996.
12. Murray CJL, Lopez AD. *The global burden of disease: A comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020*. Harvard School of Public Health (on behalf of WHO and the World Bank), distributed by Harvard University Press, 1996.
13. Greenwood BM, Bradley AK, Greenwood AM, et al. Mortality and morbidity from malaria among children in a rural area of The Gambia, West Africa. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1987; 81(3): 478-86.
14. Brewster DR, Kwiatkowski D, White NJ. Neurological sequelae of cerebral malaria in children. *Lancet* 1990; 336(8722): 1039-43.
15. Zimicki S. Promotion in Sub-Saharan Africa. In: Lengeler C, Cattani J. and de Savigny D., ed. *Net Gain: a new method for preventing malaria deaths.* IDRC/WHO, 1996: 111-147.
16. Lines JD. The technical issues. In: Lengeler C, Cattani J. and de Savigny D., ed. Net Gain: a new method for preventing malaria deaths. IDRC/WHO, 1996: 17-53.
17. Lengeler C. Insecticide-treated bednets and curtains for malaria control (Cochrane Review). In *The Cochrane Library* Issue 3, 1998: Oxford, Update Software.
18. Curtis CF, Myamba J, Wilkes TJ. Various pyrethroids on bednets and curtains. *Memorias do Instituto Oswaldo Cruz* 1992; 3: 363-70.
19. Chavasse D, Reed C, Attawell K. *Insecticide Treated Net Projects: A Handbook for Managers*, London and Liverpool Malaria Consortium, 1999: 1-173.
20. Picard J, Aikins M, Alonso PL, Armstrong Schellenberg JR, Greenwood BM, Mills A. A malaria control trial using insecticide-treated bed nets and targeted chemoprophylaxis in a rural area of The Gambia, West Africa. 8. Cost-effectiveness of bed net impregnation alone or combined with chemoprophylaxis in preventing mortality and morbidity from malaria in Gambian children. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1993; 2: 53-7.
21. Aikins MKS. *Cost-effectiveness analysis of insecticide-impregnated mosquito nets (bednets) used as a malaria control measure: a study from the Gambia*. PhD Thesis, Department of Public Health and Policy, London School of Hygiene and Tropical Medicine, University of London, 1995.
22. Binka FN, Mensah OA, Mills A. The cost-effectiveness of permethrin impregnated bednets in preventing child mortality in Kassena-Nankana district of Northern Ghana. *Health Policy* 1997; 41: 229-239.
23. Some ES. *Optimizing the community effectiveness of insecticide-impregnated bednets used for malaria control in coastal Kenya: Implications of perceptions, programme organization, compliance, and costs.*

PhD Thesis, Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, University of London, 1998.
24. Aikins MK, Fox-Rushby J, D'Allessandro U, et al. The Gambian National Impregnated Bednet Programme: Consequences and net cost-effectiveness. *Social Science and Medicine* 1998; 46(2): 181-191.
25. Curtis CF, Maxwell CA, Finch R, Njunwa KJ. A comparison of use of a pyrethroid either for house spraying or for bednet treatment against malaria vectors. *Tropical Medicine and International Health* 1998; 3(8): 619-631.
26. Feilden RM. Experiences of implementation. In: Lengeler C, Cattani J. and de Savigny D., ed. *Net Gain: a new method for preventing malaria deaths.* IDRC/WHO, 1996: 55-110.
27. Miller JE, Lindsay SW, Schellenberg J, Adiamah J, Jawara M, Curtis CF. Village Trial of bednets impregnated with wash-resistant permethrin compared with other pyrethroid formulations. *Medical and Veterinary Entomology* 1995; 9(1): 43-49.
28. Curtis CF. Should DDT continue to be recommended for malaria vector control? *Medical and Veterinary Entomology* 1994; 8(2): 107-112.
29. Chavasse DC, Yap HH. Chemical methods for the control of vectors and pests of public health importance. WHO Pesticide Evaluation Scheme, 1997.
30. Molineaux L. The impact of parasitic diseases and their control, with an emphasis on malaria and Africa. In: Vallin J, Lopez, A., ed. *Health Policy, Social Policy and Mortality Prospects*. Liège: Ordina Editions, 1985: 13-44.
31. Zahar AR. Vector bionomics in the epidemiology and control of malaria, Part 1, Section III (A), WHO Report. 1985.
32. Hill JA, Lake S, Meek SR, Mehra S, Standing H. *Approaches to malaria control in Africa, Part I: analysis and opportunities for malaria control support in selected countries in Africa*. London/Liverpool Malaria Consortium, 1996.
33. Vundule C, Mharakurwa S. Knowledge, practices, and perceptions about malaria in rural communities of Zimbabwe - Relevance to malaria control. *Bulletin of The World Health Organization* 1996; 74(1): 55-60.
34. Songane FF. Cost-effectiveness of malaria control programmes in Beira-Mozambique - thesis submitted in partial fulfilment of MSc in Financial Economics. School of Oriental and African Studies, University of London, 1997.
35. Julvez J. The cost of a campaign against malaria. General considerations. *Bulletin de la Société de Pathologie Exotique* 1990; 83(2): 211-6.
36. Wery M, Coosemans M. Les coûts du paludisme et son impact socio-économique en Afrique. *Cahiers Santé* 1993; 3: 323-30.
37. El Gaddal AA, Haridi AAM, Hassan FT, Hussein H. Malaria control in the Gezira-Managil Irrigated Scheme of the Sudan. *Journal of Tropical Medicine and Hygiene* 1985; 88: 153-159.
38. Hedman P, Brohult J, Forslund J, Sirleaf V, Bengtsson E. A pocket of controlled malaria in a holoendemic region of West Africa. *Annals of Tropical Medicine and Parasitology* 1979; 73(4): 317-25.
39. Wernsdorfer G, Wernsdorfer WH. Social and economic aspects of malaria and its control. In: Wernsdorfer WH, and McGregor, I., ed. *Malaria: Principles and Practice of Malariology Volume II*. Churchill Livingstone, 1988: 1421-1471.
40. Menon A, Snow RW, Byass P, Greenwood BM, Hayes RJ, N'Jie ABH. Sustained protection against mortality and morbidity from malaria in rural Gambian children by chemoprophylaxis given by village health workers. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1990; 84(6): 768-72.
41. Greenwood BM, Greenwood AM, Bradley AK, et al. Comparison of two strategies for control of malaria within a primary health care programme in the Gambia. *Lancet* 1988; 1(8595): 1121-7.
42. Allen SJ, Snow RW, Menon A, Greenwood BM. Compliance with malaria chemoprophylaxis over a five-year period among children in a rural area of The Gambia. *Journal of Tropical Medicine and Hygiene* 1990; 93(5): 313-22.
43. Kaseje DC, Sempebwa EK, Spencer HC. Malaria chemoprophylaxis to pregnant women provided by community health workers in Saradidi, Kenya. I. Reasons for non-acceptance. *Annals of Tropical Medicine and Parasitology* 1987; 81(1): 77-82.
44. MacCormack CP, Lwihula G. Failure to participate in a malaria chemosuppression programme: North Mara, Tanzania. *Journal of Tropical Medicine and Hygiene* 1983; 86(3): 99-107.
45. British Medical Association and Royal Pharmaceutical Society of Great Britain. British National Formulary. 1997.
46. Picard J, Mills A, Greenwood B. The cost-effectiveness of chemoprophylaxis with Maloprim administered by primary health care workers in preventing death from malaria amongst rural Gambian children aged less

than five years old. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1992; 86(6): 580-1.

47. Walt G. *Community health workers in national programmes: Just another pair of hands?* Milton Keynes: Open University Press, 1990.
48. Delacollette C, Van der Stuyft P, Molima K. Using community health workers for malaria control: experience in Zaire. *Bulletin of the World Health Organization* 1996; 74(4): 423-30.
49. Kaseje DC, Spencer HC, Sempebwa EK. Characteristics and functions of community health workers in Saradidi, Kenya. *Annals of Tropical Medicine and Parasitology* 1987; 81(1): 56-66.
50. Management Sciences for Health. *International Drug Price Indicator Guide*. Boston: MSH, 1996.
51. WHO. Vector resistance to pesticides, Fifteenth Report of the WHO Expert Committee of Vector Biology and Control. Geneva: 1992.
52. MartinezTorres D, Chandre F, Williamson MS, et al. Molecular characterization of pyrethroid knockdown resistance (kdr) in the major malaria vector Anopheles gambiae S.S. *Insect Molecular Biology* 1998; 7(2): 179-184.
53. Elissa N, Mouchet J, Rivière F, Meunier J-Y, Yao K. Resistance of Anopheles gambiae s.s. to pyrethroids in Côte d'Ivoire. *Annales de la Société Belge de Médecine Tropicale* 1993; 73: 291-294.
54. Curtis CF, Miller JE, Hassan Hodjati M, Kolaczinski JH, Kasumba I. Can anything be done to maintain the effectiveness of pyrethroid-impregnanted bednets against malaria vectors? *Philosophical Transactions of the Royal Society of London* 1998; B(353): 1769-1775.
55. WHO/CTD. *Assessment of therapeutic efficacy of antimalarial drugs for uncomplicated falciparum malaria in areas with intense transmission*. Geneva: WHO/MAL/96.1007.
56. Allen SJ, Otoo LN, Cooke GA, A OD, Greenwood BM. Sensitivity of Plasmodium falciparum to Maloprim after five years of targetted chemoprophylaxis in a rural area of The Gambia. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1990; 84(5): 666-7.
57. Snow RW, Bastos de Azevedo I, Lowe BS, et al. Severe childhood malaria in two areas of markedly different falciparum transmission in East Africa. *Acta Tropica* 1994; 57(4): 289-300.
58. Snow RW, Omumbo JA, Lowe B, et al. Relation between severe malaria morbidity in children and level of Plasmodium falciparum transmission in Africa. *Lancet* 1997; 349(9066): 1650-4.
59. Trape JF, Rogier C. Combating malaria morbidity and mortality by reducing transmission. *Parasitology Today* 1996; 12(6): 236-240.
60. Greenwood BM, David PH, Otoo-Forbes LN, et al. Mortality and morbidity from malaria after stopping malaria chemoprophylaxis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1995; 89(6): 629-33.
61. Otoo LN, Snow RW, Menon A, Byass P, Greenwood BM. Immunity to malaria in young Gambian children after a two-year period of chemoprophylaxis. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1988; 82(1): 59-65.
62. Bradley Moore AM, Greenwood BM, Bradley AK, et al. Malaria chemoprophylaxis with chloroquine in young Nigerian children. I. Its effect on mortality, morbidity and the prevalence of malaria. *Annals of Tropical Medicine and Parasitology* 1985; 79(6): 549-62.
63. Menendez C, Kahigwa E, Hirt R, et al. Randomised placebo-controlled trial of iron supplementation and malaria chemoprophylaxis for prevention of severe anaemia and malaria in Tanzanian infants. *Lancet* 1997; 350(9081): 844-50.
64. Coleman PG, Goodman CA, Mills A. Rebound mortality and the cost-effectiveness of malaria control: potential impact of increased mortality in late childhood following the introduction of insecticide treated nets. *Tropical Medicine and International Health*, 1999; 4: 175-86.
65. Lindsay SW, Alonso PL, Armstrong Schellenberg JR, et al. A malaria control trial using insecticide-treated bed nets and targeted chemoprophylaxis in a rural area of The Gambia, West Africa. 7. Impact of permethrin-impregnated bed nets on malaria vectors. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1993; 2: 45-51.
66. Quiñones ML, Lines JD, Thomson MC, Jawara M, Greenwood BM. Permethrin-treated bed nets do not have a "mass killing effect" on village populations of *Anopheles gambiae s.l.* in The Gambia. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1998; 92: 373-378.
67. Karch S, Garin B, Asidi N, Manzambi Z, Salaun JJ, Mouchet J. Impregnated bednets against malaria in Zaire. *Annales de la Société Belge de Médecine Tropicale* 1993; 73(1): 37-53.
68. Magesa SM, Wilkes TJ, Mnzava AEP, et al. Trial of pyrethroid impregnated bednets in an area of Tanzania holoendemic for malaria. 2. Effects on the malaria vector population. *Acta Tropica* 1991; 49(2): 97-108.

69. Greenwood BM, Greenwood AM, Snow RW, Byass P, Bennett S, Hatib-N'Jie AB. The effects of malaria chemoprophylaxis given by traditional birth attendants on the course and outcome of pregnancy. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1989; 83(5): 589-94.
70. Menendez C, Todd J, Alonso PL, et al. The effects of iron supplementation during pregnancy, given by traditional birth attendants, on the prevalence of anaemia and malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1994; 88(5): 590-3.
71. Lines J. Review: mosquito nets and insecticides for net treatment: a discussion of existing and potential distribution systems in Africa. *Tropical Medicine and International Health* 1996; 1(5): 616-32.
72. De Ferranti D. Paying for health services in developing countries: an overview. World Bank Staff Working Paper, No. 721. Washington, DC: World Bank, 1985.
73. Murray CJ, Lopez AD, Jamison DT. The global burden of disease in 1990: summary results, sensitivity analysis and future directions. *Bulletin of the World Health Organization* 1994; 72(3): 495-509.
74. Alonso PL, Lindsay SW, Armstrong Schellenberg JR, et al. A malaria control trial using insecticide-treated bed nets and targeted chemoprophylaxis in a rural area of The Gambia, West Africa. 5. Design and implementation of the trial. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1993; 2: 31-6.
75. Habluetzel A, Diallo DA, Esposito F, et al. Do insecticide-treated curtains reduce all-cause child mortality in Burkina Faso? *Tropical Medicine and International Health* 1997; 2(9): 855-62.
76. Mouchet J. DDT and public health. *Santé* 1994; 4(4): 257-62.
77. Schofield CJ. DDT and malaria vector control [Letter]. *International Pest Control* 1992; May/June: 88-89.
78. Tinker A, Koblinsky MA. *Making motherhood safe*. Washington D.C.: The World Bank, 1992.
79. Attanayake AMGNK. *Cost-effectiveness of anti-malaria activities in Sri Lanka.* PhD Thesis, Department of Public Health and Policy, London School of Hygiene and Tropical Medicine, University of London, 1994.
80. USAID. Manual on malaria control in primary health care in Africa. Washington D.C.: Bureau for Africa, 1982.
81. WHO. Control of the leishmaniases. Report of a WHO Expert Committee. *World Health Organization Technical Report Series* 1990; 793: 1-158.
82. Hudson. Sprayer and duster price list. Chicago: 1996.
83. Phillips MA, Mills AJ. The operational costs of spraying residual insecticides: a case study from Nepal. *Journal of Tropical Medicine and Hygiene* 1991; 94: 130-139.
84. United Nations. Demographic Yearbook, 1995. New York: 1997.
85. Foster SD. Pricing, distribution, and use of antimalarial drugs. *Bulletin of The World Health Organization* 1991; 69(3): 349-363.
86. World Bank. *Tanzania - Role of Government: Public Expenditure Review, Volume 1.* Washington DC: World Bank, 1994.

Chapter 4 – Prevention of Malaria in Pregnancy

4.1 Introduction

Pregnant women are particularly vulnerable to malaria. Infection may cause harmful effects for the mother, and placental parasitemia retards the growth of the foetus and increases the prevalence of low birth weight (LBW), the proportion of newborns weighing less than 2,500g[1-3]. This is of particular concern because LBW is associated with increased neonatal mortality[4]. In areas of high transmission the effects are most marked in women during their first pregnancy (primigravidae). The reason for this is unclear; it is probable that immunosuppression is more marked in primigravidae, but it is also possible that protective immunity may be acquired in the reproductive tract through malaria infection during the first pregnancy, reducing susceptibility in later pregnancies[5].

ITNs have been shown to be effective in preventing malaria and reducing mortality in children under 5 years of age[6-8], but the results for their impact on maternal or foetal health when used during pregnancy are inconclusive[9-11]. However, chemoprophylaxis or intermittent treatment with antimalarials during pregnancy has been shown to reduce the risk of malaria infection in all pregnant women and to increase significantly the birth weight of babies born to primigravidae[12]. In 1986 WHO recommended that all pregnant women in malaria endemic areas receive regular prophylaxis[13], but this has rarely been accomplished effectively in practice. By the late 1980s few African countries had achieved coverage of even half of the population of pregnant women, and in a survey of four countries only 1% to 18% of women reported using an antimalarial drug on a weekly basis at a dosage that approximated the WHO recommendation[13]. WHO have continued to recommend chemoprophylaxis for pregnant women as part of the Global Malaria Control Strategy, although it is recognized that the success of this policy is hampered by both increasing drug resistance and poor compliance with therapy[14].

This analysis assesses whether a drive to increase the coverage of strategies to prevent malaria in pregnancy is justified on the basis of cost-effectiveness. It combines data from a meta-analysis of strategies for preventing malaria in pregnancy[12] with information on costs and compliance from a range of published and unpublished sources, and explores the impact of prophylaxis and intermittent treatment on neonatal mortality via its effect on birth weight. A model of birth weight and child survival is presented and used to estimate the cost per DALY averted by prophylaxis or intermittent treatment in the three economic strata.

The intervention was defined as the provision of chemoprophylaxis or intermittent treatment as an addition to standard ANC services, with antimalarial drugs distributed during ANC visits in the second and third trimesters. Two potential drugs were considered: CQ, the most widely used prophylactic, and SP. CQ is taken prophylactically, in a weekly dose of 300 mg, with tablets prescribed at ANC visits and then taken home by women. With increasing resistance to CQ in many areas of Africa, intermittent treatment with SP is now being considered as a potential alternative, and has been introduced in Malawi[13], and approved in Kenya[15]. In contrast with the CQ regimen, which is designed to achieve sustained levels of the drug in the blood throughout the second half of pregnancy, the intermittent therapy with SP is designed to ensure that infections are cleared fairly

rapidly if they occur[a]. Apart from lower levels of drug resistance, SP has the additional advantage over CQ that it is taken in only two doses (of 1,500 mg/75 mg), and is therefore likely to have higher rates of compliance than the weekly CQ regimen.

4.2 A model of birth weight and child survival

It was assumed that birth weight distributions were normal and, therefore, fully defined by their mean m and standard deviation s[b]. A range of estimates for m and s for babies born to women who had not received prophylaxis or intermittent treatment were gathered from published data on birth weights in primigravidae in malarious settings in SSA[18-21]. Birth weight distributions were described in terms of the relative birth frequency, f, of weight x kg. Birth weights were assumed to lie in the range of 1.0 to 4.5 kg and were grouped to the nearest 0.1 kg.

Birth weight specific neonatal mortality m_x was defined as the proportion of live new-borns of birth weight x kg who die during the neonatal period, the first 28 days of life. A Wilcox-Russell model of mortality[17, 22, 23] was fitted directly to empirical neonatal mortality observations[c] as

$$m_x = k + \frac{e^{a-bx}}{1+e^{a-bx}} + \frac{e^{a'+bx}}{1+e^{a'+bx}} \qquad \text{Equation 1}$$

where k, a, a', and b are constants. Data on birth weight specific mortality for Africa are limited[24] and empirical observations were restricted to two studies, conducted in The Gambia[25] and Malawi[26][d]. The empirical m_x data points and the fitted model are shown in Figure 4.1. The estimates for the parameters in Equation 1 were k = 0.0249, a = 6.3749, a' = -37.2204 and b = 4.3301. Whereas previous models used a cut-off of 2,500 g, and ascribed different neonatal mortality rates to children above and below this threshold[27], this model incorporated the continuum of birth weights and birth weight specific mortality.

[a] SP is too dangerous to be used as a regular prophylactic, as it has been shown to be associated with Stevens Johnson syndrome and death when used in this way[16].

[b] It would be more accurate to describe birth weights as a combination of two distributions, a predominantly normal distribution with a second residual distribution for low birth weights with a much lower mean[17]. By assuming that the whole distribution can be approximated as normal, the prevalence of low birth weight and therefore effectiveness will be slightly underestimated, making the estimates of cost-effectiveness conservative.

[c] Empirical m_x values were assumed to have binomial errors and the model was fitted using the forward differencing quasi-Newton iterative method available in Microsoft Excel® to maximize the likelihood between the observed and fitted values.

[d] The Malawi study included still births in estimates of mortality, while The Gambia study presented calculations of m_x based on deaths among live births only. The m_x estimates from the Malawi study are therefore overestimates of the neonatal death rate. However, as no still birth rate was presented it is not possible to correct from perinatal to neonatal mortality.

The crude neonatal mortality rate (NNMR) was calculated from the f_x distribution and m_x curve as

$$\text{NNMR} = \sum_{x=1.0}^{x=4.5} f_x m_x \qquad \text{Equation 2}$$

4.2.1 Effectiveness

Antenatal chemoprophylaxis or intermittent treatment was considered to lead to a shift in the birth weight frequency distribution, increasing m by i kg relative to no protection. The proportion of high birth weights (greater than 3.5 kg), was assumed to be the same with or without the intervention[e] [20, 28]. It follows that if m_u and s_u describe the birth weight distribution in women who did not receive the intervention (referred to as unprotected) and m_p and s_p the distribution in those who did (referred to as protected) then

$$\frac{3.5 - m_u}{s_u} = \frac{3.5 - m_p}{s_p} \qquad \text{Equation 3}$$

Therefore, with estimates of i, m_u and s_u the birth weight distributions in both unprotected and protected women may be defined.

The average magnitude of i was reported in the Cochrane meta-analysis of malaria prevention in pregnancy[12]. In studies including all pregnant women, the overall impact on birth weight was not significant. However where only primigravidae were considered, the mean birth weight in the protected group was significantly greater than in the unprotected group (difference of 0.101 kg with a standard deviation (s.d.) of 0.042 kg). The analysis was therefore initially restricted to primigravidae. It was assumed that the SP and CQ regimens were equally effective in increasing birth weight in the absence of resistance to either drug. Although none of the studies included in the meta-analysis used the SP regimen, it was assumed that a similar effect on birth weight would be obtained, as this regimen is highly effective in decreasing the prevalence of both placental parasitaemia and severe maternal anaemia[29, 30].

The difference, d, between NNMRs in protected and unprotected primigravidae was calculated from the two birth weight distributions. An example of the model is shown in Figure 4.2, using the best estimates for m_u, s_u and i of 2.788 kg, 0.476 kg and 0.101 kg, respectively, and the m_x curve described by the parameter estimates listed above. In this example the crude NNMRs in unprotected and protected primigravidae were 0.045 and 0.034, respectively, giving a d of 0.011.

The difference, d, is the maximum level of effectiveness achieved in a situation of complete malaria parasite sensitivity to the drugs, where all pregnant woman complied fully with the correct regimen and there were no still births. This will not occur in practice for several reasons: resistance to CQ is already high in many areas of Africa and resistance to SP is starting to grow; attendance at antenatal services is often intermittent; and compliance with drug therapy has been shown to be very low[31-33].

[e] In order to keep the proportion of babies greater than 3.5 kg the same in the protected and unprotected groups whilst increasing the mean birth weight, it was necessary to assume that the standard deviation for the protected group was slightly lower than that for the unprotected group. This meant that the model predicted that the proportion of children at very high weights (e.g. greater than 4 kg) would fall very slightly. However this simplifying assumption had no impact on the effectiveness outcome.

It was therefore necessary to adjust *d* by taking into account the level of drug resistance, *r*, and the probability of attending the antenatal clinic in the first or second trimester, v_1, returning for a second clinic visit, v_2, and compliance to the correct drug regimen, g[f]. It was also necessary to adjust for the still birth rate, *s*, as it was assumed that the intervention does not affect the primigravidae still birth rate[18], and so the benefits of increased birth weight on survival are not experienced by these births. Resistance, *r*, was defined as RII/III resistance (no clearance of parasitemia within 7 days of drug administration). It was assumed that parasitological cure was required to increase birth weight[13].

It was assumed that the regimens were only effective if women made their first visit before the end of the second trimester, and made at least two visits per pregnancy. These are conservative assumptions, as it is possible that there would be some beneficial effects if chemoprophylaxis or intermittent treatment were started later in the pregnancy or fewer doses were received[30].

Full compliance implies that the drugs were procured, the correct dose was taken, and the doses were taken at the correct time. Estimates were made of patient compliance, considering only the probability of underdosing. The probability of overdosing and incorrect timings were ignored, although over-dosing could potentially lead to a risk of toxic side-effects. Estimates for under-dosing with CQ prescribed during ANC were taken from two studies in Malawi. Heymann *et al.* (1990)[34] found a compliance rate of 36% based on the presence of CQ in urine samples on return ANC visits, and Helitzer-Allen *et al.* (1993)[32] found a baseline compliance of 25%, which rose to 57% following the introduction of a new health education message[g]. A range of between 25% and 57% was therefore selected for CQ, and this was assumed to reflect average compliance during pregnancy. No data were available for compliance with SP, but it was assumed that as it is taken in a series of single doses rather than on a weekly basis, compliance would be much higher than with CQ. However, it will not necessarily be 100% because patients may not take it if, for example, they are anxious about side-effects. Compliance was therefore set at between 85% and 95% for each dose, giving a figure of between 72% and 90% for the two doses. In some cases of non-compliance with CQ, only minor under-dosing may occur. The impact of underdosing on effectiveness is not known, but it is very unlikely that all those who underdose receive zero effects. In the absence of drug resistance, it was assumed that underdosing with the two-dose SP regimen, led to zero effectiveness, but that with a multi-dose drug such as CQ, the proportion of underdosed cases where the drug was still effective (*z*) was between 0.1 and 0.3.

The effective reduction in the NNMR, *D*, was calculated as

$$D = d \times (1 - s) \times (1 - r) \times \left(g + [1 - g]z\right) \times v_1 \times v_2 \qquad \text{Equation 4}$$

The parameter values for s, v_1, v_2, z and g were estimated from the published literature, and consultation with researchers and practitioners. D was calculated as a function of resistance, r, which was allowed to vary between 0 (complete sensitivity) and 1 (complete resistance).

[f] It was assumed that the efficacy data incorporated in the meta-analysis were based on study cohorts with close to full compliance, in the absence of drug resistance, and therefore represent the maximum effectiveness that could be achieved.

[g] A rate of 87% was achieved using sugar-coated pills, and a rate of 91% using a new health education message and sugar-coated pills. The estimates based on coated pills have not been included, as such tablets are not included in the specified intervention.

The possibility of side-effects from the drug regimens was not included, but they are not expected to be important. CQ is known to be safe in pregnancy. Fatal side effects have been observed with SP at a rate of between 1:11,000 and 1:25,000 when used as weekly prophylaxis[16], but are likely to be much less frequent with intermittent treatment.

The effective reduction in the NNMR, *D*, was converted to DALYs averted per primigravidae, considering only discounted years of life lost YLLs, as no morbidity or disability effects were included in the model. All effectiveness input parameters are listed in Table 4.1.

The DALYs averted per primigravidae with CQ were on average 0.09 for very low and middle income countries and 0.10 for higher income countries, and with SP 0.14 for very low and middle income countries and 0.16 for higher income countries. More DALYs were averted per woman in higher income countries because a life table with a higher life expectancy at birth was used. SP was more effective than CQ even when there was no resistance to either drug because compliance was assumed to be lower with CQ than with SP.

4.2.2 Costs

The incremental cost per primigravidae receiving ANC included the cost of the drug, incremental staff time, training, and the production of health education materials. The costing was based on adding the service to an existing ANC programme. Patient travel and time costs were not included, as they were assumed to be incurred whether or not the additional antimalarial service was provided.

Implementing the intervention would require additional time from ANC and supervisory staff. The cost of this time was included since staff could be undertaking other useful activities if they were not involved in this intervention (i.e. their time has an opportunity cost). It was estimated that the intervention would add 10 minutes to the first visit and 5 minutes to the second visit, allowing time to explain the rationale of the intervention, answer questions, and provide counselling on the importance of compliance. It was estimated that an additional 15 minutes of supervisory time would be required per month to discuss the intervention.

Salary costs were assumed to vary by per capita income level, but all other costs were held constant. A full course of SP consisted of two doses of 1,500 mg/75 mg, and a full course of CQ of 16 doses of 300 mg, based on an average first recruitment time of 22 weeks[33], and an average gestational age at delivery of 38 weeks. Costs were also included for one flip-chart and five posters per clinic to be used for health education, and the cost of these materials was annualised over an estimated useful life of 4 years. It was estimated that two staff members would be trained per clinic at a one-day workshop, and this cost was annualized over a two- year period. The cost of treating drug-related side-effects was not included. All cost input variables are listed in Table 4.2.

The incremental cost varies with v_2 (probability of returning for second clinic visit), as the cost of the additional visit would not be incurred if the woman failed to return. It was assumed that the cost was independent of compliance, as the drug cost would be incurred whether or not the tablets were taken as prescribed, and independent of v_1 (attendance before the end of the second trimester), as

drugs would be prescribed even when the first visit took place during the third trimester (although it was assumed that this would result in zero effectiveness).

Cost-effectiveness of a particular intervention can be calculated including only the incremental costs of adding the intervention to an existing service, but some analyses incorporate a share of the service overheads into the intervention costs. To enable comparison with such studies, an average cost of the intervention was calculated, by scaling up staff costs to account for a share of the time of ANC staff spent on administration and non-specific activities, and scaling up all recurrent costs to make an allowance for a share of ANC capital costs and overheads.

The mean incremental costs per pregnancy for the CQ and SP regimens are shown in Table 4.3. The incremental cost with SP was $1.13 in very low income countries, $1.25 in middle income countries, and $2.14 in higher income countries; the increase in costs in higher income countries being explained by higher salaries. In very low and middle income countries, drugs and staff each accounted for approximately one-third of the incremental cost, with health education and training making up the remaining third. In higher income countries, salary costs made up about two-thirds of the incremental cost, with drugs falling to only 15%. The mean average cost with SP in very low, middle and higher income countries, was $2.24, $2.58 and $5.17 respectively. All costs were higher with the CQ regimen because of the higher drugs cost per pregnancy. The mean incremental cost with CQ was $1.30 in very low income countries, $1.42 in middle income countries, and $2.31 in higher income countries, and the mean average cost $2.51 in very low income countries, $2.84 in middle income countries, and $5.44 in higher income countries. Although the average drug cost per dose was higher with SP than with CQ, the CQ regimen demanded an average of 16 doses per pregnancy, giving a higher total drug cost per pregnancy (mean of $0.50 compared with $0.32 for SP). Drugs therefore were the most important element of incremental costs with CQ for very low and middle income countries, although salaries remained the most important for higher income countries.

4.3 Cost-effectiveness

The incremental CER was calculated as the cost per primigravidae divided by the number of DALYs averted per primigravidae. For each drug and each income level in a situation of zero resistance, the mean cost per DALY averted and range within which 90% of CERs fell was calculated. The mean and range were calculated as a function of r for both CQ and SP. The simulation was halted after 1,600 iterations at which point all output variables had reached convergence.

The ranges for the CER for SP and CQ at complete drug sensitivity ($r = 0$) for a very low income country, using incremental costs, are shown in Figure 4.3 (all results are summarized in Table 4.4). The mean CER of using SP in a very low income country was $12, and 90% of the simulation results fell in the range $4 to $26. CQ was slightly less cost-effective than SP, because of both higher costs per primigravidae and lower DALYs averted. The mean CER in very low income countries was $21, with a 90% range of between $7 and $47. As current levels of resistance to CQ are much higher than those for SP in SSA, in practice this difference between the two drug regimens would be accentuated.

Figure 4.4 shows the CER for SP for the three different income levels (again with zero resistance and using incremental costs). There was little difference between the CERs for very low and middle income countries (mean of $13 compared with $12) but the CER was significantly higher in countries with higher per capita incomes (mean of $20, range $7 to $43), as the impact of increased costs due to higher salaries outweighed the increased DALYs averted due to the higher life expectancy. For all income levels, the ranges for SP clearly fell below $45 per DALY averted. The intervention would be considered an "attractive" option for all economic strata with either drug regimen as over 95% of the iterations had a CER below $150. However one could not be reasonably certain that the CER was below the "highly attractive" threshold of $25 with either drug.

The CERs reported above include only the *incremental* costs of adding the intervention to existing ANC services. Results are shown in Figure 4.5 for SP using *average* costs for the three economic strata. This raised the range for the cost per DALY averted in very low income countries to between $8 and $51. The results show that intermittent SP treatment would still fall into the "attractive" category in all income groups, even using average CERs.

Rank order correlation coefficients for the input variables that were most important in explaining the variation in the CER were calculated. The increase in birthweight as a result of the intervention, *i*, and the standard deviation of birthweights in the unprotected population, σ_p, were the most important variables (both positively related to effectiveness), followed by the number of ANC visits per clinic per annum (negatively related to costs). The latter variable was important because it affected the proportion of fixed costs, such as training and health education, attributed to each woman, demonstrating the importance of economies of scale in delivering the service.

The above results were all based on full drug sensitivity. Allowing for some degree of drug resistance reduced effectiveness and caused the CER to increase. The relationship between the incremental CER and the level of drug resistance for very low income countries is shown for CQ and SP in Figures 4.6a and 4.6b. At any level of resistance below 69%, the CER range for CQ fell below $150. For SP, up to resistance levels of 83%, the range fell below the $150 threshold.

4.4 Discussion

The results show that in the absence of drug resistance, the intervention is clearly a good use of resources in SSA countries. For both CQ and SP, the CERs were well below the $150 threshold for all economic strata, and for SP in very low income countries the upper end of the range only marginally exceeded the $25 threshold. Even when resistance is allowed for, both drug regimens remained cost-effective up to high levels of resistance.

The results demonstrate the advantage of using intermittent treatment doses rather than weekly prophylactic doses, as this improves compliance and, therefore, effectiveness and cost-effectiveness. Further analysis highlighted the potential benefits to be gained from improving compliance with CQ. For example, increasing compliance with CQ by an average of 20% would reduce the mean CER by 23%. The cost-effectiveness of interventions such as the use of coated tablets (to remove the bitter taste of CQ), pre-packaging of drugs, or intensified health education should therefore be

explored where CQ remains the drug of choice. However, even with resistance levels of over 40%, the SP regimen would on average still be more cost-effective than the CQ regimen with zero CQ resistance[h], and in reality resistance to CQ is much greater than to SP in SSA[31], explaining the change to an SP antenatal regimen in Malawi in 1992/3[13].

The intervention appeared highly cost-effective despite the relatively narrow definition of health benefits included. The model incorporated only reduced mortality in the neonatal period, excluding increased survival for children older than 28 days, and potential benefits from reductions in morbidity and mortality for mothers. Chemoprophylaxis or intermittent treatment in primigravidae is associated with a significant reduction in the number of malaria episodes treated for the mother relative to unprotected primigravidae[12]. Although this morbidity reduction in mothers would be unlikely to have a significant effect on the DALYs averted (because of the low disability weighting and short duration of a malaria episode), it could lead to significant cost-savings for households and providers due to the reduction in treatment seeking. In addition, the impact on maternal anaemia was not incorporated. Malaria infection is strongly associated with moderate and severe anaemia in primigravidae, which in turn is associated with increased maternal morbidity and mortality[1]. The interventions could therefore also have an impact on the maternal mortality rate, which could have spin-off effects on the health and well-being of the whole household[35].

Several limitations to the analysis should be noted. Whilst the impact of prophylaxis and intermittent treatment on birth weight in primigravidae has been clearly shown, the sample sizes of the studies included in the meta-analysis were too small to demonstrate a significant impact on neonatal mortality, even amongst primigravidae[12]. It was therefore necessary to model the impact on mortality based on empirical evidence of birth weight distributions and birth weight specific NNMRs. However, the available data on birth weights and mortality are limited, and are unlikely to be representative of the whole of SSA. One might expect that birth weights would be positively correlated with economic development, and birth weight specific mortality rates negatively correlated. As the data on birth weights in unprotected primigravidae and birth weight specific mortality all came from studies conducted in middle and very low income countries, it is possible that the model overestimates effectiveness in higher income countries.

The model assumed a direct relationship between increases in birth weight and reductions in neonatal mortality, without distinguishing between different causes of LBW. LBW can arise due to pre-term birth or retarded intrauterine growth, which results in the infant weighing less than expected for gestational age at birth. The NNMR at a given birth weight is higher for a pre-term baby than for a full-term baby with retarded growth[36]. Whilst there is evidence that malaria affects both gestational age and weight for age[36], no studies have demonstrated that prophylaxis or intermittent treatment reduces the prevalence of pre-term births[12]. It is possible that the intervention could have a differential impact, with for example a bigger impact on the birth weight for gestational age than on the gestational age at delivery, and may therefore not have the impact on neonatal mortality predicted by the model. The effectiveness of the interventions may therefore be overestimated.

It was not possible to analyse the variation in cost-effectiveness by length of transmission season because the increase in birth weight from the Cochrane review was based on a meta-analysis

[h] Despite the assumption that under-dosing was effective with CQ between 10% and 30% of the time but never with SP.

combining studies conducted under both perennial and seasonal conditions. The relationship between length of transmission season and effectiveness is likely to be complex and difficult to predict, due to the lower levels of acquired immunity in populations experiencing shorter transmission seasons.

The analysis was restricted to primigravidae because the Cochrane review reported that prophylaxis or intermittent treatment had a significant effect on LBW only in the first pregnancy. However for several reasons it may be inappropriate or impractical to restrict the intervention to this group. First there may be some benefit for multigravidae. Although no trials have shown a significant effect on second or third pregnancies, there is some evidence that the risk of infection increases in grandemultigravidae[18]. Moreover, HIV infection may increase the risk for multigravidae[37], and in low transmission areas where acquired immunity is low, all pregnant women may be at risk. Finally, it is possible that protecting women during their first pregnancy could lead to enhanced susceptibility to malaria during their second pregnancy[38]. Greenwood *et al.* (1994)[5] did not find evidence of increased risk in second pregnancies in a study of Gambian women who had received prophylaxis as primigravidae, but it is not possible to rule this out as long as the reasons for increased susceptibility in primigravidae women are not fully understood.

In view of these areas of uncertainty, together with the complexity of offering different services to different groups of women, and the political problems involved in excluding some women from what is perceived to be a valuable service, it may be deemed preferable to offer the intervention to all pregnant women, and this policy was recently adopted in Kenya[15]. Even if there are some positive effects in multigravidae, it is likely that their inclusion would reduce average effectiveness markedly and would therefore make the intervention less attractive in terms of cost-effectiveness. To explore this, Figure 4.7 shows the CER for SP (very low income, zero resistance) if all women were included, but as a worst case scenario, the increase in birth weight, *i*, was set at zero for multigravidae. Whilst the average effectiveness was substantially reduced, the cost per woman also fell due to economies of scale in supervision, training and health education. For example, with SP in a very low income country, the expected incremental cost per woman fell to $0.79 compared with $1.13 for primigravidae alone (total costs would of course rise). The net result was an increase in the mean CER from $12 to $32, with an increase in the upper end of the range from $26 to $70, meaning that the intervention remained cost-effective at the $150 per DALY averted threshold.

Evidence is emerging that two doses of SP per pregnancy are inadequate for HIV positive women, and that more frequent doses may be preferable[39, 40]. Rates of HIV infection in SSA are increasing fast; a recent review of the global HIV/AIDS epidemic[41] reported a median HIV prevalence among antenatal women in SSA of 5% in rural areas and 6% in urban areas, with rates as high as 47% reported in rural areas of Zimbabwe. Due to the costs and difficulties involved in screening all pregnant women for HIV, it may be necessary to administer the additional doses to all women in areas with high rates of HIV prevalence. The potential impact on the cost-effectiveness of intermittent treatment is shown in Figure 4.8. Costs were increased to include one extra dose of SP and an extra clinic visit, and effectiveness was reduced to account for lower compliance with a three-dose regimen. For a very low income country with no SP resistance, the mean incremental CER rose from $12 to $21, and the upper end of the range increased from $26 to $46, meaning that the intervention remained cost-effective at the $150 per DALY averted threshold. Unprotected birth weights were assumed to be the same in populations with high rates of seropositivity. However,

HIV infection diminishes the capacity of a pregnant woman to control malaria infection[37], and may therefore increase the prevalence of LBW and potentially the effectiveness of the intervention.

Although the intermittent treatment intervention consistently appeared cost-effective even with the inclusion of multigravidae or the use of a three-dose regimen, these adaptations would have an impact on the total cost of the intervention. To assess affordability, the expected total cost to government was estimated for SP in a very low income country, using Tanzania as an example (Table 4.5) . The expected incremental cost per pregnancy with SP for primigravidae only was $1.13, giving a total annual cost of $156,000, representing 0.17% of the existing government health care budget. The incremental cost of a three-dose regimen would be $1.31 per primigravidae, giving a total cost of $181,000, equivalent to 0.19% of the budget. Including all gravidae (two-dose regimen) increased the total cost to $639,000 p.a., or 0.68% of the existing budget. Under all of these scenarios, the intervention would represent only a relatively minor addition to existing government health sector expenditure.

The cost analysis was based on the assumption that ANC services were already in place, and that the new intervention could be added to this existing infrastructure. Whilst for most SSA countries, the percentage of primigravidae receiving ANC is high (median of 89% for 17 countries[33]), there are some exceptions. For instance, in Burkina Faso, only 61% of primigravidae attended ANC, and in Niger only 32%. The incremental costs to both the facility and to women would be much greater if it were necessary to set up an entirely new ANC service in order to implement the intervention. This is not fully captured in the average cost calculations, which consider only the proportion of existing ANC overheads that would be attributable to the intervention. The cost of establishing the service would depend on many factors, including local unit costs, the package of ANC offered and the existing infrastructure of health facilities. This variation is demonstrated by ANC costing studies that provide estimates of the cost of the programme per visit ranging from $0.19 to $0.26 in Tanzania[42], to $0.75 in the Gambia[43], and $8.41 and $12.53 in South Africa[44, 45].

It is possible that if wide coverage of ANC services were not attainable, community-based health workers such as TBAs or VHWs could deliver the intervention. TBAs were found to be an effective and appropriate channel for providing antimalarial and iron prophylaxis to pregnant women in The Gambia, even though they received no additional payment[18, 46]. However a well-supported VHW programme in Kenya was able to achieve only 29% coverage of primigravidae[47]. The main reasons for not taking prophylaxis were lack of awareness about the service (53%), fear of chloroquine-induced itching (10%), the VHW had no drugs (8%) and the VHW had not advised the woman to take the drugs (8%). The authors concluded that the programme was not effective in providing prophylaxis, and argued that asking VHWs to distribute the drugs was too difficult for many of them and may have overloaded them.

4.5 Summary and conclusions

Assuming the hypothesized link holds between an increase in birth weight and reduction in NNMR, prophylaxis and intermittent treatment for primigravidae are cost-effective where ANC coverage already exists. This remains true even when there is a significant degree of drug resistance, or if all

antenatal women are included. SP intermittent treatment is likely to be more cost-effective than CQ prophylaxis because the SP regimen is cheaper, compliance will be higher and there is currently less resistance to SP in SSA. In addition to being highly cost-effective, the intervention is also relatively affordable for SSA governments, with an incremental cost equivalent to less than 1% of the existing health sector budget.

However, these results are based on the addition of the new intervention to an existing infrastructure of antenatal clinics. If ANC coverage is low, the incremental costs of providing the service through clinics would be much higher. The use of community-based delivery strategies would be a potential alternative, but success would be heavily dependent on the availability of well-organized, well-supervised, and motivated VHWs.

Figure 4.1. Empirical estimates of birth weight specific neonatal mortality (m_x) from Malawi (¦) and The Gambia (±), and the fitted model (——) described by Equation 1.

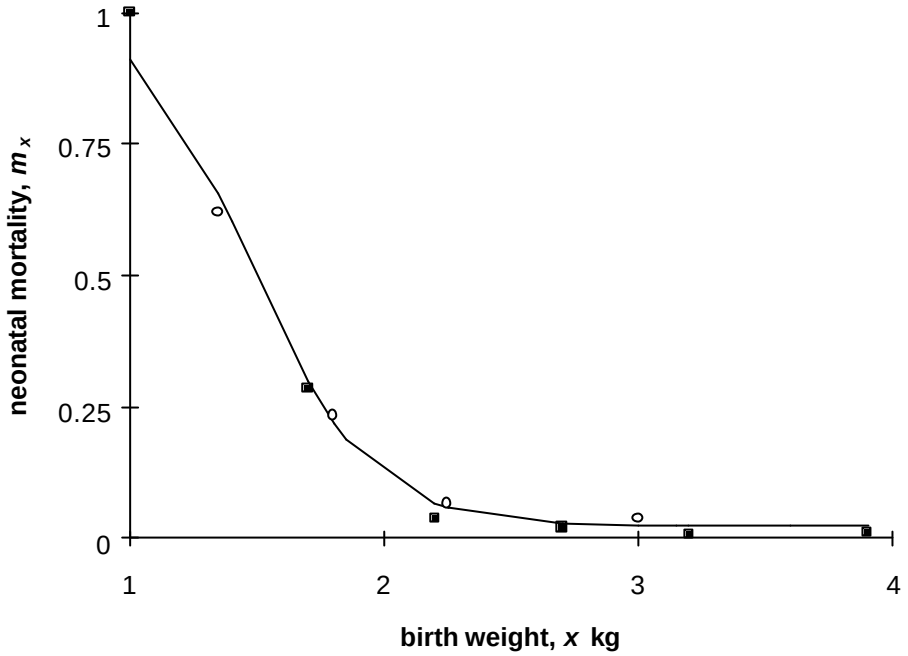


Figure 4.2. Illustrative example of the birth weight distributions in unprotected (——) and protected (- - - -) primigravidae, and the birth weight specific neonatal mortality curve (m_x) (—¦—).

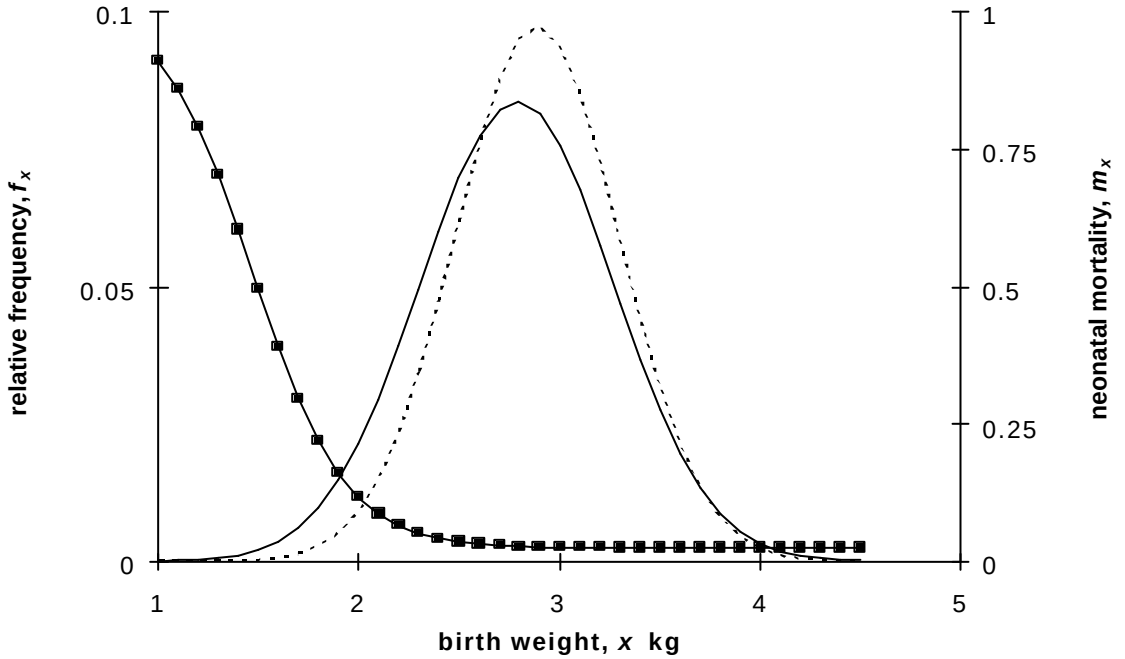


Figure 4.3. Cost-effectiveness of CQ prophylaxis and SP intermittent treatment: mean (¦) and 90% range for the incremental CER in a very low income country with no drug resistance (1995 US dollars).

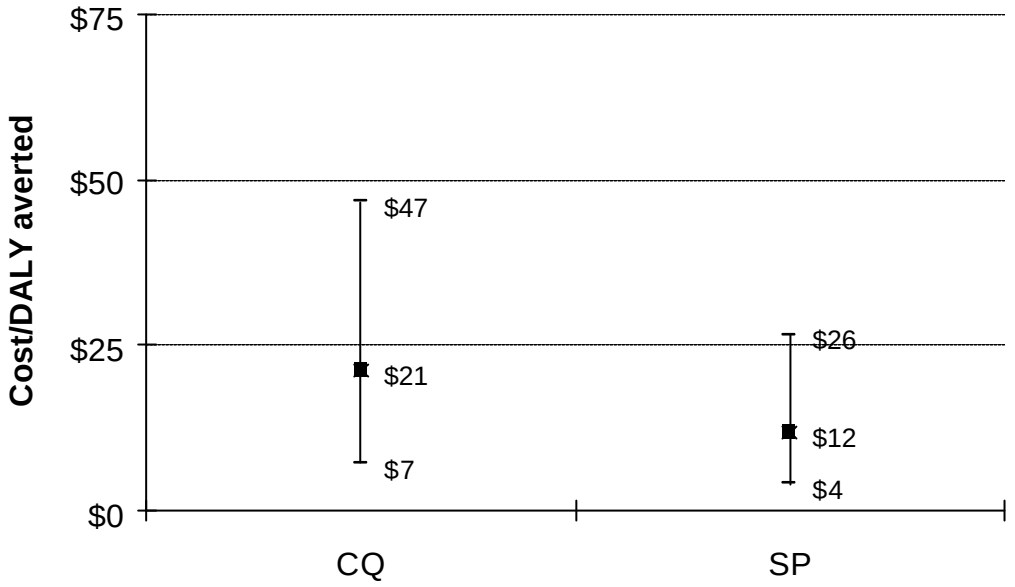


Figure 4.4. Cost-effectiveness of SP intermittent treatment for three economic strata: mean (¦) and 90% range for the incremental CER with no drug resistance (1995 US dollars).

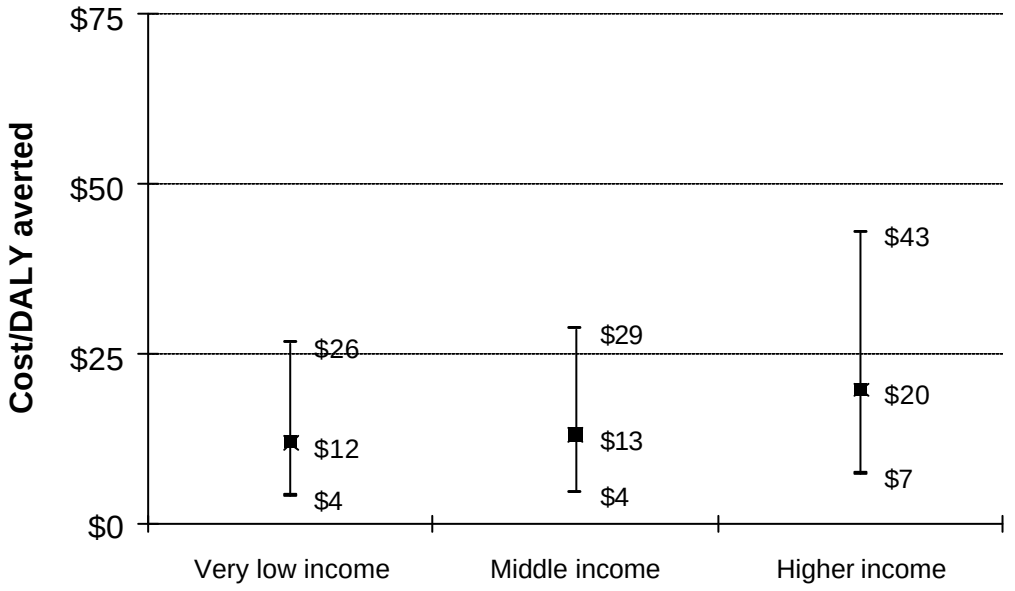


Figure 4.5. Cost-effectiveness of SP intermittent treatment using average costs: mean (¦) and 90% range for the CER in three economic strata with no drug resistance (1995 US dollars).

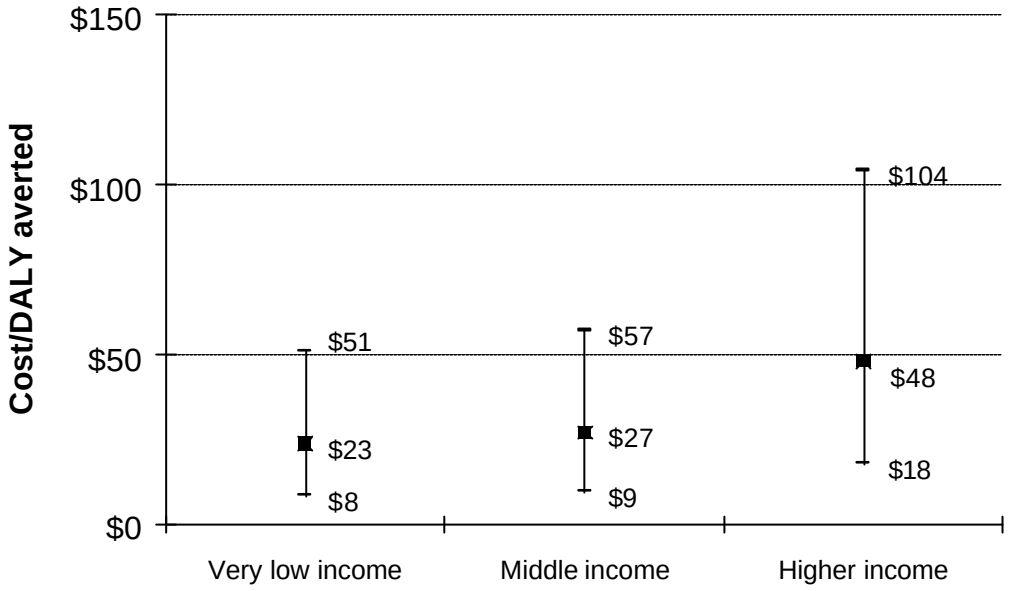


Figure 4.6. Cost-effectiveness of (a) CQ chemoprophylaxis, and (b) SP intermittent treatment as a function of drug resistance, *r*, for very low income countries with incremental costs, showing the mean CER (- - - - -) and 90% range (——) (1995 US dollars)

Figure 4.6a. CQ

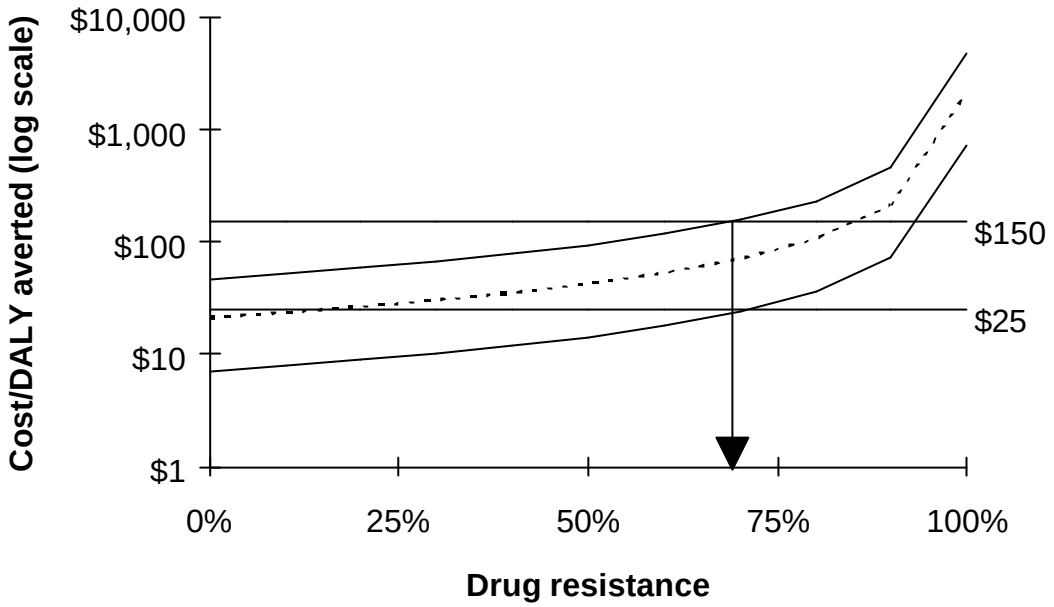


Figure 4.6b. SP

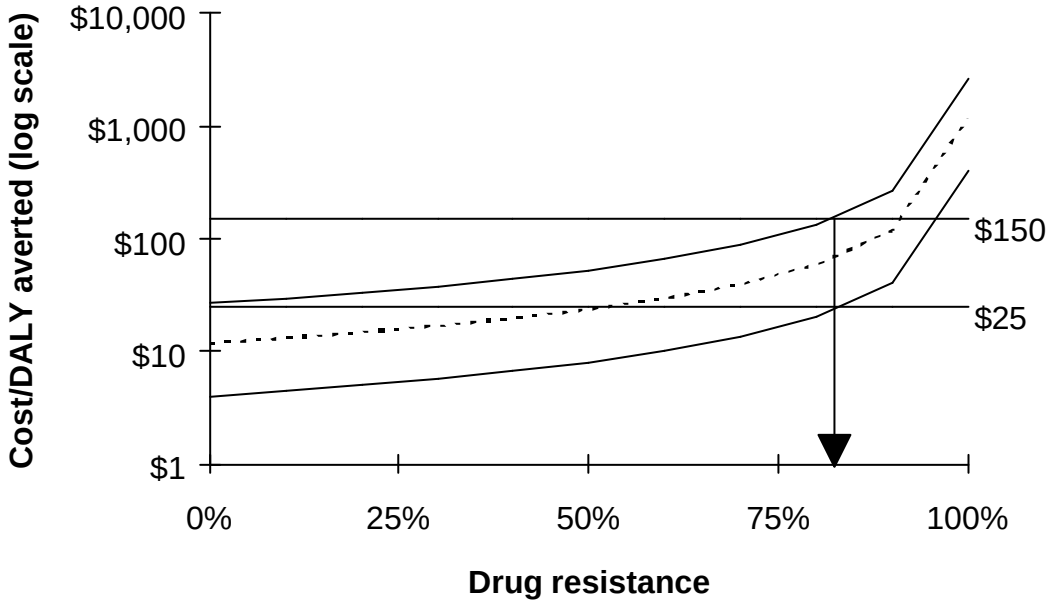


Figure 4.7. Cost-effectiveness of providing CQ chemoprophylaxis or SP intermittent treatment to all pregnant women compared with primigravidae only: mean (¦) and 90% range for the incremental CER in a very low income country with no drug resistance (1995 US dollars).

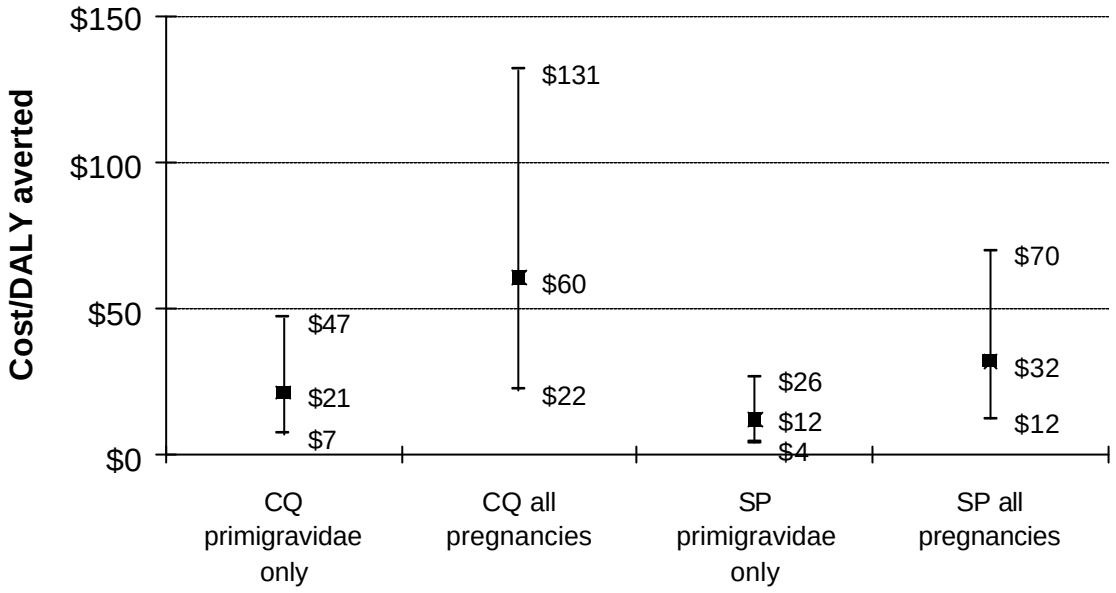


Figure 4.8. Cost-effectiveness of intermittent treatment with SP using a 2 dose or 3 dose regimen: mean (¦) and 90% range for the incremental CER in a very low income country with no drug resistance (1995 US dollars).

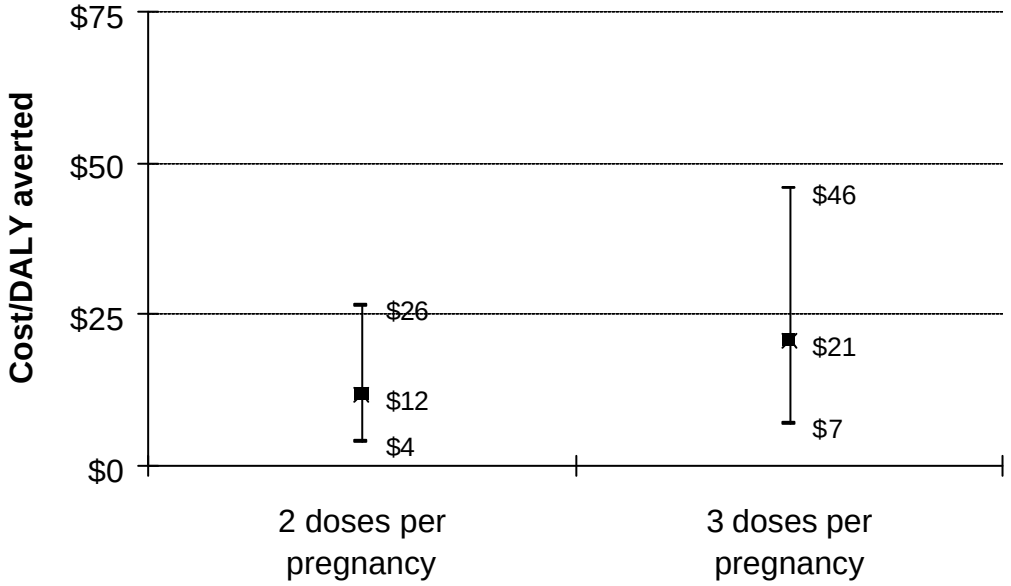


Table 4.1. Effectiveness input variables used in the analysis of antenatal prophylaxis or intermittent treatment

Input variable	Probability Distribution	Distribution parameters			Source
Mean birth weight in unprotected primigravidae, m_u	Truncated normal	m = 2.788 s = 0.082			Cot *et al*. 1995[20], Fleming *et al*. 1986[21], Greenwood *et al*. 1989[18], Menendez *et al*. 1994[19].
Standard deviation of birth weight, s_u	Truncated normal	m = 0.476 s = 0.098			Cot *et al*. 1995[20], Fleming *et al*. 1986[21], Greenwood *et al*. 1989[18], Menendez *et al*. 1994[19].
Increase in birth weight, i	Truncated normal	m = 0.101 s = 0.042			Gülmezoglu & Garner 1997[12].
		Minimum	**Maximum**	**Best estimate**	
Still birth rate in primigravidae, s	Uniform	0.062	0.116		Greenwood *et al*. 1994[28].
Initial clinic visit in first or second trimester, v_1	Triangular	0.540	0.936	0.868	DHS 1997[33]
Probability of returning for second clinic visit, v_2	Triangular	0.835	0.989	0.937	DHS 1997[33]
Probability of returning for third clinic visit, v_3 (relevant where HIV prevalence is high)	Triangular	0.481	0.942	0.796	DHS 1997[33]
Compliance to prescribed drug, g					
CQ (average for whole course)	Uniform	0.25	0.57		Helitzer-Allen *et al*. 1993[32], Heymann *et al*. 1990[34], Schultz *et al*. 1996[48].
SP (per dose)	Uniform	0.85	0.95		
Proportion of underdosed cases which are effective, z	Triangular	0.1	0.3		

Table 4.2. Cost input variables used in the analysis of antenatal prophylaxis or intermittent treatment

	Probability distribution	Distribution parameters			Source
					All costs in 1995 US dollars
		Minimum	**Maximum**	**Best estimate**	
Drug cost					
CQ					
Cost of 150mg tablet	triangular	0.008	0.013	0.01	International drug price indicator guide, 1996[49]
Tablets per dose				2	WHO Model Prescribing Information: Drugs used in Parasitic Diseases, 1995[50]
Doses per pregnancy				16	
SP					
Cost of 500/25mg tablet	triangular	0.032	0.040	0.036	International drug price indicator guide, 1996[49]
Tablets per dose				3	WHO Model Prescribing Information: Drugs used in Parasitic Diseases, 1995[50]
Doses per pregnancy				2	WHO Model Prescribing Information: Drugs used in Parasitic Diseases, 1995[50]
Delivery cost as % of warehouse cost				25%	Foster, 1991[51]
Wastage of drugs				25%	
Salaries p.a.					
Health Centre Staff FTE					
very low income countries	uniform	1934	2617		Extrapolation from Tinker & Koblinsky, 1992[52], plus and minus 15%
middle income countries	uniform	2544	3442		
higher income countries	uniform	7312	9893		
Supervisory Staff					
very low income countries	uniform	3137	4244		Extrapolation from Tinker & Koblinsky, 1992[52], plus and minus 15%
middle income countries	uniform	4127	5584		
higher income countries	uniform	11868	16057		
Days worked per year				236	
Hours worked per day				8	
Health Centre staff time per pregnancy (mins)				15	
Supervisory staff time per pregnancy (mins)				2.16	

Table 4.2. Cost input variables used in the analysis of antenatal prophylaxis or intermittent treatment (cont.)

	Probability Distribution	Distribution parameters			Source
					All costs in 1995 US dollars
		Minimum	**Maximum**	**Best estimate**	
Health education					
Cost per flipchart	uniform	10.95	14.81		Helitzer-Allen *et al*., 1993[32],
Cost per book/poster	uniform	4.11	5.55		L. Kumaranayake, personal communication
Number of flipcharts per clinic				1	
Number of books/posters per clinic				5	
Life time of health education materials (years)				4	
Training					
Cost of training per person				10	
Number of staff trained per clinic				2	
Life time of training (years)				2	Picard *et al*., 1993[53]
Utilisation data					
No. of ANC visits per clinic per year	uniform	209	1056		Hanson & Chindele, 1992[54], Hanson & Nkunzimana, 1992[55], Ogunbekun *et al*., 1996[56]
% primigravidae				0.25	
No. of visits per pregnancy	triangular	0.7	5.6		DHS 1997[33]
Scale up factors to calculate total cost					
Administration and TWSA* as a % of staff time	uniform	0.35	0.58		Gilson, 1992[42]
Capital costs and overheads as a % of total cost	uniform	0.25	0.46		Gilson, 1992[42], Fabricant *et al*., 1994[43], Broomberg *et al*., 1993[45]

*time without specific activity

Table 4.3. Expected incremental and average cost per primigravidae, adjusted for non-compliance (1995 US dollars)

Drug Regimen		Economic strata		
		very low income	**middle income**	**higher income**
SP	Drugs	$0.32 (29%)	$0.32 (26%)	$0.32 (15%)
	Staff	$0.36 (32%)	$0.48 (38%)	$1.38 (64%)
	Health Education & Training	$0.44 (39%)	$0.44 (36%)	$0.44 (21%)
	Mean incremental cost	$1.13 (100%)	$1.25 (100%)	$2.14 (100%)
	Mean average cost	$2.24	$2.58	$5.17
CQ	Drugs	$0.50 (38%)	$0.50 (35%)	$0.50 (21%)
	Staff	$0.36 (28%)	$0.48 (34%)	$1.38 (59%)
	Health Education & Training	$0.44 (34%)	$0.44 (31%)	$0.44 (19%)
	Mean incremental cost	$1.30 (100%)	$1.42 (100%)	$2.31 (100%)
	Mean average cost	$2.51	$2.84	$5.44

Table 4.4. Mean CER and the range within which 90% of all CERs fell (no drug resistance) (1995 US dollars)

Drug	Economic strata	Costing	Mean CER	Range within which 90% of all CERs fell
CQ	very low	Incremental	$22	$7 - $47
	middle		$23	$8 - $50
	higher		$33	$12 - $72
SP	very low	Incremental	$12	$4 - $26
	middle		$13	$4 - $29
	higher		$20	$7 - $43
CQ	very low	Average	$41	$14 - $91
	middle		$46	$16 - $102
	higher		$78	$28 - $173
SP	very low	Average	$23	$8 - $51
	middle		$27	$9 - $57
	higher		$48	$18 - $104
CQ (all gravidae)	very low	Incremental	$60	$22 - $129
	very low	Average	$125	$45 - $271
SP (all gravidae)	very low	Incremental	$32	$12 - $70
	very low	Average	$70	$26 - $146
SP (3 doses)	very low	Incremental	$21	$7 - $46
	very low	Average	$41	$14 - $92

Table 4.5. Annual mean incremental cost implications for Tanzania (very low income country) of introducing SP antenatal regimen (1995 US dollars)

	Government cost p.a.	Cost as % Government health budget
Two-dose regimen, primigravidae only	$155,896	0.17%
Two-dose regimen, all pregnant women	$639,474	0.68%
Three-dose regimen, primigravidae only	$180,729	0.19%

Based on the following estimates for Tanzania:

- Population of 29.2m[57]
- Crude birth rate of 42.6/1000[58]
- 17% of all births born to primigravidae
- 93.2% of primigravidae, and 91.8% of all pregnant women receive ANC[33].
- 70% of population at high risk of malaria
- Government health budget p.a. of $94 million (including donor contributions)[59]
- No cost recovery

References

1. Shulman CE, Graham WJ, Jilo H, et al. Malaria is an important cause of anaemia in primigravidae: evidence from a district hospital in coastal Kenya. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1996; 90(5): 535-9.
2. Brabin BJ. An analysis of malaria in pregnancy in Africa. *Bulletin of the World Health Organization* 1983; 61(6): 1005-16.
3. McGregor IA. Epidemiology, malaria and pregnancy. *American Journal of Tropical Medicine and Hygiene* 1984; 33(4): 517-25.
4. McCormick MC. The contribution of low birth weight to infant mortality and childhood morbidity. *New England Journal of Medicine* 1985; 312(2): 82-90.
5. Greenwood AM, Menendez C, Alonso PL, et al. Can malaria chemoprophylaxis be restricted to first pregnancies? *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1994; 88(6): 681-2.
6. Alonso PL, Lindsay SW, Schellenberg J, et al. A malaria control trial using insecticide-treated bed nets and targeted chemoprophylaxis in a rural area of the Gambia, West-Africa. 6. The impact of the interventions on mortality and morbidity from malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1993; 87(S2): 37-44.
7. D'Alessandro U, Olaleye BO, McGuire W, et al. Mortality and morbidity from malaria in Gambian children after introduction of an impregnated bednet programme. *Lancet* 1995; 345(8948): 479-83.
8. Binka FN, Kubaje A, Adjuik M, et al. Impact of permethrin impregnated bednets on child mortality in Kassena-Nankana district, Ghana: a randomized controlled trial. *Tropical Medicine and International Health* 1996; 1(2): 147-54.
9. D'Alessandro U, Langerock P, Bennett S, Francis N, Cham K, Greenwood BM. The impact of a national impregnated bed net programme on the outcome of pregnancy in primigravidae in The Gambia. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1996; 90(5): 487-92.
10. Dolan G, Terkuile FO, Jacoutot V, et al. Bed nets for the prevention of malaria and anaemia in pregnancy. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1993; 87(6): 620-626.
11. Shulman CE, Dorman EK, Talisuna AO, et al. A community randomized controlled trial of insecticide-treated bednets for the prevention of malaria and anaemia among primigravid women on the Kenyan coast. *Tropical Medicine and International Health* 1998; 3(3): 197-204.
12. Gülmezoglu AM, Garner P. Malaria in pregnancy in endemic areas (Cochrane Review). *The Cochrane Library* 1998; Issue 3: Oxford, Update Software.
13. Steketee RW, Wirima JJ, Campbell CC. Developing effective strategies for malaria prevention programs for pregnant African women. *American Journal of Tropical Medicine and Hygiene* 1996; 55(1 Suppl): 95-100.
14. WHO. Implementation of the global malaria control strategy - Report of a WHO Study Group on the implementation of the global plan of action for malaria control 1993-2000. *WHO Technical Report Series 839* 1993.
15. Government of Kenya. *National guidelines for diagnosis, treatment and prevention of malaria for health workers*. Nairobi: Ministry of Health, 1997.
16. Miller KD, Lobel HO, Satriale RF, Kuritsky JN, Stern R, Campbell CC. Severe cutaneous reactions among American travelers using pyrimethamine-sulfadoxine (Fansidar) for malaria prophylaxis. *American Journal of Tropical Medicine and Hygiene* 1986; 35(3): 451-8.
17. Wilcox AJ, Russell IT. Birthweight and perinatal mortality: I. On the frequency distribution of birthweight. *International Journal of Epidemiology* 1983; 12(3): 314-8.
18. Greenwood BM, Greenwood AM, Snow RW, Byass P, Bennett S, Hatib-N'Jie AB. The effects of malaria chemoprophylaxis given by traditional birth attendants on the course and outcome of pregnancy. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1989; 83(5): 589-94.
19. Menendez C, Todd J, Alonso PL, Lulat S, Francis N, Greenwood BM. Malaria chemoprophylaxis, infection of the placenta and birth weight in Gambian primigravidae. *Journal of Tropical Medicine and Hygiene* 1994; 97(4): 244-8.
20. Cot M, Le Hesran JY, Miailhes P, Esveld M, Etya'ale D, Breart G. Increase of birth weight following chloroquine chemoprophylaxis during the first pregnancy: results of a randomized trial in Cameroon. *American Journal of Tropical Medicine and Hygiene* 1995; 53(6): 581-5.
21. Fleming AF, Ghatoura GB, Harrison KA, Briggs ND, Dunn DT. The prevention of anaemia in pregnancy in primigravidae in the guinea savanna of Nigeria. *Annals of Tropical Medicine and Parasitology* 1986; 80(2): 211-33.

22. Wilcox AJ, Russell IT. Birthweight and perinatal mortality: II. On weight-specific mortality. *International Journal of Epidemiology* 1983; 12(3): 319-25.
23. Wilcox AJ, Russell IT. Birthweight and perinatal mortality: III. Towards a new method of analysis. *International Journal of Epidemiology* 1986; 15(2): 188-96.
24. Ashworth A, Feachem RG. Interventions for the control of diarrhoeal diseases among young children: prevention of low birth weight. *Bulletin of the World Health Organization* 1985; 63(1): 165-84.
25. Greenwood AM, Armstrong JR, Byass P, Snow RW, Greenwood BM. Malaria chemoprophylaxis, birth weight and child survival. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1992; 86(5): 483-5.
26. McDermott JM, Wirima JJ, Steketee RW, Breman JG, Heymann DL. The effect of placental malaria infection on perinatal-mortality in rural Malawi. *American Journal of Tropical Medicine and Hygiene* 1996; 55(1 SS): 61-65.
27. Schultz LJ, Steketee RW, Chitsulo L, Wirima JJ. Antimalarials during pregnancy: a cost-effectiveness analysis. *Bulletin of The World Health Organization* 1995; 73(2): 207-14.
28. Greenwood AM, Menendez C, Todd J, Greenwood BM. The distribution of birth weights in Gambian women who received malaria chemoprophylaxis during their first pregnancy and in control women. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1994; 88(3): 311-2.
29. Schultz LJ, Steketee RW, Macheso A, Kazembe P, Chitsulo L, Wirima JJ. The efficacy of antimalarial regimens containing sulfadoxine-pyrimethamine and/or chloroquine in preventing peripheral and placental Plasmodium falciparum infection among pregnant women in Malawi. *American Journal of Tropical Medicine and Hygiene* 1994; 51(5): 515-22.
30. Shulman CE, Dorman EK, Cutts F, et al. Intermittent sulfadoxine-pyrimethamine to prevent severe anaemia secondary to malaria in pregnancy: a randomised placebo-controlled trial. *Lancet* 1999; 353(9152): 632-636.
31. World Health Organization. *Antimalarial Drug Policies: Data requirements, treatment of uncomplicated malaria and management of malaria in pregnancy*. Geneva: World Health Organization - Division of Control of Tropical Diseases, 1994.
32. Helitzer-Allen DL, McFarland DA, Wirima JJ, Macheso AP. Malaria chemoprophylaxis compliance in pregnant women: a cost-effectiveness analysis of alternative interventions. *Social Science and Medicine* 1993; 36(4): 403-7.
33. Stewart MK, Stanton CK, Ahmed O. *Maternal Health Care, DHS Comparative Studies No. 25*. Calverton, Maryland: Macro International Inc., 1997.
34. Heymann DL, Steketee RW, Wirima JJ, McFarland DA, Khoromana CO, Campbell CC. Antenatal chloroquine chemoprophylaxis in Malawi: chloroquine resistance, compliance, protective efficacy and cost. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1990; 84(4): 496-8.
35. WHO. *Mother-baby package: Implementing safe motherhood in countries*. Maternal Health and Safe Motherhood Programme, Division of Family Health, 1994.
36. Steketee RW, Wirima JJ, Hightower AW, Slutsker L, Heymann DL, Breman JG. The effect of malaria and malaria prevention in pregnancy on offspring birth-weight, prematurity, and intrauterine growth-retardation in rural Malawi. *American Journal of Tropical Medicine and Hygiene* 1996; 55(1 SS): 33-41.
37. Steketee RW, Wirima JJ, Bloland PB, et al. Impairment of a pregnant woman's acquired ability to limit Plasmodium falciparum by infection with human immunodeficiency virus type-1. *American Journal of Tropical Medicine and Hygiene* 1996; 55(1 Suppl): 42-9.
38. McGregor IA. Thoughts on malaria in pregnancy with consideration of some factors which influence remedial strategies. *Parassitologia* 1987; 29(2-3): 153-63.
39. Verhoef H, Bos R. Development and vector-borne diseases. *World Health* 1992; 15-7.
40. Wolfe EB, Steketee RW, Haddix AC, Parise ME. Cost-effectiveness of sulfadoxine-pyrimethamine for the prevention of low birth weight caused by placental malaria. Abstract of Paper presented at 47th Annual Meeting of the American Society of Tropical Medicine and Hygiene, Puerto Rico, October 18-22 1998. *American Journal of Tropical Medicine and Hygiene* 1998; 59(3 (supplement)): 286-7.
41. UNAIDS/WHO. *Report on the global HIV/AIDS epidemic*. Geneva: UNAIDS, 1998.
42. Gilson LJ. *Value for Money?: The Efficiency of Primary Health Units in Tanzania*. London School of Hygiene and Tropical Medicine, University of London: PhD Thesis, 1992.
43. Fabricant S, Newbrander W. *The Gambia Health Facilities Cost Study*. Management Sciences for Health, Boston, Massachusetts, USA, 1994.
44. Valli A, Ferrinho PD, Broomberg J, Wilson TD, Robb D. Costs of primary health care at the Alexandra Health Centre. *South African Medical Journal* 1991; 80(8): 396-9.
45. Broomberg J, Rees H. Delivering at the right price--the costs of primary maternity care at the Diepkloof Community Health Centre, Soweto. *South African Medical Journal* 1993; 83(4): 272-5.

46. Menendez C, Todd J, Alonso PL, et al. The effects of iron supplementation during pregnancy, given by traditional birth attendants, on the prevalence of anaemia and malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1994; 88(5): 590-3.
47. Kaseje DC, Sempebwa EK, Spencer HC. Malaria chemoprophylaxis to pregnant women provided by community health workers in Saradidi, Kenya. I. Reasons for non-acceptance. *Annals of Tropical Medicine and Parasitology* 1987; 81(1): 77-82.
48. Schultz LJ, Steketee RW, Chitsulo L, Macheso A, Kazembe P, Wirima JJ. Evaluation of maternal practices, efficacy, and cost-effectiveness of alternative antimalarial regimens for use in pregnancy: chloroquine and sulfadoxine-pyrimethamine. *American Journal of Tropical Medicine and Hygiene* 1996; 55(1 Suppl): 87-94.
49. Management Sciences for Health. *International Drug Price Indicator Guide*. Boston: MSH, 1996.
50. WHO. *Model Prescribing Information: Drugs used in Parasitic Diseases*. Geneva: WHO, 1995.
51. Foster SD. Pricing, distribution, and use of antimalarial drugs. *Bulletin of The World Health Organization* 1991; 69(3): 349-363.
52. Tinker A, Koblinsky MA. *Making motherhood safe*. Washington D.C.: The World Bank, 1992.
53. Picard J, Aikins M, Alonso PL, Armstrong Schellenberg JR, Greenwood BM, Mills A. A malaria control trial using insecticide-treated bed nets and targeted chemoprophylaxis in a rural area of The Gambia, West Africa. 8. Cost-effectiveness of bed net impregnation alone or combined with chemoprophylaxis in preventing mortality and morbidity from malaria in Gambian children. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1993; 2: 53-7.
54. Hanson K, Chindele F. *Costs, resource use and financing: a study of Monze District, Zambia*. New York: Bamako Initiative Technical Report Series, UNICEF, 1992.
55. Hanson K, Nkunzimana F. *Les coûts et l'utilisation des ressources dans les centres de santé de la province de Muyinga, Burundi*. New York: Bamako Initiative Technical Report Series, UNICEF, 1992.
56. Ogunbekun I, Adeyi O, Wouters A, Morrow RH. Costs and financing of improvements in the quality of maternal health services through the Bamako Initiative in Nigeria. *Health Policy and Planning* 1996; 11(4): 369-84.
57. World Bank. *World Development Report 1997. The state in a changing world*. New York: Oxford University Press, 1997.
58. UNDP. *Human Development Report*. Oxford University Press, 1997.
59. World Bank. *Tanzania - Role of Government: Public Expenditure Review, Volume 1*. Washington DC: World Bank, 1994.

Chapter 5 – Improving Malaria Case Management

5.1 Introduction

WHO has argued that appropriate and timely case management should be seen as not only a key component of any malaria control programme, but also a fundamental right of all populations affected by malaria[1]. In reality, case management is often highly inadequate. Inappropriate drugs are prescribed, compliance with the recommended regimen is low, drugs are often ineffective due to resistance or poor quality, and patients with severe malaria are managed inappropriately[2-5]. Inadequate care results in higher morbidity and mortality from malaria, and may also encourage the development of drug resistance[6].

Several interventions have been proposed to improve case management: for example, using more effective drugs, improving compliance, strengthening diagnosis, and using combination therapies[6-8]. Evaluation is hampered by a lack of information on both costs and effects, and the few studies that do consider such strategies generally do not report health outcomes. In order to address some of the key issues, a model of the treatment of outpatients with suspected uncomplicated malaria was developed to translate changes in intermediate outcomes, such as compliance and drug efficacy, into final health outcomes. The analysis was restricted to this group of patients, although it is recognized that many cases are not seen at formal outpatient facilities, and alternative strategies would have to be employed to reach these patients.

The model of case management is presented below, and used to estimate the costs and effects of the following interventions: improving compliance through pre-packaging and training; improving the availability of second and third line drugs; changing the first line drug for treatment; using combination therapies to reduce the growth of resistance; the introduction of new diagnostic techniques. The interventions are considered in two epidemiological strata (high and low transmission) and the three socio-economic strata.

5.2 A model of case management

5.2.1 Health effects

The outcome of treatment for people presenting at an outpatient facility with suspected uncomplicated malaria is modelled using a decision tree framework, depicted in Figure 5.1. Patients enter the tree at point A, when they are given the first line drug[a]. There is a probability P0 that their illness is caused by malaria. Of those who are suffering from malaria, the first line drug fails with a probability P1. Given that the first line drug has failed, the patient will either develop severe malaria

[a] The first line treatment refers to the drug routinely prescribed for a case of uncomplicated malaria at a health facility (patients may have already self-treated with chloroquine or another drug). The second line treatment is the drug used for treating either a case of uncomplicated malaria that has not been cured by the first line treatment, or one for which the first line drug is contra-indicated.

(with a probability P2), or continue to suffer from uncomplicated malaria. If severe malaria develops, inpatient care may be sought (probability P3), when the patient will receive intravenous quinine. The probability is then estimated of full recovery, recovery with neurological sequelae (NS) and death, with inpatient care (P4, P5 and P6), and without inpatient care (P7, P8 and P9).

If the patients still have uncomplicated malaria after failing with the first line drug, they may choose to seek further outpatient care (probability P10), when they are prescribed the second line drug. In the event of a failure of the second line drug (probability P11), it is again possible that severe malaria will develop (probability P12), or that uncomplicated malaria will persist. If severe malaria develops, patients may or may not seek inpatient care, as described above. If uncomplicated malaria persists, patients will again decide whether to attend outpatients (probability P13), and if they do they will be given the third line drug. If the third line drug fails (probability P14), patients will either ultimately recover (probability P15), recover with NS (P16) or die (P17). The probabilities of death or NS for patients with uncomplicated malaria who do not seek outpatient care (P19 and P20) were assumed to equal the probability of developing severe malaria (P2) multiplied by the probability of death or NS if severe without inpatient care (P8 and P9)[b]. The risk of lethal side-effects was also considered with each drug. The outcomes for the suspected cases which were not malaria were not calculated that as they were assumed to be unaffected by the interventions to improve malaria treatment.

The probability of failure with an outpatient drug is defined as

$$\text{Probability of failure} = 1 - (\text{Cure rate} \times \text{Compliance rate})$$

where the cure rate refers to the "adequate clinical response rate" (ACR), and "resistance" is defined as (1-ACR)[c]. The preventive interventions were initially analysed in a situation of zero drug or insecticide resistance (see Chapters 3 and 4). However, chloroquine resistance is common throughout Africa, and in fact is the rationale for several of the case management interventions, so some degree of drug resistance was included in all of the analyses. The initial cure rate of chloroquine (CQ) was varied. The initial ACR for SP was given a range of 63% to 99% (based on a review by Hill, 1996[10]). Estimates for quinine (QN) were presumed to be very high (99.5% to 100%) as reports of resistance to this drug in Africa are extremely rare, and the initial ACR for AQ was estimated to fall within the range of 80% to 90%.

Estimates of compliance were obtained from the literature[3] and through discussions with researchers. It is likely that drugs taken over several days, such as CQ, AQ and QN, will have lower patient compliance than those taken in a single dose, such as SP, and that compliance will be lower with drugs that have more common unpleasant side-effects, such as CQ and QN. Compliance with CQ was set at 20% to 50%, SP at 85% to 95%, AQ at 30% to 60%, and QN at 10% to 25%. In some cases of non-compliance with multiple dose drugs, only minor under-dosing may have

[b] The probability of full recovery, death and NS was assumed to be the same for all those with severe malaria not seeking formal treatment (P7, P8 and P9), which includes those who use self-treatment, or traditional medicine and those who do nothing. This may not hold if some patients are obtaining effective over the counter drugs, but no effectiveness data are available on this.

[c] The response to treatment is classified as adequate clinical response if the patient does not suffer from treatment failure in the first two weeks after treatment, and by day 14 either does not have parasitaemia or does not have a temperature higher than 37.5°C (as defined by WHO[9]).

occurred. Although the impact on effectiveness of under-dosing with different drugs is not known, it is possible that there could still be some therapeutic effect. In the absence of drug resistance, it was therefore assumed that under-dosing with multi-dose drugs, such as CQ, AQ and oral QN, would be effective in between 10% and 30% of cases under-dosed. Under dosing with a single dose drug, such as SP, was assumed to have zero effectiveness.

The model is inevitably a simplified reflection of the complex patterns of treatment-seeking behaviour that occur in practice. Whilst the decision tree represents treatment as a linear progression through a series of stages, in reality, care-seeking pathways tend to be highly varied[11]. Patients may alternate between formal and informal providers, and may use more than one source of care at the same time. It may also be difficult to distinguish between treatment failure and reinfection, so that the end of one episode and the beginning of another may be hard to discern.

The decision tree was used to calculate the probability of an outpatient with malaria entering the system surviving, dying or surviving with NS. These probabilities were then converted to expected DALYs per patient[d]. Estimates were made separately for patients over and under 5 years of age, and the overall expected DALYs were calculated as an average weighted by each group's share of the total population. The impact of an intervention to improve case management was modelled as a change in one or more of the probabilities in the decision tree. The expected DALYs per patient were recalculated using the new probabilities, and compared to the results for the original tree to calculate the effectiveness of the intervention as the expected DALYs averted per patient.

In order to estimate each of the probabilities in the decision tree, it was necessary to combine estimates from a wide range of SSA countries. For some variables there were simply no data available, so estimates had to be made following discussions with experts in the field. The ranges and sources used for the probabilities in the decision tree are documented in Table 5.1. The effectiveness of the case management interventions was estimated for the two broad epidemiological strata of low and high transmission. To characterize these two zones, different input parameters were used for the average age at death, the proportion of presenting cases that were children, the positive predictive value of clinical diagnosis, and the probability of developing severe malaria (see Table 5.1). All other variables were kept the same in both zones.

5.2.2 Costs

Costs were also attached to the branches of the decision tree where relevant, so that a cost could be estimated for each possible path that an outpatient could take. The expected cost per outpatient could then be calculated by multiplying the cost of each path by the probability that it would be followed. Cost estimates used in the decision tree are documented in Table 5.2. The average cost

[d] Morbidity and chronic anaemia from malaria episodes could also be included in the YLDs, but would be relatively insignificant compared with mortality and neurological sequelae. In their calculations of the burden of disease, Murray & Lopez (1996[12]) found that morbidity from episodes and anaemia made up only 1.5% of the DALYs due to malaria in SSA.

per adult treatment with CQ was $0.13, with SP $0.14, with AQ $0.20, and with QN (7 day course) $2.68[e].

An intervention to improve case management will lead to incremental costs, for example due to higher expenditure on drugs, prepackaging, or education. The decision tree was used to calculate the expected cost per outpatient both with and without the intervention in order to assess the incremental cost per patient.

In addition to the incremental costs of an intervention, cost-savings, or "cost-offsets", may arise if the effectiveness of case management improves. Reductions in the number of persistent cases of uncomplicated malaria and the number of cases developing to severe malaria would lead to lower treatment-seeking costs for both providers and households. Costs were therefore attached to the decision tree to cover the cost of outpatient visits, inpatient visits, and the cost of seeking care from alternative non-formal sources. The total expected net cost for an outpatient was then calculated. Estimates for treatment-seeking costs were obtained through a literature review, covering both costs to the health system and out-of-pocket costs to patients and their families, and are shown in Table 5.2.

It is unlikely that the full cost of treating each inpatient or outpatient case averted will actually be saved, because some proportion of the costs will be fixed, at least in the short term, meaning that they will not vary with the number of patients. This will generally include buildings and equipment, supervision and training, and may also include most staff costs. On the other hand, items such as drugs, reagents and food can be expected to vary with utilisation. All capital costs were assumed fixed and estimates were taken from the literature of the percentage of recurrent costs fixed, of 25% to 40% for outpatients, and of 50% to 75% for inpatients[13, 14]. It was therefore assumed that averting an outpatient visit saved 60% to 75% of the outpatient recurrent unit cost, and that averting an inpatient day saved 25% to 50% of the inpatient recurrent cost per day.

The change in the expected cost per outpatient after the introduction of an intervention could then be calculated, as a gross cost, including only the additional intervention costs, and as a net cost, including both the additional costs and the cost-offsets. Where cost-offsets were included, it was possible that in some circumstances the net cost of an intervention could be negative, i.e. there would be overall cost-savings because the cost-offsets exceeded the incremental costs.

5.2.3 Cost-effectiveness

The cost-effectiveness of an intervention was calculated by comparing the expected incremental cost per outpatient and the expected DALYs averted per outpatient. Results were classified as falling within one of the four quadrants of the cost-effectiveness plane shown in Figure 5.2.

The horizontal axis of the plane represents the difference in effects from the intervention, a positive effect meaning that DALYs were averted. The vertical axis represents the difference in costs. If the intervention would lead to negative effects (increase in DALYs) and would be more costly the result

[e] Doses: CQ and AQ: 25mg/kg over 3 days, SP: 25mg/kg S + 1.25mg/kg P in a single dose, QN: 10mg/kg every 8 hours for 7 days. Costs were not adjusted for compliance, or possible variations in staff time for prescribing different drugs. The cost of treating side-effects was also not included.

would fall in quadrant IV, and the intervention would be "dominated" by the status quo. If the intervention would lead to positive effects (reduction in DALYs), and would be less costly the result would fall in quadrant II, and the intervention would be the "dominant" option. If the intervention would lead to positive effects but would be more costly the result would fall in quadrant I: the choice between implementing the intervention and maintaining the status quo would not be clear, and would depend on an assessment of cost-effectiveness. In this quadrant the cost-effectiveness ratio (CER) can be calculated as the cost per DALY averted (expected incremental cost per outpatient divided by the expected DALYs averted per outpatient). As an example, the $25 per DALY averted cut-off suggested by the Ad Hoc Committee on Health Research Relating to Future Intervention Options[15] is also shown in quadrant I; any results falling below this line would be considered cost-effective using this criterion.

The simulation was run for 3,000 iterations. With gross costs, where at least 95% of the iterations had CERs below $150 or $25 it was concluded that one could be "reasonably certain" that the intervention was cost-effective at this level. Where net costs were used, when at least 95% of the iterations were dominant (fell in quadrant II), it was concluded that one could be "reasonably certain" that the intervention was cost-saving.

5.3 Using pre-packaging, training and health education to improve compliance with antimalarials

Compliance with drug treatment is very low in SSA for several reasons. The correct regimen may not be prescribed, due to inadequate knowledge or poor communication skills on the part of the prescriber. Providers may deliberately under-prescribe, in order to preserve drug stock for other patients, or deliberately over-prescribe if they gain financially from drug sales. The appropriate drugs may not be available due to inadequate stock at the health facility and a lack of alternative outlets. Patients may choose not to obtain the drugs if the price charged is unaffordable, or if they are not aware of the importance of taking a full course. Finally, patients may not take the correct doses at the correct time if they forget or misunderstand the instructions, or decide to discontinue treatment when their symptoms appear resolved and to reserve the remaining drugs for later use[2, 3, 16-19].

Several strategies have been proposed to improve compliance, such as training providers, training care-takers, and pre-packaging drugs. It was assumed that pre-packaging would make it easier for patients to understand and remember how to take their drugs, improving patient compliance, and would simplify dispensing, improving provider compliance. In Burkina Faso, an intervention to train mothers and distribute CQ and paracetamol pre-packaged in simple plastic bags by VHWs led to an increase in the number of children taking an adequate dose of CQ from 3% to 49%, and an increase in the number following a treatment regimen of adequate length from 21% to 72%[20]. Compliance was also found to increase following a similar pre-packaging intervention in Ghana[21]. Studies in South-East Asia showed positive results with blister packaging of antimalarials, increasing compliance from 83% to 97% in China, compared to handing out drugs in simple envelopes[22]. It was noted at a workshop on pre-packaging in Liverpool in 1997 that the average increase in compliance reported in various intervention studies was approximately 20%, although the impact on compliance might vary depending on the existing level of compliance, the age of the target group, education levels and the regimen of the drug in question[23].

Little information is available on the cost of these strategies. In Burkina Faso, the cost of the simple plastic bags, labels and packing was $0.015 per treatment, and the total non-drug cost of the intervention per treatment was $0.07 (which included the cost of training and health education, bags, labels and packaging of drugs, incentives to VHWs, supervision and distribution). Blister packs are much more expensive, and were reported to add $0.84 to the cost of a treatment course of CQ, although costs may fall if mass production were possible[24]. However, whereas pills packaged in loose plastic bags need to be used within 35 days, blister packs can last up to 13 months, and should also be more difficult to forge than low-technology plastic bags[23].

The cost-effectiveness of an intervention to improve compliance was evaluated using the case management model, with CQ as first line drug, SP as second line and oral QN as third line and inpatient drug. The intervention was assumed to include training of providers, health education for patients and care-takers, and the pre-packaging of CQ in plastic bags, and to cost between $0.05 and $0.15 per case treated[f]. The intervention was assumed to lead to an increase of between 10% and 30% in the percentage of patients receiving at least the minimum dose. The increase in compliance serves to reduce P1, the probability of failure of the first line drug, thus increasing the proportion of cases cured overall and reducing morbidity and mortality, and the costs of treatment for persistent uncomplicated malaria and cases that develop to severe malaria. The model was used to estimate the cost per DALY averted by the intervention for different levels of CQ resistance.

5.3.1 Improving compliance: cost-effectiveness results

The results for a very low income country with high transmission using gross costs are in Figure 5.3a, which shows the mean and 90% range for the CER as CQ resistance varies. For example, with no resistance to CQ, the CER range is below $5, and with 50% resistance, below $11. As resistance increases the intervention becomes less cost-effective, because the CER rises as the benefits of improved compliance are not reaped with ineffective drugs. However, one can be reasonably certain that the intervention has a CER under $25 up to CQ resistance of 77%.

The CER at given resistance levels was much higher in low transmission areas as shown in Figure 5.3b (very low income countries). With no resistance to CQ, the CER range was below $18, and with 50% resistance, below $36. One could be reasonably certain that the intervention had a CER under $25 only up to CQ resistance of 24%, but the range remained below $150 up to 87% resistance. The intervention was not as cost-effective in low transmission areas because the true prevalence of malaria among suspected cases was lower, meaning that the benefits of improved compliance with antimalarials were experienced by a smaller percentage of the patients. The results with gross costs for middle and higher income countries were very similar to those for very low income countries in both types of transmission area.

The model was also run using net costs (i.e. including cost-offsets) to assess whether the intervention was likely to lead to overall cost-savings. The results show that one could not be reasonably certain that there would be net cost-savings in very low and middle income countries at any level of CQ

[f] Using a range around the estimate for the intervention described by Pagnoni *et al*[20], which cost $0.07. The upper limit was set at $0.15 to allow for an increase in the quantity of CQ prescribed.

resistance. The same was true for higher income countries in low transmission areas, but for higher income countries in high transmission areas, one could be reasonably certain that there would be cost-savings at any level of resistance below 61%. The intervention was more likely to be cost-saving in higher income countries because the treatment-seeking costs saved were assumed to be larger.

5.3.2 Improving compliance: discussion

The results indicate that interventions to improve compliance are potentially highly cost-effective, especially in high transmission areas, and may be cost-saving in higher income countries. Moreover, the intervention may lead to other cost-savings not included in the model, such as a reduction in over-prescription, unnecessary use of injections and polypharmacy[21]. It is also possible that a reduction in the proportion of cases being treated with sub-optimal doses would reduce the speed at which resistant parasites are selected[25].

The results should be interpreted cautiously as the implication from the model that the increase in compliance will be translated into a reduction in morbidity and mortality has not been validated empirically. It is also not clear whether the substantial improvements in compliance observed would be maintained over time. For example, in Ghana, in-service training of providers improved prescribing performance in the short-term, but was not found to be an effective means of changing prescribing decisions in the long-term[2]. Care should also be taken in extrapolating the available results to other settings. The existing studies focus on the use of CQ, and may not be generalizable to other drugs such as SP, which involve different regimens and different compliance issues. Moreover, the effectiveness of training, education and pre-packaging in improving compliance will depend on the underlying reasons for non-compliance in a specific setting. For example, effectiveness is likely to be greater if low compliance is due to inadequate provider knowledge or to patients/caretakers misunderstanding or forgetting the correct regimen. However, it is less likely to be effective if patients buy a sub-optimal dose because they cannot afford the full regimen, if drugs are frequently unavailable, or if strong incentives remain for providers to deliberately over- or under-prescribe. Finally, the results are sensitive to the cost per patient. If, for example, the cost were as high as $0.50 per outpatient, one could never be reasonably certain that the CER would be below $25, even at zero resistance.

In conclusion, interventions to improve compliance are a promising area for further exploration, and could be of value in the formal and informal private sector as well as the public sector. More research is urgently needed to design reliable and affordable packaging, and to provide more information on intervention costs and effects and the sustainability of improvements in compliance over time.

5.4 Improving access to the second and third line drugs for treatment failures

The model is based on the assumption that there is a clear hierarchy of drugs for the treatment of uncomplicated malaria. If uncomplicated malaria persists after treatment with the first line drug and the patient returns to an outpatient facility, it was assumed that the second line drug would be

prescribed, and that if the patient returns a third time having failed with the second line, the third line would be given. However, in reality, access to second and third line drugs may be very poor. For example, in Zambia, SP was the official second line drug, but was only available by physician prescription at referral hospitals. In 1996 the Zambian Government decided to improve access to SP by making it available at health centres for people with persistent or recurrent symptoms after treatment with CQ[26].

The model was used to assess the cost-effectiveness of such a change, by comparing a situation where only CQ is available at outpatient facilities, with one where SP and QN are available as second and third line drugs respectively for patients identified as treatment failures. In the case where only CQ is available, all first line failures due to parasite resistance automatically fail with a repeat CQ treatment, and only those failures due directly to non-compliance have a chance of a cure when CQ is prescribed again. The use of the more effective drugs for second and third line treatment leads to a reduction in the failure rates, P11 and P14. The incremental costs of the intervention are the additional costs of the more expensive second and third line treatments, and the cost of training health care staff to manage the more complicated regimen. The latter was assumed to be the same as the costs of training, health education and regulatory revisions for changing the first line drug (see below). The model was simulated to estimate the CER for different levels of CQ resistance.

5.4.1 Improving access to second and third line drugs: cost-effectiveness results

The results for a very low income country with high transmission using gross costs are in Figure 5.4a, which shows the mean and 90% range for the CER as CQ resistance varies. For example, with no resistance to CQ, the 90% CER range was below $14, and with 50% resistance, below $2. As resistance increases, the intervention becomes more cost-effective because it becomes more important to provide an effective drug in the event of treatment failure. One could be reasonably certain that the intervention had a CER under $25 at any level of CQ resistance.

The intervention is slightly less cost-effective in low transmission areas as shown in Figure 5.4b (very low income countries). With no resistance to CQ, the CER range is below $37, and with 50% resistance, below $4. However one could be reasonably certain that the intervention had a CER of under $25 at any level of CQ resistance greater than 6%. The intervention is not as cost-effective in low transmission areas because the true prevalence of malaria among suspected cases is lower, meaning that the benefits of more effective drugs are experienced by a smaller percentage of the patients. The results with gross costs for middle and higher income countries were very similar to those for very low income countries in both types of transmission area.

The results using net costs for high transmission areas are shown in Figure 5.5. One could be reasonably certain that there would be net cost-savings over a threshold level of CQ resistance of 40% in very low income, 22% in middle income and 3% in higher income countries. In low transmission areas one could never be reasonably certain of cost-savings in very low income countries, but in middle and higher income countries cost-savings were reasonably certain above 77% and 19% CQ resistance respectively.

5.4.2 Improving access to second and third line drugs: discussion

The results indicate that improving the availability of second and third line drugs is potentially highly cost-effective, and possibly cost-saving where there is significant resistance to the first line drug. However, the assumption that the training will provide health care staff with the necessary skills to identify treatment failures and implement the more complicated regimen may be optimistic in some settings, meaning that the new regimen would not be implemented as planned. Another possible cause for concern is that making second and third line drugs widely available would increase the growth of resistance to these drugs, potentially compromising the treatment of severe malaria and reducing the cure rates of potential replacements to CQ. However these drugs may be already widely available in the private sector, so that resistance would be increasing anyway. The intervention could be combined with strategies to improve provider practice and patient compliance, in order to minimize this danger.

5.5 Changing the first line drug for the treatment of uncomplicated malaria

For decades CQ has been the official first line drug for the treatment of uncomplicated malaria in nearly all African countries as it is cheap, effective and safe, causing only minor side-effects. CQ resistance first appeared in Africa in the late 1970s. It spread very slowly at first, but from the mid-1980s the rate of growth accelerated rapidly, and it is now common in practically all endemic countries in SSA[4]. Resistance has made it increasingly difficult to provide effective treatment and has been associated with a rise in malaria related mortality[27]. There has been considerable debate over when the first line drug should be changed, and the choice of replacement drug[8]. A common candidate is SP, another relatively cheap and safe antimalarial which currently faces much lower rates of resistance than CQ. A change from CQ to SP has been fully implemented in Malawi[26] and in some provinces of South Africa, and Kenya has now decided to follow suit. All other SSA countries still use CQ as the first line drug, despite frequently high rates of resistance.

The growth of resistance to the replacement drug is a major cause of concern for policy- makers, who fear that this drug will be difficult to replace in turn, because few safe, effective and affordable antimalarials are currently available. For example, in Thailand, SP replaced CQ as the first line treatment in 1973. Although morbidity and mortality fell over the next seven years, by 1981 there were reports of diminishing efficacy, and in 1983 a new first line drug was introduced in some areas[28]. Whereas SP and CQ are relatively similar in price per treatment, the potential replacements for SP are much more expensive. QN is not considered to be a suitable first line drug because of the length of the regimen, its side effects and the importance of maintaining its efficacy as a treatment for severe malaria. In South-East Asia it has been common to make the second switch from SP to mefloquine, which has a cost per treatment 30 to 40 times greater than CQ, and is unlikely to be affordable in SSA. It is uncertain whether any more affordable alternatives will become available, especially as there are limited incentives for pharmaceutical companies to invest in drugs for which the ability to pay is so low[6].

A key question for policy-makers is at what level of resistance to CQ a change in drug policy should be implemented. Several authors have attempted to provide guidelines[8, 29-31], but no consensus has yet been reached. This decision involves complex trade-offs between higher drug costs, immediate reductions in morbidity and mortality and reductions in the associated cost of treatment, and

potential increases in resistance to replacement drugs which could lead to higher morbidity and mortality in the future.

The model was used to analyse these trade-offs by simulating a change in the official regimen. The analysis builds on previous work by Phillips *et al.*, Sudre *et al.* and Schapira *et al.*[29, 31, 32] on the economics of changing the first line antimalarial, and draws insights from the work by Coast *et al.*[33, 34] on resistance to antibiotics in developed countries. Two possible drug policy regimens are considered: in the initial situation, Regimen 1, CQ is the first line drug, SP is the second line drug and oral QN is the third line drug. A change is considered to Regimen 2, where SP is the first line drug, AQ the second line drug, and oral QN remains the third line. The expected DALYs per outpatient with each regimen were calculated from the decision tree, using the failure rates and compliance rates for each drug described in Table 5.1. The costs and effects of changing from Regimen 1 to Regimen 2 are first considered in a static framework, where resistance to each drug is held constant. The model is then extended to consider the costs and effects over a 10-year period, incorporating the growth in drug resistance over time.

Changing the first line drug would lead to incremental costs from any increase in the costs of new first and second line drugs. In addition there will be costs associated with the policy change itself, due to the need to revise treatment guidelines, train staff and produce new health education materials. The cost of the policy change in Malawi was approximately $575,000 (see Table 5.3). This was standardized for country size by calculating an annualized cost per outpatient visit, using an expected life time of the new regimen (between 5 and 10 years), and dividing by the annual number of outpatients attributed to malaria in Malawi, to give a range of between $0.02 and $0.03[g]. The expected gross cost of switching from Regimen 1 to Regimen 2 was calculated as the expected change in outpatient drug costs plus the cost per outpatient of the accompanying training, health education and regulatory revisions. Potential cost-offsets from reduced treatment-seeking were included to calculate the net expected cost of switching. The expected DALYs averted and costs incurred per outpatient from moving from Regimen 1 to Regimen 2 were calculated for different levels of resistance to CQ.

5.5.1 Cost-effectiveness results in a static framework

With resistance to the drugs held constant over time, the results clearly showed that switching to Regimen 2 would be cost-effective. Using gross costs, in high transmission areas of very low income countries, even with no CQ resistance, 95% of all results fell below the $25/DALY averted cut-off, and when there was some CQ resistance, the switch appeared even more attractive. Using net costs, threshold analysis showed that at any level of CQ resistance greater than 10%, over 95% of results showed the switch to be cost-saving. Regimen 2 appeared much more cost-effective than Regimen 1 in the static framework, even when the failure rates of the two drugs were similar, because compliance to the single dose drug, SP, was much higher than compliance to CQ. This meant that the failure rate with the first line drug, P1, was much lower under Regimen 2, and the DALYs per outpatient were therefore lower. The increase in cost for the first line drug was very small, as treatments of SP and CQ were similar in price, and the additional costs of the replacement

[g] The costs involved in monitoring drug efficacy have not been included as it is assumed that these activities should be conducted whether or not a decision is made to change drug, so the costs are not incremental.

second line drug and implementing the policy change appeared good value for money relative to the benefits of the increased cure rate.

For middle and higher income countries, one could be reasonably certain that the switch was cost-saving even at 0% CQ resistance. In countries with higher per capita GNP, the threshold levels of resistance were lower because the DALYs averted per death prevented were greater due to the higher life expectancy, and where cost-offsets were included, the savings from reduced treatment were higher due to higher salary costs and better quality health services.

In areas of low transmission, at zero CQ resistance one could be reasonably certain that the switch was cost-effective at the $25 cut-off in all economic strata, and cost-saving in higher income countries. The threshold level of resistance at which the switch became cost-saving was slightly higher in very low and middle income countries (30% and 10% respectively). This is due to the lower proportion of suspected outpatient cases that are actually caused by malaria in low transmission areas, meaning that the benefits of the more effective drug were experienced by a smaller percentage of the patients.

If the analysis was considered only in this static framework, the implication would be that switching to Regimen 2 was highly cost-effective, even at zero resistance to CQ. All countries in SSA are already experiencing some degree of CQ resistance, and therefore would be advised to initiate a change, especially as it has taken Malawi more than two years to implement the new policy fully[10].

5.5.2 Extending the model to allow for the growth of drug resistance

The static analysis does not allow for an increase in drug resistance over time. This ignores one of the main concerns of policy-makers, which is that resistance to the replacement first line drug will rapidly increase once it is widely adopted, reducing the effectiveness of the new regimen.

The model was thus extended to allow resistance to the drugs to increase over time (see Table 5.4). As no models were available which could endogenously predict resistance growth rates, it was necessary to make assumptions for each of the drugs. Resistance to CQ when used as a first line drug was assumed to grow at a constant exponential rate of between 7% and 15% per year (to encompass the 11% growth rate estimated by Schapira *et al.* (1993) from a review of African evidence[31]). Once SP was adopted as the first line drug, the growth rate of resistance was assumed to be twice that of CQ resistance. It is expected that resistance will grow more quickly to SP than to CQ, due to its long half-life and the drug-specific mechanisms underlying the development of resistance[10, 35]. Resistance to SP when used as a second line drug was assumed to increase at only 20% of its rate of growth as a first line drug, as it would be much less widely used and the prevalence of drug use has theoretically been shown to be the most important factor in determining the rate of spread of resistance[36]. Resistance to AQ when used as a second line drug was estimated to increase at 20% of the rate of growth of resistance to CQ as a first line drug. In view of the possibility that there may be cross-resistance between CQ and AQ[37, 38], it was assumed that when Regimen 1 was in place, resistance to AQ would grow at 10% of the rate of growth of resistance to CQ as a first line drug, even though AQ was not part of the official regimen. As resistance to QN has remained low in SSA despite its widespread use as a referral drug, the growth of resistance to QN as a third line drug was assumed to be zero. To illustrate these growth rates,

Figure 5.6 shows the paths of the ACR for each drug if a switch from Regimen 1 to Regimen 2 took place after 5 years, assuming an initial CQ resistance rate of 20%.

The model enables the total costs and total effects over a 10-year period of either remaining with Regimen 1 or switching to Regimen 2 in each of the 10 years to be calculated. For example, a switch from Regimen 1 to Regimen 2 after 5 years (as shown in Figure 5.6) would involve the costs and effects of using Regimen 1 for 5 years, plus the costs and effects of using Regimen 2 for 5 years. Costs and effects were converted to their present values using a discount rate of 3%. Initial rates of resistance to SP, AQ and QN were kept at the rates used in the main model. Initial CQ resistance was varied.

5.5.3 Cost-effectiveness results in a dynamic framework

The extended model was initially run with a sample starting level of CQ resistance of 20%. The mean incremental costs and effects of switching in each year, relative to not switching over the 10-year period, are shown in Figure 5.7a, using gross costs. Only the mean points are shown although the simulation results showed variations around these points. The arrows show how the mean incremental costs and effects changed as the year of switch was delayed. For example, switching after 1 year would lead to an average gross cost per outpatient of $0.71, and an average of 0.14 DALYs averted per outpatient, whereas switching after 8 years would involve a gross cost of $0.06 and 0.13 DALYs averted per outpatient. It can be seen that the maximum number of DALYs are averted by switching after 4 or 5 years. Switching in any earlier year is clearly dominated, as the total effects over the 10 years would be lower and the total costs higher. Switching in a later year would be less effective but also less costly. To calculate the optimal year of switch, pairwise comparisons were made of the results for switching in consecutive years. Either the dominant year was identified (more effective and less costly), or one year was identified as more effective but more costly. In the latter case the incremental cost-effectiveness ratio (CER) was calculated. The CER was then compared to the cut-off of $25 per DALY averted to assess whether it was preferable to bring forward the switch by one year. Beginning with no switch (the origin in Figure 5.7a) the costs and effects of using Regimen 1 for all 10 years were compared with switching to Regimen 2 after 9 years. If over 95% of the iterations showed switching after 9 years compared with not switching to be dominant or to have a CER under $25, it was concluded that switching after 9 years was preferable to not switching. The costs and effects of switching after 9 years were then compared with switching after 8 years, and so on until less than 95% of the iterations showed bringing the year of switch forward by one more year to be cost-effective. This gave an "optimal year of switch" using the cost-effectiveness criteria of year 6, when CQ resistance would be 59%.

The analysis was repeated using net costs (see Figure 5.7b). Switching any time from year 3 onwards was demonstrated to lead to cost-savings over the 10-year period compared to not switching. Switching in years 7, 8 or 9 was dominated by year 6, and switching in years 0, 1, 2 or 3 was dominated by years 4 and 5. Having eliminated these dominated years, the optimal year of switch was calculated. Despite the inclusion of cost-savings, the optimal year remained year 6, as with the gross cost analysis. At a starting level of 20% CQ resistance, this did not vary for other income levels, or for areas of low transmission.

The effect on the optimal year of switch of varying the initial value of CQ resistance is shown in Table 5.5 for a very low income country with high transmission. With higher initial CQ resistance, the optimal year of switch was brought forward. For example, with an initial level of 30% CQ resistance, the optimal year of switch would be year 5, and with an initial level of 60% CQ resistance, the optimal year of switch would be year 3.

5.5.4 Changing the first line drug: discussion

If the growth of drug resistance is ignored, an immediate switch to Regimen 2 appears highly cost-effective, whatever the level of CQ resistance. By contrast, using a dynamic framework leads to strikingly different conclusions. With a starting CQ resistance of 20%, there should be a delay of 6 years before a switch is implemented, which would inevitably lead to higher rates of mortality in the short to medium term. The analysis can be used as an analytical tool to help structure the problem, explicitly explore the trade-offs involved, and pinpoint areas where further research would be beneficial to reduce parameter uncertainties. However, it cannot aim to provide policy-makers with a definitive answer on when to switch drugs, because the results are highly dependent on both empirical and subjective parameter estimates used in the model.

There is a high degree of uncertainty about both existing levels of resistance and likely growth rates. The resistance data available in SSA are mainly in terms of parasitological failure (e.g. RII/RIII); there is little information on the clinical failure rates required for this model, and the relationship between parasitological and clinical failure is complex and varies depending on the epidemiological conditions[39].

The estimates for the resistance growth rates are very speculative, and are based on extremely limited empirical data, often from settings which are not typical of SSA. Constant growth rates were assumed, but in practice it is likely that rates may vary over time. For example, the growth rate may accelerate after a certain threshold is reached, and then perhaps plateau off at high levels of resistance. Varying resistance growth rates substantially influence the results. A higher growth rate of resistance to SP relative to CQ as a first line drug would delay the optimal year of switch. If resistance to SP were assumed to grow three, rather than two times as fast as resistance to CQ, the expected optimal year of switch would be delayed from year 6 to year 7. On the other hand, if the resistance growth rates of the two drugs as first line treatments were the same, the optimal year would be year 4.

The model is based on the premise that the growth rate of drug resistance depends on the role of the drug in the official regimen. This may over-emphasize the importance of the public sector in drug distribution, as between 40% and 60% of antimalarials in SSA are distributed through private providers[40]. If a drug becomes widely available in the private sector it is likely that resistance will grow rapidly, even if it is not part of the official regimen. For example in Cambodia, mefloquine was widely used by privileged groups in the private sector so that by the time it was introduced into the official regimen, its efficacy was already declining rapidly[41].

Other key factors affecting the results are the time-frame and discount rate used in the model. A discount rate on health benefits was used to reflect the preference of individuals and governments to receive the benefits of reduced mortality earlier rather than later (time preference), and to reflect the

increased uncertainty about receiving predicted benefits further into the future (risk premium). The discount rate was set at 3% to ensure comparability with other economic evaluations[42] and to maintain consistency with the treatment of costs. Reducing the discount rate for health benefits from 3% to 1% leaves the optimal year of switch at year 6, but increasing the discount rate to 10% brings forward the optimal year to year 5 (assuming initial CQ resistance of 20%). A 10-year time-frame was chosen to reflect the number of years over which one could predict the availability of therapies with some confidence. Beyond 10 years it is very difficult to anticipate which new drugs will be registered and what their prices will be, and therefore not possible to include them in the model. It may be considered that 10 years is actually an over-estimate of the period over which we can predict, and that it would be prudent to shorten the time-frame of the dynamic analysis. However this view needs to be balanced with a concern for intertemporal equity, which could be compromised by putting a lower weight on health implications further into the future, or by not considering them at all[33, 34].

The time-frame considered and the discount rate used affect the model results, and as these parameters represent the preferences of policy-makers, research in the field of policy analysis is required to explore the objectives of those responsible for malaria drug policy. Currently, little is known about the motives behind policy changes, and the nature of the information required by decision-makers is therefore unclear. It is possible that the use of expected health outcomes in the model may not fully encompass policy-makers' attitudes to risk. There is potential for a catastrophic outcome where there is high resistance to all cheap drugs and no effective, affordable antimalarials available. It may therefore be preferable to consider drug policy to have some characteristics of a decision about insurance, where decision makers may be prepared to accept a lower expected overall health outcome in order to reduce the risk of the catastrophic scenario[34].

Increases in resistance may lead to behavioural changes that are not incorporated in the model, but which would have implications for both costs and health outcomes. For example, providers or patients may respond to a decline in efficacy by increasing the dosage, leading to an increase in serious side effects. Alternatively, widespread perception that a drug is no longer effective could result in a shift away from formal treatment services. A change in the first line drug could lead to an increase in outpatient utilization rates if treatment is perceived to be more effective, or a decrease in utilization if patients lose confidence when a long-familiar drug is replaced[11].

The analysis is based on a shift in drug regimen for all patients in all areas of a country. However, rates of clinical failure are often highly variable, being more common in certain regions, or in non-immunes. Policy-makers may therefore wish to consider changing regimen only in particular geographical areas, or for particular age groups. For example, in Thailand, the recommended therapy has been changed only in areas of most severe drug resistance[43]. The benefits of such a targeted approach must be weighed against the potentially higher health education and training costs, the confusion that could arise from having a more complex drug policy, and the potential political problems of denying access to a more effective therapy for certain groups.

5.6 Combination drug therapies

The use of combination drug therapies has been advocated to reduce the spread of resistance[44]. The rationale is that if two drugs are used together, the chance that a mutant will emerge that is simultaneously resistant to both drugs is much lower than if the drugs are used alone (assuming that the genetic mutations which confer resistance to the two drugs are not linked)[35]. In Thailand, a combination of SP and mefloquine was introduced in 1984 in an attempt to reduce the development of resistance, but the strategy met with little success because resistance to SP was already high, and the pharmokinetic properties of the drugs were not well matched[39]. However, since 1992, mefloquine has been prescribed with artemisinin on the western Thai border, with no decline in the efficacy of the combination regimen[45]. It has been suggested that similar success could be achieved through combining other antimalarials with artemisinin (ART)[39]. As ART is fast acting, most parasites are eliminated quickly, leaving only a small residual for the second drug to remove, so the opportunity for the selection of resistant parasites is reduced, and patients will recover more quickly[35].

The extended case management model was used to assess the cost-effectiveness of using combination therapies over 10 years, by modelling the trade-off between increased drug costs and slower development of resistance. A situation was considered where a decision had been taken to replace CQ as the first line drug and two options were being considered: introducing Regimen 2 (SP as first line, AQ as second line and QN as third line), or introducing a Combination Regimen, where every first line treatment with SP was accompanied by ART (with AQ and QN as second and third line drugs respectively, as in Regimen 2). It was assumed that the growth of SP resistance would be lower under the Combination Regimen, but as empirical data are not available on the extent of this reduction, the cost-effectiveness of the intervention was evaluated for a range of percentage reductions in the growth of SP resistance. It is not clear what the failure rate of the first line combination would be as SP resistance increases, so to be conservative it was assumed that all treatments would fail if there was resistance to SP, whether or not there was susceptibility to ART. Costs were based on the assumption that the SP dose would be the same under both regimens (25 mg/1.25 mg/kg). The accompanying ART dose used in the Combination Regimen was assumed to be 600 mg over 3 days for patients over 5 years of age, and 120 mg for patients under 5, with a cost per treatment of $1.25 and $0.25 respectively[h]. Compliance with ART was estimated at between 30% and 60% as with AQ, as they are both taken over 3 days but have relatively few minor side-effects. The costs of training, health education and regulatory revisions were not included as they would be incurred whichever regimen was adopted when CQ was replaced, and would therefore not be incremental costs.

5.6.1 Combination therapies: cost-effectiveness results

The results for a very low income country with high transmission using gross costs are in Figure 5.8, which shows the mean and 90% range for the CER as the percentage reduction in the growth rate of SP resistance increases. For example, with a 10% reduction, the CER range was below $200, with a 50% reduction, below $30, and with an 80% reduction, below $15. One could be reasonably certain that the intervention had a CER under $150 at any reduction in SP resistance growth of 14% or more, and under $25 if the reduction was greater than 58%.

[h] Based on a cost of $1 for a pack of 12 50 mg tablets for artesunate in Vietnam (N. White, personal communication) plus 25% for transport, insurance and delivery.

The intervention is less cost-effective in low transmission areas. With a 50% reduction in the growth of resistance, the CER range was below $140; and with an 80% reduction, below $72. One could be reasonably certain that the intervention had a cost per DALY averted of under $150 at any reduction in SP resistance growth of 47% or more, but even with a 100% reduction in the growth rate one could not be reasonably certain that it was under $25. The intervention was not as cost-effective in low transmission areas because the true prevalence of malaria among suspected cases is lower, meaning that the benefits of more effective drugs were experienced by a smaller percentage of the patients. The results for middle and higher income countries were very similar to those for very low income countries in both types of transmission area. The model was also run using net costs to assess whether the intervention was likely to lead to overall cost-savings. One could never be reasonably certain of cost-savings in very low, middle or higher income countries.

5.6.2 Combination therapies: discussion

The results indicate that the use of combination regimens is potentially cost-effective in high transmission areas, but this is dependent on the extent of the reduction in the growth of resistance to SP. To be reasonably certain that the intervention is cost-effective at the $25 cut-off, the resistance growth rate must be at least halved. However this is likely to be a conservative estimate of the cost-effectiveness of combination therapies because it was assumed that the therapy would not be effective if there was resistance to SP, even if ART was still effective.

The likelihood of reductions in the growth of resistance to SP occurring should be considered in the context of less than perfect compliance with the combination therapy. In particular, it is likely that SP would be distributed widely outside the government sector by formal and informal providers, when it would probably be taken on its own, contributing to faster resistance growth. Moreover, it is possible that making ART widely available would lead to an increase in resistance to this drug, reducing the efficacy of a potentially important drug for treating severe malaria. Whilst it has been argued that the combination will also protect artemisinin from the development of resistance[46], patients may decide to take it alone, especially if they perceive its rapid action as an indication of high efficacy[47].

5.7 Introducing new diagnostic tools

Malaria diagnosis in African health facilities is usually based on clinical symptoms, but as malaria is difficult to distinguish from several other diseases, there is a high rate of over-diagnosis and unnecessary prescription of antimalarials. An alternative would be to use diagnostic tests, such as microscopy or the new antigen detection dipsticks, and only prescribe antimalarials to patients with positive test results. As the health impact of introducing diagnostic tools is not clear, the analysis was restricted to an evaluation of net costs. The potential cost savings from using tests were assessed by comparing the incremental cost per test with the potential savings in drugs prescribed.

The dipstick technique requires only a small blood sample, is relatively quick to do, and does not require sophisticated laboratory skills or equipment. Some of the tests can identify only *p. falciparum*, but newer tests are becoming available which can distinguish between parasite

species[48]. The incremental cost per test was calculated based on a cost per dipstick of between $1 and $1.65, plus additional supplies (cotton swab, lancet, and gloves), between 7 and 9 minutes of incremental staff time, and a day's training per staff member[49]. This gave a cost between $1.26 and $1.84 in the very low income stratum, between $1.30 and $1.89 for middle income countries and between $1.69 and $2.31 in higher income countries.

The most common method of malaria diagnosis is to take a blood sample, prepare a stained thick smear and examine for parasites using a light microscope. In most African countries microscopy is not available in rural health centres but may be used at the district hospital level or in larger clinics. The incremental cost per test was estimated, including the annualized cost of the microscope, supplies, staff time and training, scaled up by 20% to 30% to account for the supervision and overhead costs required for the operation of a successful service.

The microscopy cost per test was cheaper than the dipstick test in very low income countries (between $0.31 and $0.58), and in middle income countries (between $0.37 and $0.73), but there was some overlap with the dipstick cost for higher income countries (between $0.84 and $1.85). This overlap occurred in the top economic stratum because of the slightly higher staff time required for microscopy, weighted by the relatively high salary costs. The cost of additional patient waiting time was not included although this can be substantial, at an average of about an hour for microscopy, and 30 minutes for a dipstick test[49, 50]. All cost input variables are listed in Table 5.2.

The savings in drug costs per patient from the use of a diagnostic test depend on the accuracy of clinical diagnosis, the accuracy of the test, and the cost of drugs used. The probability that a suspected case was caused by malaria was taken from the main model (35% to 58% of clinical diagnoses in high transmission areas, and in 10% to 20% in low transmission areas). There is little difference between the accuracy of the two tests. For the dipstick a range of 81% to 99.5% was used for specificity, and 84% to 94% for sensitivity[49]. Microscopy sensitivity was assumed to be between 83% and 91%, and specificity between 91% and 100%[51]. The average drug cost per treatment was calculated as a weighted average of the cost per adult and the cost per child, assuming that in low transmission areas 20% of patients presenting would be under 5 years of age, and in high transmission areas, 50%. The drug cost per treatment at which the tests would become cost saving was calculated (Table 5.6) and compared to the weighted average cost for commonly used antimalarials.

5.7.1 Net costs of diagnostic technologies

Despite the low positive predictive values for clinical diagnosis, it is apparent that the use of additional diagnostic technology is very unlikely to be cost-saving in SSA because the current range of first line antimalarials are relatively inexpensive drugs. Neither dipsticks nor microscopy would be cost-saving with CQ, SP or AQ, which all have an average treatment cost of well under $0.20. In the very low income stratum, dipsticks would be cost-saving with drugs with an average cost per treatment greater than $2.87 in high transmission areas and $1.95 in low transmission. The results were only slightly higher for the middle income strata, but in the higher income stratum the drug cost would have to be over $3.70 in high transmission areas and over $2.51 in low transmission. Drug cost-savings per case were larger in low transmission areas because a higher proportion of cases are adults, requiring a higher drug dose, and clinical diagnosis is generally less accurate. As the cost per

test was lower with microscopy, it would be cost-saving with less expensive drugs. For example, for very low income countries, microscopy was cost-saving with any drug with an average cost greater than $0.78 in high transmission areas and $0.61 in low transmission settings. A comparison with mefloquine, one of the more expensive antimalarials, showed that both tests were clearly cost-saving with mefloquine in low transmission areas (weighted average cost per treatment of $3.35-$4.40). For very low and middle income countries, microscopy would also be cost-saving with mefloquine under high transmission (average cost of $2.39-$3.14), but the results were ambiguous for higher income countries, and for all countries with dipsticks.

The robustness of these conclusions to any reasonable changes in the assumptions was tested for CQ. There were no net cost-savings with either dipsticks or microscopy even when the accuracy of clinical diagnosis was assumed to be only 1%, or when only adults were considered, or when staff time was reduced by assuming that tests were done in batches. Moreover, there was no possible price per dipstick at which they would become cost-saving with CQ, because the cost of the staff time and other supplies alone was greater than the drug costs saved per case. One possible exception was where CQ syrup or injections are widely used, as these forms are much more expensive than tablets.

It is possible that the cost-savings are overestimated. As the tests are not 100% sensitive, some positive cases will be missed, and a sub-set of these patients may remain sick and return to the facility, incurring additional costs for themselves and the health system. It is also possible that drugs will be prescribed for patients who test negative. Health workers may substitute a different prescription, such as antibiotics, or persist in prescribing antimalarials because they are afraid of missing a severe case of malaria[52], or because patients demand them[2]. For example, in Zambia, on average 35% of patients with negative blood slides were still prescribed antimalarials[53].

5.7.2 Potential health effects of diagnostic technologies

Even where diagnostic tests are not cost-saving, they could be considered cost-effective if their use led to significant improvements in health outcomes. The evidence on this issue is inconclusive. The use of tests could lead to more rapid diagnosis and appropriate management of non-malarial cases if prescribers look more actively for other explanations of symptoms and treat them appropriately. A reduction in unnecessary drug treatment would lead to fewer drug-related side-effects. In addition, the knowledge that an accurate test is available may encourage more people to come to health facilities for treatment. In a situation of epidemic malaria, dipsticks could be used as part of a flexible programme of surveillance, which would help programme managers to target interventions[54]. Perhaps most importantly, a reduction in drug treatment could reduce the development of drug resistance, although the potential impact is currently unknown. The health benefits from slowing the development of resistance could be large, but they would have to be considered relative to the costs of implementation.

5.8 Other interventions

Other strategies to improve the case management of uncomplicated malaria include the introduction of the Integrated Management of Childhood Illness (IMCI), and improving the quality of drugs.

Anecdotal evidence indicates that drug quality is a major problem in some countries, although no wide-ranging review is available[5]. The implications of increasing drug quality, while recognized to be potentially important, are very difficult to assess due to the lack of available information on the proportion of drugs that are currently sub-standard, the reasons for this low quality, the improvements that could be expected with better surveillance and enforcement, and the costs of any interventions.

IMCI is an approach currently being piloted in a few African countries, which aims to improve the treatment of the most common childhood diseases and conditions (acute respiratory infections, measles, malaria, diarrhoea and malnutrition). Due to the considerable overlap in the signs and symptoms of these diseases, a single diagnosis for a sick child is often inappropriate, and may lead to other serious and potentially life-threatening conditions being overlooked. To tackle this problem, IMCI involves the training of health workers in integrated case management and the development of guidelines. Other strategies to improve treatment services include the strengthening of drug supply, management and supervision systems. An evaluation of IMCI is beyond the scope of this analysis, as it involves consideration of the benefits for several disease areas. The World Development Report (1993[55]) reported that IMCI was highly cost-effective, with a CER of between $30 and $50 in low income countries, but this did not reflect the incremental cost-effectiveness of introducing IMCI over and above current treatment practices. A comprehensive study to estimate the incremental costs of the substantial training required and the drugs involved, and to model the potential incremental health impact is required.

It would also have been desirable to include analysis of interventions to improve the case management of severe malaria, but data were not available on either the costs or the health effects. However, as an illustration, the introduction of artesunate suppositories for patients with severe malaria is discussed in Box 1. This preliminary analysis indicated that this intervention could be highly cost-effective, and it is plausible that this could also be the case for other interventions to improve the treatment of severe cases. More research is urgently needed in this area.

Box 1. Using artesunate suppositories to improve access to inpatient care

Poor access to inpatient care is potentially an important cause of morbidity and mortality from severe malaria. Prompt access is vital for patients who cannot take oral medication, as resources required for administering intravenous drugs, such as infusion sets, sterilizing equipment and skilled personnel, are rarely available at peripheral facilities[56]. However, in practice, long delays frequently occur.

Artesunate suppositories could be administered to patients being referred with severe malaria, to prevent the onset of complications and so increase their chance of survival both en route and once they arrive in hospital. Artesunate is an artemisinin derivative that has recently been manufactured in a suppository form. WHO/TDR is currently undertaking trials of the suppositories to examine their potential for patients with severe malaria en route to hospital, who are unable to take oral drugs[57]. Results so far are described as "optimistic", but have not yet been released in full. The suppositories can be given by minimally trained staff, and have the added advantage that there is no risk of HIV or hepatitis infection that could occur with parenteral injections[56].

Cost-effectiveness was explored by assuming that the suppositories were administered to all children with suspected severe malaria on referral and that their use reduced the rates of mortality and persistent NS they experienced in hospital. It was assumed that the true cause of illness was malaria in 90% of severe cases being referred. The price per suppository was estimated at $0.50, although this is still very speculative. The CER was calculated for a range of possible reductions in the mortality and NS rates, for a very low income country with high transmission using gross costs.

The results are in Figure 5.9, which shows the mean and 90% range for the CER as the percentage reduction in the mortality and NS rates increase. With a 10% reduction, the CER range was below $2, and as the percentage reduction increased the range was even lower. Even with only a 5% reduction, the range was under $4, well below the $25 threshold.

This simple analysis indicates that artesunate suppositories may be highly cost-effective. However only a sub-set of severely ill patients will benefit from the intervention. Failure to receive prompt inpatient treatment may arise from a variety of causes, including inadequate training of health centre staff, lack of transport, and financial barriers, such as high fees charged at hospital facilities, none of which would be resolved by the introduction of this new technology. However, these issues could be tackled by introducing the suppositories as part of a package, which also included in-service training on the recognition of cases requiring referral, or the provision of additional transport.

5.9 Affordability

The government budget required to implement the interventions on a nationwide scale for a very low income country such as Tanzania was estimated (Table 5.7). Improving compliance, and increasing the accessibility to second and third line drugs, are relatively low cost interventions, both representing well under 1% of the existing government health care budget. Switching from CQ to SP as first line drug would require a relatively small increase in the government health budget, of approximately 0.2% per year. However, switching to mefloquine, a potential replacement for SP, would require an 18% increase, which would have serious implications for the allocation of the health budget as a whole, and would be unlikely to be affordable in most SSA countries without substantial external assistance. The introduction of combination therapy was estimated to require a 5% annual increase to the current health care budget.

The universal implementation of dipstick tests would represent a very high cost for African health services. Taking into account CQ savings, and the case of a very low income country with high transmission, the net cost of using dipsticks for every suspected malaria outpatient case was estimated to be $7.8 million, or around 8% of the existing health sector budget. The use of microscopy would be less costly, at only $2m for full coverage, but would require trained staff, well maintained equipment and a reliable electricity supply, which would be extremely difficult to provide for many peripheral facilities.

5.10 Summary and conclusions

Relatively low-technology, simple interventions that are available to improve case management are potentially highly cost-effective. The limited data indicate that strategies to improve compliance or increase the availability of second and third line therapies are likely to have a cost per DALY averted well below $25 in most settings. These interventions are also likely to be affordable, even for low income SSA countries, with an annual cost of less than 1% of the current public sector health care budget. There is a need for operational research on such strategies to provide more data on their costs and effects.

Changing the first line drug is a highly complex issue, involving a series of trade-offs between current and future costs and effects. There is considerable uncertainty about whether any new safe, effective and low-cost antimalarials will become available, and analysis of the cost to government of changing the drug regimen demonstrates that this is a crucial concern. A dynamic framework is essential to evaluate this decision, but cost-effectiveness analysis cannot provide a definitive threshold resistance level at which change should take place. The identification of the optimal year of switch is dependent on both empirical factors (for which there are very few data) and subjective factors, relating to the preferences and priorities of policy makers, and their attitudes to risk. The collection and dissemination of relevant information on this issue should be a key priority, and constructive advice should be provided to policy makers to help them to weigh up the complicated trade-offs involved.

In the light of the grave threat posed by increasing drug resistance, there is an urgent need for research to investigate the factors that contribute to its development, and for the design and implementation of strategies to reduce its growth. Whilst data in this area are extremely limited at

present, preliminary analysis demonstrates that the increased costs of using a combination therapy could be justified if it produces a significant deceleration in the resistance growth rate. Other strategies that could have a beneficial impact on the growth rate, such as improving compliance, and restricting prescription to confirmed diagnoses, require investigation.

It is possible that there will be trade-offs between the two aims of first, making prompt, effective treatment as accessible as possible, and secondly, limiting the spread of drug resistance[58]. For example, in order to maximize the provision of prompt, effective treatment it would be preferable to use a long half-life drug that can be taken in a single dose. On the other hand, strategies to minimize the growth of resistance might include using short half-life drugs that have to be taken in multiple doses, or more complex combination therapies. The first aim might best be achieved by treating all patients with fever at the most peripheral level, but this could thwart the second aim, which would require tighter control of drug distribution, and the prescription of drugs only to patients with a confirmed diagnosis. Evaluation of these strategies will require a modelling framework, which can incorporate the trade-offs involved with each approach.

Figure 5.1. Case Management Decision Tree

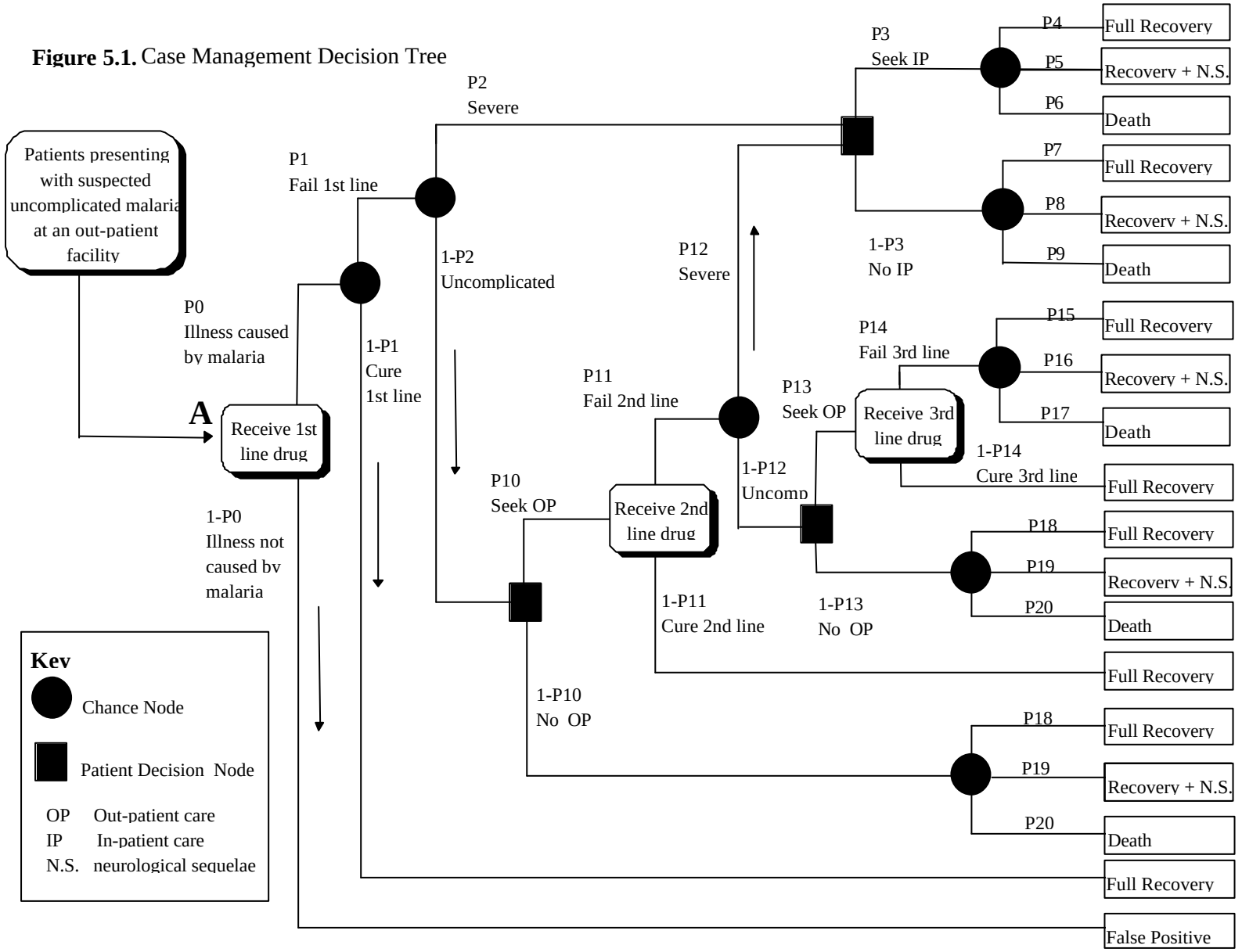


Figure 5.2. Cost-effectiveness plane

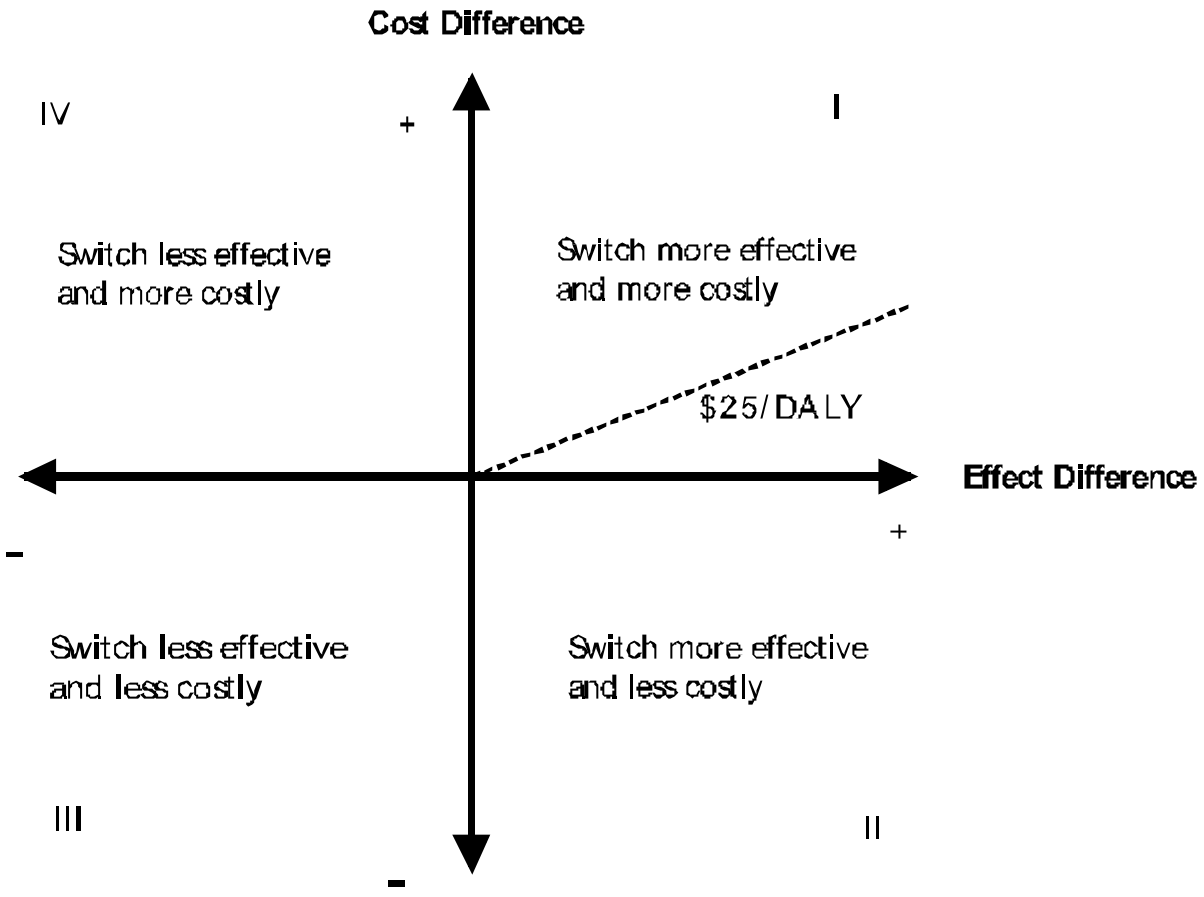
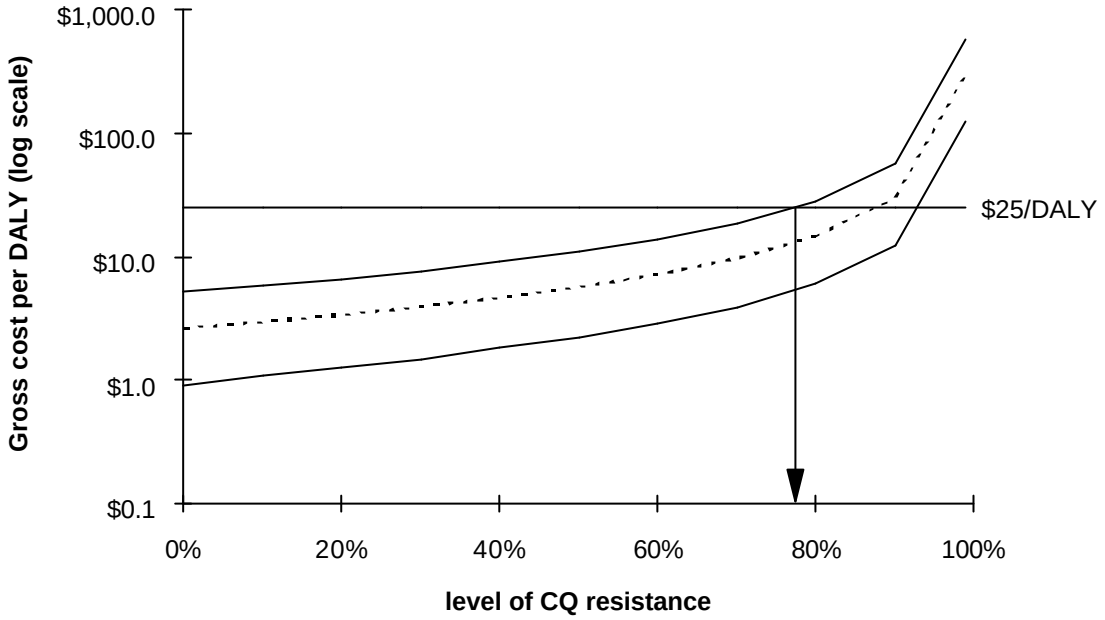


Figure 5.3a and **5.3b**. Pre-packaging and training to improve compliance: gross cost per DALY averted as a function of CQ resistance, for very low income countries and (a) high, and (b) low transmission, showing the mean CER (- - - -) and the 90% range (—) (1995 US dollars)

a. High transmission



b. Low transmission

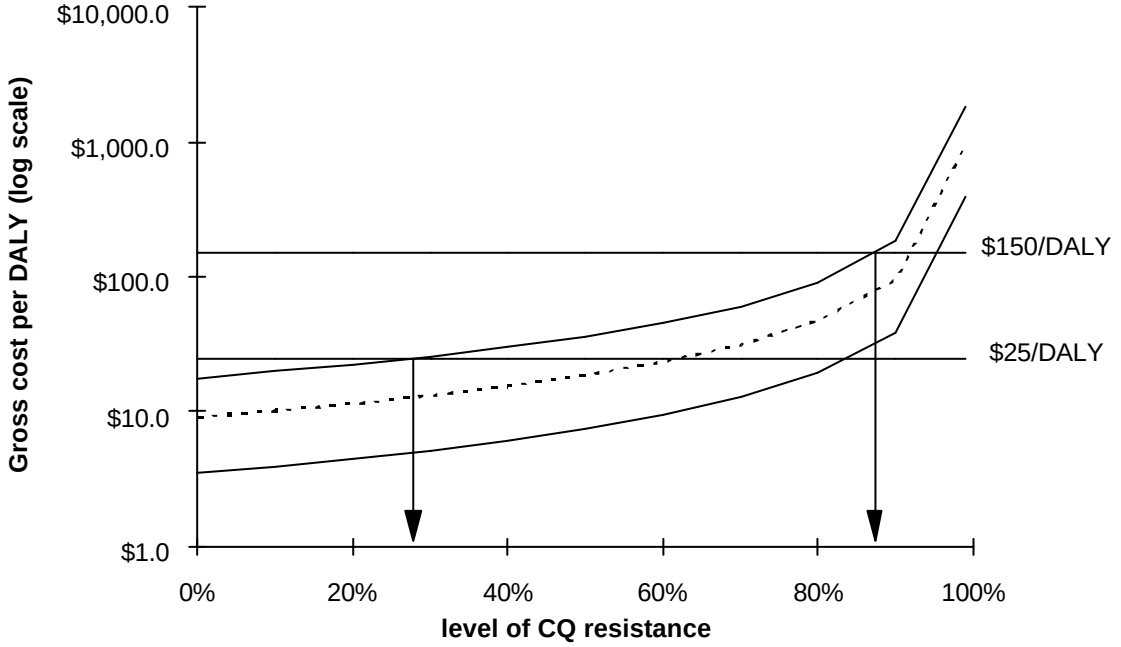
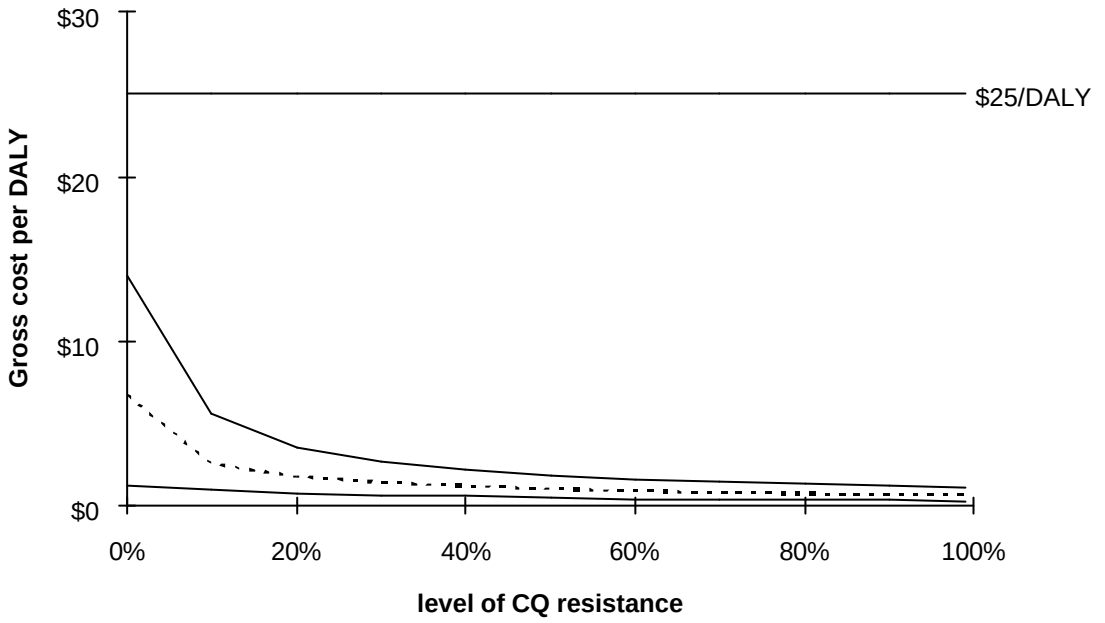


Figure 5.4a and **5.4b**. Improving access to the second and third line drugs: gross cost per DALY averted as a function of CQ resistance, for very low income countries and (a) high transmission, and (b) low transmission, showing the mean CER (- - - --) and the 90% range (——) (1995 US dollars)

a. High transmission



b. Low transmission

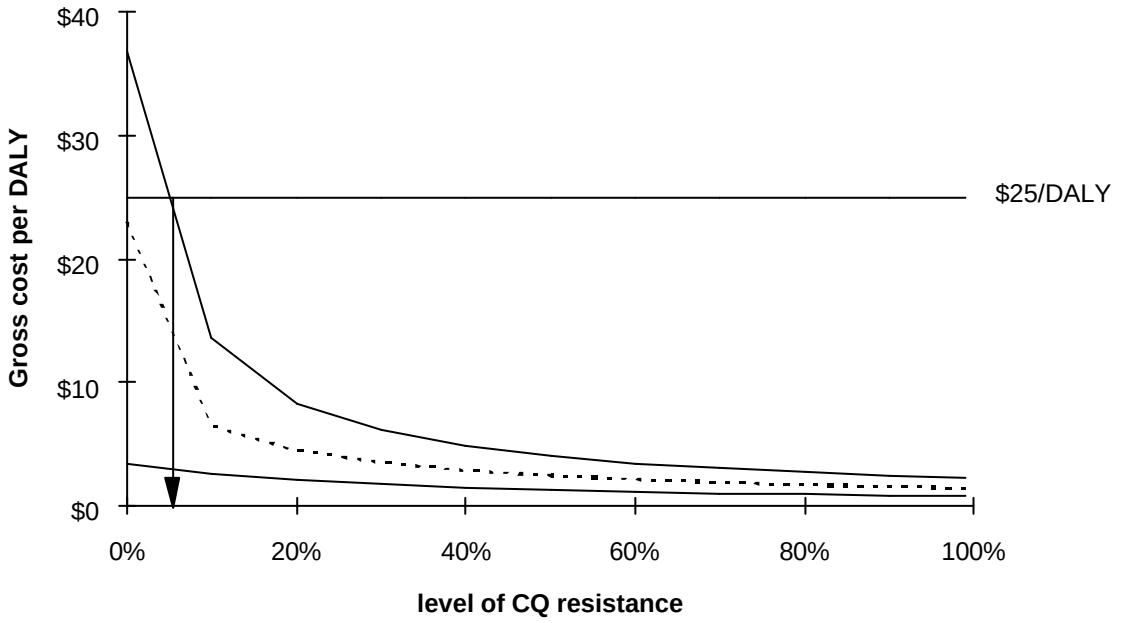


Figure 5.5. Improving access to the second and third line drugs: percentage of iterations that are cost-saving as a function of CQ resistance, using net costs for very low income countries and high transmission areas.

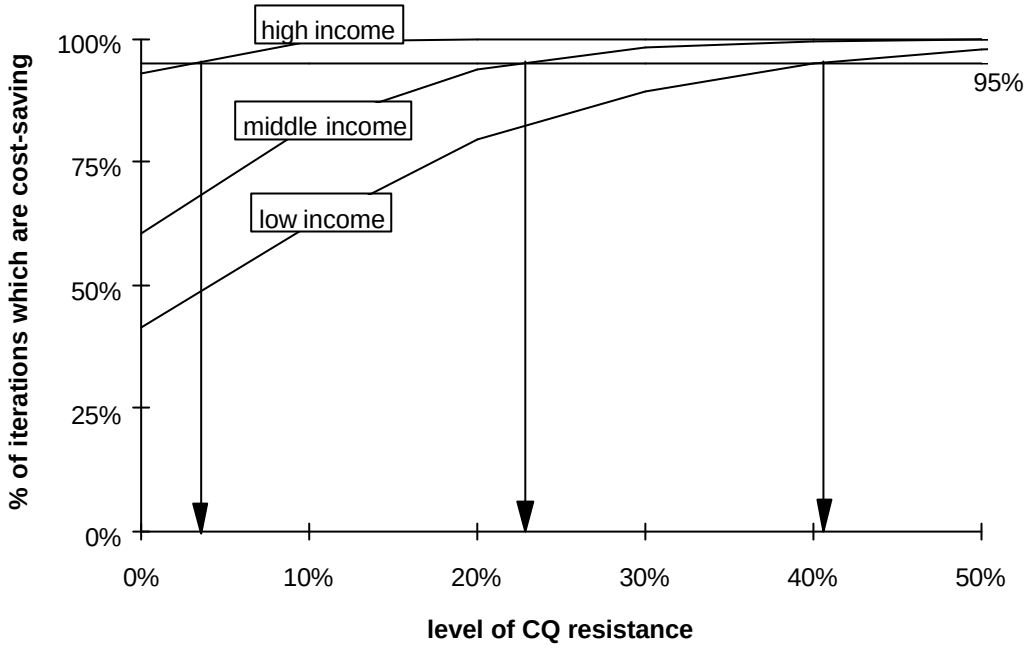
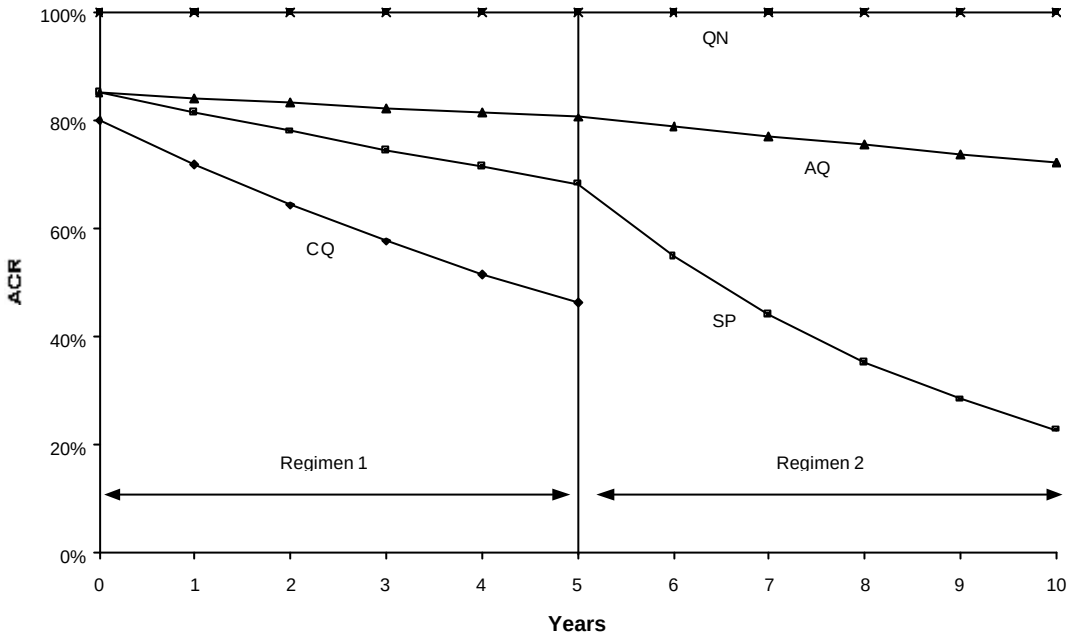


Figure 5.6. Path of ACR to each drug over time if switch from Regimen 1 to Regimen 2 takes place after 5 years (initial CQ resistance of 20%)

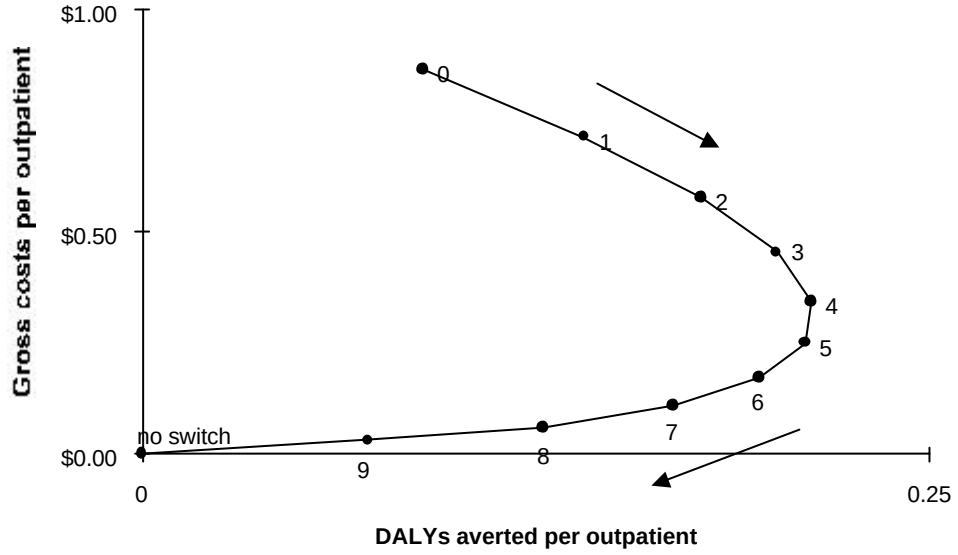


Notes

Regimen 1:	First line - CQ
	Second line - SP
	Third line - oral QN
Regimen 2:	First line - SP
	Second line - AQ
	Third line - oral QN

Figure 5.7a and **5.7b**. Mean incremental effects and costs of switching to Regimen 2 in each year compared to not switching (origin) using the dynamic framework. The numbers next to the data points refer to the year of switch. The simulation used an initial CQ resistance of 20% (1995 US dollars).

a. Using gross costs



b. Using net costs

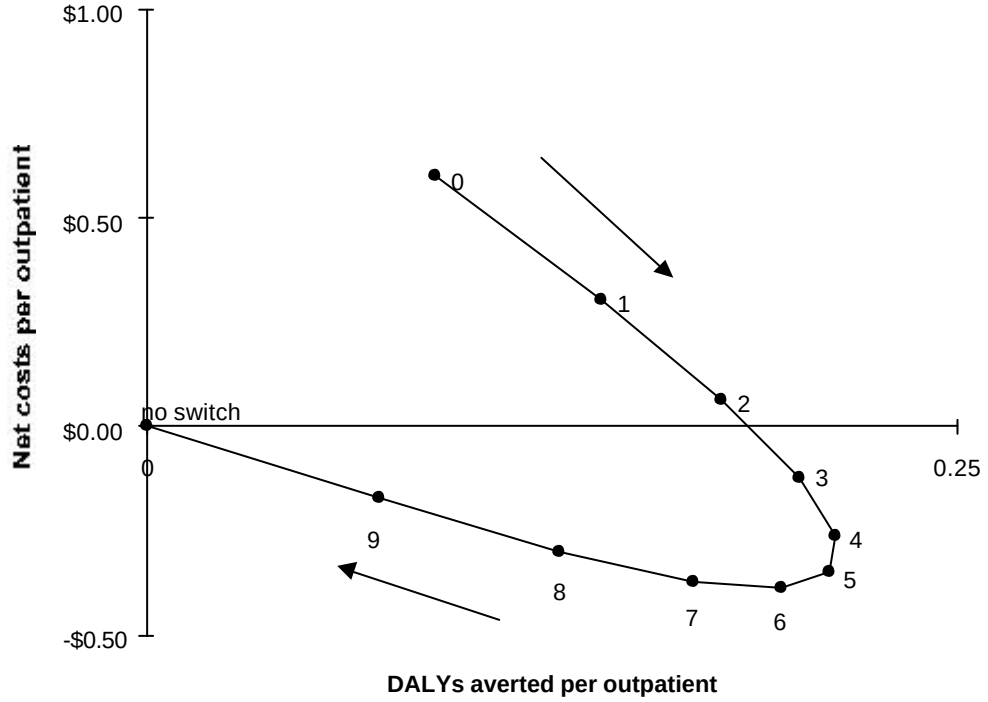


Figure 5.8. Use of combination therapies: gross cost per DALY averted as a function of the percentage reduction in the growth rate of SP resistance, for very low income countries and high transmission, showing the mean CER (- - - - -) and the 90% range (——) (1995 US dollars)

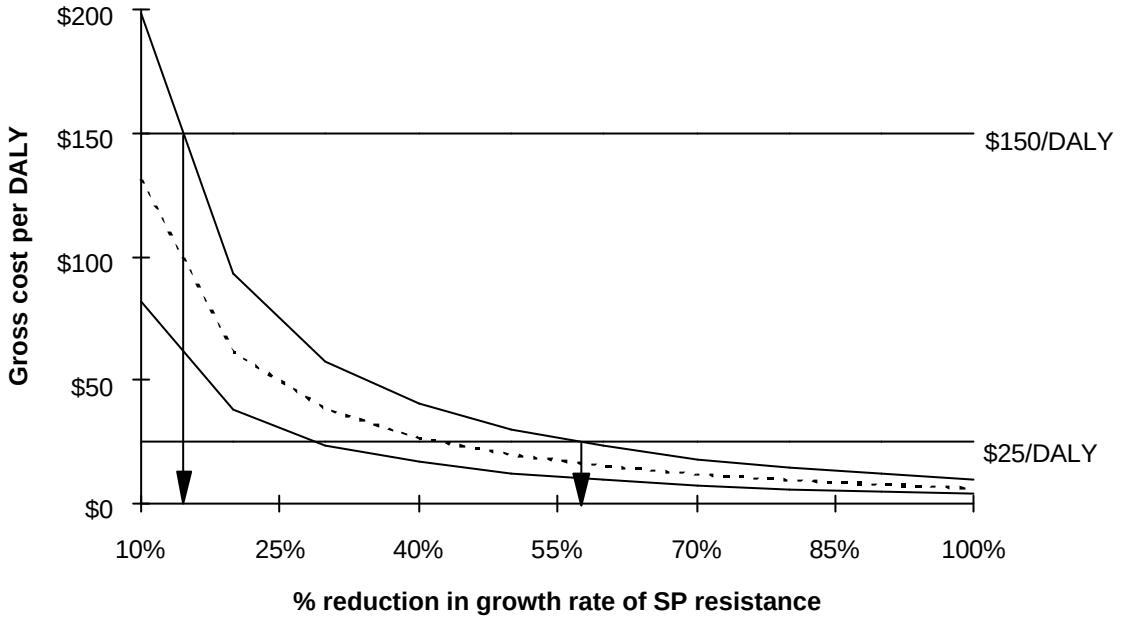


Figure 5.9. Use of artesunate suppositories on referral: gross cost per DALY averted as a function of the percentage reduction in rates of inpatient mortality and neurological sequelae, for very low income countries and high transmission, showing the mean CER (- - - - -) and the 90% range (——) (1995 US dollars)

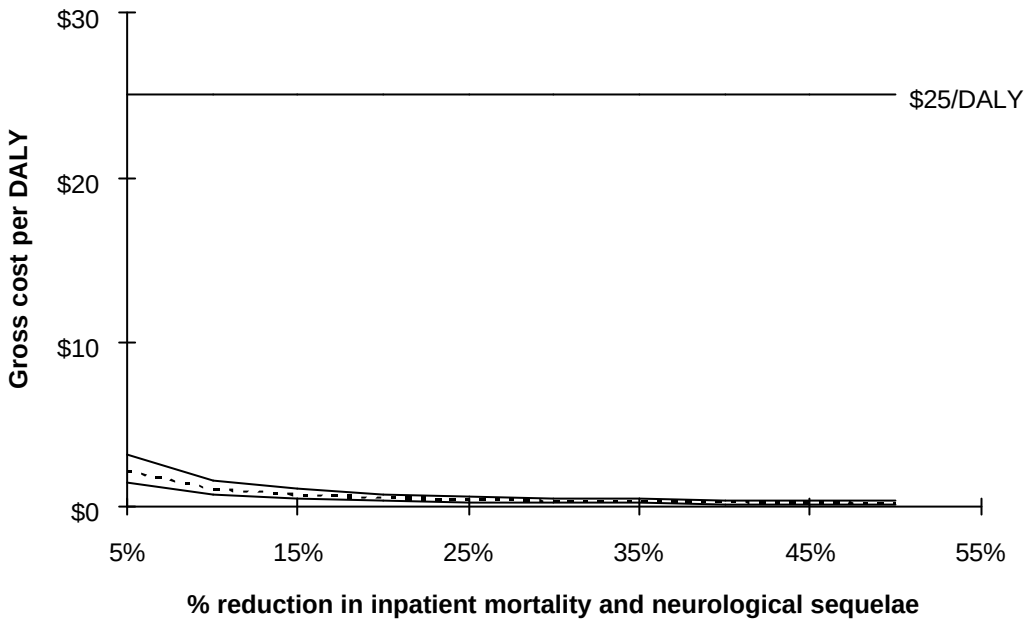


Table 5.1. Effectiveness input variables used in the case management model
(Where no source is given, data were not available and the estimates are based on discussions with researchers in the field.)

Effectiveness input variable	Type of probability distribution	Best estimate	Low estimate	High estimate	Source
Average age of death due to malaria					
High transmission age <5	point estimate	1.2 years			Snow *et al.*, 1994[59]
High transmission age >5	point estimate	20 years			
Low transmission age <5	point estimate	2 years			Snow *et al.*, 1994[59]
Low transmission age >5	point estimate	30 years			
Proportion of cases <5 years of age:					
High transmission	point estimate	0.5			
Low transmission	point estimate	0.2			
Compliance:					
CQ	uniform		0.200	0.500	Slutsker *et al.*, 1994[3], personal communications I.
SP	uniform		0.850	0.950	Ageypong, M. Ettling, O. Nwanyanwu, S. P. Kachur
QN	uniform		0.100	0.250	and C. Baume
AQ	uniform		0.300	0.600	
% non-compliers for whom treatment is effective:					
CQ	triangular	0.2	0.1	0.3	
SP	triangular	0	0	0	
QN	triangular	0.2	0.1	0.3	
AQ	triangular	0.2	0.1	0.3	

Table 5.1. Effectiveness input variables used in the case management model (cont.)

Effectiveness input variable	Type of probability distribution	Best estimate	Low estimate	High estimate	Source
Initial ACR:					
CQ	(varied)				
SP	triangular	0.93	0.630	0.990	Hill, 1996[10]
QN	uniform		0.995	1.000	
AQ	triangular	0.85	0.80	0.90	
P0 Suspected outpatient case is caused by malaria[a]					
High transmission	uniform		0.350	0.580	Hill, 1996[10], Olivar *et al.*, 1991[60], Stein & Gelfand,
Low transmission	uniform		0.10	0.20	1985[61], Guiguemde *et al.*, 1997[62], Brinkmann & Brinkmann[63]
P1 Failure first line drug	1-{Cure rate x (Compliance rate + (non-compliance rate * % non-compliers for whom treatment is effective))}				
P2 Develop severe malaria after failing 1st line[b]					
High transmission age <5	triangular	0.050	0.030	0.070	
High transmission age >5	triangular	0.010	0.005	0.015	D. Evans personal communication
Low transmission age <5	triangular	0.050	0.030	0.070	
Low transmission age >5	triangular	0.050	0.030	0.070	Nájera & Hempel, 1996[64]
P3 Seek inpatient care if fail 1st line and severe[c]	triangular	0.48	0.19	0.88	McCombie, 1996[65]
P4 Full recovery if seek inpatient care		1 – (P6+P5)	1 – (P6+P5)	1 – (P6+P5)	

Table 5.1. Effectiveness input variables used in the case management model (cont.)

Effectiveness input variable	Type of probability distribution	Best estimate	Low estimate	High estimate	Source
P5 NS if seek inpatient care					
age <5	triangular	0.0132	0.0041	0.0224	
age >5	triangular	0.005	0.0025	0.0075	Brewster *et al*., 1990[66]
P6 Death if seek inpatient care:					
age <5	triangular	0.192	0.100	0.300	Brewster *et al.*, 1990[66], Nájera & Hempel, 1996[64],
age >5	triangular	0.100	0.075	0.125	Greenberg *et al.*, 1989[67]
P7 Full recovery if severe and do not seek inpatient care		1-(P8+P9)	1-(P8+P9)	1-(P8+P9)	
P8 NS if severe and do not seek inpatient care		P5	P5	P5	
P9 Death if severe and do not seek inpatient care					
age <5	triangular	0.5	0.4	0.6	Nájera & Hempel, 1996[64]
age >5	triangular	0.25	0.2	0.3	Nájera & Hempel, 1996[64]
P10 Seek outpatient care if fail 1st line and uncomplicated[c]		P3	P3	P3	
P11 Failure second line drug	1-{Cure rate x (Compliance rate + (non-compliance rate * % non-compliers for whom treatment is effective))}				
P12 Develop severe malaria after failing 2nd line		P2	P2	P2	
P13 Seek outpatient care if fail 2nd line and uncomplicated[c]		P3	P3	P3	
P14 Failure third line drug	1-{Cure rate x (Compliance rate + (non-compliance rate * % non-compliers for whom treatment is effective))}				

Effectiveness input variable	Type of probability distribution	Best estimate	Low estimate	High estimate	Source
P15 Full recovery if fail 3rd line		1-(P16+P17)	1-(P16+P17)	1-(P16+P17)	

Table 5.1. Effectiveness input variables used in the case management model (cont.)

Effectiveness input variable	Type of probability distribution	Best estimate	Low estimate	High estimate	Source
P16 NS if fail 3rd line		P2*P5	P2*P5	P2*P5	
P17 Death if fail 3rd line		P2*P9	P2*P9	P2*P9	
P18 Full recovery if uncomplicated and do not seek outpatient care[b]		1-(P19+P20)	1-(P19+P20)	1-(P19+P20)	
P19 NS if uncomplicated and do not seek outpatient care[b]		P2*P5	P2*P5	P2*P5	
P20 Death if uncomplicated and do not seek outpatient care[b]		P2*P9	P2*P9	P2*P9	
Death from side effects CQ	point estimate	0	0	0	Sudre *et al.*, 1992[29]
Death from side effects SP	uniform		1/25000	1/11000	Miller *et al.*, 1986[68]
Death from side effects QN	point estimate	1/100000			
Death from side effects AQ	uniform		1/25000	1/11000	White, 1996[69]
Pre-packaging, training and health education to improve compliance					
Increase in compliance	triangular	0.2	0.1	0.3	Meeting on pre-packaging at Liverpool School of Tropical Medicine[23]
Combination therapy					
Compliance with ART	uniform		0.3	0.6	

Effectiveness input variable	Type of probability distribution	Best estimate	Low estimate	High estimate	Source
Artesunate Suppositories					
True prevalence of malaria among patients being referred with severe disease	point estimate	0.9			

Table 5.1. Effectiveness input variables used in the case management model (cont.)

Effectiveness input variable	Type of probability distribution	Best estimate	Low estimate	High estimate	Source
Diagnostic Techniques					
Sensitivity of dipstick test	triangular	0.891	0.836	0.939	WHO, 1996[49]
Specificity of dipstick test	triangular	0.97	0.811	0.995	WHO, 1996[49]
Sensitivity of microscopy	uniform	-	0.83	0.914	Barat *et al*., 1999[53], Craig *et al.*, 1997[51], Humar *et al.*, 1997[70]
Specificity of microscopy	uniform	-	0.91	1	Barat *et al*., 1999[53], Craig *et al.*, 1997[51], Humar *et al.*, 1997[70]

Notes:

[a] Probability P0 that a suspected case is actually caused by malaria was estimated for high and low transmission zones from a review of studies on the accuracy of clinical diagnosis, assuming that microscopy facilities are not used for outpatients with suspected uncomplicated malaria.

[b] Probability of developing severe malaria in the event of a treatment failure, P2, was assumed to be equal to the proportion of all malaria cases that are severe. This probability was held constant for failure of first, second and third line drugs.

[c] Given treatment failure, the probability that a patient would return to a formal health care facility was based on a review of treatment seeking behaviour by McCombie, (1996[65]), and was assumed to be the same for inpatient and outpatient care (P3, P10 and P13).

Table 5.2. Cost input variables used in the case management model (all costs in 1995 US dollars)

Cost Input Variables	Type of probability distribution	Best estimate	low estimate	high estimate	Sources and Assumptions
Cost per outpatient visit of training, health education and regulatory revisions accompanying a change in regimen	uniform		0.02	0.03	See Table 5.3
Drug Costs (per person >5 per treatment)[a]					International Drug Price Indicator Guide, 1996[(71)], WHO Model Prescribing Information: Drugs Used in Parasitic Diseases, 1995[(72)].
CQ	triangular	0.125	0.100	0.163	25mg/kg over 3 days
SP	triangular	0.135	0.120	0.150	25mg/kg sulfadoxine + 1.25mg/kg pyrimethamine in a single dose
AQ	triangular	0.200	0.180	0.210	25mg/kg over 3 days
Oral Q (7 day)	triangular	2.678	2.363	3.150	10mg/kg every 8 hours for 7 days
IV Q (initial dose)	triangular	0.470	0.390	0.575	20mg/kg over 4 hours
IV Q (per day thereafter)	triangular	0.705	0.585	0.863	10mg/kg every 8 hours
Drug costs for <5 as a % of >5	point estimate	20%			Average <5 weight of 12kg.
Transport, insurance & delivery as % of drug price	point estimate	25%			Foster, 1991[(40)]
Wastage of drugs	point estimate	25%			D. Evans, personal communication
Outpatient visit costs[b]					
Health centre outpatient recurrent facility cost per visit:					
Very low income	triangular	0.61	0.29	1.14	Ettling *et al.* 1992[(73)], Gilson, 1992[(13)], Hanson *et al.*, 1992[(74)], Mills, 1990[(75)]
Middle income	triangular	0.96	0.63	1.29	Fabricant *et al.*, 1994[(76)], Bennett *et al.*, 1990[(77)], Hanson *et al.*, 1992[(78)], Foster *et al, 1996*[(79)]
Higher income	triangular	7.51	4.16	10.48	BIMU, 1993[(80)], Valli *et al.*, 1991[(81)]
Hospital outpatient recurrent facility cost per visit:					
Very low income	triangular	3.30	0.77	5.15	Gilson, 1992[(13)], Barnum & Kutzin, 1993[(82)], Kirigia *et al.*, 1998[(14)]
Middle income	triangular	4.97	1.08	13.66	Fabricant *et al.*, 1994[(76)], Aikins, 1995[(83)], Gilson, 1992[(13)], Foster *et al.* (unpub.)[(79)], Barnum & Kutzin, 1993[(82)]
Higher income	triangular	38.43	6.24	76.68	Estimated based on scaled up estimates for low and middle income
% of outpatient visits that take place at hospital	point estimate	0.32			Aikins, 1995 [(83)]
% drugs in outpatient recurrent facility costs	point estimate	0.37			Average from Ettling *et al.* 1992[(73)]

Table 5.2. Cost input variables used in the case management model (all costs in 1995 US dollars) (cont.)

Cost Input Variables	Type of probability distribution	Best estimate	low estimate	high estimate	Sources and Assumptions
% of outpatient drugs that are antimalarials	point estimate	0.74			M. Ettling, personal communication
% of outpatient recurrent costs that are fixed	uniform		0.25	0.40	Gilson, 1992 [13]
Additional patient cost when visiting formal outpatient facility (exc. fees)	triangular	0.63	0.15	1.42	Asenso-Okyere *et al.*, 1997[84], Louis *et al.*, 1992[85], Sauerborn *et al.*, 1991[86], Litvack *et al.*, 1993[87]
Inpatient visit costs[b]					
Recurrent facility cost per inpatient day:					
Very low income	triangular	11.99	3.87	20.74	Nelson, 1995[88], Kirigia *et al.*, 1998[14], Barnum & Kutzin, 1993[82]
Middle income	triangular	17.11	4.22	36.08	Fabricant *et al.*, 1994[76], Aikins, 1995[83], Gilson, 1992[13], Foster *et al.* (unpub.)[79], Barnum & Kutzin, 1993[82]
Higher income	triangular	129.17	34.11	235.15	Estimated based on scaled up estimates for low and middle income
% of inpatient recurrent facility costs that are drugs	point estimate	0.17			Gilson, 1992 [13]
% of inpatient drugs that are antimalarials	point estimate	0.17			Faye *et al.*, 1995 [89]
% of recurrent inpatient costs that are fixed	uniform		0.50	0.75	Gilson, 1992 [13],Kirigia *et al.*, 1998[14]
Average length of inpatient stay if fully recover (days)	point estimate	4.5			Nelson *et al.*, 1995[88], Faye *et al.*, 1995[89]
Average length of inpatient stay if die (days)	point estimate	2			
Average length of inpatient stay if survive with neurological sequelae (days)	point estimate	10			Brewster *et al.*, 1990[66]
Additional patient cost when visiting formal inpatient facility (exc. fees)	triangular	3.25	0.94	7.94	Asenso-Okyere *et al.*, 1997[84], CNLP, 1994[90], Louis *et al.*, 1992[85], Sauerborn *et al.*, 1991[86], Sauerborn *et al.*, 1995[91], Litvack *et al.*, 1993[87]
Cost to patient of treatment in nonformal sector					
Self treatment/purchase of over-the-counter drugs:					
Very low income	triangular	0.285	0.28	0.29	Ettling *et al.*, 1994[92], CNLP, 1995[93]
Middle and higher income	point estimate	2.38			Louis *et al.*, 1992[85]
Traditional healer (all income levels):	triangular	1.14	0.67	1.44	Ettling *et al.*, 1994[92], CNLP, 1995[93]
Probability of seeking care at formal facility	uniform		0.19	0.88	McCombie, 1996[65]

Table 5.2. Cost input variables used in the case management model (all costs in 1995 US dollars) (cont.)

Cost Input Variables	Type of probability distribution	Best estimate	low estimate	high estimate	Sources and Assumptions
Of those not seeking formal care:					
Probability of self treatment/OTC drugs	triangular	0.50	0.07	0.94	McCombie, 1996 [65]
Probability of seeking care with traditional healer	triangular	0.10	0.00	0.53	McCombie, 1996 [65]
Pre-packaging, training and health education to improve compliance					
Incremental cost per case treated	uniform		0.05	0.15	Pagnoni *et al.*, 1997[20]
Improving access to 2nd & 3rd line drugs					
Cost of training, health education and regulatory revisions per outpatient case treated	uniform		0.02	0.03	Assumed to be the same as costs for changing first line drug
Combination therapy					
Cost per adult treatment of ART	point estimate	1.25			N. White, personal communication plus 25% for transport, insurance & delivery drug price
Artesunate Suppositories					
Cost per suppository	point estimate	0.50			
Diagnostic Techniques					
Staff time to do dipstick test (mins)	uniform	-	7	9.05	WHO, 1996[49], Uguen *et al.*, 1995[94] Craig *et al.*, 1997[51]
Staff time to do microscopy test (mins)	uniform	-	5.9	15	Uguen *et al.*, 1995[94], Craig *et al.*, 1997[51], Schapira, 1989 [4]
Price of dipstick test kit	uniform	-	1	1.65	
Price of lancet	point estimate	0.04			Echo Price Guide 1996[95]
Price of swab	point estimate	0.01			Echo Price Guide 1996[95]
Price of gloves	point estimate	0.01			Echo Price Guide 1996[95]
Price of slide	point estimate	0.06			Echo Price Guide 1996[95]
Price of microscope (inc 25% to scale up to CIF)	uniform	-	1214	1612	Echo Price Guide 1996[95]
Lifetime of microscope	uniform	-	8	12	Schapira, 1989[4]

Table 5.2. Cost input variables used in the case management model (all costs in 1995 US dollars) (cont.)

Cost Input Variables	Type of probability distribution	Best estimate	low estimate	high estimate	Sources and Assumptions
Price of other disposables for microscopy per test	point estimate	0.02			
Supervision and overheads for microscopy as % of other costs	uniform	-	20%	30%	
Dipstick tests per Lancet	point estimate	1			
Dipstick tests per swab	point estimate	1			
Dipstick tests per gloves (hospital)	point estimate	10			
Dipstick tests per gloves (HC)	point estimate	1			
Microscopy tests per Lancet	point estimate	1			Jonkman *et al.*, 1995[96],
Microscopy tests per slide	uniform	-	3	10	Schapira, 1989[4], Jonkman *et al.*, 1995[96]
Microscopy tests per gloves	point estimate	10			
Microscopy tests per swab	point estimate	1			
Annualised training cost per test for microscopy	point estimate	0.004			Schapira, 1989[4]
Cost of dipstick training per person per day	point estimate	10			
Dipstick tests done in training per person	point estimate	5			
Staff trained for dipstick per clinic	point estimate	2			
Life time of dipstick training investment	point estimate	2			Picard *et al.*, 1993[97]
Number of OP visits per hospital p.a.	triangular	65769	3243	75000	Gilson *et al.*, 1997[98], Foster *et al.*, unpub. [79], BIMU, 1993[80], Fabricant *et al.*, 1994[76]
Number of OP visits per clinic p.a.	triangular	12221	8770	34960	Bennett & Musambo, 1990[77], Biljmakers *et al.*, 1996[99], Fabricant *et al.*, 1994[76], Gilson 1992[13]
% OP cases suspected malaria (high transmission)	uniform		0.25	0.43	Hill 1996[10], Brinkmann *et al.*, 1991[63]
% OP cases suspected malaria (low transmission)	uniform		0.01	0.2	Hill 1996[10], Brinkmann *et al.*, 1991[63]

Table 5.2. Cost input variables used in the case management model (all costs in 1995 US dollars) (cont.)

Notes

[a] Notes on drug costs

- Drug costs were based on an average over 5 year old weight of 60 kg, and an average under 5 year old weight of 12 kg.
- It was assumed all CQ is given in the form of tablets. In reality it may be given as either syrup (especially to children) or as injections, which are both more expensive than the equivalent dose in tablets.
- Inpatient antimalarial drug costs were calculated by assuming that patients who survived received an initial dose of IV QN, followed by on average three further days IV QN and four days oral QN. Fatal cases were assumed to die on average 48 hours after being admitted, and therefore received only the initial dose and two days of IV QN. Those who survived with NS on average received an initial dose, 4.5 days of further IV QN treatment and 5.5 days of oral QN.

[b] Notes on outpatient and inpatient visit costs

- Data on the unit recurrent cost per outpatient visit and per inpatient day in the formal health care sector were reviewed, and minimum, maximum and average costs were extracted for each economic stratum, using data for both general and malaria specific cases, as there were so few data available on the latter.
- The "formal sector" was defined to include both public and private health facilities. It was assumed that the majority of private health facilities in SSA were mission run, and would follow government drug policies, and could therefore be incorporated within the model. Private for-profit facilities are an important component of care in some areas, but have not been included in this analysis.
- The costs were adjusted to remove the cost of antimalarial drugs, as these were calculated separately. This was done by estimating the proportion of outpatient and inpatient costs attributable to drugs, and the proportion of drugs given to a malaria patient that were antimalarials.
- Estimates of the additional costs to households of seeking care, such as transport, food and lodging, were obtained from literature reviews. As so few data points were available, the same maximum, minimum and best estimates were used across all economic strata, and it was also necessary to include studies that were not malaria specific. Households also bear some of the facility costs in the form of fees, but these "transfer costs" have been excluded to avoid double-counting of resources consumed.

Table 5.3. The costs of training, health education and regulatory revisions required when the first line drug was changed in Malawi (1995 US dollars)

Activities	Expenditure	
General activities		
National Meeting to revise guidelines		46,582
Printing of guidelines		20,187
Meeting with Pharmaceutical companies		6,026
Workshops to develop IEC materials		18,078
Press Conference		4,789
IEC materials - Design and production of:		
Posters		26,339
radio messages		23,945
newspaper material		2,395
school comics		21,550
Meetings to inform and train all health care staff		
Meetings with malaria control coordinators and regional staff		35,917
24 Meetings with district health staff		287,328
24 Briefing meetings with community level health providers		34,488
Training of shopkeepers/pharmacists		47,890
Total cost for country size of Malawi		575,514
Estimated expected life of new drug	5	10
Discount rate	0.03	0.03
Annualised value of cost	125,666	67,468
Number of curative OP cases attributed to malaria p.a. in 1990, all ages and providers	3,800,000	3,800,000
Cost per OP visit	0.03	0.02

Sources:
Type of activities: Steketee *et al.*, 1995[100]
Cost estimates: O. Nwanyanwu, personal communication
Number of malaria OP cases: Ettling *et al.* 1992[73]

Table 5.4. Growth rates of drug resistance assumed in the dynamic analysis

Drug	When first line	When second line	When third line	When not part of official regimen
CQ	7% - 15%			
SP	14% - 30%	2.8% - 6%		
AQ		1.4% - 3%		0.7% - 1.5%
QN			0%	

Table 5.5. Effect of varying the starting value of CQ resistance on the optimal year of switch (using gross costs and the dynamic framework, very low income country, high transmission).

Initial CQ resistance	Optimal year of switch	CQ resistance at optimal year of switch
0%	7	54%
10%	6	53%
20%	6	59%
30%	5	60%
40%	5	65%
50%	4	68%
60%	3	71%
70%	2	76%
80%	2	84%
90%	1	91%

Table 5.6. Drug cost per case above which diagnostic tests are cost-saving, mean (90% range) (1995 US dollars)

Transmission Level	Income Level	Dipsticks	Microscopy
High Transmission	very low	$2.87 ($2.15 - $3.72)	$0.78 ($0.52 - $1.10)
	middle	$2.96 ($2.23 - $3.82)	$0.96 ($0.63 - $1.35)
	higher	$3.70 ($2.87 - $4.68)	$2.36 ($1.43 - $3.45)
Low Transmission	very low	$1.95 ($1.54 - $2.36)	$0.61 ($0.40 - $0.89)
	middle	$2.01 ($1.60 - $2.43)	$0.74 ($0.48 - $1.04)
	higher	$2.51 ($2.06 - $2.99)	$1.69 ($1.06 - $2.36)

Table 5.7. Gross average annual cost implications of interventions to improve case management for Tanzania (high transmission, very low income country) (1995 US dollars).

	Incremental cost per OP visit	Total annual incremental cost to government	Cost as % of public health budget
Pre-packaging, training and health education to improve compliance	$0.09	$0.5m	0.5%
Improving access to second and third line drugs	$0.06	$0.3m	0.3%
Change in first line drug:			
from CQ to SP	$0.04	$0.2m	0.2%
from CQ to MF	$3.23	$16.7m	18%
Combination therapy (SP + ART), compared to SP alone	$0.90	$4.6m	5%
Using dipstick test for every suspected outpatient malaria case	$1.51	$7.8m	8%
Using microscopy for every suspected outpatient malaria case	$0.39	$2.0m	2%

Notes:
Based on the following assumptions:

- Estimated number of suspected outpatient malaria visits per annum of 5,159,000 (number of outpatient visits recorded as malaria for all ages (1,857,361) scaled up to account for low number of facilities reporting (36%)) (Tanzania MOH Health Statistics Abstracts for 1995[101])
- Government health budget p.a. of $94 million (including donor contributions)[102]
- Average cost per adult treatment of mefloquine of $4.59[71]

References

1. WHO. Implementation of the global malaria control strategy - Report of a WHO Study Group on the implementation of the global plan of action for malaria control 1993-200. *WHO Technical Report Series 839* 1993.
2. Ofori-Adjei D, Arhinful DK. Effect of training on the clinical management of malaria by medical assistants in Ghana. *Social Science and Medicine* 1996; 42(8): 1169-76.
3. Slutsker L, Chitsulo L, Macheso A, Steketee RW. Treatment of malaria fever episodes among children in Malawi: results of a KAP survey. *Tropical Medicine and Parasitology* 1994; 45(1): 61-4.
4. Schapira A. Chloroquine resistant malaria in Africa: the challenge to health services. *Health Policy and Planning* 1989; 4(1): 17-28.
5. Shakoor O, Taylor RB, Behrens RH. Assessment of the incidence of substandard drugs in developing countries. *Tropical Medicine and International Health* 1997; 2(9): 839-45.
6. Gomes M, Wayling S, Pang L. Interventions to improve the use of antimalarials in South-East Asia: an overview. *Bulletin of The World Health Organization* 1998; 76(Supp. 1): 9-19.
7. WHO. *Roll Back Malaria: A global partnership*. Geneva: WHO, 1998.
8. Bloland PB, Kazembe PN, Oloo AJ, Himonga B, Barat LM, Ruebush TK. Chloroquine in Africa: critical assessment and recommendations for monitoring and evaluating chloroquine therapy efficacy in sub-Saharan Africa. *Tropical Medicine and International Health* 1998; 3(7): 543-552.
9. WHO/CTD. *Assessment of therapeutic efficacy of antimalarial drugs for uncomplicated falciparum malaria in areas with intense transmission*. Geneva: WHO/MAL/96.1077.
10. Hill JA, Lake S, Meek, SR, Mehra S, Standing H. *Approaches to malaria control in Africa, Part I: analysis and opportunities for malaria control support in selected countries in Africa*. London/Liverpool Malaria Consortium, 1996.
11. Kachur SP, Adeniyi JD, Mwenesi H. *Rational use of antimalarial drugs to slow the development of resistance: education and training for health care workers and the community*. Harare: Draft Position Paper prepared for meeting on "Confronting the challenge of antimalarial drug resistance in Africa", 1998.
12. Murray CJL, Lopez AD. *The global burden of disease: A comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020*. Harvard School of Public Health (on behalf of WHO and the World Bank), distributed by Harvard University Press, 1996.
13. Gilson LJ. *Value for Money?: The Efficiency of Primary Health Units in Tanzania*. London School of Hygiene and Tropical Medicine, University of London: PhD Thesis, 1992.
14. Kirigia JM, Snow RW, Fox-Rushby J, Mills A. The cost of treating paediatric malaria admissions and the potential impact of insecticide treated mosquito nets on hospital expenditure. *Tropical Medicine and International Health* 1998; 3: 145-150.
15. WHO. *Investing in Health Research and Development: Report of the Ad Hoc Committee on Health Research Relating to Future Intervention Options.* Geneva: TDR/Gen/96.1, 1996.
16. Makubalo EL. *Malaria and chloroquine use in Northern Zambia*. London School of Hygiene and Tropical Medicine, University of London: PhD Thesis, 1991.
17. Yeneneh H, Gyorkos TW, Joseph L, Pickering J, Tedla S. Antimalarial drug utilization by women in Ethiopia - a knowledge-attitudes-practice study. *Bulletin of The World Health Organization* 1993; 71(6): 763-772.
18. Vundule C, Mharakurwa S. Knowledge, practices, and perceptions about malaria in rural communities of Zimbabwe - Relevance to malaria control. *Bulletin of The World Health Organization* 1996; 74(1): 55-60.
19. Massele AY, Mpundu MN, Hamudu NA. Utilisation of antimalarial drugs by pregnant women attending the antenatal clinic at Muhimbili Medical Centre, Dar es Salaam. *East African Medical Journal* 1997; 74(1): 28-30.
20. Pagnoni F, Convelbo N, Tiendrebeogo J, Cousens S, Esposito F. A community-based programme to provide prompt and adequate treatment of presumptive malaria in children. *Transactions of The Royal Society of Tropical Medicine and Hygiene* 1997; 91: 512-517.
21. WHO. The advantages of pre-packaged antimalarials. *TDR news* 1997; No. 54: 5.
22. Qingjun L, Jihui D, Laiyi T, et al. The effect of drug packaging on patients' compliance with treatment for Plasmodium vivax malaria in China. *Bulletin of The World Health Organization* 1998; 76(Supp. 1): 21-27.
23. Liverpool School of Tropical Medicine & WHO/TDR. Meeting on the Packaging of Antimalarials in Africa. Liverpool: 1997.
24. Hill J. Report of the meeting on the packaging of antimalarials in Africa. Liverpool School of Tropical Medicine: 1997.

25. White NJ. Antimalarial drug resistance: the pace quickens. *Journal of Antimicrobial Chemotherapy* 1992; 30(5): 571-85.
26. Barat LM, Himonga B, Nkunika S, et al. A systematic approach to the development of a rational malaria treatment policy in Zambia. *Tropical Medicine and International Health* 1998; 3(7): 535-542.
27. Trape JF, Pison G, Preziosi MP, et al. Impact of chloroquine resistance on malaria mortality. *C. R. Acad. Sci. Paris, Sciences de la vie* 1998; 321: 689-697.
28. World Health Organization. *Antimalarial Drug Policies: Data requirements, treatment of uncomplicated malaria and management of malaria in pregnancy*. Geneva: World Health Organization - Division of Control of Tropical Diseases, 1994.
29. Sudre P, Breman JG, McFarland D, Koplan JP. Treatment of chloroquine-resistant malaria in African children: a cost-effectiveness analysis. *International Journal of Epidemiology* 1992; 21(1): 146-54.
30. Bloland PB, Lackritz EM, Kazembe PN, Were JB, Steketee R, Campbell CC. Beyond chloroquine: implications of drug resistance for evaluating malaria therapy efficacy and treatment policy in Africa. *Journal of Infectious Diseases* 1993; 167(4): 932-7.
31. Schapira A, Beales PF, Halloran ME. Malaria - Living With Drug-Resistance. *Parasitology Today* 1993; 9(5): 168-174.
32. Phillips M, Phillips-Howard PA. Economic implications of resistance to antimalarial drugs. *Pharmacoeconomics* 1996; 10(3): 225-238.
33. Coast J, Smith RD, Millar MR. Superbugs - Should antimicrobial resistance be included as a cost in economic-evaluation. *Health Economics* 1996; 5(3): 217-226.
34. Coast J, Smith RD, Millar MR. An economic perspective on policy to reduce antimicrobial resistance. *Social Science and Medicine* 1998; 46(1): 29-39.
35. White NJ, Olliaro PL. Strategies for the prevention of antimalarial drug resistance: Rationale for combination chemotherapy for malaria. *Parasitology Today* 1996; 12(10): 399-401.
36. Curtis CF, Otoo LN. A simple model of the build-up of resistance to mixtures of anti-malarial drugs. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1986; 80(6): 889-92.
37. Draper CC, Hills M, Kilimali VA, Brubaker G. Serial studies on the evolution of drug resistance in malaria in an area of east Africa: findings from 1979 up to 1986. *Journal of Tropical Medicine and Hygiene* 1988; 91(5): 265-73.
38. Basco LK. Inefficacy of amodiaquine against chloroquine-resistant malaria [letter]. *Lancet* 1991; 338(8780): 1460.
39. White NJ. Assessment of the pharmacodynamic properties of antimalarial drugs in vivo. *Antimicrobial Agents and Chemotherapy* 1997; 41(7): 1413-22.
40. Foster SD. Pricing, distribution, and use of antimalarial drugs. *Bulletin of The World Health Organization* 1991; 69(3): 349-363.
41. Meek S. *Antimalarial drug usage in the context of national malaria control programmes: the critical issues*. Malaria Consortium, London School of Hygiene and Tropical Medicine / Liverpool School of Tropical Medicine, 1998.
42. Jamison DT, Mosley WH, Measham AR, Bobadilla JL. *Disease control priorities in developing countries*. New York: Published for the World Bank by Oxford University Press, 1993.
43. Thimasarn K, Ettling M. *Twenty-five years of malaria treatment policy in Thailand 1973-1997*. Harare: Draft Position Paper prepared for meeting on "Confronting the challenge of antimalarial drug resistance in Africa", 1998.
44. White NJ, Nosten F, Looareesuwan S, et al. Viewpoint: Averting a malaria disaster. *The Lancet* 1999; 353: 1965-7.
45. Price RN, Nosten F, Luxemburger C, et al. Artesunate/mefloquine treatment of multi-drug resistant falciparum malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1997; 91(5): 574-7.
46. White NJ. *Combination Antimalarials*. Harare: Draft Position Paper prepared for meeting on "Confronting the challenge of antimalarial drug resistance in Africa", 1998.
47. Shwe T, Lwin M, Aung S. Influence of blister packaging on the efficacy of artesunate + mefloquine over artesunate alone in community-based treatment of non-severe falciparum malaria in Myanmar. *Bulletin of The World Health Organization* 1998; 76(Supp. 1): 35-41.
48. Makler MT, Palmer CJ, Ager AL. A review of practical techniques for the diagnosis of malaria. *Annals of Tropical Medicine and Parasitology* 1998; 92(4): 419-33.
49. WHO. WHO Informal Consultation: a rapid dipstick antigen capture assay for the diagnosis of falciparum-malaria. *Bulletin of The World Health Organization* 1996; 74(1): 47-54.

50. Barat LM. *Assessment of microscopic diagnosis of malaria at six health centers in Zambia - Final Trip Report*. Atlanta: CDC, 1997.
51. Craig MH, Sharp BL. Comparative evaluation of four techniques for the diagnosis of Plasmodium falciparum infections. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1997; 91(3): 279-82.
52. Nabiswa AK, Makokha JDS, Godfrey RC, Lore W. Management of malaria before and after introduction of a treatment protocol at the Eldoret District Hospital. *East African Medical Journal* 1994; 71(1): 9-13.
53. Barat L, Chipipa J, Kolczak M, Sukwa T. Does the availability of blood slide microscopy for malaria at health centers improve the management of persons with fever in Zambia? *American Journal of Tropical Medicine and Hygiene* 1999; 60(6): 1024-30.
54. Verle P, Binh LN, Lieu TT, Yen PT, Coosemans M. ParaSight-F test to diagnose malaria in hypo-endemic and epidemic prone regions of Vietnam. *Tropical Medicine & International Health* 1996; 1(6): 794-796.
55. World Bank. *World Development Report 1993. Investing in Health*. New York: Oxford University Press, 1993.
56. Arnold K. Early treatment of malaria in the community using artemisinin--hope or hazard? *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1994; 88(1): S47-9.
57. WHO. Artesunate Rectocaps: a life-saving intervention. *TDR news* 1997; No. 53: 1-2.
58. Bloland PB. *Introduction: the challenges and dilemmas.* Harare: Draft Position Paper prepared for meeting on "Confronting the challenge of antimalarial drug resistance in Africa", 1998.
59. Snow RW, Bastos de Azevedo I, Lowe BS, et al. Severe childhood malaria in two areas of markedly different falciparum transmission in East Africa. *Acta Tropica* 1994; 57(4): 289-300.
60. Olivar M, Develoux M, Chegou Abari A, Loutan L. Presumptive diagnosis of malaria results in a significant risk of mistreatment of children in urban Sahel. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1991; 85(6): 729-30.
61. Stein CM, Gelfand M. The clinical features and laboratory findings in acute Plasmodium falciparum malaria in Harare, Zimbabwe. *Central African Journal of Medicine* 1985; 31(9): 166-70.
62. Guiguemde TR, Ouedraogo I, Ouedraogo JB, Coulibaly SO, Gbary AR. Malaria morbidity in adults living in urban Burkina Faso. *Medecine Tropicale Marseilles* 1997; 57(2): 165-8.
63. Brinkmann U, Brinkmann A. Malaria and health in Africa: the present situation and epidemiological trends. *Tropical Medicine and Parasitology* 1991; 42(3): 204-13.
64. Nájera JA, Hempel J. *The burden of malaria*. WHO CTD/MAL/96.10, 1996.
65. McCombie SC. Treatment seeking for malaria - a review of recent research. *Social Science and Medicine* 1996; 43(6): 933-945.
66. Brewster DR, Kwiatkowski D, White NJ. Neurological sequelae of cerebral malaria in children. *Lancet* 1990; 336(8722): 1039-43.
67. Greenberg AE, Ntumbanzondo M, Ntula N, Mawa L, Howell J, Davachi F. Hospital-based surveillance of malaria-related paediatric morbidity and mortality in Kinshasa, Zaire. *Bulletin of the World Health Organization* 1989; 67(2): 189-96.
68. Miller KD, Lobel HO, Satriale RF, Kuritsky JN, Stern R, Campbell CC. Severe cutaneous reactions among American travelers using pyrimethamine-sulfadoxine (Fansidar) for malaria prophylaxis. *American Journal of Tropical Medicine and Hygiene* 1986; 35(3): 451-8.
69. White NJ. Can amodiaquine be resurrected? *Lancet* 1996; 348(9036): 1184-5.
70. Humar A, Ohrt C, Harrington MA, Pillai D, Kain KC. Parasight F test compared with the polymerase chain reaction and microscopy for the diagnosis of Plasmodium falciparum malaria in travelers. *American Journal of Tropical Medicine and Hygiene* 1997; 56(1): 44-8.
71. Management Sciences for Health. *International Drug Price Indicator Guide*. Boston: MSH, 1996.
72. WHO. *Model Prescribing Information: Drugs used in Parasitic Diseases*. Geneva: WHO, 1995.
73. Ettling M, McFarland DA. *Economic impact of malaria in Malawi*. Virginia: Vector Biology Control Project, 1992.
74. Hanson K, Nkunzimana F. *Les coûts et l'utilisation des ressources dans les centres de santé de la province de Muyinga, Burundi*. New York: Bamako Initiative Technical Report Series, UNICEF, 1992.
75. Mills AJ. The economics of hospitals in developing countries. Part II: costs and sources of income. *Health Policy and Planning* 1990; 5(3): 203-218.
76. Fabricant S, Newbrander W. *The Gambia Health Facilities Cost Study*. Management Sciences for Health, Boston, Massachusetts, USA, 1994.
77. Bennett S, Musambo M. *Report on community financing and district management strengthening in Zambia*. New York: Bamako Initiative Technical Report Series, UNICEF, 1990.

78. Hanson K, Chindele F. *Costs, resource use and financing: a study of Monze District, Zambia*. New York: Bamako Initiative Technical Report Series, UNICEF, 1992.
79. Foster S. *Socio-economic impact of HIV/AIDS in Monze District, Zambia*. PhD Thesis, London School of Hygiene and Tropical Medicine, University of London, 1996.
80. Bamako Initiative Management Unit. *Cost, resource use and financing of district health services: a study of Otjiwarongo District, Namibia*. New York: Bamako Initiative Technical Report Series, UNICEF, 1993.
81. Valli A, Ferrinho PD, Broomberg J, Wilson TD, Robb D. Costs of primary health care at the Alexandra Health Centre. *South African Medical Journal* 1991; 80(8): 396-9.
82. Barnum H, Kutzin J. *Public hospitals in developing countries: resource use, cost, financing*. Published for the World Bank, The Johns Hopkins University Press, Baltimore and London, 1993.
83. Aikins MKS. *Cost-effectiveness analysis of insecticide-impregnated mosquito nets (bednets) used as a malaria control measure: a study from the Gambia*. PhD Thesis, Department of Public Health and Policy, London School of Hygiene and Tropical Medicine, University of London, 1995.
84. Asenso-Okyere WK, Dzator JA. Household cost of seeking malaria care. A retrospective study of two districts in Ghana. *Social Science and Medicine* 1997; 45(5): 659-667.
85. Louis JP, Trebucq A, Gelas H, et al. Malaria in Yaounde (Cameroon). Cost and antivectorial control at the family level. *Bulletin de la Société de Pathologie Exotique* 1992; 85(1): 26-30.
86. Sauerborn R, Shepard DS, Ettling MB, Brinkmann U, Nougtara A, Diesfeld HJ. Estimating the direct and indirect economic costs of malaria in a rural district of Burkina Faso. *Tropical Medicine and Parasitology* 1991; 42(3): 219-23.
87. Litvack JI, Bodart C. User fees plus quality equals improved access to health care: results of a field experiment in Cameroon. *Social Science and Medicine* 1993; 37(3): 369-383.
88. Nelson E, Weikert M, Phillips JA. Paediatric treatment costs and the HIV epidemic. *Central African Journal of Medicine* 1995; 41(5): 139-44.
89. Faye O, N'dir O, Gaye O, Fall M, Diallo S, Billon C. Care charges and direct costs related to hospitalization of Senegalese children with cerebral malaria. Study of 76 cases in the Albert-Royer Hospital in Dakar in 1991-1992. *Sante* 1995; 5(5): 315-8.
90. CNLP. Un traitement pour toutes les bourses. *CNLP Presse* 1994; 1(3): 1-4.
91. Sauerborn R, Bodart C, Essomba RO. Recovery of recurrent health service costs through provincial health funds in Cameroon. *Soc-Sci-Med* 1995; 40(12): 1731-9.
92. Ettling M, McFarland DA, Schultz LJ, Chitsulo L. Economic impact of malaria in Malawian households. *Tropical Medicine and Parasitology* 1994; 45(1): 74-9.
93. CNLP. Où traites-tu ton palu? Combien dépenses-tu? *CNLP Presse* 1995; 2(4): 1-4.
94. Uguen C, Rabodonirina M, De Pina JJ, et al. ParaSight-F rapid manual diagnostic test of Plasmodium falciparum infection. *Bulletin of the World Health Organisation* 1995; 73(5): 643-9.
95. ECHO International Health Services Ltd. *Medical equipment, instruments and consumables price guide*. Surrey: 1996.
96. Jonkman A, Chibwe RA, Khoromana CO, et al. Cost-saving through microscopy-based versus presumptive diagnosis of malaria in adult outpatients in Malawi. *Bulletin of the World Health Organization* 1995; 73(2): 223-7.
97. Picard J, Aikins M, Alonso PL, Armstrong Schellenberg JR, Greenwood BM, Mills A. A malaria control trial using insecticide-treated bed nets and targeted chemoprophylaxis in a rural area of The Gambia, West Africa. 8. Cost-effectiveness of bed net impregnation alone or combined with chemoprophylaxis in preventing mortality and morbidity from malaria in Gambian children. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1993; 2: 53-7.
98. Gilson L, Adusei J, Arhin D, Hongoro C, Mujinja P, Sagoe K. Should African governments contract out clinical health services to church providers? In: Bennett S, McPake, B. & Mills, A., ed. Private Health Providers in Developing Countries". London: Zed Press, 1997.
99. Biljmakers L, Chihanga S. *District health systems in Zimbabwe: cost, resource adequacy, efficiency and the core service package*. New York: Bamako Initiative Technical Report Series, UNICEF, 1996.
100. Steketee R, Macheso A, Heyman D, et al. *A decade of progress in malaria policy and program development in Malawi: 1984-1993*. Washington DC: USAID, 1995.
101. Government of Tanzania. *HMIS Health Statistics Abstracts*. Dar es Salaam: MOH, 1997.
102. World Bank. *Tanzania - Role of Government: Public Expenditure Review, Volume 1.* Washington DC: World Bank, 1994.

Chapter 6 – The Economic Impact of Malaria[a]

6.1 Introduction

This chapter summarizes the available evidence on the economic impact of malaria in SSA, and specifically considers evidence on:

- the economic costs of malaria in terms of labour efficiency and land use
- the effect of malaria on school attendance, performance and cognitive impairment
- the economic costs of malaria in terms of expenditures by households and the public health sector.

While it would have been desirable to include literature on the economic benefits of malaria control and cost-benefit analyses, only one study was identified, for Sudan(1), contained in a government document and of doubtful quality[b].

The literature regards the two key determinants of the economic costs of malaria as the direct costs of prevention and treatment and the indirect costs of productive factor time lost due to malaria. The latter draws on the human capital approach, which has been widely used to assess the productivity losses from illness or injury as measured by income forgone due to morbidity, disability and mortality. In developed societies, labour force participation rates and earnings of affected individuals are used to calculate the value of productivity losses due to morbidity and premature mortality. In developing societies with more informal employment arrangements, various proxies for the labour force and earnings have been used.

A central problem in assessing the impact of malaria, worth highlighting in advance, is the identification of a suitable indicator for the presence of disease. On the one hand, studies of indirect costs have tended to use parasitaemia, although this may bear an unclear relationship to clinical disease. On the other hand, studies of direct costs of treatment usually assess expenditure on fever as a proxy for malaria. This creates a major difficulty in interpreting and extrapolating from the existing literature.

6.2 Review of studies

6.2.1 Effect of malaria on labour productivity

Most studies on the economic impact of malaria in SSA have focused on the informal traditional sector and only a few have considered the formal industrial, agricultural and service sectors of the economy(2). Two analytical approaches have been used to assess the effects of malaria on labour

[a] This chapter is based on the research done and the report written by Reginald Ikechukwu Chima, Lecturer, Department of Economics, University of Nigeria, when he was a WHO/TDR Post-doctoral Fellow and Visiting Scientist at the London School of Hygiene and Tropical Medicine.

[b] It gave a benefit-cost ratio of 4.6.

productivity: the production function method, which relies on models of the Cobb-Douglas type, and the wage rate method, which relies on the relationship between the wage and the value of labour.

Production function method

A couple of studies have applied this method with specifications of models of the Cobb-Douglas production function. The main study of this type is by Audibert (1986)[3], who estimated the relationship between health status and agricultural non-wage peasant production using a generalized production function and data from rice farmers in Cameroon. The area was said to be meso-endemic for malaria. The key variables were output of rice (kg/acre); number of seasons of experience in specific crop farming; family size; the size of the working population as measured by the total number of persons who effectively work in the farms (this may include children) and by the number of adults working in the farms; prevalence of malaria and schistosomiasis among adults and family members; duration of transplanting for rice farmers; surface area of cultivated land; fertility of cultivated soil; millet output; and number of millet fields. A seasonal dummy variable was incorporated to explain the various effects of changes in climatic conditions on rice growing and output. Capital inputs such as mechanical ploughing, seedlings, water and fertilisers were not included as determinants of individual production because the rice farmers studied received equal amounts of these capital inputs.

Audibert found that malaria prevalence was not a significant explanation of rice output, whereas schistosomiasis prevalence did significantly affect output. However, this conclusion should be regarded with caution: the study appears to base prevalence of malaria on levels of parasitaemia, though how these data were obtained was not explained and they seem to apply to the dry season (when prevalence would have been lower than during the rainy season when crops are cultivated). The level of parasitaemia is anyway likely to be a poor proxy of the physiological effects of malaria, since immune adults may have parasites but experience no clinical symptoms.

Wage rate method

Most studies of the economic impact of malaria have based their estimates on the amount of time lost by the sick person (or the carer in the case of child illness) multiplied by some value of a day of work. Key variables are thus the amount of time lost and the assumed value of that time. Table 6.1 summarizes these variables for the studies located by the review. Table 6.2 lists studies that measured time lost but did not attempt valuation.

Sauerborn *et al.* (1995)[4] provided a detailed specification of the wage rate method of assessing the time costs of illness. The time cost was defined as the sum of the opportunity cost of wages forgone by the sick individual due to illness, and the opportunity costs of healthy household members' time spent on treating or attending to the sick person or accompanying them for treatment. Sauerborn *et al.* equated the opportunity cost of time with the marginal cost of labour, approximated by the price of hired labour.

As Table 6.1 indicates, other authors have made similarly approximate estimates of the value of time. Most studies have used some estimate of the average wage, adjusted or unadjusted, with the implicit assumption that wages reflected marginal product[5]. One study used the market value of the average output per person of the main produce in each of two seasons[6].

All studies assumed that the value of a day of work lost could be treated as the gain that would result if malaria were reduced or eliminated. There are two key problems with this assumption. First, the potential for substitution of labour crucially affects whether or not the loss of time is translated into a loss of output. At times of the year when there is underemployment or unemployment, substitution may be feasible without any consequent loss of output. Only one study was located that examined this issue in Africa (Nur 1993[7]; Nur and Mahran 1988[8]). The latter paper showed that in the Gezira in the Sudan, 62% of the loss of work hours due to malaria and schistosomiasis was compensated for by family members. In the case of malaria, labour hours lost to agriculture were completely compensated for, though primarily by women and children whose household activities and schooling suffered as a result.

Secondly, estimates of loss based on the average product or wage may also be an overestimate of the actual gains because the increase in labour supply would not be accompanied by changes in other factors of production.

Conversely, however, there are good grounds for believing that these estimates (including any derived from a production function approach) underestimate the impact of malaria. In particular, malaria (and poor health status more generally) may have a pervasive effect on the economic incentives, behaviour and strategies of households[9, 10]. Thus the long run effect of improved health status may be quite different from the effect predicted from observing the current impact of ill health. Recent work that uses economic growth models to assess the effect of malaria prevalence on depressing economic growth rates suggests that this is likely to be the case[11] (see section 6.3).

The productivity consequences of mortality – as opposed to morbidity – have received relatively little attention, probably because in areas of stable transmission, adult mortality from malaria is very rare. Shepard *et al.* (1991)[12] included in their calculations the present value of future earnings lost due to mortality. In two of the four country case studies it was possible to assess the relative importance of morbidity as opposed to mortality as a cause of loss of work time. The value of loss of time due to mortality accounted for 74% of total indirect costs in Rwanda[13], and 88% in a district in Burkina Faso[6]. Adult deaths in Rwanda amounted to around 50% of all deaths attributed to malaria, whereas adult deaths attributed to malaria in Burkina Faso were very unusual. It is therefore surprising that mortality contributed more to indirect costs in the latter. However, these studies do indicate that more attention should be paid to the mortality consequences of malaria in areas where adults are at risk.

Malaria may also affect productivity through its effect on:

- work capacity (since repeated malaria attacks may cause debility)
- decisions on land use (in terms both of extent of land cultivated and choice of crops[c])
- labour quality (since malaria can affect the cognitive development and school performance of children).

Evidence on these is examined in the following sections.

[c] As found by Conly (1975)[14] in Paraguay.

6.2.2 Impact of malaria on physical work capacity

For some diseases such as schistosomiasis, research has explored their impact on physical capacity to work, but similar literature on malaria is scanty. Brohult *et al.* 1981[15] looked at the impact of malaria on the working capacity of Liberian males living in areas with different malario-metric indices. They found no major differences between farmers living in holo-endemic areas and mining company workers living in meso-endemic areas. A further study by Pehrson *et al.* 1984[16] found no difference in the work capacity of industrial workers who received malaria prophylaxis and those who did not.

6.2.3 Impact of malaria on land use

Malaria also affects productivity through its impact on agricultural land use, but the literature on this relationship is virtually non-existent. Wang'ombe and Mwabu (1993)[17] examined the extent to which malaria affected agricultural land use patterns in several districts in Kenya. The study related the total cultivated acreage of cassava to total family size and the total number of malaria cases in households over a period of three months. They concluded that malaria had no statistically significant effect on cassava production nor the acreage cultivated. They suggested that this may be explained by coping strategies of households including household labour hiring practices aimed at cushioning the effects of malaria on income; and increased efforts made by other household members at the time of the illness. As in the case of Audibert (1986)[3], the study suffers from using prevalence of parasites as indicative of the level of illness due to malaria. Moreover, it is possible that malaria has long term effects on economic strategies relating to land exploitation at the community level; these are unlikely to be identifiable through a study of households living within a similar disease and economic environment.

6.2.4 Impact of malaria on children's school attendance, performance and cognitive skills

A number of studies have associated malaria with anaemia, epileptic convulsions and growth faltering during the first three years of life[18, 19]. Shiff *et al.* (1996)[18] found that children unprotected by impregnated bednets grew less in a 5-month period and were twice as likely to be anaemic as protected children, although presumptive treatment was available to both groups. There is good evidence on the association between iron deficiency anaemia (IDA) and poor performance in infant development scales, IQ and learning tasks in pre-school children and educational achievement among school-age children[20-22]. Lozoff *et al.* (1991)[23] observed that IDA among infants predicted poorer performance in cognitive tests at a later developmental period. Iron supplementation has been associated with improvement in mental development scale scores in infants[24] and significant increases in school achievement scores[25]. It is not clear whether these findings for IDA apply equally to children with the type of anaemia[26] associated with malaria. Children presenting with severe anaemia associated with malaria might develop secondary loss of iron through severe loss of appetite and very poor nutrition, although there is no evidence on this. Anaemia within the first two years of life would have serious developmental consequences that might include cognitive impairment[21].

In Africa, malaria is considered the single most important cause of seizures in early childhood. In Kenya, Waruiru *et al.* (1996)[19] found that malaria accounted for 31.3% cases of seizures. Asindi

et al. (1993)[27] and Axton and Siebert (1982)[28] have provided further evidence on the proportion of seizures attributed to malaria, ranging from 70% in Nigeria to 16% in Zimbabwe. Epileptic seizures can cause serious learning disabilities in children, resulting in poor cognitive performance and reduced school attendance[29].

Around 10% of children with cerebral malaria and 1% to 3% of adults have residual neurological sequelae[30]. Brewster *et al.* (1990)[31] followed up Gambian children with cerebral malaria, and found that 11% of survivors had neurological sequelae at discharge, of whom half made a full recovery and 26% had major residual handicaps, mainly severe cerebral palsy and blindness. They suggested that the possibility that cerebral malaria produced intellectual impairment in children who have apparently recovered could not be discounted.

Leighton and Foster (1993)[2] provided evidence on the number of school days lost due to malaria in Kenya and Nigeria, based largely on information from focus group discussions. Efforts were made to ensure that responses related to malaria rather than just "fever". In Kenya, primary school students were considered to have on average four episodes of malaria per year and to miss five school days per episode, amounting to 20 school days missed per child per year and 11% out of Kenya's 186 day school year. For secondary schoolchildren, the numbers were eight days lost per year or 4.3% of a school year. In the case of Nigeria, school days missed varied between the rural and urban primary and secondary schools within the range of 3 to 12 days per year per student or 2% to 6% of the school year. Primary school teachers in Nigeria were considered to experience three episodes of malaria per year and to miss two days per episode: 6 days of school days missed in total. A study in The Gambia of the effects of insecticide-treated mosquito nets found that whereas before the intervention there was no significant difference between control and intervention areas in school absenteeism due to fever, in the year of the intervention, absenteeism because of fever was significantly higher in the control group[32].

Variations in reasoning ability, cognitive skill, and years of schooling are considered to be important explanations for future variations in productivity and earnings of individuals[33, 34]. Thus it is very likely that the effect of malaria on children, mediated via severe anaemia, epilepsy, seizures, and school absenteeism, will affect their productivity in later life. However, there is currently no direct evidence to support this assertion, and even the effects of severe malaria and anaemia on cognitive development are only beginning to be explored.

6.2.5 Impact of malaria on household expenditure

Household expenditures on malaria consist of two main components: expenditure on malaria (and mosquito nuisance) prevention; and expenditure on treatment. With respect to malaria prevention, preventive measures such as mosquito coils, aerosol sprays, bednets and mosquito repellents are used, to very differing degrees in different areas and by different households. Figure 6.1 shows the available evidence on monthly per capita household expenditures, which ranged between $0.05 and $2.08 per person, equivalent to between $0.23 and $15 per household. Expenditures tend to be highly skewed: for example, in Malawi, only 10% of households reported any preventive expenditures in the preceding month[35].

Household expenditure on malaria-related treatment includes out-of-pocket expenditures for treatment fees, drugs, transport and the cost of subsistence at a distant health facility. Figure 6.2 shows available data on monthly per capita expenditure on malaria-related treatment, which ranged between $0.39 and $3.84 per person, equivalent to between $1.79 and $25 per household. These data derive from household surveys and thus include all sources of care accessible to households.

These data are inadequate to permit generalization beyond the original setting. It is likely that expenditure levels are affected by per capita income - for example, in Malawi, only 4% of very low income households spent money on malaria prevention as opposed to 16% of other households[35] - but the data are inadequate to explore this fully. Most studies have been done in urban areas, and thus are unlikely to represent expenditure in rural areas. In addition they report expenditure in a specific time period (usually a month) which cannot be extrapolated to an annual figure without good information on the seasonal distribution of malaria and cash availability.

6.2.6 Public health sector expenditures on malaria

No attempts have been made to estimate overall public expenditure on malaria prevention and treatment. Most expenditure is incurred by health facilities providing treatment, and thus malaria-related expenditures are not disaggregated from other health service costs in budgeting and accounting systems. Where governments have a budget line for malaria, this generally relates to specific preventive expenditures (e.g. purchase of insecticide) which are likely to be a very small percentage of total malaria-related expenditures. The numbers of patients seeking care for suspected malaria and estimates of the unit cost of treatment suggest that public expenditure on malaria is likely to be substantial. For example, around 20% to 40% of outpatient visits in SSA are for 'fever'[d], and suspected malaria amongst inpatients ranges in different studies from between 0.5% to 50% of admissions[36-38]. Very few studies are available on the unit costs of malaria treatment. The average recurrent cost per outpatient visit for suspected malaria was $0.96 in government and mission facilities in Malawi[39], and inpatient treatment for severe malaria cost $35 per admission in a typical Kenyan district hospital (1995 US dollars)[40]. Ettling *et al.* (1991)[13] estimated that approximately 19% of the operating budget of the Rwandan MOH was spent on malaria treatment in public facilities. Kirigia *et al.* (1998)[40] estimated that 15% of the annual recurrent costs of inpatient care in the Kilifi district hospital, and 9% in the adjacent Malindi sub-district hospital (both on the Kenyan coast) were absorbed by paediatric malaria admissions. A small portion of these costs may be recouped through user fees, which would be also recorded as a household expenditure, but the majority of the costs would be borne by the government.

6.2.7 Overall economic cost of malaria in Africa

Only one study, by Shepard *et al.* 1991[12], has attempted to put data together to estimate the overall economic cost of malaria in Africa. Based on extrapolations from four country case studies[e], the total direct and indirect cost in 1987 was estimated to be $791 million, $2.34 per capita, and 0.6% of the sub-Saharan Africa gross domestic product (GDP). These data are reported here since they have been widely quoted, but it should be noted that first, the results are based on many

[d] The proportion of these that are actually malaria will vary greatly by area and season.
[e] Burkina Faso (one district); Chad (one district); Brazzaville, Congo; Rwanda.

assumptions and approximations, and secondly the methodology for valuing indirect costs has all the problems associated with the wage-rate method.

Two further studies providing country-specific estimates also relied on the wage-rate method to estimate indirect costs. Ettling *et al.* (1994)[35], in a study on the economic impact of malaria on Malawian households, which relied to a greater extent than Shepard *et al.* (1991) on specially collected data, found that direct costs of treatment amounted to 28% of household income among very low income households, and 2% among the rest. Indirect costs were 3.1% and 2.2% for the same income groups, and total costs 32% and 4.2%[f].

Leighton and Foster (1993)[2] used rapid assessment methods based on focus group discussions and interviews to produce high and low estimates for days lost from morbidity[g], decreased productivity, and value of production lost by economic sector, urban and rural populations, and sex for Kenya and Nigeria. They estimated that the total annual value of malaria-related production loss was 2% to 6% of GDP in Kenya and 1% to 5% in Nigeria, and that 3% to 14% of workdays were lost in Kenya and 1% to 8% in Nigeria. 58% of losses were in the agricultural sector in Kenya and 7% in the industrial sector: in Nigeria these figures were 50% and 10%. Total household costs as a percentage of annual income for rural small farmers amounted to 8.8% to 17.6% in Kenya, and 7.2% to 13.2% in Nigeria. These figures for agribusiness labourers in Kenya were 0.8% to 5.2%, and for urban self-employed in Nigeria 11.2% to 18.7%. As with other studies, since these proportions were calculated by aggregating up from information on days lost per episode and values of days lost, there is the potential for minor errors in unit values to have a major effect on totals. Moreover, no validation was done of the focus group approach to obtaining this sort of data, so it is not possible to assess whether the estimates are of the correct order of magnitude.

The widely different methodologies, sources of data, and often heroic assumptions make it impossible to draw conclusions from these studies. Even judgements of the relative importance of direct and indirect costs varied greatly, with Ettling *et al.* (1991)[13] and Sauerborn *et al.* (1991)[6] showing that indirect costs dominated, and Leighton and Foster (1993)[2] arguing that if mortality costs were ignored as being of little relevance to households in the short term, direct costs represented a greater burden to households than indirect costs.

6.3 Overall comments on the literature

The human capital approach to assessing the economic impact of malaria has very limited value, and it does not adequately measure an individual's contribution to society. The approach largely excludes benefits experienced by those who are not part of the labour force. It values earnings and housekeeping services but not leisure time, and it may undervalue the productivity of groups whose productivity value is not fully reflected in earnings (Haddix and Shaffer, 1996[42]).

[f] Costs per episode were used to make annual estimates based on average household size and average predicted episodes per year: there is thus the possibility that the annual estimates are inaccurate, especially given seasonal differences in both malaria and cash availability (Sauerborn, 1996[41]).
[g] Mortality effects were excluded.

The economic setting of SSA poses considerable challenges to the human capital approach. Seasonal unemployment is prevalent and farming is often undertaken communally, in households or extended families. This means that in the event of temporary or permanent disability of any member of the household, the family workforce provides a cushion for the period of absence of the disabled member and allowances need to be made for this. Child- care is often shared among the extended family, making it difficult to discern the impact on adults of a child's illness[32]. Not all production in SSA is peasant production. Small modern sectors do exist such as mining and quarrying, manufacturing, building and construction, commercial large-scale agriculture, and general commercial services. However, most studies have looked at the impact of malaria on the rural, subsistence farming sector.

The alternative to the human capital approach for valuing benefits, the willingness to pay (WTP) approach, has theoretical attractions, but its value as a practical tool is severely limited by difficulties in obtaining relevant data. So far WTP studies in the malaria field, and in the health field more broadly, have concentrated on using WTP estimates to set prices rather than to value benefits, although work is forthcoming using WTP methods to value malaria prevention in Ethiopia[43].

A holistic view of the productivity effects of malaria should incorporate the implications of depleted capital stock and lost savings due to indebtedness or expenditures on prevention and treatment of malaria; the labour supply responses including limiting specialization of labour and maintaining labour reserves to reduce the risk of labour shortages at key times of the year; and the pervasive influence of risk of ill health on the incentive to invest[10]. At very low levels of income, the approach of households to prevention and treatment costs may be to sell arable land, economic trees and livestock[44]. This ultimately affects supply or production through low saving and investment. Furthermore, it means that the direction of causality of the economic impact of malaria may not necessarily be through uncultivated arable land and sick labour only, but also through lost capital and purchasing power. However, what happens on the demand-side has been left out of considerations of the economic impact of malaria, except in including estimates of actual expenditure on prevention and treatment.

An important first step in determining the economic impact of disease on individuals in any environment is to delineate and characterize the type of economy in which they function as economic agents. However, in most analyses of the economics of malaria there is a gross lack of definition and characterization of the nature and structure of the economies in which malaria is prevalent. Typically, studies move rapidly from a brief description of the epidemiological background to conclusions on economic costs of malaria.

Studies have also suffered from insufficient attention given to the nature of malaria and how it might affect economic activity. The few studies that seek to study directly the impact of malaria (as opposed to estimating it from data on days lost and wage rates) all encounter the problem of the measurement of health status. This is a particular difficulty in the case of malaria since those who are regularly exposed to infection are known to develop immunity, which shortens the period of illness for adults compared with children (see Tables 6.1 and 6.2). The impact of malaria on adults in a high transmission area may be more manifest in the costs of caring for sick children, though this has still to be fully explored. Brinkmann and Brinkmann (1991)[37] suggest that approximately 60% of the population of SSA lives in areas of stable malaria transmission where protective immunity develops

from about the age of 5; 30% live in areas of seasonal transmission where protection is gained rather later (around the age of 10); and 10% live in areas of unstable transmission where epidemics may occur with substantial consequences for adult morbidity and mortality. Immunity is gradually lost in the absence of reinfection; thus the population of large cities where transmission does not occur are at risk when travelling outside the city. Future research needs to explore the implications of malaria for these population groups exposed to malaria in different ways and thus likely both to suffer and to respond differently.

Work in progress by Gallup and Sachs is exploring the macro-economic impact of malaria by including the amount of malaria as an explanatory variable in economic growth models. The amount of malaria was proxied by a "malaria index", which was calculated as the product of the fraction of land area with endemic malaria and the fraction of malaria cases that are *P. falciparam*. Preliminary results suggest that countries with a substantial amount of malaria grew 1.3% per year less (controlling for other influences on growth), and that a 10% reduction in malaria was associated with 0.3% higher growth per year[11]. These findings reinforce the concerns presented here on the value of past micro-economics work, and further highlight the need to develop a detailed understanding of the mechanisms by which malaria affects households and economies.

6.4 Conclusion

The weakness of the literature available on the economic impact of malaria is clearly evident. No studies can be highlighted as models of good methodology. Excessive effort has been devoted to indirect studies that use often very weak data on earnings and days lost to make gross and potentially misleading estimates. Studies often ignore both the detailed economic circumstances and behaviour of rural households, and the specific characteristics of malaria - especially in relation to incidence by age and immune status. Much more sophisticated approaches to research are required. A key deficiency is the complete absence of studies that attempt to address the benefits from malaria control.

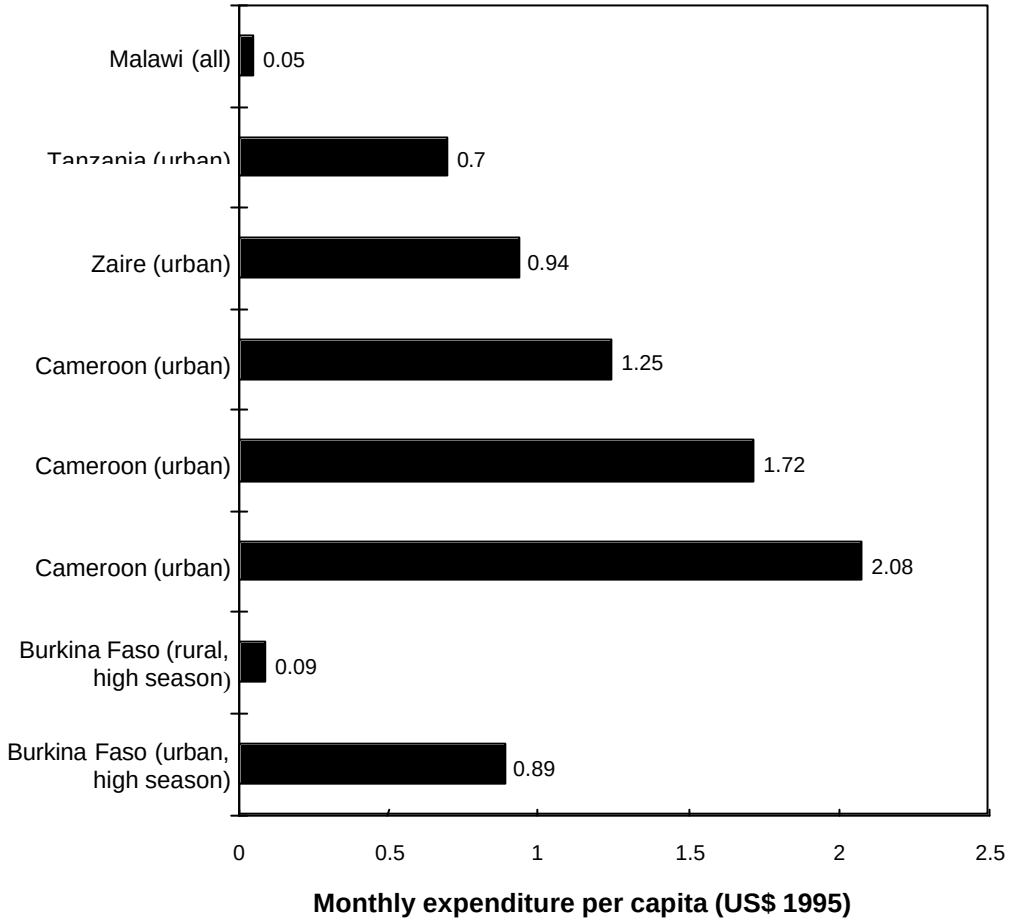
Studies that estimate economic costs of malaria are of limited relevance on a number of grounds. In particular, studies fail to consider:

- the coping strategies of households that reduce the impact (but which may also have costs)
- the possible pervasive effect of malaria in affecting the productive environment and production possibilities and incentives of households
- the extent to which resources devoted to treatment might be released or diverted to other high priority health problems if the burden of malaria were reduced.

In addition, given the known variations in transmission levels and health impact of malaria across Africa, the haphazard set of country and area data reviewed here are of little use in making generalizations. A much more systematic and carefully thought through effort is required to ensure that key differences in economic environments and malaria epidemiology are taken into account, and that both shorter and longer run consequences of malaria are considered.

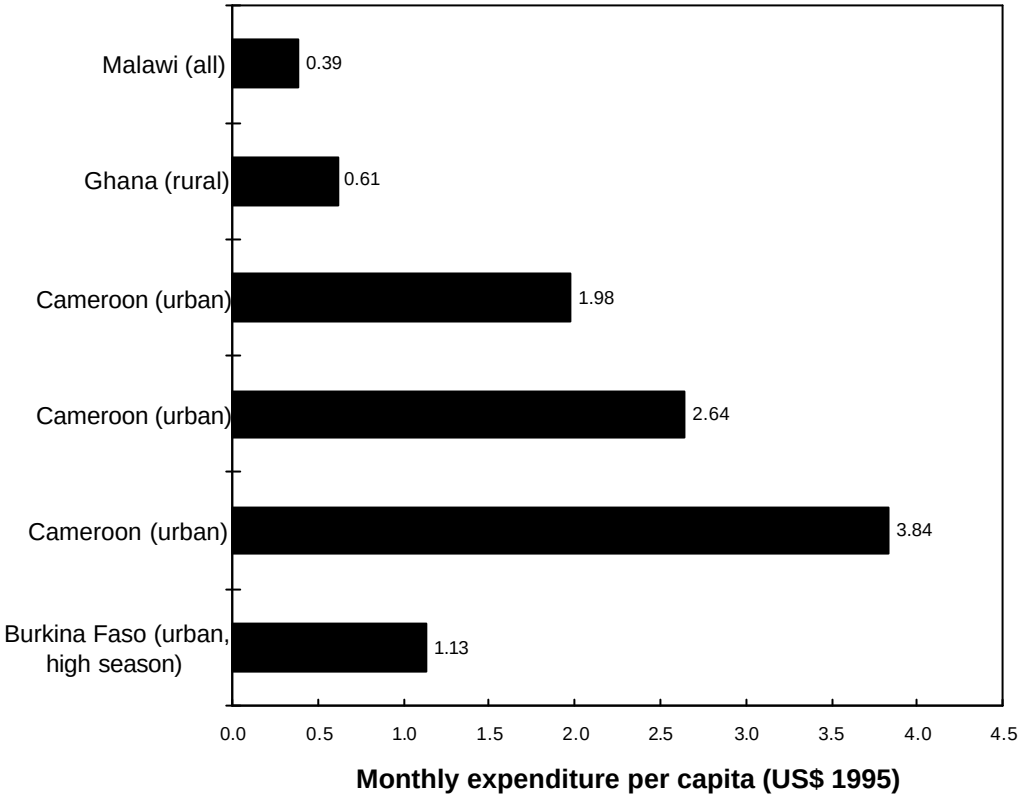
Such research should help to publicize and justify a major malaria control effort. However, this information, if suitably disaggregated, can also be used to design and target control interventions. Better information on economic impact is required to identify the population groups and regions most at risk of adverse economic effects. In particular, it is remarkable that good information is lacking on the relative incidence of malaria by socio-economic group, and especially its impact on the poorest. Furthermore, economic impact data could be used to identify the control interventions that make the largest contribution to reducing the economic burden. For example, anti-vector interventions, such as residual spraying or ITNs, are likely to act as substitutes to some degree for expenditure on coils and sprays, but this is unlikely to be the case for chemoprophylaxis. Preventive interventions that reduce transmission levels could have a significant impact on prevailing economic incentives for investment and saving. The improvement of treatment services may have little impact on direct preventive expenditure, but may lead to a change in the risks faced by households and therefore their productive and demographic decisions. The addition of these considerations to current knowledge on the gross costs and health effects of control interventions would enrich the planning process, and facilitate the identification of packages of interventions that have the greatest community-wide benefits.

Figure 6.1. Monthly per capita expenditure by households on prevention-related activities



Source: Mills (1998)[45].

Figure 6.2. Monthly per capita expenditure on malaria-related treatment by households



Source: Mills (1998)[45].

Table 6.1. Estimates used to calculate productivity costs of a malaria episode using the wage rate method

Authors	Country	Method of valuing time	Period of time lost	
			By sick adult	By child carer
Aikins (1995)[32]	The Gambia	marginal value of work time on crops cultivated by women		2.16 hours per day per child for 4 days
Ettling *et al*. (1991)[13]	Rwanda	marginal product proxied by average rural wage x .85[h]	3 days	1 day
Ettling *et al*. (1994)[35]	Malawi	mean per capita income from survey	2.7 days	1.2 days
Guiguemdé *et al*. (1997)[46]	Burkina Faso	mean annual income per worker by occupational group	4 days (all ages; 73% were <5)	Assumed to be 1.2 days
Leighton and Foster (1993)[2]	Kenya	average wage by sector	2-4 days (plus allowance for lower productivity for 2 days)	2-4 days
Leighton and Foster (1993)[2]	Nigeria	average wage by sector	1-3 days (plus allowance for lower productivity for 2 days)	1-3 days
Sauerborn *et al*. (1995)[4]	Burkina Faso	local wage for hired labour	3.5 days	2.7 days
Sauerborn *et al*. (1991)[6]	Burkina Faso	market value of average output per person for main produce in each of 2 seasons	mild illness 1 day; severe 5 days	1/3 of adult illness time

Table 6.2. Other estimates of period of illness caused by malaria

Authors	Country	Period of time lost
Bruce-Chwatt (1963)[47]	Nigeria (psychiatric patients, Lagos)	2.6 days (untreated)
Gazin *et al*. (1988)[48]	Burkina Faso (factory)	3.5 days
Hall and Wilkes (1967)[49]	Tanzania	1.16 days per person per year
Miller (1958)[50]	West African men	4.2 days per episode; 3 workdays lost per year
Nur and Mahran (1988)[8]	Gezira, Sudan	6 days of disability, plus 5 at 50% productivity

[h] Justification not provided.

References

1. Barlow R, Grobar LM. Cost and benefits of controlling parasitic diseases. Population, Health and Nutrition Department, World Bank, 1986.
2. Leighton C, Foster R. *Economic impacts of malaria in Kenya and Nigeria*. Bethesda, Maryland: Abt Associates, Health Financing and Sustainability Project, 1993.
3. Audibert M. Agricultural non-wage production and health-status - a case-study in a tropical environment. *Journal of Development Economics* 1986; 24(2): 275-291.
4. Sauerborn R, Ibrango I, Nougtara A, et al. The economic costs of illness for rural households in Burkina Faso. *Tropical Medicine and Parasitology* 1995; 46(1): 54-60.
5. Mills A. The economics of malaria control. In: Targett G, ed. Waiting for the Vaccine. Chichester: Wiley & Sons, 1991: 333-47.
6. Sauerborn R, Shepard DS, Ettling MB, Brinkmann U, Nougtara A, Diesfeld HJ. Estimating the direct and indirect economic costs of malaria in a rural district of Burkina Faso. *Tropical Medicine and Parasitology* 1991; 42(3): 219-23.
7. Nur ET. The impact of malaria on labour use and efficiency in the Sudan. *Social Science and Medicine* 1993; 37(9): 1115-9.
8. Nur ET, Mahran HA. The effect of health on agricultural labour supply: A theoretical and empirical investigation. In: Herrin AN, Rosenfield, P.L., ed. Economics, Health and Tropical Diseases. Manila: University of the Philippines, School of Economics, 1988.
9. Stevens CM. Health and economic development: longer-run view. *Social Science and Medicine* 1977; 11(17-18): 809-17.
10. Over M, Ellis RP, Huber JH, Solon O. The consequences of adult ill-health. In: Feachem RGA, Kjellstrom T, Murray CJL, Over M & Phillips MA, ed. The Health of Adults in the Developing World. Washington DC: Published for the World Bank by the Oxford University Press, 1992: 161-207.
11. Gallup JL, Sachs JD. The economic burden of malaria. Cambridge, MA: Center for International Development at Harvard University, 1998.
12. Shepard DS, Ettling MB, Brinkmann U, Sauerborn R. The economic cost of malaria in Africa. *Tropical Medicine and Parasitology* 1991; 42(3): 199-203.
13. Ettling MB, Shepard DS. Economic cost of malaria in Rwanda. *Tropical Medicine and Parasitology* 1991; 42(3): 214-8.
14. Conly GN. The impact of malaria on economic development : a case study. Washington, DC.: Pan American Health Organisation Scientific Publication, 1975.
15. Brohult J, Jorfeldt L, Rombo L, et al. The working capacity of Liberian males: a comparison between urban and rural populations in relation to malaria. *Annals of Tropical Medicine and Parasitology* 1981; 75(5): 487-94.
16. Pehrson PO, Bjorkman A, Brohult J, et al. Is the working capacity of Liberian industrial workers increased by regular malaria prophylaxis? *Annals of Tropical Medicine and Parasitology* 1984; 78(5): 453-8.
17. Wang'ombe JK, Mwabu GM. Agricultural land use patterns and malaria conditions in Kenya. *Social Science and Medicine* 1993; 37(9): 1121-30.
18. Shiff C, Checkley W, Winch P, Premji Z, Minjas J, Lubega P. Changes in weight-gain and anemia attributable to malaria in Tanzanian children living under holoendemic conditions. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1996; 90(3): 262-265.
19. Waruiru CM, Newton CR, Forster D, et al. Epileptic seizures and malaria in Kenyan children. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1996; 90(2): 152-5.
20. Pollitt E. Iron deficiency and educational deficiency. *Nutrition Reviews* 1997; 55(4): 133-41.
21. Pollitt E. Iron deficiency and cognitive function. *Annual Review of Nutrition* 1993; 13: 521-37.
22. Soewondo S, Husaini M, Pollitt E. Effects of iron deficiency on attention and learning processes in preschool children: Bandung, Indonesia. *American Journal of Clinical Nutrition* 1989; 50(3 Suppl): 667-73.
23. Lozoff B, Jimenez E, Wolf AW. Long-term developmental outcome of infants with iron deficiency. *New England Journal of Medicine* 1991; 325(10): 687-94.
24. Pollitt E, Saco Pollitt C, Leibel RL, Viteri FE. Iron deficiency and behavioral development in infants a nd preschool children. *American Journal of Clinical Nutrition* 1986; 43(4): 555-65.
25. Soemantri AG, Pollitt E, Kim I. Iron deficiency anemia and educational achievement. *American Journal of Clinical Nutrition* 1985; 42(6): 1221-8.

26. Marsh K. Immunology of human malaria. In: Gilles HM, and Warrell, D.A., ed. Bruce-Chwatt's Essential Malariology 3rd edition. London: Edward Arnold, 1993.
27. Asindi AA, Ekanem EE, Ibia EO, Nwangwa MA. Upsurge of malaria-related convulsions in a paediatric emergency room in Nigeria. Consequence of emergence of chloroquine-resistant Plasmodium falciparum. *Tropical and Geographical Medicine* 1993; 45(3): 110-3.
28. Axton JH, Siebert SL. Aetiology of convulsions in Zimbabwe children three months to eight years old. *Central African Journal of Medicine* 1982; 28(10): 246-9.
29. Boyle CA, Decoufle P, Yeargin Allsopp M. Prevalence and health impact of developmental disabilities in US children. *Pediatrics* 1994; 93(3): 399-403.
30. Mai NTH. Post-malaria neurological syndrome. *Lancet* 1996; 348: 817-821.
31. Brewster DR, Kwiatkowski D, White NJ. Neurological sequelae of cerebral malaria in children. *Lancet* 1990; 336(8722): 1039-43.
32. Aikins MKS. *Cost-effectiveness analysis of insecticide-impregnated mosquito nets (bednets) used as a malaria control measure: a study from the Gambia*. PhD Thesis, Department of Public Health and Policy, London School of Hygiene and Tropical Medicine, University of London, 1995.
33. Boissier M, Knight JB, Sabot RH. Earnings, schooling, ability and cognitive skills. *American Economic Review* 1985; 75(December): 1016-1030.
34. Knight JB, Sabot RH. *Education Productivity and Inequality: The East African Natural Experiment*. The World Bank, Oxford University Press, 1990.
35. Ettling M, McFarland DA, Schultz LJ, Chitsulo L. Economic impact of malaria in Malawian households. *Tropical Medicine and Parasitology* 1994; 45(1): 74-9.
36. Hill JA, Lake S, Meek SR, Mehra S, Standing H. *Approaches to malaria control in Africa, Part I: analysis and opportunities for malaria control support in selected countries in Africa*. London/Liverpool Malaria Consortium, 1996.
37. Brinkmann U, Brinkmann A. Malaria and health in Africa: the present situation and epidemiological trends. *Tropical Medicine and Parasitology* 1991; 42(3): 204-13.
38. Nájera JA, Hempel J. *The burden of malaria*. WHO CTD/MAL/96.10, 1996.
39. Ettling M, McFarland DA. *Economic impact of malaria in Malawi*. Virginia: Vector Biology Control Project, 1992.
40. Kirigia JM, Snow RW, Fox-Rushby J, Mills A. The cost of treating paediatric malaria admissions and the potential impact of insecticide treated mosquito nets on hospital expenditure. *Tropical Medicine and International Health* 1998; 3: 145-150.
41. Sauerborn R, Nougtara A, Hien M, Diesfeld HJ. Seasonal variations of household costs of illness in Burkina Faso. *Social Science and Medicine* 1996; 43(3): 281-290.
42. Haddix AC, Shaffer PA. Cost-effectiveness analysis. In: Haddix AC, Teutsch, SM, Shaffer, PA and Dunet, DO, ed. Prevention Effectiveness: A guide to decision analysis and economic evaluation. Oxford: Oxford University Press, 1996.
43. Cropper ML, Lampietti JA, Haile M, Poulos C, Whittington D. *The value of preventing malaria in Tigray, Ethiopia (Preliminary draft)*. Washington DC: The World Bank, 1999.
44. Sauerborn R, Adams A, Hien M. Household strategies to cope with the economic costs of illness. *Social Science and Medicine* 1996; 43(3): 291-301.
45. Mills A. Operational research on the economics of insecticide-treated mosquito nets: lessons of experience. *Annals of Tropical Medicine and Parasitology* 1998; 92(4): 435-447.
46. Guiguemde TR, Coulibaly N, Coulibaly SO, Ouedraogo JB, Gbary AR. An outline of a method for estimating the calculated economic cost of malaria cases: its application to a rural area in Burkina Faso (Western Africa). *Tropical Medicine and International Health* 1997; 2(7): 646-53.
47. Bruce-Chwatt LJ. A longitudinal survey of natural malaria infection in a group of West African adults, Parts I & II. *West African Medical Journal* 1963; 12: 141-173 & 199-217.
48. Gazin P, Freier C, Turk P, Gineste B, Carnevale P. Malaria in employees of an African industrial enterprise (Bobo Dioulasso, Burkina Faso). *Annales de la Société Belge de Médecine Tropicale* 1988; 68(4): 285-92.
49. Hall SA, Wilks NE. A trial of chloroquine-medicated salt for malaria suppression in Uganda. *American Journal of Tropical Medicine and Hygiene* 1967; 16(4): 429-42.
50. Miller MJ. Observations on the natural history of malaria in the semi-resistant West African. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1958; 52: 152-168.

Chapter 7 – Policy Implications

The aim of this final chapter is to reflect on the economic evidence available to underpin Roll Back Malaria by:

- bringing the cost-effectiveness results provided in previous chapters together and reflecting on their policy implications
- addressing the question of the cost of packages of malaria control measures
- highlighting implementation issues that need further and urgent consideration, including sources of finance, choice of distribution and provision strategies, and the broader policy environment, including regulation
- documenting key gaps in knowledge that are identified by the cost-effectiveness analyses and the economic impact of malaria review, and that need to be addressed by research.

7.1 Comparison of the cost-effectiveness of malaria control strategies

The cost-effectiveness of each intervention is dependent on many factors, such as the level of drug resistance and the length of the transmission season. This makes it difficult to make simple comparisons between interventions. However, to give a broad indication of relative cost-effectiveness, results are shown in Figure 7.1 for a range of interventions in a very low income country with high transmission (see Notes to Figure 7.1 for assumptions made for each intervention).

The key message from this analysis is that all the interventions would be considered an attractive use of resources: the range for the cost per DALY averted clearly falls below $150 in each case for very low income countries. It is possible to make rough comparisons with CERs for other health interventions, although the methodology used may not be strictly comparable. For example, the cost-effectiveness of measles vaccination is between $2 and $17 per DALY averted, onchocerciasis vector control between $120 and $230, and the medical management of hypertension greater than $2,000[a].

For the childhood preventive interventions, the level of existing infrastructure is a crucial factor in determining the most cost-effective strategy. ITNs are a highly attractive use of resources if net coverage is already high, and chemoprophylaxis for children is highly cost-effective if a VHW network already exists. Under these conditions the cost-effectiveness of both interventions falls in a similar range to measles vaccination. If this baseline infrastructure is not in place, the costs of the two interventions are significantly increased, although one can still be reasonably certain that the CERs remain under $150.

The choice between childhood preventive interventions is not clear-cut because there is considerable overlap in the CER ranges. If two spraying rounds are required a year, the mean CER for residual spraying is similar to that for "Nets and Insecticide Treatment", although the range for ITNs is much

[a] Data from Jamison *et al.*, 1993[1], converted to 1995 US dollars.

broader. If only one spraying round is required, the mean CER is significantly lower than for "Nets and Insecticide Treatment", although considerable overlap remains in the ranges. In practice, therefore, country-specific information on factors such as input prices, likely compliance and capacity to implement would have to be considered in order to select the best strategy. All results for prevention in childhood should also be considered in the light of the potential risk of reduction in acquired immunity, and the impact of insecticide and drug resistance.

Malaria prevention in first pregnancies is also highly cost-effective, assuming ANC coverage exists and that an increase in birth weight leads to a reduction in neonatal mortality. SP intermittent treatment is likely to be more cost-effective than CQ chemoprophylaxis due to lower costs, higher compliance and lower drug resistance. However, the CQ regimen is still cost-effective, with a CER under $150 up to levels of RII/RIII resistance of 69%. Even using average rather than incremental costs (i.e. including an allowance for ANC overheads), the CQ and SP regimens continue to look cost-effective up to levels of resistance of 40% and 65% respectively in very low income countries.

The case management interventions shown in Figure 7.1 (improving compliance with the first line drug, and improving the accessibility of the second and third line drugs) are the most cost-effective of all, with CERs clearly below $10, under the assumptions used in Figure 7.1. However data on the costs and effects of these interventions are very limited so further investigation is required to validate these results. Results for the other case management interventions are not shown in Figure 7.1. Combination therapies and artesunate suppositories are excluded because so little is known about their effectiveness. The introduction of new diagnostic techniques is not included because only changes in costs were considered, as the impact on health outcomes is not known. The issues involved in changing the first line drug for treatment cannot be summarized in a single CER, as this is a highly complex issue, involving a series of trade-offs between current and future costs and effects. Results are dependent on both empirical factors (for which there are very little data) and subjective factors relating to the preferences and priorities of policy makers, and their attitudes to risk.

Despite the limitations of the information available, it is clear that many interventions to improve case management are potentially extremely good value for money, and further investigation of cost-effectiveness is urgently required. This should incorporate potential trade-offs between the two objectives of making prompt, effective treatment as accessible as possible, and controlling drug use to reduce the growth rate of resistance.

The cost-effectiveness of the interventions was also compared in the other economic strata. For middle income countries, the results were very similar to very low income countries; the relative cost-effectiveness of the interventions was unchanged, and the CERs in each case were only very slightly higher. For all interventions, the CER ranges fell clearly below $150. In higher income countries, the CERs were significantly higher for all of the prevention interventions, but very similar for the interventions to improve case management, further reinforcing the attractiveness of these strategies. In this economic stratum it was no longer clear that ITNs including net distribution, residual spraying with two rounds a year, or chemoprophylaxis for children when a VHW network must be established were below the $150 cut-off. However, it is plausible that higher ability to pay for health care interventions would mean that a higher CER cut-off was appropriate in these countries.

Cost-effectiveness depends on a range of factors specific to each intervention, but certain common influences can be identified. The length of the transmission season has an important influence on annual costs for spraying and chemoprophylaxis for children, and all interventions are affected by the price of key commodities (such as nets and drugs), and behavioural factors (such as compliance with drug regimens and re-treatment rates for nets). The degree of drug or insecticide resistance has an important impact on all interventions. Local susceptibility of parasites and vectors significantly affects cost-effectiveness, and as resistance will inevitably change over time, constant monitoring is required to identify any changes that would affect relative cost-effectiveness.

The level of existing infrastructure significantly affects incremental costs, and therefore cost-effectiveness for ITNs, chemoprophylaxis for children and prevention in pregnancy. This raises the crucial issue of a potential conflict between efficiency and equity. According to these results it would be more cost-effective to direct resources to areas where, for example, there is good ANC coverage, a network of VHWs exists, or net utilization is already high. However, if resource allocation were based only on this analysis, it would be likely that the better-off regions and households would benefit most. Those potentially excluded would be the poorer, more remote regions, which are currently underserved, and households without nets, or with poor access to health services. It is therefore essential that the cost-effectiveness of interventions is always considered in conjunction with information on the characteristics of those benefiting. Where additional costs are required to reach those in greatest need, it is appropriate that benefits accruing to those groups be given greater weight.

7.2 Packages of malaria control measures

In practice, malaria control policy involves the selection of a package of complementary interventions. The effectiveness of interventions implemented together is difficult to estimate, as the total effects of combined interventions may be less than the sum of their incremental effectiveness when implemented alone. For example, when only chemoprophylaxis was provided to children in The Gambia there was a dramatic reduction in all cause mortality, but when chemoprophylaxis was combined with ITNs in another trial, the addition of chemoprophylaxis had no incremental effect on the reduction in mortality already achieved with ITNs[2, 3]. Similarly, for example, one would expect that if residual spraying has already taken place, the additional impact of providing prophylaxis to pregnant women would be reduced, and that the impact of any preventive intervention on childhood mortality would be lower if effective treatment services were already in place. In view of the inadequate understanding of the relationship between transmission and effectiveness, it has not been possible to make estimates of the combined effectiveness of a package of control measures.

Whilst incremental effectiveness could be reduced by providing interventions together, the incremental costs of implementing interventions could also be lower if resources were shared and therefore used more efficiently. This is unlikely to be significant for most of the interventions considered here, as the delivery strategies are fairly separate. It has therefore been assumed that the cost of a package can be estimated by simply adding together the costs of the individual interventions. Table 7.1 shows the total gross cost of some possible packages for a very low income

SSA country, such as Tanzania[b] (potential cost-savings from reduced expenditure on treatment services, or from a reduction in use of other preventive measures, have not been included).

Package 1 represents a situation where resources are not available to undertake a large-scale prevention programme, so the package includes only intermittent treatment for primigravidae, and two interventions to improve case management. This gives a modest total annual cost of less than $1 million, equivalent to only $0.03 per capita or less than 1% of the existing health sector budget, which appears relatively affordable for most African countries. High coverage with a childhood prevention strategy can be achieved at relatively low cost if, for example, net usage is already high. Package 2 includes the same interventions as Package 1 but with the addition of net treatment, giving a total annual cost of $4 million, $0.14 per capita or approximately 4% of the existing health sector budget. However, if net usage is currently low, and no network of VHWs already exists to deliver chemoprophylaxis to children, the incremental costs of achieving high coverage with a childhood prevention intervention will be very high. Package 3 includes the Package 1 interventions, plus an ITN programme where nets are also distributed. The total cost is $23.7 million, equivalent to $0.81 per capita or a quarter of the current health sector budget. Finally Package 4 shows the cost of a package in perennial transmission providing full coverage with two rounds of residual spraying, intermittent treatment for all pregnant women (rather than only primigravidae), interventions to improve compliance and accessibility of second and third line drugs, and the introduction of dipstick tests for every suspected case. The total cost is over $60 million, which would require an increase in the health sector budget of 64%. This is equivalent to an incremental cost of over $2 per capita.

7.3 Other economic issues in malaria control policy formulation

The analyses presented in this report emphasize that highly cost-effective strategies are available to control malaria. However, key questions of how best to implement these strategies have still to be addressed.

7.3.1 Financing

The cost analysis above indicates certain strategies to be readily affordable within the context of existing public health services, and others to be extremely expensive if high coverage is to be achieved. Cost-effectiveness analysis leaves unanswered the question of who is to pay for the different control interventions. This issue requires an assessment on the one hand of the characteristics of the goods and services required, the willingness of people to pay for them directly, and the extent to which the benefits accrue to those individuals who purchase those goods and services or to others as well. In technical terms, these are questions of the extent of positive externalities and the public good characteristics of interventions. If either of these phenomena are important, relying purely on individuals to make their own consumption decisions will result in a sub-optimal level of demand.

On the other hand, basing the selection of appropriate financing mechanisms solely on the characteristics of the goods and services completely neglects the fundamental problem of

[b] These are mean cost estimates, and there may be considerable variation around these figures.

accessibility for the great majority of the African population, which is lack of purchasing power. Hence poverty and equity considerations are powerful arguments for a strong public role in financing. However, there is a substantial cost attached to high coverage with a number of the interventions, particularly those focused on prevention of childhood malaria. It is therefore likely that a prominent donor role in financing will be required.

7.3.2 Alternative distribution and provision strategies

In order to undertake the cost-effectiveness analyses, assumptions had to be made on the most appropriate delivery strategies to assess. In reality, very little evidence is available for any of the interventions on the costs and effects of alternative approaches to distribution. Key issues include the extent to which interventions can be integrated into existing activities; and the choice between public, non-governmental organizations (NGOs) and commercial distribution channels. The majority of malaria episodes in Africa are treated through the private sector[4-7]. This fact alone means that ways of working with the private sector must be found, regardless of the relative economic merits of public and private delivery strategies. In the case of preventive interventions, those which require the widespread distribution of goods for use in the home, such as nets and insecticide, are likely to benefit from building on the extensive private sector distribution channels that already exist in Africa. Private distribution is by no means incompatible with public subsidies. However, research is urgently needed on how subsidies for the poorest can be combined with efficient distribution systems whilst ensuring that those who can afford to pay, do so.

7.3.3 Regulation

The analyses presented in this report have focused on intervention-specific strategies. However, there are a number of policies that act at a higher level, which may have an important influence on the cost-effectiveness of malaria control interventions. Regulatory policy is an important example, which affects malaria control activities in a number of ways. In theory, the pharmaceutical market in all countries is regulated to some degree to safeguard consumers. However, such regulations often do not work well or are not enforced: anecdotal evidence indicates that drug quality is a major problem in some countries, although no wide-ranging review is available[8]. Regulations also usually exist to control the licensing of both doctors and paramedical staff, and the facilities they practise from. Again, these are often flouted or ignored[9], and typically do not encompass the informal sector[10]. Although improvement of the regulatory system is now being identified as a key issue in health sector reform[11], it has yet to be addressed in the context of a major malaria control effort.

7.4 Knowledge gaps

7.4.1 The impact of interventions on health outcomes

Estimation of the effectiveness of all control interventions is severely hampered by the lack of a transmission model of malaria with incidence as an outcome. The relationship between transmission intensity, malaria morbidity and mortality, and the effectiveness of interventions is very poorly understood, so it is not possible to predict effectiveness in different epidemiological zones, and the long-term health impact of preventive interventions is unknown.

This methodological gap is mirrored on the empirical side by the small number of trials that report health outcomes, and the even smaller number which have information on mortality:

- Mortality data for residual spraying is very old and not comprehensive.
- Only one trial of chemoprophylaxis for children has mortality as an outcome.
- No studies on prophylaxis or intermittent treatment in pregnancy have shown a significant effect on infant mortality.
- Very little information is available on the effectiveness of improving the case management of severe or uncomplicated malaria, and the available data generally do not include evidence on health outcomes.
- No information is available on the effectiveness of environmental management, epidemic control or personal protection, so evaluation of these interventions was not feasible.

7.4.2 Intervention costs

Analysis is also restricted by the lack of information on costs:

- Although good cost data are available from the ITN trials, information is lacking on the costs of other delivery strategies, such as social marketing.
- Surprisingly, no full costings of residual spraying or of the addition of prophylaxis/ intermittent treatment to antenatal care were found.
- Cost information is very limited for interventions to improve case management.
- No cost data are available for environmental management or epidemic control.

7.4.3 The development and impact of drug and insecticide resistance

Analysis of all interventions involving antimalarials is hampered by the state of knowledge on drug resistance:

- Information is limited on current levels of parasitological resistance and clinical failure, and the relationship between the two.
- Hardly any data are available on growth rates of resistance over time, or on the factors that are associated with this growth. There is no model with which to predict the impact of proposed strategies to reduce resistance growth, such as combination therapies or the use of confirmed diagnosis in treatment decisions.
- There is a similar lack of information on the development and impact of vector resistance to insecticides.

7.5 Recommendations for further research on the economics of malaria

7.5.1 Research on the economic benefits of malaria control

Systematic studies of the potential benefits of malaria control are required, disaggregated by region and population group. The analysis needs to incorporate:

- the specific nature of the disease burden from malaria
- a detailed characterisation of the local economy
- the coping strategies of households and their potential costs
- the effect of malaria on the productive environment and production possibilities and incentives of households.

7.5.2 Collection of information on the costs of interventions

Where possible, effectiveness trials should be accompanied by rigorous costings, and comparable data should also be collected on costs in operational settings. In particular, it is a high priority to collect information on:

- the costs of alternative delivery strategies for ITNs
- simple interventions to improve case management
- interventions to improve the management of severe malaria.

7.5.3 Operational research on delivery strategies

Research is needed on ongoing projects and programmes to draw out transferable lessons on the effectiveness, efficiency and equity of different delivery strategies. In particular, information is needed on:

- ways to encourage net ownership to a level where a treatment programme would be feasible
- strategies to increase ITN re-treatment rates
- ways of providing residual spraying services in a manner appropriate to community needs
- affordable ways to improve compliance with chemoprophylaxis and drug treatment.

7.5.4 Analysis of the actual and potential roles of the public and private sectors

The remit of malaria control policy should be broadened beyond government services to incorporate the whole health sector, and the interrelationships between public and private components. Market analysis is required to assess the nature of demand and supply for prevention and treatment services, and to consider the ways in which policy can improve the performance of both sectors.

7.5.5 The adaptation of generalized estimates of cost-effectiveness for use by country level policy-makers

Adapting generalized estimates for use at the country level involves the use of local epidemiological and cost data, such as the level of drug resistance and local input prices, and the consideration of specific country conditions, such as the impact of existing infrastructure on incremental costs. It will be necessary to adapt estimates of the cost-effectiveness of individual interventions to devise a package of control measures, and to consider the implications of epidemiological and economic variation within countries. Finally a framework is required for policy development that combines cost-effectiveness data with other relevant information on equity, affordability, managerial capacity and the costs of resource reallocation.

7.5.6 Generation of comparable estimates of cost-effectiveness

The widespread use of cost-effectiveness information requires that comparable estimates are available for other health care interventions, so that the opportunity costs of the resources involved can be clearly understood. This requires the development of a common cost-effectiveness methodology, which is broadly accepted and well disseminated.

7.5.7 Capacity building in health economics

The achievement of these recommendations on the scale required in SSA, with adequate inputs of local knowledge, would severely overstretch the limited existing health economics capacity. Considerable investment is therefore required to develop a cadre of researchers and programme managers with training and experience in economics and epidemiology.

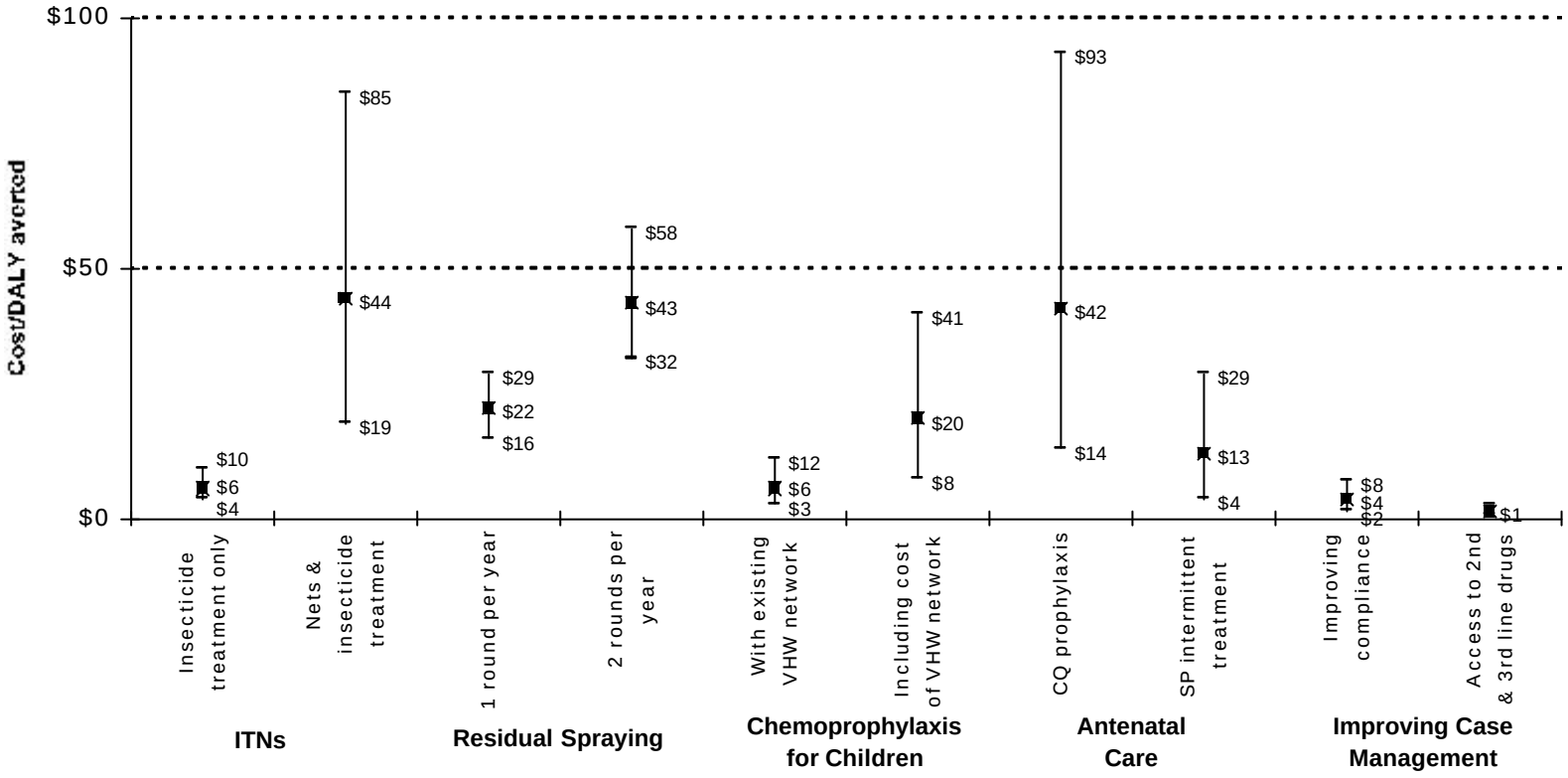


Figure 7.1. Cost-effectiveness in a very low income country with high transmission: mean and 90% range for the cost/DALY averted (1995 US dollars)

Notes:
ITNs: one treatment of deltamethrin a year, no insecticide resistance.
Residual spraying: lambda-cyhalothrin, Approach 1 to calculate effectiveness, no insecticide resistance .
Chemoprophylaxis for children: Maloprim®, perennial transmission, no resistance to Maloprim®.
Antenatal: Incremental costs, primigravidae only, 50% CQ RII/RIII resistance, 10% SP RII/RIII resistance

Case management: gross costs, CQ as first line drug with 30% clinical failure.

Table 7.1. Gross average annual cost implications of packages of malaria control measures in Tanzania (high transmission, very low income country) (1995 US dollars)

Package 1	
Antenatal intermittent treatment (primigravidae only, ANC services exist)	$0.2m
Intervention to improve compliance	$0.5m
Improving the accessibility of 2nd and 3rd line drugs	$0.3m
Total cost	$1.0m
Cost per capita	$0.03
Cost as % of existing health sector budget	1%
Package 2	
Net treatment (deltamethrin, one treatment per year)	$3.1m
Antenatal intermittent treatment (primigravidae only, ANC services exist)	$0.2m
Intervention to improve compliance	$0.5m
Improving the accessibility of 2nd and 3rd line drugs	$0.3m
Total cost	$4.1m
Cost per capita	$0.14
Cost as % of existing health sector budget	4%
Package 3	
Net distribution and treatment (deltamethrin, one treatment per year)	$22.7m
Antenatal intermittent treatment (primigravidae only, ANC services exist)	$0.2m
Intervention to improve compliance	$0.5m
Improving the accessibility of 2nd and 3rd line drugs	$0.3m
Total cost	$23.7m
Cost per capita	$0.81
Cost as % of existing health sector budget	25%
Package 4	
Residual spraying (lambda-cyhalothrin, 2 rounds a year)	$51.2m
Antenatal intermittent treatment (all pregnant women, ANC services exist)	$0.6m
Intervention to improve compliance	$0.5m
Improving the accessibility of 2nd and 3rd line drugs	$0.3m
Confirmed diagnosis for every suspected case	$7.6m
Total cost	$60.2m
Cost per capita	$2.06
Cost as % of existing health sector budget	64%

Source: Tables 3.12, 4.5 and 5.7.

References

1. Jamison DT, Mosley WH, Measham AR, Bobadilla JL. *Disease control priorities in developing countries*. New York: Published for the World Bank by Oxford University Press, 1993.
2. Menon A, Snow RW, Byass P, Greenwood BM, Hayes RJ, N'Jie ABH. Sustained protection against mortality and morbidity from malaria in rural Gambian children by chemoprophylaxis given by village health workers. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1990; 84(6): 768-72.
3. Alonso PL, Lindsay SW, Schellenberg J, et al. A malaria control trial using insecticide-treated bed nets and targeted chemoprophylaxis in a rural area of the Gambia, West-Africa. 6. The impact of the interventions on mortality and morbidity from malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1993; 87(S2): 37-44.
4. Deming MS, Gayibor A, Murphy K, Jones TS, Karsa T. Home treatment of febrile children with antimalarial drugs in Togo. *Bulletin of the World Health Organization* 1989; 67(6): 695-700.
5. Ejezie GC, Ezedinachi EN, Usanga EA, Gemade EI, Ikpatt NW, Alaribe AA. Malaria and its treatment in rural villages of Aboh Mbaise, Imo State, Nigeria. *Acta Tropica* 1990; 48(1): 17-24.
6. Mwabu GM. Health care decisions at the household level: results of a rural health survey in Kenya. *Social Science and Medicine* 1986; 22(3): 315-9.
7. Snow RW, Peshu N, Forster D, Mwenesi H, Marsh K. The role of shops in the treatment and prevention of childhood malaria on the coast of Kenya. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 1992; 86(3): 237-9.
8. Shakoor O, Taylor RB, Behrens RH. Assessment of the incidence of substandard drugs in developing countries. *Tropical Medicine and International Health* 1997; 2(9): 839-45.
9. Kumaranayake L. The role of regulation: influencing private sector activity within health sector reform. *Journal of International Development* 1997; 9(4): 641-649.
10. Foster SD. Pricing, distribution, and use of antimalarial drugs. *Bulletin of The World Health Organization* 1991; 69(3): 349-363.
11. Mills A. Reforming health sectors: fashions, passions and common sense. In: Mills A, ed. *Reforming health sectors*. London: Kegan Paul, 1999.