# 'An economic evaluation of malaria early warning systems in Africa: a population dynamic modelling approach'

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Philosophy by

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Declaration

This thesis has not been submitted for any other application for a degree and is the result of my own work and composition

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| | |
|---|---|
| ANC | Ante Natal Clinic |
| Aq | Amodiaquine |
| CBA | Cost Benefit Analysis |
| C-E ratio | Cost-Effectiveness Ratio |
| CEA | Cost Effectiveness Analysis |
| CMA | Cost Minimisation Analysis |
| CQ | Chloroquine |
| Cq | Chloroquine |
| CUA | Cost Utility Analysis |
| DALY | Disability Adjusted Life Year |
| DEHO | District Environmental Health Officer |
| DHLY | Discounted Healthy Life Year |
| DLYG | Discounted Life Year Gained |
| EDC | Epidemiology and Disease Control Unit |
| EHT | Environmental Health Technician |
| EIR | Entomological Inoculation Rate |
| ENSO | El Niño Southern Oscillation |
| GIS | Geographical Information System |
| GMS | Government Medical Stores |
| GoZ | Government of Zimbabwe |
| HK | Human Capital |
| HYE | Healthy Year Equivalent |
| IPD | In-Patient |
| ITBN | Insecticide Treated Bed Net |
| ITMN | Insecticide Treated Mosquito Nets |
| LDC | Less Developed Countries |

| | |
|---|---|
| MDA | Mass drug administration |
| MEWS | Malaria Early Warning Systems |
| MoH | Ministry of Health (Generic Term) |
| MoH&CW | Ministry of Health and Child Welfare (GoZ) |
| NGOs | Non-Governmental Organisations |
| NIBP | Gambian National Impregnated Bednet Programme |
| NMCP | National Malaria Control Programme |
| OPD | Out-Patient |
| PEHO | Provincial Environmental Health Officer |
| PHC | Primary Health Care |
| QALY | Quality Adjusted Life Year |
| RBM | Roll Back Malaria |
| RCT | Randomised Control Trial |
| RHC | Rural Health Centre |
| SARCOF | Southern Africa Climate Outlook Forum |
| SCN | State Certified Nurse |
| SHM | School Health Masters |
| SP | Sulfadoxine-pyrimethamine (Fansidar®) |
| SRN | State Registered Nurse |
| UN | United Nations |
| US$ | United States Dollar |
| VCH | Village Chloroquine Holder |
| VHW | Village Health Worker |
| WHO | World Health Organization |
| WHO-SAMC | World Health Organization Southern Africa Malaria Control Unit |
| WTA | Willingness-to-accept |
| WTP | Willingness-to-pay |
| YLD | Years Lived with Disability |

| | |
|---|---|
| YLL | Years of Life Lost |
| Z$ | Zimbabwe Dollar |

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## ABSTRACT

The purpose of this thesis is to provide a generic framework for the economic evaluation of malaria early warning systems (MEWS) for epidemic malaria control in Africa.

A population dynamic model of malaria transmission driven by temperature and rainfall was developed to represent a MEWS based on weather monitoring and/or seasonal climate forecasts offering perfect information on the on-set time and severity of epidemics to decision-makers. Climate and population data, estimates of entomological parameters and information on the malaria control strategies employed in the Hwange district of Zimbabwe are placed in the model and used to test the models ability to predict recorded clinical malaria cases over a five year period. The model is then used to predict the number of malaria cases that would occur under alternative malaria control scenarios including a 'do nothing' alternative where no spraying was carried out and spraying scenarios with various levels of spray coverage and timing.

The residual household spraying programme and selected case management activities in Hwange district were costed. The results were combined with the model estimates of case numbers in each scenario and used to calculate a number of outcome measures for each strategy including the total cost of malaria control, the cost per case prevented and the net incremental cost per case prevented.

Assuming a MEWS offering perfect information, spraying before the onset of the rains was found to be the most cost-effective intervention in most years compared to no spraying at all and spraying later. The most cost-effective level of coverage was found to vary between years depending on the level of transmission each year, with high coverage being the most cost-effective strategy in high transmission years and low or zero coverage being the most cost-effective strategy

in low transmission years. Further analysis revealed that the information provided by a MEWS using monitored information would not be available sufficiently early for the benefits associated with a perfect system to be achieved. However, a MEWS based on monitored information would represent an improvement on the current strategy of routine annual spraying with a fixed level of coverage. Moreover, a MEWS based on monitored information may provide sufficiently timely information for other malaria control interventions with shorter implementation times to be employed in a more efficient manner.

A MEWS using seasonal climate forecasts would provide information earlier than one based on monitored weather data, however it would be subject to greater error. The added lead-time offered by using seasonal climate forecasts with 100% accuracy would still not be sufficient to achieve the benefits offered by perfect information. The extent to which using seasonal climate forecasts is more beneficial than using monitored weather information will depend upon the accuracy of the forecasts, the likely severity (cost) of the epidemic and crucially, decision makers attitude to the risks of making mistakes.

## AIMS AND STRUCTURE OF THESIS

The aim of this thesis is carry out an economic evaluation of MEWS based on meteorological transmission indicators such as temperature and rainfall. Chapter 1 provides an introduction to malaria epidemics and their determinants and a description of the background to and roles of MEWS. Methods of economic evaluation and the existing literature on the economic evaluation of malaria control interventions is then reviewed in order to select and justify an appropriate economic evaluation technique (chapter 2). The methods, roles and applications of modelling techniques in economic evaluation and in malaria control theory are then described (chapter 3). A population dynamic malaria model is developed based on existing malaria models (chapter 4). The model is then applied to a specific location in order to create a framework representing a MEWS based on the monitoring of malaria transmission indicators (temperature and rainfall) (chapter 5). The framework is assumed to offer perfect information regarding the on-set time and severity of epidemics to decision-makers. Cost data from the same location is introduced into the framework (chapter 6). The framework is then used to evaluate the cost-effectiveness of perfect and imperfect MEWS based on monitored weather information. The system is then modified to represent a MEWS based on the information offered by seasonal climate forecasts (chapter 7). Finally the costs and benefits of MEWS are discussed and described and a framework for the evaluation of MEWS from the Ministry of Health and household perspective is developed.

The aim of this thesis is to compare the impact of malaria control interventions carried out or not because of a MEWS with the impact of (the same) interventions carried out later as a result of the methods currently used in Africa to trigger malaria control interventions. Early intervention is likely to affect the severity of an epidemic, for example if used early enough vector control and parasite clearing drugs will reduce transmission and early treatment of cases will reduce the

number of severe episodes and deaths. Thus it is the impact of the timing of an intervention on its effectiveness, which is of particular interest here.

# CHAPTER 1 - MALARIA EPIDEMICS, MALARIA EARLY WARNING SYSTEMS AND THE NEED FOR ECONOMIC EVALUATION

## 1 OVERVIEW OF CHAPTER

This chapter provides an introduction to malaria epidemics. The problems of defining malaria epidemics are discussed and a definition is given for this thesis. The determinants of malaria epidemics are described and the implications for monitoring and prediction of epidemics are discussed. The background to Malaria Early Warning Systems (MEWS) is given, followed by a description of the roles of MEWS and the proposed indicators which could be used to predict the timing and severity of malaria epidemics.

## 1.1 INTRODUCTION TO MALARIA EPIDEMICS

Malaria is a life threatening disease to individuals with low immunity. Communities that are not normally exposed to high rates of malaria transmission are therefore extremely vulnerable to explosive epidemics with high case fatality rates among all age groups. Such malaria epidemics are preventable if decision-makers have access to information on the risk of epidemics occurring both in space and time. The early detection, containment and prevention of malaria epidemics has been incorporated as one of four technical elements into the Global Malaria Control Strategy (WHO 1993) on which the Roll Back Malaria (RBM) initiative is building. There is growing recognition of the need to implement programmes to predict and prevent malaria epidemics (WHO 2001) therefore an evaluation of the potential economic efficiency of such technologies is timely. This study concentrates on Africa south of the Sahara where 80% of malaria mortality occurs (WHO 1993).

## 1.2 DEFINING MALARIA EPIDEMICS

There is no universally accepted definition of what constitutes a malaria epidemic (Connor et al. 1999). This thesis considers epidemics of *P. falciparum*

malaria, caused or greatly influenced by meteorological factors (namely temperature and rainfall) where the term epidemic is defined as:

"*any sudden increase in disease incidence beyond what is considered normal will constitute an epidemic* [of malaria]" (Nájera 1998)

Nájera adds that epidemics should not be confused with previously unrecognised endemic situations or seasonal increases in the incidence of the disease. Connor *et al.* define a malaria epidemic as:

"*an increase in the disease beyond that normally experienced*" (Connor et al. 1999).

These definitions are somewhat subjective reflecting the nature of epidemics, which may only be recognised as such when health services are unable to cope with the demands placed upon them by increases in disease incidence.

## 1.3 DETERMINANTS OF MALARIA EPIDEMICS

The causal factors of an epidemic must be understood in order to forecast, prevent or control them. Most epidemics are either as a result of or greatly influenced by meteorological or social determinants.

Nájera *et. al* define malaria epidemics as the result of a:

"*disturbance of a previously existing equilibrium of the ecological system comprising human, parasite and vector populations in a particular environmental niche*" (Nájera 1998)

Epidemics may be a result of a temporary disturbance of the environment, such as those caused by abnormal meteorological conditions, or, they may be due to major changes in the environment, such as the introduction of irrigation. Both of these phenomena are described by Nájera *et al.* as "*true epidemics*" as opposed to "*resurgent outbreaks*" which are due to interruptions of malaria control measures. Whatever the cause of a particular epidemic, the path it takes will be determined by

the species of parasite, its inoculation rate and the proportion of susceptibles in the human population. In tropical Africa most epidemics are caused by a single species of parasite, *P. falciparum* (*op. cit*).

## 1.4 MONITORING AND PREDICTING MALARIA EPIDEMICS

The cyclical nature of the determinants of some epidemics and the warnings given by monitoring certain appropriate variables, makes them both predictable, and with adequately prepared health services, preventable. Socio-economic variables, case data, entomological indicators and meteorological variables can all provide information as the likelihood or status of epidemics. A description of how each of these indicators could be used to monitor or predict malaria epidemics is given below.

### 1.4.1 MONITORING SOCIO-ECONOMIC VARIABLES

There are a range of socio-economic factors which may lead to increased risk of malaria epidemics. Irrigation schemes for agricultural activities may lead to the creation of socio-economic and environmental conditions suitable for malaria epidemics. For example non-immune people may move to take advantage of an irrigation scheme where malaria control measures have not been implemented. Mass population movements, social disruption and unrest may also leave populations vulnerable to malaria epidemics as health services break down or non-immune populations move into endemic areas. Crop failures in preceding years may reduce the nutritional and economic status of communities creating an ideal environment for epidemics to take hold with devastating consequences. These variables can all be used to identify areas where epidemics may occur, however it is difficult to envisage the creation of a simple composite measure of all these that could be used to predict malaria epidemics.

### 1.4.2 CASE MONITORING

Monitoring the number of cases reporting at health facilities and comparing this with the normal level is one of the commonest ways that epidemics are detected. Thresholds for an above normal level of cases are developed from previous years' case data and are then used to trigger epidemic interventions (WHO 2001). Despite its widespread use, this method of epidemic surveillance is unlikely to provide sufficient lead time for effective preventive action particularly as reporting systems make take a number of weeks for data to reach the decision making level. Nájera states that:

"*Unfortunately, during most epidemics, once the increase in morbidity has been recognized, there may be too little time to mobilize the required resources for effective vector control before the transmission season has reached its peak*" (Nájera 1998)

This represents a lost opportunity for malaria control, however in reality the situation may be worse. If an epidemic is severe enough to become a political issue this may lead to the initiation of a vector control programme well beyond the time period in which it could effectively reduce transmission (Connor et al. 1999). If this is the case the intervention represents a waste of scarce resources. Case data provides valuable information but is not available early enough to be used in epidemic prevention, although it may be useful in epidemic mitigation.

### 1.4.3 MONITORING AND PREDICTING ENTOMOLOGICAL VARIABLES

Time lags exist between the build up of a sufficiently mature vector population, the increase in the sporozoite rate and the onset of a malaria epidemic. Theoretically it is possible to carry out routine monitoring of entomological variables (vector density, survivorship and sporozoite rates) in sufficient time to warn of a potential epidemic situation. Unfortunately the difficulty and cost associated with carrying out entomological surveys large enough to gain a representative sample

make them unfeasible in Africa. In addition to this the time to act offered by monitoring such variables may not be sufficient to carry out effective preventive measures (Nájera 1998).

The entomological inoculation rate (EIR) has been suggested as an indicator of epidemic risk (Onori and Grab 1980). The EIR is given by the mean daily number of infective bites received per person per day. It is calculated from the multiplication of the person-biting rate with the sporozoite rate. Similar problems with data collection may arise if attempts are made to measure the EIR directly, however since many of the components of the EIR are related to meteorological variables (Lindsay and Birley 1996, Onori and Grab 1980) it may be possible to derive an estimate for it using climate data. Such estimates will be limited since the gametocyte carrier rate and the sporozoite rate are only partly related to temperature and rainfall, other vital factors include population movement, control measures and vector competence.

### 1.4.4 MONITORING AND PREDICTING METEOROLOGICAL VARIABLES

In some areas, mainly either arid or semi-arid areas (e.g. the Sahel) and highland areas (e.g. Kenyan Highlands), the relationship of the malaria vector and parasite to temperature and rainfall may be a crucial determinant of epidemics. In arid areas malaria transmission will normally be limited by insufficient rainfall to provide breeding sites for vectors and low humidities which reduce survivorship. In highland areas the temperatures will normally be too low for parasite development to occur in the vectors and enable them to transmit the parasite from an infected individual to another individual. In these areas there are likely to be long periods of limited or zero transmission meaning that the human population will build up little or no immunity. This will lead to the build up of a vulnerable population with a high proportion of susceptible individuals, especially when combined with poverty, lack of

access to health services, poor nutritional status and the incidence of other infectious diseases.

When abnormal meteorological events occur, in arid areas this could be excessive, prolonged, early or later than normal rains and in highland areas this could be a longer, warmer or more humid summer, it may lead to a devastating malaria epidemic. Rainfall in arid areas is most likely to increase vector numbers because of a proliferation of breeding sites although the opposite is possible due to the flushing out of some breeding sites by increased flow of water (Lindsay and Birley 1996). Warmer temperatures in highland areas will increase the probability that the parasite will develop successfully within the life time of the vector because parasite development is accelerated in warmer conditions (Detinova 1962, Lindsay and Birley 1996, Macdonald 1957) and the vectors survival rate per gonotrophic cycle is relatively independent of temperature (Hii et al. 1990, Lindsay and Birley 1996). The likelihood that an infected vector will transmit malaria is also increased because vectors feed more frequently at warmer temperatures (Detinova 1962, Gilles 1953, Lindsay and Birley 1996).

These factors when combined with a vulnerable population have the potential to trigger an epidemic. In both cases the link between temperature and/or rainfall and malaria epidemics can be used as the basis for predicting malaria epidemics. This can be done either through the real time monitoring of climate variables and possibly by using seasonal climate forecasts (see section 1.6).

## 1.5 BACKGROUND TO MALARIA EARLY WARNING SYSTEMS

The ability to predict malaria epidemics means that they can be prevented or that their effects can be greatly reduced through effective and timely intervention. Problems of poor-intersectoral collaboration between meteorological or agricultural and health services have hindered efforts by African countries to develop simple transmission risk indices, however new tools have recently become available which

have lead to increased interest in the development of Malaria Early Warning Systems. Geographical information systems (GIS) and satellite data (often available freely or at low cost over the internet) have been used to develop early warning systems for agricultural problems in Africa and it has been suggested that the principles which underlie these systems apply to the development of MEWS for Africa (WHO 2001).

A recent WHO document provides a framework for the development of a MEWS for use in African countries (WHO 2001), since MEWS are not yet fully operational in Africa this framework document provides a description of the type of MEWS which this thesis aims to evaluate. A clarification and description of what is meant by MEWS, extracted from the WHO document, for the purpose of thesis follows below.

## 1.6 DESCRIPTION OF MALARIA EARLY WARNING SYSTEMS (MEWS)

It is proposed that Malaria Early Warning Systems (MEWS) use three main groups of indicators to predict the timing and severity of a malaria epidemic. These indicators consist of vulnerability indicators, transmission risk indicators and early detection indicators.

Vulnerability indicators may be low immunity, drug resistance, HIV, malnutrition, population movement, etc. which may be monitored continuously and are likely to predict the severity, rather than timing of an increase in malaria transmission.

Transmission risk indicators such as unusual increases in rainfall may predict the timing of an increase in malaria transmission 2-4 months before an epidemic occurs. In some situations a higher than average seasonal rainfall may be predicted from seasonal climate forecasts 1-6 months in advance – giving a maximum warning of an epidemic situation developing with 10 months early warning.

Early detection indicators from health facility malaria morbidity data and using epidemic thresholds may be used to confirm the onset of an epidemic situation and predict the magnitude of the epidemic 3-4 weeks in advance.

There is a trade off between the accuracy and timing of these indicators – for instance seasonal forecasts are available early in the planning cycle but their ability to predict the future weather is limited. On the other hand surveillance systems, which pick out higher than normal malaria in a particular area, may be a better indicator that a malaria epidemic is occurring but offers little time for effective prevention and control.

## 1.7 THE ROLES OF A MALARIA EARLY WARNING SYSTEM

The WHO document states that the role of a MEWS in the control and mitigation of malaria epidemics is: *"manifold and includes the determination of:*

- *which districts are prone to epidemics*
- *the population at risk – where, when and whom and therefore the size of the response required*
- *the timing at which decisions and actions must be made to control or mitigate malaria epidemics**
- *surveillance thresholds that may be used to verify the onset of an emerging epidemic*
- *where and how active disease surveillance needs to be strengthened – and where temporary or permanent sentinel sites need to be established*
- *the level of financing that should be invested to maintain an effective early warning system**
- *the logistics required for the control intervention(s)*

- *the technical and political relationships with stakeholders and decision-makers"**

(Those roles marked with * are of particular relevance to this thesis)

The WHO framework document also points out that:

*[The] most important factors determining patient survival are (a) the patients personal vulnerability (in terms of immunity, malnutrition, other diseases etc.) and (b) early diagnosis and prompt treatment with effective anti-malarial drugs (although even with effective treatment cerebral malaria still has a mortality rate of around 20%). Hospital studies show that on average symptoms are often only evident for 2 days before patients present and most deaths occur within 24 hours of admission to hospital [cited reference: (Jaffer et al. 1997)],*

*Of critical significance to the development of MEWS is the knowledge that for many parts of Africa over 80% of malaria cases and malaria deaths occur in the community and are not recorded at all. Early warning systems may allow preventative and curative measures to be instigated at the community level.*

### 1.7.1 PREVENTION OF AND RESPONSE TO MALARIA EPIDEMICS

Sudden or explosive epidemics of malaria determined by meteorological factors such as abnormally heavy/prolonged rains, unusually warm, humid or long summers or abnormally prolonged dry seasons in humid valleys (leading to the drying up of rivers creating pools suitable for vector breeding sites) can be contained or prevented using a number of control measures (Nájera 1998).

The main objectives of a response to control or mitigate the effects of a malaria epidemic can be separated into those aimed at reducing the case fatality rate and those aimed at reducing epidemic potential. These are described in further detail below as laid down in the WHO document (WHO 2001).

*Measures to reduce the case fatality rate can be aimed at reducing the care seeking constraints of the affected population by:*

- *Increasing public awareness of malaria symptoms to encourage early reporting at health facilities and support for malaria control activities using radio, press, community meetings, religious leaders etc.*
- *Reducing physical constraints of access to health services thorough the use of mobile clinics, field hospitals, community drug holders, mobilisation of transport for the sick*
- *Reducing economic constraints to health services through changes in charging policy to ensure drugs are free or affordable to those who need them (e.g. suspending or reducing user fees) and the provision of free transport for referrals*

*They can also be aimed at reducing care delivery constraints within the health services by:*

- *Improving health services effectiveness by improving human resources and infrastructure*
- *Improving specific malaria epidemic related health care support by providing timely financial and practical support for health services to ensure adequate staffing levels and an adequate supply of appropriate drugs and equipment*

*A reduction in epidemic potential can be brought about by improving disease prevention and case management by:*

- *Increasing public awareness of malaria control activities at the community level to encourage practical and financial support for control activities*

- *Improving case management facilities e.g. diagnostic and treatment facilities should be stocked with appropriate and effective first and second line anti-malarials to ensure that cases reaching facilities can be treated as soon as possible. Peripheral health facilities may also be provided with the necessary drugs and equipment to manage severe malaria (e.g. IV equipment and quinine) to reduce the time taken between severe cases reporting and receiving adequate treatment, thus reducing the number of deaths.*

- *Providing chemoprophylaxis to vulnerable groups such as short term travellers, pregnant women, children under five or (rarely) to the entire non-immune population where the population is settled temporarily in a malarious area*

*Reducing malaria transmission potential during or just prior to an expected epidemic should be carried out as long as the epidemic has not exhausted itself before health services have recognised it, or had time to act. This can be achieved by:*

- *Reducing the number of gametocyte carriers in the human population by the timely use of gametocidal and anti-malarial drugs either by mass fever treatment (presumptive treatment of all fever cases with anti malaria drugs) or by mass drug administration (MDA) (coverage of the whole population with anti gametocydal drugs). MDA is only appropriate in small well defined and controlled populations however it may still be difficult or undesirable due to problems of drug resistance, cost and if there are insufficient drugs* (Nájera 1998)

*The number of sporozoite positive mosquitoes can be reduced by:*

- *Reducing the capacity for mosquitoes to survive through indoor residual spraying* and/or other vector control measures such as space spraying of insecticide to rapidly reduce vector density. Space spraying may be prohibitively expensive due to cost of insecticides, it also requires special equipment and may be impossible in inaccessible areas* (Nájera 1998).
- *Reducing mosquito density through environmental management and larviciding in specific settings*

*Human exposure to infective mosquitoes can be reduced by:*

- *Moving populations away from areas of high transmission*
- *Increasing personal use of mosquito nets and insecticide impregnated mosquito nets or other materials*

## 1.7.2 REDUCING THE CONSEQUENCES OF MALARIA EPIDEMICS

The aim of a MEWS is to control and mitigate malaria epidemics in order to reduce their consequences at the individual, household, community, regional and national level. The consequences of epidemics outlined in the WHO publication (WHO 2001)as follows:

*Epidemics can:*

- *cause considerable malaria morbidity* and mortality in the affected community*
- *make vulnerable groups more susceptible to diseases other than malaria*
- *seriously disrupt health care services with consequent increases in all-cause morbidity and mortality**
- *have long term consequences for the health of unborn children**
- *add significantly to costs at the household, community and MoH level of both curative an preventative health care provision**

- *cause declines in agricultural output resulting in economic losses at both the household and commercial level*
- *result in significant school and work absenteeism*
- *seriously disrupt the social, political and economic activity in a community or country*

Again points marked with * are of particular relevance or are discussed in this thesis.

## 1.8 THE NEED FOR ECONOMIC EVALUATION OF MEWS

MEWS are being proposed for the use in epidemic prone areas in sub-Saharan Africa as part of efforts to predict and prevent malaria epidemics and as part of the wider RBM initiative to reduce the burden of malaria. Before this takes place there is a need to evaluate the potential economic implications of MEWS for improving epidemic malaria control. However, since MEWS are not yet fully operational it is only possible to evaluate certain aspects of their role and consider how these roles if fulfilled, would affect the economic efficiency of epidemic malaria control interventions.

MEWS may facilitate earlier and therefore more effective intervention in epidemic situations, which could substantially reduce the effects of epidemics, however they may also lead to the unnecessary use of resources if they incorrectly predict an epidemic. The trade off which exists between earlier intervention based on uncertain indicators of malaria (e.g. seasonal climate forecasts or rainfall monitoring) and later intervention based on monitored information of current malaria (e.g. malaria case or death data) is crucial in determining the economic benefits of using MEWS. Furthermore, if quantified the potential benefits of MEWS will give some indication of the level of resources that should be invested in them.

In a world of perfect prior information where decision makers knew exactly what was going to happen each malaria transmission, before the season, they would be able to choose the optimal malaria control strategy each year. Clearly this is not and can never be the case and decision makers will normally have limited information based mostly on previous years malaria transmission on which to base control decisions leading to sub-optimal control strategies being employed. A MEWS which provides information on the likely characteristics (timing and severity) of a forthcoming malaria transmission season is unlikely to be able to provide sufficient information for the optimal control strategy to be chosen, however it may offer improvements upon the sub-optimal strategy employed without a MEWS. Evaluating the difference in the costs and benefits of malaria and malaria control between the sub-optimal strategies with and without MEWS and compared to the optimal control strategy offers a means of measuring the economic benefit or cost of MEWS.

## 1.9 CHAPTER SUMMARY

The determinants of malaria epidemics include social, economic and meteorological factors and can be used to a greater or lesser extent to predict the timing and/or severity of a potential epidemic. MEWS based on transmission risk indicators such as rainfall and temperature can use seasonal climate forecasts and/or monitored temperature and rainfall data to predict malaria epidemics. A trade-off exists between the timing and accuracy of malaria control strategies based on a MEWS compared to malaria control strategies not based on a MEWS. Furthermore, there is a trade-off between timing and accuracy of malaria control strategies based on a MEWS using seasonal climate forecasts and malaria control strategies based on a MEWS using monitored weather data. In the former situation the information will be available sooner but is necessarily probabilistic and in the latter situation the information will be available later but is likely to be a more

accurate predictor of malaria. In both situations the MEWS is subject to the limitations regarding the understanding of the relationship between the weather variables being used and malaria. The existence of these trade-offs and their potential implications for the costs and benefits of using MEWS to inform malaria control strategy decision making form the basis of the argument for the economic evaluation of MEWS.

# CHAPTER 2 - ECONOMIC EVALUATION

## 2 OVERVIEW OF CHAPTER

Economic theory provides a range of techniques to examine the efficiency and desirability of any health intervention or activity. In this chapter the existing tools and methodologies for economic evaluation are described in turn and their limitations are explained. Following the description of each evaluation technique a critical review of its application to malaria control interventions is presented. The relevance of each evaluation technique to the question being posed in this thesis is then discussed and the most appropriate evaluation technique is selected.

## 2.1 INTRODUCTION TO ECONOMIC EVALUATION

Economic evaluation has been defined as:

"*the comparative analysis of alternative courses of action in terms of their costs and consequences.*" (Drummond et al. 1997)

An evaluation must therefore identify, measure, value and compare the costs and consequences of all the alternatives being considered. In the case of health care evaluation it is useful to distinguish between the different types of evaluation. Initially they can be characterised as partial and full evaluation methods. Techniques which fail to evaluate two or more alternatives to achieve the specified outcome, or examine only the costs or consequences of the health care activity being evaluated are only partial evaluation methods. Partial evaluation methods are useful in terms of developing an understanding of the costs and consequences of health services or programmes, however they are not sufficient to answer efficiency questions. For this full economic evaluation is required. Full economic evaluation implies that there is a comparison of two or more alternative activities or interventions and that both the costs and outputs of alternatives are examined. This can be achieved using one or a combination of methods of economic evaluation.

## 2.2 METHODS OF ECONOMIC EVALUATION

The main types of economic evaluation are: cost-minimisation analysis (CMA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-benefit analysis (CBA).

### 2.2.1 COST-MINIMISATION ANALYSIS

Cost-minimisation analysis (CMA) is a special case of cost-effectiveness analysis (CEA) where the outcomes of the alternative activities being compared is either known, presumed or turns out to be the same. In this case the outcomes can be ignored and the most efficient alternative is found by analysing and comparing the costs of each option.

Gold *et al.* suggest that while the effectiveness of alternatives is unlikely to be equal, it may be a reasonable approximation in some cases (Gold et al. 1996), however (Evans and Hurley 1995) argue that this assumption is a major limitation of CMA. They suggest that there are likely to be other outcomes of supposedly identical alternatives that are not captured by the reported outcome measure. It is rare to find examples of CMA in the published literature, particularly in developing countries.

#### 2.2.1.1 REVIEW OF PUBLISHED STUDIES USING COST-MINIMISATION ANALYSIS

No examples of CMA of malaria control interventions were found from sub-Saharan Africa, therefore examples from Sri Lanka and the Solomon Islands were included instead.

Konradsen *et al.* undertook a CMA of a range of preventive and curative interventions for malaria in Sri Lanka (Konradsen et al. 1999). The analysis was based on the use of standardised cost estimating procedures, taking into account costs borne by both the government and households, and what the authors describe as "comparable units of effective outputs". The curative interventions compared

were hospital diagnosis and treatment, mobile clinic diagnosis and treatment and village treatment centre diagnosis and treatment, the units for comparison of cost-effectiveness were cost per blood slide examined by microscopist and cost per blood slide found to be malaria positive and treated. The preventive treatments compared were residual spraying, bednet impregnation (of nets existing in the community), larviciding and water management and the unit for comparison was cost per person protected per year or season. It was assumed that all curative interventions were equally as effective and that of the preventive interventions bednets and spraying were equally as effective, but that it was too difficult to estimate the effectiveness of the other preventive interventions.

The results of Konradsen and colleagues analysis indicated that, from the government perspective, hospital facilities are the most cost-effective in terms of cost per positive case detected and treated, followed by village level treatment and then by mobile clinics. From the household perspective both mobile clinics and village level treatment centres had zero cost however, the hospital treatment cost an estimated US$1 per positive case treated. Overall from the joint government and household perspective village level treatment centres were the most cost-effective, followed by hospital based diagnosis and treatment and the mobile clinics.

The assumption that the effectiveness of the three curative interventions is equal does not capture certain aspects of each intervention adequately. For example the added flexibility achieved through the use of mobile clinics in the malaria control programme is not included, also the possible benefit of earlier treatment achieved through village level facilities is ignored. This example illustrates one of the major limitations of CMA; namely that examining and comparing costs alone may neglect other important non-cost factors. The main weakness of this study is the choice of evaluation techniques (i.e. CMA) which is inappropriate since

it has not been established that the effectiveness of each intervention compared is equal.

Kere and Kere used a cost minimisation analysis in the Solomon Islands to compare the cost per capita of distribution and annual re-impregnation of bednets (using permethrin) and residual household spraying with DDT for malaria control (Kere and Kere 1992). The results of the analysis showed that the cost per person per year of a spray programme would be SI$8.53, compared to SI$3.85 per person per year for bednet distribution and annual re-impregnation. The authors argued that since CEA and CBA are much more complicated and difficult to carry out in the health sector than CMA, and that because analysis of cost is an essential element of both of these types of analysis, it would provide adequate evidence for decision making. The authors also point out that the policy change from DDT house spraying to permethrin-impregnated bednets in 1991 in the Solomon Islands was based on the results of their CMA.

The authors argue that CMA was employed in these circumstances because no data on the effectiveness of the interventions under the Solomon Island conditions was available, however its use may have meant that certain important considerations were ignored. For example, the authors point out that the operating costs of a bednet programme may be lower than for a spray programme because villagers are more willing to volunteer to participate in the running of the programme than in a spray programme. This may mean that the programme is more affordable to the government since the costs are shared with households. No information is given on the operational efficacy of either intervention it is therefore questionable that the interventions will achieve the goal of controlling malaria to exactly the same extent. An essential pre-requisite for CMA is therefore not met.

### 2.2.1.2 RELEVANCE OF COST-MINIMISATION ANALYSIS TO MALARIA CONTROL INTERVENTIONS

CMA is appropriate when it can be shown or reasonably assumed that alternative activities achieve an output to the same extent without any additional positive or negative effects. In the case of malaria control interventions it is unlikely that two different interventions will be equivalent in all ways other than cost. Peoples attitudes to different interventions, and the different operational circumstances and problems associated with each intervention are likely to affect acceptability, feasibility and the efficiency of interventions in real situations, even if they seem equivalent in trials.

An example of the degree to which the effectiveness of interventions can vary dramatically due to a small change is illustrated by the results of Helitzer-Allen *et al.* who found that the compliance with malaria chemoprophylaxis in pregnant women in Malawi could be increased from 25% to 87% simply by coating the tablets with a non-bitter substance (Helitzer-Allen et al. 1993).

CMA is too blunt an analytical tool to capture the subtleties of malaria control interventions, which may vary only slightly in terms of cost, but dramatically in terms of effectiveness. Moreover, differences in costs may be offset by differences in effectiveness that would not be captured through the use of CMA; this may lead to the results of a CMA being dramatically altered if a CEA were carried out.

The cost of MEWS and of intervention strategies employed as a result of them must be captured but will not provide sufficient information alone to establish the relative economic efficiency of the alternatives being considered. Using CMA would fail to capture changes in the effectiveness of malaria control strategies based on alternative types of MEWS as compared to malaria control strategies devised without information from a MEWS. For this reason and for the reasons outlined above CMA is not a suitable analytical technique for this study.

## 2.2.2 COST-EFFECTIVENESS ANALYSIS

Cost-effectiveness analysis is used to compare the effects/outcomes and costs of alternative interventions, where outcomes are expressed in terms of physical units as opposed to monetary units (as in CBA) or units of utility (as in CUA). CEA is useful if each intervention method being examined has different costs and successes in achieving a common outcome. The outcome indicators used may be either intermediate or final and the results of a CEA are expressed as a cost-effectiveness ratio (see section 2.2.2.2), which is used to compare the intervention of interest with a suitable alternative.

Drummond *et al.* suggest two conditions, one of both of which must hold, for cost-effectiveness to be the appropriate form of analysis. Firstly, they recommend that there should be one unambiguous objective of the intervention(s), which offers the outcome by which the effectiveness can be assessed for example detecting cases or treating infections. In this situation it may be possible to examine outcomes using either an intermediate measure (for example cases prevented) or a final outcome measure (for example years of life gained). Secondly, they point out that there may be many objectives, which the alternatives achieve to the same extent. In this case the analysis becomes a CMA as, since the outcomes are equivalent in every way, only the cost of performing them need be used to compare efficiency (Drummond et al. 1997) .

### 2.2.2.1 INTERMEDIATE AND FINAL OUTCOME MEASURES

If the results of CEA are required to choose between alternative means of achieving the same intermediate output, e.g. cost per case detected for a specific condition, then the results can be presented and compared in the form of cost per intermediate output.

Intermediate outcome measures are used as a proxy for health improvements achieved by a given intervention based on the assumption that the

measure has a consistent relationship with health improvement (Evans and Hurley 1995). For example if the intermediate outcome measure used is "malaria cases detected and treated" (for example in (Mills 1992)) it is implicitly assumed that detection and treatment of cases is correlated with final health improvements. Furthermore, it is assumed that case detection and treatment will achieve the same unit of health improvement for each case. This is seen as a limitation to the use of intermediate outcome indicators, because it is unlikely that the health improvement gained for each unit of intermediate outcome achieved is the same. For example the health improvement gained by detecting and successfully treating a severe malaria case, which may have been more likely to result in death is larger than the health improvement gained by detecting and treating a simple malaria case, which may have resulted in only a few days of morbidity.

In some situations intermediate outcome measure are extrapolated to give a final outcome measure (see section 3.5 for further discussion of extrapolation and modelling in cost-effectiveness analysis), as long as the link used is adequately established by previous research this is an acceptable technique (Drummond et al. 1997). An example of this can be found in Picard *et al.* concerning a CEA of bed net impregnation alone or combined with chemoprophylaxis to prevent malaria in Gambian children (Picard et al. 1992). The number of deaths and clinical episodes of malaria averted by the interventions was extrapolated from the difference in mortality rates between the protected group and a control group from published data (Greenwood et al. 1988). Estimates were also made of the cost per discounted healthy life years (DHLY) gained by estimating the difference between life expectancy at death and median age at death.

The use of intermediate outcome measures in CEA may not be sufficient to fully capture the impact of the intervention on health, however this limitation should be considered in the light of the availability and accuracy of final outcome indicators,

which may be limited. Moreover, whenever an intermediate outcome measure is being used it is important that it has value and meaning in its own right (Drummond et al. 1997), thus selection of intermediate outcome measures should be carefully considered so that the results of the CEA are relevant and useful. For example Helitzer-Allen and colleagues compared different strategies for increasing malaria chemoprophylaxis compliance in Malawi women (Helitzer-Allen et al. 1993) . They used an intermediate outcome measure - compliance with treatment- because the short-term nature of their analysis did not allow for the use of an outcome measure such as malaria cases prevented or deaths averted. In this case it is likely that the intermediate outcome measure of improved compliance is correlated with health improvements, and given the limitations of short-term research outlined by the authors the use of an intermediate outcome measure is therefore acceptable and useful in this case.

A further criticism of the use of intermediate outcome indicators is that they may only be used to compare interventions which aim to produce or achieve the same output, for example the outcome "malaria cases prevented" can only be used to compare schemes which aim to prevent malaria cases. To overcome this problem, final outcome indicators such as the number or lives saved or years of life saved by interventions may be used, this enables comparison of very different programmes as long as the outcomes can be expressed in such units. CEA can therefore be used to compare radically different health interventions as long as they can be expressed using a common final unit of output, such as cost per life year saved, or cost per disability days avoided.

#### 2.2.2.2 THE COST-EFFECTIVENESS RATIO

The results of a CEA on a particular pair or group of interventions are generally expressed in terms of a cost-effectiveness ratio (C-E ratio). A C-E ratio is the incremental price of obtaining a unit health effect from a given health

intervention when compared with an alternative (Gold et al. 1996). For example consider a situation where the existing malaria control strategy (A), costs $1250 and prevents 300 malaria cases, may be replaced with an alternative strategy (B) which costs $1500, and prevents 400 malaria cases. The C-E ratio of switching from strategy A to B is given by the difference in cost between A and B, divided by the difference in effectiveness between A and B (shown in Box 2-1). Therefore the incremental cost per case prevented using strategy B compared to strategy A is $2.5 per case prevented.

Box 2-1 Cost per unit of Output

| | | |
|---|---|---|
| Strategy A | = | $1250/300 |
| Strategy B | = | $1500/400 |
| C-E Ratio | = | (1500-1250)/(400-300) |
| | = | 250/100 or $2.5 per case prevented |

Alternatively C-E ratios may be expressed in terms of the output achieved per unit of cost, as shown in Box 2-2, where the incremental case prevented per dollar spent using strategy B, compared to strategy A is 0.4 cases prevented per additional dollar spent. This way of expressing the C-E ratio is useful if a budget constraint exists, for example if decision makers know how much they have to spend and want to know what they can expect to gain from spending the money on alternative strategies.

Box 2-2 Output per unit of Cost

| | | |
|---|---|---|
| Strategy A | = | 300/$1250 |
| Strategy B | = | 400/$1500 |
| C-E ratio | = | (400-300)/(1500-1250) |
| | = | 100/250 or 0.4 cases prevented per $ spent |

The C-E ratio is used to decide whether interventions are considered worthwhile either through a comparison with the C-E ratio of other alternatives or using guidelines for the level of cost-effectiveness required for an intervention to be considered desirable. One example of such guidelines is provided in the report of the WHO Ad Hoc Committee on Health Research Relating to Future Intervention Options, based on work by (Jamison et al. 1993, WHO 1996). This suggests that any intervention costing less than US$25 per DALY averted should be considered as "highly attractive" and that those interventions costing less than US$150 per DALY averted should be considered as "attractive" to a low-income country (with *per capita* GNP of less than US$765 in 1995).

Regardless of the manner in which the C-E ratio is used to inform decisions, the value of a unit of health effect is the greatest "price", or incremental C-E ratio, that we would pay for an intervention relative to its less costly alternative (Gold et al. 1996). In other words, the intervention will be considered desirable, if the cost per health effect (for example case prevented, treated or detected) given by the C-E ratio is lower or equal to the value placed on that health effect by society or the decision maker.

Evans and Hurley (Evans and Hurley 1995) point to a possible draw back of using C-E ratios to inform decisions, suggesting that they may not provide sufficient information to make choices. Firstly, they suggest that once the preferred option has been chosen, information must be available to make a judgement regarding the affordability of that intervention, thus the authors call for information on the total costs of the chosen intervention. This may be necessary if a completely new intervention is being considered, however it could also be argued that where different strategies or additional measures are to be adopted or added on to an existing programme, information need only be available on the costs of the changes

or additions. This is because the existing programme may be assumed to be affordable as it is already being implemented.

Secondly, Evans and Hurley argue that even if an intervention is shown to be affordable a question still remains regarding its efficiency compared to all other possible uses of the money necessary to fund it. In order to answer this question information would need to be available on the C-E ratios of all other possible activities both within and outside the health sector, which is clearly an unrealistic demand. In response to this point it can be argued that the use of CEA to assess the efficiency of an intervention necessarily implies that the outcome being pursued is considered desirable and that the point of interest is in identifying the most efficient way of achieving that outcome. If this is not the case and the desirability of the outcome being pursued, compared to other possible outcomes that could be pursued is in question, CBA would be the most appropriate form of analysis to use. This point then becomes a question regarding the choice of the most appropriate economic evaluation technique to use in any particular circumstance rather than a criticism of CEA and the use of C-E ratios.

Thirdly, Evans and Hurley point out that, if the alternative with the lowest C-E ratio is chosen over an alternative which has a higher C-E ratio (because it is more costly but more effective), it may be desirable to pay the extra amount for the additional effectiveness if the funds are available. Fourthly, the authors suggest that the desirability of using the extra funds for this particular intervention compared with all other possibilities would also need to be questioned. This raises questions regarding the total costs of the more effective programme and whether or not the use of these additional resources in this sector would be the most appropriate and efficient use. In answer to these points it could be argued that in the context of malaria control in Africa it is unlikely that the additional resources would be available due to the scarcity of health care resources for even the most basic of health

services. Moreover, even if the resources were available, the arguments levelled against points one and two above would apply to points three and four here. In other words information would only be required on the additional resources required to add to the existing programme and if the desirability of the programme being supplemented is in question, CBA and not CEA should be the analytical tool used to answer the question.

### 2.2.2.3 DISABILITY ADJUSTED LIFE YEARS

The global burden of disease study developed the disability adjusted life year (DALY) as opposed to using the existing quality adjusted life year (QALY) (see section 2.2.3). The DALY has been described as an attempt to move towards a more economic measure of the benefits of improvements in health status, by the introduction of productivity weights, age weights and discounting, however it is admitted that such adjustments are based on arbitrary assumptions with little basis in welfare economic theory (Jack 1999). DALYs are defined as:

"*a composite measure of the burden of each health problem*"

with the DALYs for a given condition being:

"*the sum of years of life lost due to premature mortality and the number of years of life lived with disability, adjusted for the severity of the disability.*" (Murray and Lopez 1996)

Using the DALY framework, the World Development Report 1993 (World Bank 1993) estimated that malaria cost 32 million DALYs per year in Africa alone. This study involved the calculation of DALYs from intermediate outcome measures and therefore constitutes a CEA with DALYs as the final outcome measure and not a modified version of CUA as it has been described by some authors (Evans and Hurley 1995).

The DALY differs from the QALY in a number of ways. Firstly, the utility weights in DALYs were set by a panel of experts as opposed to by relevant groups of individuals, (unlike some of the methods used to derive utility weights for the QALY this method has no basis is economic theory). Secondly, states of disability, as opposed to states of health, were identified and placed into six categories of disability. Thirdly, unlike QALYs, DALYs are age weighted in favour of adults of a productive age. This is based in the assumption that adults are responsible for dependants and so more weight should be given to their health as the health of others may depend up on it (Evans and Hurley 1995).

### 2.2.2.4 REVIEW OF PUBLISHED STUDIES USING COST-EFFECTIVENESS ANALYSIS

Cost-effectiveness analysis is most commonly used in the economic evaluation of malaria control strategies to compare alternative intervention strategies. The results of such analyses are sometimes used by the authors to draw conclusions as to the desirably of malaria control strategies compared to intervention strategies for other common conditions in developing countries (Picard et al. 1993). A critical review of the existing CEA of malaria control strategies in Africa follows below presented by intervention type.

#### 2.2.2.4.1 COST-EFFECTIVENESS ANALYSES OF INSECTICIDE TREATED BEDNETS OR MOSQUITO NETS (ITBN/ITMN)

Picard and colleagues (Picard et al. 1993) compared the cost-effectiveness of insecticide impregnation of existing bednets with a strategy combining impregnation with chemoprophylaxis, for the prevention of malaria mortality and morbidity in Gambian children. To estimate effectiveness the authors used primary data from a large malaria control trial (of which their study was part) to calculate estimates of the number of deaths and episodes averted by each intervention strategy, based on comparison of the rates of each event in the intervention and control groups. The cost data was collected by the authors and included

expenditure and time costs met by both the government and the village level volunteers. Estimates were also made of the resources saved by preventing childhood malaria in terms of saved treatment and caring expenses and averted funeral and mourning costs, although these were considered too small for it to be worthwhile including them in the calculation of cost-effectiveness.

The results of the study (*op cit*) showed that the cost per case averted with the single intervention strategy was higher at US$28.33 than the dual intervention strategy at US$19.41. However, these results were reversed for the cost per death averted, with the dual strategy costing US$257.13 compared to US$187.53 for the single intervention strategy. This was because adding chemoprophylaxis had an effect on morbidity but no effect on mortality. Combining the effects of morbidity and mortality using the measure of cost per DHLY (discounted health life year saved) showed that the single intervention strategy was more cost-effective at a cost of US$7.90 per DHLY saved, compared to US$10.84 for the dual intervention strategy. The additional marginal cost per case prevented by adding chemoprophylaxis was reported to be $10. Sensitivity analysis revealed that the results were sensitive to changes in estimated effectiveness and the price of insecticides. The authors also provided information on the relative cost-effectiveness of the study interventions compared to other intervention trials, pointing out that they ranked alongside immunisation costs per death averted in Indonesia, and were only slightly higher per death averted than immunisation costs per death averted in Kenya. Thus the authors concluded that bed net impregnation was an efficient means of improving the health of rural Gambian children. However, they also warned that the high existing bed net usage in The Gambia and the wide variations in the epidemiology of malaria might limit the transferability of the results to other settings.

The strengths of this study lie in the fact that primary data on cost and effectiveness from a large scale field trial were used. However, limitations exist in

transferring the results of a CEA carried out on a pilot intervention study to the CEA which would result from the wider implementation of the intervention, for example lower levels of intervention efficacy are likely to occur when interventions are scaled up. These may be offset to some extent if economies of scale can be exploited in the larger intervention programme although problems of administrating, managing and supervising a large programme may in turn off-set these effects (Graves 1998).

Aikins *et al.* investigated the net cost-effectiveness of the National Impregnated Bednet Programme (NIBP) launched by The Gambian Ministry of Health and Social Welfare (MoH) in 1992, which followed the success of the study described above (Aikins et al. 1998). The object of the programme was to introduce insecticide treated bednets (ITBN's) into all primary health care villages in the Gambia over a period of 2-3 years. In this study primary data was collected on NIBP costs to the health sector, households and community. The health effects were measured through mortality surveillance, monitoring of primary school attendance and through the estimation of morbidity rates from a case control study. Resources saved in the health service and community were also measured.

The study was unable to detect any significant difference in ill health in schools between the study and control group, however it did demonstrate a significantly larger level of absenteeism due to fever in the non-intervention group. Resource savings were found to be made in treatment costs for hospitalised patients (a saving for the government) and also to the households in terms of reduced expenditure on treatment costs, time saved, postponed funeral costs and expenditure on mosquito coils. Overall the study reported the net cost-effectiveness of the intervention as US$27 per illness averted and US$471 per death averted. Using a discount rate of 6% (double that used in the (Picard et al. 1993) study) the authors found a net cost per discounted life year gained (DLYG) in children age 1-9 years of US$32. Sensitivity analysis revealed that insecticide costs, government

and household treatment costs and the number of cases seeking treatment were all very important variables which could influence the cost-effectiveness of the intervention.

The authors concluded that the NIBP was a highly cost-effective nation-wide approach to reducing child deaths. They also noted that crucial funding decisions must be made by governments in order to choose between higher costs to governments, giving higher effectiveness, or higher costs to households, which may reduce coverage and therefore effectiveness. The study goes a long way to provide information so that well-informed decisions can be made regarding this difficult trade off. The strengths of this study are that primary data on costs and effectiveness was collected, and also that it was a net cost-effectiveness analysis which means that resource savings resulting from the intervention were taken into account. It has limited use for providing information to other countries however, because of the high initial level of bed net usage in the Gambia which means that the intervention was more likely to be accepted and understood by the communities. The inclusion of the cost of purchasing nets in the sensitivity analysis revealed that the cost-effectiveness ratios increased more than 3 fold, even without the inclusion of other factors such as the increased need for community education and sensitisation.

Evans *et al.* used a modelling approach to estimate the cost-effectiveness of insecticide treated mosquito nets (ITMN's) (Evans et al. 1997). They applied the percentage reduction in mortality found in the Gambian study (D'Alessandro et al. 1995) to a cohort of 10000 newborns who would face standard West African death rates and life expectancies without the used of ITMN's. The analysis was designed to be different from the Picard (Picard et al. 1993) and Aikins (Aikins et al. 1998) studies in a number of ways. Firstly, the use of a cohort allowed the effects of the intervention to be followed over a long period of time rather than the one year period used in both of the previous Gambian studies. Secondly, the Evans study

investigated the effects of the intervention on those under 1 year of age, unlike the Gambian studies, which did not include this age group. Thirdly, the use of the standard West African death rates and life expectancies was used in an attempt to more accurately reflect actual non-trial conditions, rather than the lower death rates which were reported in the control groups in both of the previous studies. It was argued that the lower death rates would have been due to ethical reasons which meant that the clinicians involved in a trial would not allow children in the control study to die in the interests of getting accurate results. Cost data was taken from the Picard (Picard et al. 1993) study using the figure quoted for the purchase and distribution of locally produced nets at as well as annual impregnation, annualised over a five year period this gave a cost of purchase and reimpregnation of US$6.24 per year. Effectiveness was measured in terms of the number of lives and DALYs saved by the use of impregnated nets.

In the baseline case (without the intervention) the cohort was followed to death using model West African age specific mortality rates with a life expectancy of 50 years (taken from a UN life table (United Nations 1991)). In the intervention group, it was assumed that nets would be provided for those aged 0-4 years with two children under each net. The nets were assumed to reduce all cause mortality by 25% in children until they reached the age of five [taken from The Gambian study (D'Alessandro et al. 1995)] and life years gained were discounted at 3%. Sensitivity analysis was used to explore the effects of variations in assumptions regarding the number of children sleeping under each net, the target age group, the price of nets, life expectancy, compliance and the impact nets on morbidity. However, no justification was given for the range of values employed in the sensitivity analysis.

The study reported the following results, with 100% compliance in children aged 0-4 the cost per DALY averted was US$9.97, increasing to US$18.88 if the intervention were only offered to children aged 1-4. Reducing compliance to a more

realistic 50% these figures were increased to US$20.21 and US$38.04 respectively. Further sensitivity analysis revealed that if nets were offered to 0-4 year olds, with 50% compliance, but that 3 nets had to be distributed per child (instead of 0.5 in order to ensure that the nets protected children) the cost per DALY saved would be US$121.27. Including the impact of morbidity on the baseline assumptions of 100% compliance, 0-4 years included and 0.5 nets per child, gives a cost of US$8.84 per DALY gained, with 50% compliance this figure increased to US$16.58. The authors concluded that the critical variable in the analysis was the degree of protection against all cause mortality (even though other variables seemed to dramatically affect the results, particularly the number of nets per child which is unrealistic at 0.5 according to other studies for example (Picard et al. 1993)). They also concluded that, for the level of protection found in trials and for most combinations of realistic assumptions, ITMN's represent an excellent use of public health resources in areas where malaria mortality is high.

The study uses secondary data to model the long-term consequences of the intervention programme which highlights the need for on-going evaluation of the effects of programmes. This is particularly important if the impact of interventions may alter over time or have other long term consequences such as delaying the impact of disease to later in life due to a reduction in the acquisition of immunity. A number of studies have suggested that the implementation of ITMNs in high transmission areas may shift the risk of clinical disease to older children due to delayed acquisition of functional immunity (Menendez 1997, Snow and Marsh 1998, Snow et al. 1997). However the resulting impact of this on intervention effectiveness is subject to debate. Snow *et al.* suggest that a reduction in transmission could in the long term result in subsequent increased mortality (Snow et al. 1997). Others argue that the overall gain may remain unchanged (Trape and

Rogier 1996) or that reducing exposure will always be beneficial because of the indirect impacts of malaria on mortality (Molineux 1997).

Two studies have investigated the impact of possible 'rebound mortality' on the cost-effectiveness of ITBN's (Guyatt et al. 1999) and (Coleman et al. 1999). The first study used a modified version of the methodology employed in the Evans study (Evans et al. 1997) described above, considering two alternative delivery scenarios, (i) that the intervention was delivered to 0-9 year olds and (ii) that it was delivered to 0-4 year olds. Effectiveness was defined as the discounted years of life lost (YLL) averted by the intervention and calculated by comparing the number of survivors with and without the intervention over each year of the cohorts life time. It was assumed that mortality would be reduced by 0.18 and that 65% compliance would be achieved. The mean annual cost per child protected was taken as US$8.06 assuming that all nets were re-impregnated and that the number of nets per child was 2.96 (cited source: personal communication with P. Coleman, C. Goodman and A. Mills).

The impact of the intervention was evaluated by examining its effect on a cohort of 10000 new-borns. The baseline situation (without the intervention) was calculated from a standard life table (United Nations 1991) as in the (Evans et al. 1997) above. The impact of the intervention was calculated by reducing the mortality in the age groups targeted and by including the impact of malaria specific shifted mortality, which was calculated from the rates of age specific incidence in two transmission settings (low to moderate and high). Sensitivity analysis was used to explore the impact of variations in the number of nets per child, reduction in all cause mortality, malaria attributable mortality and malaria specific shifted mortality. Optimisation analysis was also carried out in order to identify situations in which the cost per year of life lost averted by the intervention was below US$25.

The study results revealed that key parameters affecting the cost-effectiveness of the intervention were the reduction in all cause mortality achieved; the age group receiving the intervention; the timing and extent of the changes in malaria specific mortality risk caused by reducing the force of infection and the proportion of mortality attributable to malaria. Certain scenarios resulted in the overall number of survivors with the intervention being lower than the number without it. The crucial parameter was found to be the speed at which the increased mortality risk develops, with an immediate increase in mortality risk causing the intervention to cost more lives than it saved under certain scenarios. At one extreme without shifted mortality risk the intervention could cost as little as US$25-30 per YLL averted. Conversely with immediate shifted mortality risk the intervention could cost more lives than it saved. With a two year delay in mortality risk the intervention was still found to save lives and was considered to be cost-effective for most assumptions about the other parameters.

Due to the paucity of existing information on the epidemiology of malaria under different transmission settings and the impact of certain interventions on the acquisition of immunity the study was unable to draw firm conclusions regarding the cost-effectiveness of ITBN's given the risk of delayed immune acquisition. However, it did pinpoint the most important variable in this problem, which was found to be the timing of the delayed immune acquisition in other words at what point the lack of acquired immunity causes an increase in mortality risk.

A similar study to the one described above was carried out by Coleman and colleagues (Coleman et al. 1999) using effectiveness, cost and behavioural (compliance) parameters drawn from the literature. This study differed from the Guyatt *et al.* (1999) study in that it used range, rather than point estimates, and a Monte Carlo simulation (see section 3.2 for a description of Monte Carlo simulation) in order to calculate cost-effectiveness. It also used the DALY measure to include

the impact of morbidity as well as mortality. The rebound rate was varied from 0% upwards and its effects on different age ranges were considered.

The results showed that without rebound mortality the cost-effectiveness of ITBN's would be considered attractive (less than US$150 per DALY averted) in over 95% of the iterations run in the Monte Carlo simulation. If rebound mortality occurred in the 5-9 age range the intervention would be likely (in 95% of simulations) to be cost-effective up to a rebound rate of 39% compared to baseline morbidity and mortality levels. The age range over which the rebound effect occurred was found to be a critical determinant of the threshold rebound rate at which it was not possible to be reasonably certain that the intervention remained cost-effective over time. This conclusion is in line with the findings of Guyatt and colleagues (Guyatt et al. 1999) and points to the importance of long term monitoring and evaluation of malaria control interventions.

The use of Monte Carlo simulation represents an effective means of combining a variety of data into a model in a meaningful and flexible way. A major strength of both the Guyatt *et al.* and Coleman *et al.* studies is that they have used different methodologies, but have identified the same variable as being the most important in terms of its effect on the likely cost-effectiveness of ITBN's in the event of rebound mortality. These results strengthen calls for further research into the long-term impact of the intervention in areas of high transmission where the normal process of immunity acquisition may be disturbed by ITBN's or any other intervention which may affect the acquisition of immunity.

A further study which used the results from The Gambian study is that of (Graves 1998) who used a decision analysis model to compare the cost-effectiveness of bednet impregnation (with permethrin) with a vaccination strategy for a cohort of children born in The Gambia in 1990. Cost data for the impregnation strategy was taken from Picard *et al.* (Picard et al. 1993) (excluding village costs

since Evans' study perspective was that of the government). Cost data for the vaccination strategy was derived from a study of hepatitis-B vaccine in The Gambia (Hall et al. 1993) which was used to estimate the cost of adding the malaria vaccination to the expanded programme of immunisation. Estimates of the efficacy of both strategies were derived from published studies from the Gambia for both reductions in the risk of clinical attacks and malaria deaths. Effectiveness estimates were derived from estimates of the predicted number of cases and deaths in the cohort without either intervention (taken form published studies from The Gambia), which were compared to estimates of the number of cases and deaths averted with each intervention.

The results showed that the cost per death averted for the net impregnation strategy was US$711, compared to US$252 for the vaccination strategy. The cost per malaria attack averted was US$12.75 for net impregnation, compared to only US$3.71 for the vaccine strategy. However, the absolute numbers of attacks and deaths averted with the bednet impregnation strategy were higher than with the vaccine strategy, 69415 attacks and 1537 deaths averted with impregnation compared to 50502 attacks and 743 deaths averted with the vaccine strategy. Sensitivity analysis revealed that the cost per malaria attack averted was always lower for the vaccine strategy, with all levels of efficacy tested, however at efficacies of 10% and 63% against death for the vaccine and impregnation strategies respectively, the nets became more cost-effective in terms of cost per death averted. The results were also sensitive to the cost of both the vaccine and insecticide, however even at the highest vaccine cost and lowest insecticide costs tested the vaccine was still more cost-effective for both attacks and deaths averted.

The main conclusions drawn from the study were that up to a vaccine efficacy of 48%, bednet impregnation would prevent more attacks and deaths, however the cost per attack and death prevented with the impregnation strategy was

higher. The author suggests therefore that although bednet impregnation should be supported currently, care should be taken so that when a vaccine becomes available it is possible to switch to the alternate strategy. Graves also suggests that due to the lower cost as a proportion of The Gambian annual health budget, vaccines (2.8%) are much more affordable than bednet impregnation (16.4%). This difference would be increased dramatically in a country where bednet usage was not widespread so that the cost of nets would have to be included in the programme costs for the impregnation strategy.

Although the study used secondary data, care was taken to ensure that all data was from the relevant country and the assumptions were clearly stated. The use of a decision analysis model allows the question to be structured clearly and also gives flexibility to the analysis. The model illustrated could be adapted for other country studies as long as the relevant epidemiological and demographic data was available along with good quality economic data.

Goodman *et al.* (Goodman et al. 2000, Goodman et al. 1999) used mathematical models to provide information on the cost-effectiveness of a range of malaria control interventions in sub-Saharan Africa, focussing on interventions designed to prevent malaria in childhood and to improve treatment. The preventive interventions examined included insecticide treated nets (ITMNs), residual spraying of houses, chemoprophylaxis for children, and chemoprophylaxis for pregnant women using one of two alternative treatment regimens. The interventions to improve malaria treatment examined were improved compliance, improved availability of second line and third line drugs and changes in the first line drug. In order to follow the categorisation of cost-effectiveness analyses by intervention type in this literature review, a brief description of the methodology used in the Goodman *et al.* study will now be given, followed by the studies results for ITMNs. The results

for the other interventions examined by Goodman *et al.* will be given in the relevant sections of this thesis (below).

In the Goodman *et al.* study (*op cit.*) the baseline population for the analysis was described using standard life tables, with baseline levels of all-cause and malaria mortality, and malaria morbidity being estimated from a number of sources. The efficacy of interventions was established from an extensive review of both published and unpublished literature, with the results being adjusted to represent actual effectiveness rather than efficacy. Cost estimates for each intervention were calculated using the ingredients approach (Phillips et al. 1993) and a variety of published and unpublished data. Deaths and morbidity/disability averted due to each intervention were then calculated for different age classes and converted into YLLs (years of life lost) and YLDs (years of life lived with disability) averted per child. These were then converted into DALYs averted per child. Probabilistic sensitivity analysis was used such that ranges, rather than point estimates were assigned to the value of uncertain parameters. The cost-effectiveness ratios of each intervention were calculated using a Monte Carlo simulation where the value of input variables is selected at random from the specified range and a large number of iterations are run until the results show convergence.

Two possible scenarios for ITMNs were considered firstly, net delivery and insecticide treatment and secondly, insecticide treatment of existing nets. Two types of pyrethroid insecticide were also considered; permethrin (with a 6 month effectiveness thus requiring two re-treatments per year, depending on the length of transmission season) and deltamethrin (with a 1 year effectiveness thus requiring annual re-treatment). The intervention also included staff and community training, procurement and transport of insecticide and nets, and initial and subsequent re-treatment of nets. The effectiveness of ITMNs was estimated from a published meta-analysis (Lengeler 1998), which estimated a 19% reduction in all cause

mortality and a 46% reduction in clinical episodes. The estimates for the input parameters for the cost of the programmes were drawn from a number of published (Aikins 1995, Binka et al. 1996, Picard et al. 1993, Some 1998) and unpublished sources, with estimates of between 2 and 3.9 nets per child being considered.

The study results (Goodman et al. 1999) showed that in a very-low-income country the cost-effectiveness range for insecticide treatment of existing nets was between US$4 and US$10 per DALY averted. The cost-effectiveness ratio for provision and treatment of nets ranged between US$19 and US$85 per DALY averted. If two treatments per year were required the ratios increased to between US$9-23 and US$25-96 respectively.

The strengths of the Goodman *et al.* analysis lie in its ability to combine the existing data on the costs and effectiveness of providing ITMNs in sub-Saharan Africa. However the accuracy of the C-E ratios reported depends upon the quality of the data which has been used to estimate them. In the case of ITMNs there are a relatively large number of studies available from which to derive cost and effectiveness information, however most of these are from the same country (The Gambia) which may limit applicability to other situations. On one hand, the range estimates given in this study may be preferable to the point estimates and sensitivity analysis reported in other studies. This is because they may reduce the risk of inappropriate estimates of cost-effectiveness being applied to very diverse situations without regard for the implications of the results of sensitivity analyses reported or the variety of epidemiological and economic situations in sub-Saharan Africa. However, the range estimates may make decisions difficult if there is significant overlap in the ranges of C-E ratios reported for alternative interventions. It may also have been beneficial to present the results of the study in terms of cost per intermediate outcome (for example cost per case or death averted) as well as in

terms of cost per DALY averted, to facilitate comparison with other studies which do not use the DALY measure.

There exists a relatively large number of good quality CEA on ITMNs for malaria control in Africa, compared to the number available for other interventions. However, the fact that most of the studies come from the same country is a limitation, particularly since the level of existing bednet usage in The Gambia (58%) is unusual compared to other countries (Ghana < 10%, low rates in Kenya, Tanzania and Malawi) (Goodman et al. 2000). The studies on the cost-effectiveness of ITMNs have also been limited to areas of high transmission, which may make drawing conclusions on their cost-effectiveness in other epidemiological settings difficult. (Mills 1998) points out a number of reasons as to why it may be difficult to generalise results of cost-effectiveness analysis across settings including, differences in existing infrastructure, variability of input costs, differences in the scale of programmes, and the acceptability of interventions in different settings. Bednets may also impact on other vector borne diseases for example on lymphatic filariasis in West Africa and leishmaniasis in Sudan, none of the studies on the cost-effectiveness of ITMN's for malaria control attempt to quantify the additional benefits of controlling other diseases.

Overall the conclusions from the above studies suggest that ITMNs represent an efficient use of resources and can be effective at preventing mortality and morbidity in children in Africa. Concerns regarding the possible rebound mortality effects of ITMNs have been addressed using a modelling approach in two studies (Coleman et al. 1999, Guyatt et al. 1999). Both studies concluded that the crucial factor affecting the cost-effectiveness of ITMNs in the event of rebound mortality, is the timing of the effect or in other words the age group in which the effects occurred. Given that evidence has also been presented that the effects of rebound mortality are insignificant relative to all cause mortality benefits, more data

is required on this factor before ITMNs can be fully endorsed as a cost-effective intervention. In addition, the study by Graves (Graves 1998) suggested that if a vaccine with a high enough level of efficacy becomes available it is likely to be far more cost-effective than ITMN. Moreover, concerns have been raised about the affordability of the intervention in terms of the health budgets of African countries (Aikins et al. 1998, Evans et al. 1997, Goodman et al. 2000, Goodman et al. 1999, Graves 1998, Mills 1998) and it has been recognised that extensive external assistance is likely to be required in order to fund wide scale implementation of ITMNs in African countries (Goodman et al. 1999).

#### 2.2.2.4.2 COST-EFFECTIVENESS OF RESIDUAL SPRAYING

Studies on the cost-effectiveness of residual spraying in Africa are extremely limited and are rarely done well (Phillips et al. 1993). Those which do exist tend to be from studies over 15 years old which may make them out dated as a result of changes in insecticide cost and resistance (Bruce-Chwatt and Archibald 1959, El Gaddal et al. 1985, Hedman et al. 1979, Molineaux and Grammicia 1980, Walsh and Warren 1979). Mills used these (and other) studies to calculate C-E ratios using the outcome indicators of annual cost per person protected, cost per case prevented and/or cost per death averted (Mills 1991). The results from Mills' reanalysis for those studies including vector control or spraying in Africa are reported in Table 2-2 and selected studies are discussed below.

The study by Hedman *et al.* examined the effectiveness of a malaria control programme, carried out by the mine company including indoor spraying, chemoprophylaxis and anti-larval measures in a mining town, Yekepa, in Northern Liberia (Hedman et al. 1979). The spleen rate in the town was compared to control groups from the surrounding area and was considerably lower, 10.7% compared to 95%, thus the authors concluded that the interventions resulted in reducing the level of transmission to hypoendemic as opposed to holoendemic. A significant

difference was also found between the enlarged spleen rates and parasite rates estimated in Yekepa (1.8 and 12.6% respectively) and the surrounding area (2.7 and 67% respectively). The costs to the company were reported broken down into vector control costs (manpower, chemicals and equipment) and chemoprophylaxis costs (drugs and drug administration). These costs were used by the authors to calculate a cost per person protected of US$4-5 including all control costs. The incremental costs and effects of each intervention were not estimated separately so it is not possible to estimate the cost-effectiveness of the household spraying alone, however, Mills estimated a cost per person protected by the control programme of US$6.64 and a cost per case prevented of US$12.30 (in 1984 US$). Hammer recalculated these results and came up with values of US$14 per case prevented and US$143 per discounted QALY saved (US$1987) (Hammer 1993).

This study is unlikely to be representative of the cost-effectiveness of household spraying programmes in Africa since it was carried out by a mining company who are likely to have had considerably more resources at their disposal than many government run programmes. The combination of interventions also makes it difficult to separate the effectiveness of the household spray component of the programme moreover, the style of dwellings in the town was reported to be "western" making comparison with effectiveness of spray programmes targeting more traditional style dwellings.

Walsh and Warren cited references reporting that in tropical regions and savannas of Africa, twice yearly spraying had decreased the crude death rate by approximately 40% and infant mortality by 50% (Kousnetsov 1977, Payne et al. 1976, Payne et al. 1978). They used a WHO estimate of the average cost for house-to-house spraying with DDT of US$2 per capita annually (Anonymous 1974), to estimate the cost per adult and infant death averted (US$250) and the cost per infant death averted (US$600). Mills re-calculated these estimates to estimate the

annual cost per person protected with vector control (US$2.97) and the cost per death averted (US$892.20) (both in 1984 US$). Hammer recalculated these estimates and suggested a cost of US$990 per death averted and US$34 per discounted QALY saved (in 1987 US$) (Hammer 1993) . These estimates are at best crude and take no account of the variety of epidemiological settings in which vector control measures could be used.

The Garki project in a highly endemic area of Nigeria attempted to estimate the effects of house spraying alone or in combination with mass drug administration. Although cost-effectiveness ratios were not calculated, information was provided on the cost of the Garki project (Molineaux and Grammicia 1980). Mills estimated that the cost per case prevented by case detection and treatment and vector control was US$233.15 (in 1985 US$) (Mills 1991). Hammer calculated that the costs per discounted QALY saved and per case prevented using vector control and drug therapy during the Garki project were US$1500-2650 and US$259 respectively (in US$1987) (Hammer 1993).

El Gaddel *et al.* (1985) described the malaria control problems in an irrigated area of the Sudan. Efforts to control the disease using house spraying were successful, but the fast development of insecticide resistance in the early 1980's forced the authorities to switch from the use of malathion at a cost of US$0.50 per capita, to fenitrothion, increasing the cost to US$0.60 per capita. In spite of the increasing costs, household spraying was still a very effective means of reducing malaria prevalence. Unfortunately specific cost-effectiveness ratios were not reported in the study however, Mills recalculated the figures presented in the study to produce an estimate of US$0.75 per person protected in 1985 US$ (Mills 1991).

Goodman *et al.* considered a government-run residual spray programme with locally hired and trained staff employed to spray houses in their area (Goodman et al. 2000). The costs of training staff, sensitisation of the community, procurement

and transport of insecticide and spraying of houses was included in the analysis and four separate insecticides were considered. The insecticides considered were DDT, malathion, deltamethrin and lambda-cyhalothrin since these were all found to be used in sub-Saharan Africa (WHO 1994).

Due to the paucity and dated nature of data on the effectiveness of spraying on health outcomes (only three exist from the 1950s and 1960s (Molineaux 1985)) Goodman *et al.* also considered a scenario based on the assumption that the effectiveness of residual spraying was equivalent to that of ITMNs. In the scenario based on the published studies a reduction in infant mortality of between 41% and 59% was assumed in the model (Molineaux 1985). The scenario based on the assumption of equal effectiveness of residual spraying and bednets was based on a study by Curtis *et al.* which found no difference in the rate of re-infection after parasite clearance with spraying or ITMNs (Curtis et al. 1998) . Therefore the results of the Cochrane review meta-analysis of ITMNs was used, so that children aged 1-59 months living in sprayed houses were assumed to face a reduction in all cause mortality rates of 0.19% and a reduction in rates of neurological sequelae and anaemia of 0.46%. Insecticides were assumed to have equal effectiveness and one spray round per year was assumed for seasonal transmission areas and two rounds for areas with perennial transmission. Effectiveness estimates were adjusted for compliance which was estimated to be between 70-90%.

Cost data was collected from a number of published studies and converted into US$1995. The cost per house sprayed ranged between US$3.71-$8.93 and the cost per capita was estimated to lie between US$0.24 and US$6.70 (Curtis et al. 1998, El Gaddal et al. 1985, Hedman et al. 1979, Julvez 1990, Songane 1997, Wernsdorfer and Wernsdorfer 1988, Wery and Coosemans 1993). The quality and consistency of the reported data was not considered to be reliable therefore, the costs of spraying were estimated using the ingredients approach using data from

available sources and expert opinion. Using the ingredients approach the mean cost per child was found to be US$7.33 per child in very low income countries with one spray round per year and US$14.65 with two rounds per year.

The scenario where the reduction in infant mortality was taken from trials (scenario 1) found the mean C-E ratio for one spray round per year (seasonal transmission) in a very low income country to be US$16-29 per DALY averted, rising to US$32-58 if two spray rounds are required (perennial transmission). In scenario 2 (effectiveness assumed to be equal to ITMNs) the cost per DALY averted in an area of seasonal transmission was estimated to be between US$18-36, rising to US$35-72 if two rounds were required. The C-E ratios for scenario 2 are slightly higher than for scenario 1 and the need for two spray-rounds doubles the C-E ratio. The analysis for middle income countries produced very similar results to the low-income country analysis however the C-E ratios for higher income countries were considerably higher. In scenario 1 with one spray round per year the C-E ratio was between US$60-120 per DALY averted, with two spray rounds per year this was doubled. In scenario 2 the C-E ratio with one round per year was US$113-242 in higher income countries, doubled if two rounds were needed.

The authors concluded that with one round per year spraying would be considered an attractive option for all income levels (apart from scenario two which would not be attractive in higher income countries), however the C-E were not sufficiently low for it to be considered a highly attractive option. If two rounds per year were necessary spraying would be considered attractive in low and middle-income countries but not in higher income countries. The authors warned that the results should be interpreted with caution due to the lack of up to date information on the effectiveness of residual spraying and problems of interpreting results to areas with different transmission intensities and lengths of transmission season.

Generally studies on the cost-effectiveness of residual spraying are very poor and out of date. The attempt at modelling cost-effectiveness carried out by Goodman *et al.* is severely hampered by a lack of adequate effectiveness data, particularly relating to specific epidemiological conditions. This analysis also concentrated solely on children protected by the intervention, which will underestimate the effects of spraying on the adult population, particularly in areas without a high degree of adult immunity, for example epidemic prone areas.

Spraying is recommended and used to control epidemic outbreaks, particularly in Southern Africa (Nájera and Teklehaimanot 1998, WHO 2001) and no information is available on the cost-effectiveness of the intervention in such circumstances. Moreover it is possible that the use of this intervention in such circumstances may be carried out too late to achieve the effectiveness reported in any of the field trails carried out in the past (Nájera 1998) and at a considerably higher cost due to additional costs of emergency activities. The cost-effectiveness of interventions under such circumstances is in urgent need of being assessed, this thesis sets out to address this gap in the existing literature on the economic efficiency of malaria control interventions.

#### 2.2.2.4.3 COST-EFFECTIVENESS ANALYSES OF CHEMOPROPHYLAXIS OR INTERMITTENT TREATMENT FOR PREGNANT WOMEN

A study by Heymann and colleagues examined the impact of patient compliance and drug resistance on the cost per malaria case prevented using antenatal chloroquine chemoprophylaxis in Malawi (Heymann et al. 1990). The study only included the cost of drugs (chloroquine); other costs such as service delivery costs were excluded since it was argued that these expenses would be expected to continue even if chloroquine were not provided. The result of the analysis are therefore not strictly cost-effectiveness ratios since they do not fully

capture the economic cost of providing the intervention, however they are of interest and so will be reported here.

The protective efficacy of the drug was calculated from the differences in attack rates in a group of women tested for chloroquine ingestion and *P. falciparum* infection. Drug costs were estimated using data on the cost of chloroquine (Malawi Central Pharmacy 1986), multiplied by the dose required for women by trimester of pregnancy. The authors reported that the cost per attack prevented with an estimated protective efficacy against *P. falciparum* infection of 8%, was US$10.87. If compliance could be increased from the 36% found in the study, to 80% the authors estimated the cost per infection prevented would fall to US$1.09. Another alternative would be to provide chloroquine to women in their first and second pregnancies only; in this case the cost per infection prevented would decrease to US$4.18.

The study results cannot be compared to other CEA since they fail to take into account important cost factors such as staff time and health education requirements of the programme. However, it does identify key variables, namely compliance and the target group receiving the chemoprophylaxis (by pregnancy number), which may affect the cost-effectiveness of the intervention.

A study by Helitzer-Allen and colleagues went on to further investigate the cost-effectiveness of antenatal malaria chemoprophylaxis in Malawi, with particular reference to the impact of measures designed to improve compliance on cost-effectiveness (Helitzer-Allen et al. 1993). Three alternative interventions for improving compliance were examined and compared to the original programme of chloroquine distribution combined with a health education message. Firstly, distribution of chloroquine combined with a revised health education message, secondly, distribution of a non-bitter tasting chloroquine tablet with the original

health education message and finally the distribution of a non-bitter tasting chloroquine tablet with a revised education message were examined.

The study was carried out in the period after the rainy season when malaria transmission is highest. Compliance was measured by urine specimens and effectiveness was defined as the level of compliance achieved by each alternative. Only the incremental costs of each intervention were included. These were calculated from drug cost statistics multiplied by drug requirements by trimester of pregnancy with the addition, where appropriate, of the costs of the additional health education message materials and training. Cost-effectiveness for each strategy was calculated by dividing the cost of the intervention by the estimated maximum number of compliant women assuming that the intervention was applied to the number of pregnant women in Malawi in 1988.

The results showed that the current programme which achieved an estimated 25% compliance, would have a cost per compliant woman of US$1.67. Chloroquine and a new health education message were estimated to raise compliance to 57% at a cost of US$1.27 per compliant woman. Non-bitter chloroquine and the old health education message were estimated to improve compliance to 87% at a cost of US$1.20 per compliant woman. Finally, non-bitter chloroquine and a new health education message were estimated to improve compliance to 91% with an estimated cost of US$1.48 per compliant woman.

All of the alternative interventions tested were more cost-effective than the existing strategy, however the introduction of both a new health education message and the non-bitter chloroquine was seen as redundant since it was less cost-effective than the other alternatives. Of the two most cost-effective interventions, non-bitter chloroquine and the original health education message (US$1.20 per compliant woman) was slightly more cost-effective than chloroquine and a new message (US$1.27). However, concerns were raised about the ability to maintain

the impact of the new health education message and the additional cost of providing non-bitter chloroquine.

The author's point out that the cost-effectiveness analysis carried out does not answer the resource allocation decisions faced by decision-makers but it does add to their "analytical tool-kit". The results of this study may have allowed a more informed policy decision to be made and raised awareness of the trade-off's involved in such resource allocation questions. The results of the study cannot be compared to the results from other CEA since they are expressed in terms of intermediate outputs, however this was relevant to the specific question that the research set out to answer given the constraints of time mentioned by the authors.

Schultz *et al.* examined the cost-effectiveness of three different drug regimens for antenatal chemoprophylaxis in Malawi for the prevention of low birth weight deliveries (Schultz et al. 1995) and infant deaths (Schultz et al. 1996). In both papers the authors used a decision analysis model to follow a hypothetical cohort of 10000 women in their first or second pregnancy. The three regimens compared (in both studies) were chloroquine (CQ) treatment (25mg/kg) followed by weekly chloroquine (300mg) (CQ/CQ), sulfadoxine-pyrimethamine (SP) treatment followed by weekly CQ (300mg) (CQ/SP) and SP treatment during the second trimester, repeated at the beginning of the third trimester (SP/SP). The variables included in the model were choice of regimen, and the probabilities of first attendance at antenatal clinic (ANC), second attendance at ANC, compliance with treatment, placental malaria, low birth weight deliveries and, in the 1996 study, infant death. The probabilities for each of these variables were obtained from studies carried out in Malawi over the period 1987-1992. Cost data was included on the drug costs for each regimen only; no other costs were included in the analysis. Univariate and multivariate sensitivity analyses were carried out on the model in both studies.

In the 1995 study the cost per low birth weight delivery prevented for each regimen was found to be US$113.05 for CQ/CQ, US$62.01 for SP/CQ and US$9.66 for SP/SP. Univariate and multivariate sensitivity analysis revealed that SP/SP remained the most cost-effective alternative in all circumstances tested.

In the 1996 study the cost per infant death prevented of each regimen was found to be US$542 for the CQ/CQ regimen, US$481 for the SP/CQ regimen and US$75 for the SP/SP regimen. Sensitivity analysis revealed that the price of anti-malarials, duration of CQ prophylaxis, drug efficacy and compliance were the most important variables in terms of their effect on the results. The univariate and multivariate sensitivity analyses carried out also revealed that SP/SP was the most cost-effective alternative under the range of parameters tested, consistently having a C-E ratio of between US$75-91 per infant death averted.

Both of these studies are limited by the fact that only drug costs are included in the cost estimates. No estimation of the costs to the women of attending ANC has been made for the alternative regimens, this is important since it may have an impact on compliance and therefore cost-effectiveness with each regimen if one requires more ANC attendance than the other does. There may be justification for not including these costs since women attending ANC would incur them regardless of whether or not chemoprophylaxis is provided (Goodman et al. 2000). The neglect of the cost of staff time ignores the opportunity cost of spending time on these interventions as opposed to alternative activities. The potential long-term implications for accelerating the development of parasite resistance to SP have also been neglected in the analysis and discussion provided in both studies. In spite of these limitations the results of the studies are reported to have been responsible for a policy change from CQ/CQ to SP/SP in Malawi. Although limited in some ways, the studies provided some much-needed information on the economic

considerations involved in decisions regarding choice of drug regimen for antenatal anti-malarials in Malawi.

Goodman *et al.* used a modelling approach to examine the cost-effectiveness of anti-malaria treatment or chemoprophylaxis in first pregnancy (primagravidae) (Goodman et al. 2000). They constructed a normal distribution for birth weight in Africa without prophylaxis or treatment using the available data from a variety of countries (Cot et al. 1995, Fleming et al. 1986, Greenwood et al. 1989, Menendez et al. 1994) and a model of birth weight specific mortality in Africa from available (more limited) sources (Greenwood et al. 1992, McDermott et al. 1996). The impact of chemoprophylaxis or intermittent treatment was assumed to shift the birth weight frequency distribution, increasing the mean birth weight in relation to the situation without either intervention and therefore reducing mortality according to the model of birth weight specific mortality. The magnitude of the shift in birth weight was taken from a Cochrane meta-analysis of malaria prevention in pregnancy (Gülmezoglu and Garner 1998), corrected for drug resistance, probability of first and second clinic attendance, compliance and the still birth rate. The model was then used to calculate the reduction in the neo natal mortality rate resulting from the interventions. This was in turn used to calculate the number of DALYs averted per primagravidae treated in terms of years of life lost (morbidity was not included). The DALYs averted per primagravidae were 0.09 for CQ in a very-low -income country and 0.14 for SP in a very-low-income country, assuming zero drug resistance.

Cost data was collected on drug costs, incremental staff time, training and health education material costs from various sources. Patient costs were not included since it was assumed that these would have been incurred with visits to the ANC regardless of any treatment given.

The incremental cost-effectiveness ratio (C-E ratio) of each intervention was defined as cost per primagravidae divided by the number of DALYs averted per

primagravidae. In the "no resistance" scenario the mean C-E ratio of intervention with SP was US$12 with 90% of all iterations falling between $4-$26, for CQ these figures were US$21 with 90% of all iterations falling between $7-47. Sensitivity analysis revealed that important variables were the increase in birthweight achieved by each intervention and the standard deviation of birthweight in the unprotected population. The number of ANC visits per clinic per year was also important as this affected the economies of scale achieved by the project (by reducing the proportion of fixed costs attributed to each woman).

When drug resistance was included in the model the effectiveness of the interventions was reduced causing the C-E ratio to increase, however at levels of resistance lower than 69% CQ still had a C-E ratio of less than $150 per DALY averted. In the case of SP the C-E ratio remained below US$150 for all levels of drug resistance below 83%. The authors suggest that because resistance to CQ is generally higher than for SP, SP is likely to be more cost-effective in many settings. However, they go on to suggest that if CQ is the drug of choice, measures to improve compliance (for example coating the tablets with sugar, pre-packaging doses and improved health education) may improve its cost-effectiveness in certain settings.

The results of this model are subject to the quality of the data used to formulate it, which as the author's point out, is limited. They also note that it was not possible to analyse the variation in cost-effectiveness by length of transmission season. This may be important in interpreting the results of the study for use in different epidemiological settings. Although the analysis assumes that the intervention would only be offered to primagravidae the authors point out that this may be impractical in reality. The authors investigated the possible impact of HIV prevalence on the cost-effectiveness of the intervention, which may necessitate additional drugs and found that using the SP regimen this would still be an attractive

intervention. Although the effectiveness of the intervention depends upon the level of ANC attendance and clinic coverage in a country, the authors suggest that the use of such measures to reduce malaria risk in pregnancy would be affordable, requiring less than 1% of the annual health budget of a very-low-income country.

Most of the studies on the cost-effectiveness of anti malaria measures for pregnant women are from Malawi and tend to exclude important aspects of cost. The Goodman (Goodman et al. 2000) analysis includes estimates of all incremental costs, however the data on which the analysis is based is still limited. In spite of these limitations the prevention of malaria in pregnancy does seem to represent a cost-effective health intervention, however information on its cost-effectiveness in different settings is lacking. In particular where transmission season length varies and the level of ANC attendance is lower.

#### 2.2.2.4.4 COST-EFFECTIVENESS OF CHEMOPROPHYLAXIS IN INFANTS

A study carried out in The Gambia estimated the cost-effectiveness of chemoprophylaxis with Maloprim® distributed by village volunteers in preventing death from malaria in children under five (Picard et al. 1992). Cost data was gathered from the actual expenses incurred during the trail, including costs of time and money to the public authorities and village volunteers. The estimates of effectiveness were made using the reduction in mortality achieved in the study population compared to a control (Greenwood et al. 1988). The cost per child protected per season was reported to be US$2.84 (in 1990 US$), and the cost per childhood death averted was US$143. The authors concluded that in areas of holoendemic malaria, chemoprophylaxis could be an economically efficient means of controlling childhood malaria that is comparable with other measures to prevent deaths from childhood diseases. The study results were combined with further results from The Gambian study to compare the cost-effectiveness of insecticide treatment of nets alone to a strategy combining chemoprophylaxis and insecticide

treatment of nets. This study was discussed in detail above in the section on the cost-effectiveness of ITMNs, however the main conclusions were that the cost per death averted was higher with the combined strategy, but the cost per clinical episode averted was higher with the insecticide treatment strategy.

A study in Tanzania estimated the cost-effectiveness of iron supplementation and malaria chemoprophylaxis in the prevention of anaemia and malaria among infants (Alonso González et al. 2000). The study compared the cost-effectiveness of providing iron supplementation alone, malaria chemoprophylaxis (with Deltaprim) alone and a combined strategy, to routine case management. The efficacy of each alternative was assessed against a placebo group and then used to calculate the number of years of life lost (YLLs), years lived with disability (YLDs) and DALYs saved for each strategy. Cost data was gathered from relevant sources to reflect the cost of each strategy to health care providers. Data was also gathered to allow the calculation of treatment costs for episodes of each condition, which was used to calculate net cost-effectiveness ratios for each strategy compared to the case management strategy. Household treatment costs were also collected through a survey of mothers of sick children. Univariate and bivariate sensitivity analysis was carried out on the results.

The results showed that the dual strategy was the most cost-effective strategy for both conditions. The cost (in 1996 US$) per DALY averted for Deltaprim and iron was US$7.9 for anaemia and US$9.7 for malaria from the health care provider perspective. These costs increased slightly to US$8.9 and US$11.1 respectively from the social perspective. Deltaprim chemoprophylaxis alone cost US$10.2 (health care provider perspective) or US$12.2 (social perspective) per DALY averted and so was less cost-effective than the joint strategy for the prevention of malaria. Sensitivity analysis upheld the conclusions that preventive measures were more cost-effective than case management alone, although the

cost-effectiveness ratios were very sensitive to effectiveness estimates used, however even with low effectiveness estimates the joint strategy remained below US$25 per DALY gained.

Net cost-effectiveness ratios were reported in the Alonso González *et al.* study (the cost saving from treatment costs not incurred as a result of successful prevention are included). This means that it cannot be easily compared to other studies which do not take this into account, however the authors point out that estimates of the cost per child year protected reported in their study is similar to that of other studies (Picard et al. 1993, Picard et al. 1992). They conclude that the combination of malaria chemoprophylaxis and iron supplementation is both cost-effective and cost saving in Tanzania, and suggest that such strategies should perform well in areas with a similar malaria morbidity load and health system structure as their study area.

The strengths of this study are that first-hand data on costs and effectiveness data from a randomised placebo-controlled clinical trial were used, giving it internal validity (see section 3.3). The use of net cost-effectiveness analysis illustrates the importance of the expense averted through effective preventive interventions, however it is possible that these cost savings would not actually be realised as a reduction in total health care expenditure of governments. This is because work time or resources freed up by malaria prevention (e.g. hospital beds) would still incur costs even if malaria was dramatically reduced, however it does reflect the fact that such resources could then be used for other diseases or conditions. The study was carried out in an area of high perennial transmission of *P. falciparum* malaria, it is therefore difficult to draw conclusions as to how similar interventions as the ones examined here would translate to other epidemiological zones, however it is likely that they would be less cost-effective.

The Picard data (Picard et al. 1992) was used by Goodman *et al.* to model the cost-effectiveness of chemoprophylaxis for children. The analysis assumed that chemoprophylaxis (Maloprim®) was distributed fortnightly to children between the ages of 6-59 months by village health workers (VHWs) working on a voluntary basis. Cost estimates included the costs of training VHWs and other health workers, community sensitisation and drug distribution and procurement costs. Drug costs were estimated from the British National Formulary (British Medical Association and Royal Pharmaceutical Society of Great Britain 1997) with the addition of 25% for freight and distribution and 25% for wastage. Other costs were taken from (Picard et al. 1992). Costs were separated into fixed and variable costs to allow adjustment for two transmission season lengths, 6 months and 12 months. Cost-effectiveness was also estimated for countries with an existing network of VHWs and for countries where one would have to be established in order to carry out the intervention.

The estimates of the effectiveness of the intervention were limited since only one trial large enough to show a reduction in malaria mortality exists from The Gambia (Greenwood et al. 1988, Menon et al. 1990). The reduction in mortality from this trial was 0.49% and the reduction in clinical episodes was found to be 0.73%. The reduction in the incidence of neurological sequelae and the prevalence of malaria associated anaemia was assumed by Goodman *et al.* to be equal to the reduction in clinical episodes. The effectiveness estimates from the Greenwood *et al.* and Menon *et al.* papers were from an area of seasonal transmission, Goodman *et al.* assumed that the effectiveness would be the same in areas of perennial transmission. The effectiveness was adjusted for non-compliance assuming a linear relationship between the two such that the 72% compliance achieved in The Gambia resulted in the efficacy found in that trial and zero compliance resulted in zero effectiveness.

Using their model, Goodman *et al.* estimated that the C-E ratio for a very-low-income country with an existing network of VHWs and perennial transmission would be between US$3-12, if transmission were seasonal this figure would fall to US$2-7 per DALY averted. If the VHWs network had to be established these C-E ratios would increase to US$8-41 and US$7-36 per DALY averted for perennial and seasonal transmission respectively. Results for countries in the middle income strata as defined by Goodman *et al.* were similar to those for the very low income countries, however results for higher income countries were higher due to higher costs and lower DALYs averted. Goodman *et al.* concluded that chemoprophylaxis for children could be considered a highly attractive intervention in very low and medium income countries with an existing network of VHWs, and an attractive intervention in higher income countries. Without an existing VHW network the intervention would still be attractive in very low and middle income countries but not in higher income countries.

The Goodman *et al.* model of the cost-effectiveness of chemoprophylaxis for children is limited because of the lack of published studies from which to draw information. Since the work was completed, the study by Alonso González *et al.* (discussed above) from an area of high perennial transmission with an existing network of VHWs reported a C-E ratio of US$10.2 per DALY averted using the single intervention strategy of chemoprophylaxis with Deltaprim. This falls within the range identified by Goodman *et al.* for a very-low-income country with perennial transmission and an existing VHW network, which was reported to be US$3-12 per DALY averted. However the Goodman *et al.* study reported a C-E ratio whilst the Alonso González *et al.* study reported a net C-E ratio which took into account resources saved by a preventive intervention, hence comparison is difficult. This problem highlights the need for further standardised studies of the cost-effectiveness of this intervention in a variety of epidemiological and economic

settings, with different heath service profiles so that firmer conclusions can be drawn as the cost-effectiveness of the intervention.

## 2.2.2.4.5 COST-EFFECTIVENESS OF MALARIA TREATMENT

Sudre and colleagues carried out a study comparing the cost-effectiveness of alternative strategies (Chloroquine (Cq) Amodiaquine (Aq) and sulfadoxine pyrimethamine combination (SP)) for the treatment of childhood malaria in Africa at differing levels of chloroquine resistance (Sudre et al. 1992). They used a decision analytic model, which included the variables compliance, side effects, *P. falciparum* infection, drug sensitivity, level of resistance and parasitological cure, to calculate the cost per case cured and cost per death prevented for three alternative drug regimes. The probabilities used in the model were taken from either published studies or expert opinion (gathered formally using a Delphi[1] survey) and the costs of each drug regime were taken from drug reference price lists. The results were subject to one-way sensitivity analysis at different levels of drug resistance with the probabilities of lethal and minor side effects, risk of malaria infection, case fatality ratio and compliance being varied. The study identified that the most critical elements affecting the cost-effectiveness of alternate regimes for the treatment of paediatric malaria were cost of drugs, compliance and the level of RIII resistance. Cq was considered to be the most cost-effective regime for levels of RIII below a certain range (14-31% depending on compliance), above these levels PS was the most cost-effective treatment.

The study used a decision analytic framework for comparing three alternative regimes, however the model structure developed would be useful for testing any number of drug combinations and in different epidemiological and resistance settings. It illustrates the flexibility of decision analysis models and the authors point

out the usefulness of decision analysis models for malaria control planners with limited resources (Sudre et al. 1992).

#### 2.2.2.4.6 SUMMARY OF COST-EFFECTIVENESS ANALYSES OF MALARIA CONTROL INTERVENTIONS

This literature review has highlighted a number of weaknesses in the cost-effectiveness evaluations of malaria control interventions in Africa. Many of the analysis have been carried out or are based on the results of trial situations which may limit the applicability to the real world, these trail results have often been re-used in separate analyses which aim to draw general conclusions for all Africa based on extremely limited data. For each intervention (especially bednets and chemoprophylaxis) the data tends to come from a particular country which may limit the applicability of results to other settings as it is likely that interventions used in a particular country have been chosen because they are particularly suited to the epidemiological or social conditions within that country. In addition, most studies are based on conditions of endemic malaria and none have explicitly examined interventions for epidemic prevention or control. Studies on one intervention, residual spraying, are particularly weak and the paucity of data is highlighted by the use of ITMN data as a proxy for spraying in one study.

### 2.2.2.5 RELEVANCE OF COST-EFFECTIVENESS ANALYSIS TO THIS STUDY

In this study as well as evaluating the effectiveness of an intervention *per se,* the marginal affects of altering the timing of an intervention in relation to the development and progress of an epidemic is also of interest. Specifically the interest lies in the case where the timing of intervention is earlier than would occur in an alternative situation (without a MEWS) because a MEWS is being used. For

[1] Delphi surveys are carried out by written or telephone questions being put to a number of experts. The answers are then categorised and experts are re-contacted and requested to select the most appropriate statistic or result from the range of estimates gained from all experts sampled.

example a comparison may be made between exactly the same intervention carried out at the beginning, middle or end of an epidemic. The comparison being made is between activities that have the same common output, that of preventing malaria cases, but where costs and effectiveness may differ, consequently CEA is an appropriate tool.

Furthermore, CEA is the form of evaluation most commonly applied to malaria control interventions which means that the results of this study can be more readily compared with other studies.

### 2.2.3 COST-UTILITY ANALYSIS

As an alternative to valuing benefits in monetary terms, the outcomes of activities may be valued in terms of their utility; this type of analysis is termed cost-utility analysis (CUA). The use of cost-utility analysis overcomes some of the problems of cost-effectiveness analysis in that it allows the effects of interventions on both morbidity and mortality to be compared (Mooney and Olsen 1994). In particular it allows for the effects of changes in the quality of life offered by alternate activities to be measured.

In CUA the years of life influenced by an intervention are weighted to reflect the value placed by individuals on the quality of life experienced in each year, this calculation yields the number of quality adjusted life years (QALY) given by the intervention. Utility weightings are usually set between 0 and 1, representing death and the value of a year spent in perfect health respectively. The QALYs gained by each alternative intervention are summed, and a cost per QALY gained is then calculated and used to compare interventions.

The weights used to reflect the value of quality of life (utility measures) are obtained by asking groups of individuals questions in order to derive their implied preferences for each different outcome. A number of difficulties and problems arise with this aspect of CUA. Firstly, the choice of whom to ask may affect the utility

weightings inferred. Secondly, there is controversy over what questions should be asked, however there is some consensus that the questions should describe the possible health states associated with an intervention, in terms of a consistent set of health dimensions (Evans and Hurley 1995). For example the dimensions could represent physical function, role function (self-care and role activities), social-emotional function and the nature of the health problem (Drummond et al. 1997). Thirdly, there are a number of possible techniques that can be used to glean information on health state preferences and an analyst must choose which is the most appropriate method to use. The three main techniques are the ratings scale approach, the time trade off method and standard gamble method, alternatively results from other published studies may be used.

In the rating scale method respondents are presented with a line with clear end points, one end representing the most preferred state and the other the least preferred state. They are then given a description of health states and asked to place each state at a point on the line. The points on the line are then used to calculate the utility of each health state.

In the time trade off method, respondents are offered a series of health states for which they must choose between living in that state for a given period of time, or living in perfect health for a shorter period of time. The length of time in each health state is varied until respondents are indifferent between the choices offered, at this point utility is inferred by dividing the time in the full health by the time in less than perfect health state.

The standard gamble methodology involves giving respondents a choice between living for a time (t) in less than full health, or taking a gamble where the pay off's are total cure and living for t years or immediate death. The probability of immediate death is p and the probability of immediate cure is (1-p). The probability

p is varied until the respondent is indifferent between taking the gamble or not, at this point utility is equal to p.

Difficulties arise in using CUA since the results from each of the methods described above are likely to be different. In addition it has been suggested that results obtained through the use of the rating scale method can be misleading. The time trade off method and standard gamble approach are consistent with expected utility theory which may make them a preferable option, however the assumptions used to justify the use of expected utility theory have been shown to be violated in the real world. Due to these and other problems there is no widely accepted "gold standard" technique recommended for CUA on the basis of adherence to economic theory (Evans and Hurley 1995).

A further problem of the approach arises when QALYs are summed. This assumes that the utility of a condition is independent of the time spent in that condition, which may not be true. For example a person may consider 2 years spent in a chronic health state as more than twice as bad as one year spent in the same health state.

It has been suggested that some of the problems of using QALYs can be overcome through the use of an alternative outcome measure, the healthy year equivalent (HYE) (Mehrez and Gafni 1989). The HYE is defined as the number of years of perfect health (followed by death) that has the same utility as the lifetime path of health states under consideration. It can be measured by the standard gamble approach, using two questions, or the time trade off approach, however it is considerably more time consuming than the standard QALY approach and has been described as "empirically daunting" (Gold et al. 1996). The advantage of this approach in terms of results obtained given the additional computational and data requirements, compared to results obtained from the standard QALY approach is yet to be determined (Gold et al. 1996).

## 2.2.4 PUBLISHED STUDIES USING COST UTILITY ANALYSIS

No published studies involving the application of CUA to malaria were identified by the literature search carried out for this review.

## 2.2.5 RELEVANCE OF COST UTILITY ANALYSIS TO THIS STUDY

CUA allows the impact of an activity on both morbidity and mortality to be combined in a single measurement of utility, thus avoiding the ethical and methodological difficulties that would arise if a CBA were carried out. However, the variety of methods available for calculating the utility weights in QALYs, and the lack of consensus on the most appropriate and theoretically correct method to use, have lead to criticisms of the approach and the development of new tools such as the DALY and HYE. The DALY is commonly criticised for its lack of basis in economic theory and is in any rate not strictly a method of CUA (see section on CEA), whereas the HYE is empirically intensive which limits its usefulness in the developing country context.

It is not possible to convert the intermediate outcome measure from the MEWS model used in this analysis into an estimate of QALY's gained by the interventions for two reasons. Firstly, because the data generated by the model is not final outcome data and secondly, because further extrapolation of model results may make them too abstract to have practical relevance. CUA was therefore not considered to be the appropriate form of analysis for this study.

## 2.2.6 COST-BENEFIT ANALYSIS

Cost-benefit analysis (CBA) is used if the consequences of alternative programmes are not identical and if it is not possible to express the outcomes of each alternative in a common unit of output. For example if two alternatives (A), which prevents deaths and alternative (B), which reduces morbidity are being compared it is necessary to go beyond the actual outcomes achieved by each alternative, and attach a value to each of them which is comparable, for example a monetary value. This entails placing a monetary value on cases prevented, life

years gained or other units of output achieved by the alternative activities (Drummond et al. 1997).

CBA is the most comprehensive measure of the value of activities since it seeks to measure and place a value on all outcomes (desirable or not) including those not directly related to the specific activity (externalities). For this reason it is the most difficult type of evaluation to undertake fully, however it is possible to use CBA to compare totally different types of activities for example building a road and launching a breast cancer screening programme. In addition CBA can be used to evaluate a single activity by examining whether the net benefits of the activity are higher, lower or equal to the net costs.

The main limitation of CBA is that it requires all health and non-health effects to be given a monetary value. This presents not only methodological but also ethical difficulties such as placing a monetary value on life. The three main methods available for monetary valuation of health outcomes are the human capital approach (HK), the stated preference approach [sometimes referred to as the willingness-to-pay (WTP) or willingness-to-accept (WTA) approach] and the revealed preference approach. These approaches are discussed in turn below.

#### 2.2.6.1 THE HUMAN CAPITAL APPROACH

The human capital (HK) approach places monetary weights on healthy time gained using market wage rates. The value of the programme is then assessed by summing the present value of future earnings. The HK approach has been criticised for a number of reasons relating to both measurement problems and theoretical issues. Firstly, labour market imperfections and inequalities (often severe in developing countries) may mean that the wage rate does not equal the marginal productivity of labour for a worker (in other words the actual value of labour in terms of the value of the good or service produced), thus the estimates of the value of time

lost or gained due to a programme are likely to be inaccurate. In this case using the HK methodology would import these imperfections into the analysis.

Secondly, the HK approach may ignore the possibility that healthy time may be gained that is not sold for a wage. To avoid this problem shadow pricing must be employed, adding further complexity and methodological difficulties to the analysis. Shadow-pricing involves estimating the value a resource being used when there is no market rate for it or when the existing price does not accurately reflect the economic price or opportunity cost of resources used. It may also used to reflect social preferences for example benefits accruing to target populations (the poor, young children etc.) may be given a higher weighting in analysis.

Theoretical criticisms are also levelled at the HK approach. Namely that the valuation method employed in the HK approach is not consistent with welfare economics because it only examines the impacts of a programme on labour productivity. Welfare economics dictates that it is more relevant to establish what individuals would be willing to pay (in other words willingness to sacrifice other goods or services) to receive the effects of a given programme (Drummond et al. 1997).

(Evans and Hurley 1995) point out that the HK approach has largely been abandoned, however Gold *et al.* state that it is still used, but point out that it has been shown to be inconsistent with welfare economic theory and that it raises at least as many objections as the more theoretically sound WTP method (Gold et al. 1996). In spite of these criticisms the studies employing the HK approach still outnumber those employing the WTP approach in the malaria literature although this may change as more studies employ WTP methodologies (see below).

### 2.2.6.2 THE STATED PREFERENCE APPROACH

An alternative method of measuring benefit in monetary units, which is more consistent with welfare economic theory, involves the use of estimates of WTP or

WTA and is sometimes referred to as the stated preferences approach. In a perfect market a persons WTP reflects their valuation of the benefit of a good or service, and summing individuals' WTP reflects the societal valuation of a good. WTP is usually measured using 'contingent valuation' which involves asking people hypothetical questions about what they would be willing to pay to either reduce the risk of ill health or increase their quality of life through health gains. WTA asks similar questions regarding the amount people would be willing to accept to compensate them for an increased risk of ill health.

These methodologies are more compliant with welfare economic theory, however they are subject to many practical difficulties. Firstly, the values of WTP and WTA are often different with WTP often found to be lower than WTA estimates. Secondly, the reliability of such estimates has not been tested on repeated population samples. Thirdly, phrasing questions to obtain correct results may be very difficult. Fourthly, and perhaps most importantly, they raise serious equity issues because a more wealthy person is likely to be willing to pay a higher amount for certain, different services than a poorer person. Using WTP or WTA methodology may therefore distort the provision and valuation of health care towards the needs of the rich and away from the needs of the poor. Evans and Hurley suggest that the problems of using WTP are even more difficult to overcome in developing countries. This may be because the highest incidence of disease often occurs among poor people in isolated areas and because some of the concepts and ideas used, for example insurance and probabilities may be alien to people in many countries (Evans and Hurley 1995).

### 2.2.6.3 THE REVEALED PREFERENCE APPROACH

The revealed preference approach uses individual behaviour to infer people's preferences; it is therefore consistent with welfare economic theory. For example wage-risk studies have been used to examine the relationship between

health risks associated with particular occupations and the wages associated with those occupations. These relationships can then be used to infer people's preferences regarding the value of increased or decreased health risks. A number of theoretical and practical problems surround the use of this approach (Drummond et al. 1997) and no examples of its use were found in the malaria literature[2]. This may be because the types of data needed to infer preferences are either not available or are not of sufficient quality in developing countries. For example formal sector employment is often very low in developing countries, and labour markets and wage rates may not accurately reflect the level of risk due to an occupation.

#### 2.2.6.4 REVIEW OF PUBLISHED STUDIES USING COST-BENEFIT ANALYSIS

Studies of the cost-benefit of malaria control or eradication programmes have been undertaken in the past, a summary of the cost-benefit ratios reported for each evaluation along with details of the country and type of evaluation are given in table 2-1. The cost-benefit ratio is given by the sum of direct and indirect benefits, divided by the sum of direct and indirect costs. Intangible benefits and costs may also be included in some CBA, for example the intangible costs of grief or suffering.

The studies in Table 2-1 all have a cost-benefit ration greater than 1, suggesting that the net benefit of malaria control or eradication efforts outweighs the net cost and therefore that it is worthwhile. All of these CBA studies use the HK approach in the valuation of health benefits which means that the outcome of each programme is judged by its assumed effect on production, they are therefore subject to the criticisms of the approach as described above. In addition to these general theoretical and measurement criticisms, more specific criticisms relating to the use of the HK for valuing malaria control activities have been raised.

[2] Bids International Bibliography of the social sciences (1951-2000) using "revealed preference" + "health", "wage risk" and Ingenta Medline (1966-200) "revealed preference and health". References then further sorted by hand.

In a review of the economic and demographic research on malaria (Gomes 1993) points out that the use of the HK approach to measure the value of health is considerably difficult because of the non-monetary nature of health and because a persons stock of health can be augmented, depleted or maintained through activities other than that being evaluated. This makes it difficult to establish the causal relationship running between health investments, personal earnings and economic growth. Gomes suggests that these problems are confounded when attempting to define the economic value of removing a disease for a number of reasons. Firstly, infection does not necessarily mean that a person will be incapacitated, for example a highly immune person may be parasitaemic, but not be clinically sick, (Mills 1991) points out however that it is also possible that uninfected people may lose productive time to caring duties. Secondly, Gomes argues that even when incapacity does occur the degree of impairment will vary between individuals depending on their immunity, treatment received and other factors. Mills *op cit.* further suggests that the time lost may not have been productive time, particularly at slack times of the year. Also other people completing the work normally carried out by the sick person may have avoided lost productivity. Thirdly, Gomes suggests that the value of time lost by different groups of individuals must be considered, this causes additional problems since malaria disproportionately affects the poor who's work time is generally valued at a lower rate. Using a rate which reflects the value of lower-income lower-productivity workers may be accurate, however it raises equity issues since it implies that the value of a less productive persons life is less than another better paid or more productive person.

Further criticisms of the HK approach are outlined by Mills (Mills 1991), who points out that if a CBA is carried out prior to control being started assumptions regarding to what extent the activity will reduce malaria and at what direct and indirect cost will have to be made. Conversely if a programme exists assumptions

will have to be made about the situation that would be without it. In other words using the HK approach relies on accurately establishing the counter factual in any given situation an issue which is central to the evaluation of MEWS. In addition, it is also suggested that using the HK approach in a CBA does not match the complexity of the processes by which malaria affects the well-being of households. For example the effects of malaria on the unborn child, children and those not in work may be underestimated or ignored completely by such an approach.

Mills *op cit.* questions whether attempts to measure the costs of malaria and benefits of malaria control in terms of production gains are worthwhile and concludes that attempts to examine the rate of return to investments in health in such a way are highly ambitious. Gomes calls for far more rigour in economic analysis in order to make results useful in terms of policy decisions (Gomes 1993).

Overall the use of the HK approach to value health benefits in a CBA is methodologically unacceptable, if the principles of welfare economics are to be adhered to. It is also beset with measurement problems, which render it too crude a tool to quantify the complex nature of the malaria problem and its affects.

Although WTP has not been used to value health benefits as part of a full CBA, two studies were found in the literature, which assess the WTP for malaria control interventions. It is possible that in future the techniques for assessing WTP may be used as part of a CBA, for this reason these studies are briefly reviewed here.

Mills and colleagues investigated both the existing financing mechanisms for village activities in The Gambia and the WTP for insecticides for bednet impregnation in an attempt to resolve the question of how the treatment of nets should be financed after an initial trial. The most commonly suggested maximum and minimum amount villages suggested that they would be willing to pay for insecticide were D1 and D5 minimum and D5 and D10 maximum (D = Gambian

Dalasi). The study results were used to set the level of payment in the year following the initial trial, at D5 per net (Mills et al. 1994). However, it could be argued that they predicted poorly the real WTP since following the introduction of a charge, bednet impregnation coverage dropped from 85% and 77% in 1992 and 1993 respectively to 14% in 1994 (Müller et al. 1997).

WTP for yearly re-treatment of ITBN's in Nigeria was investigated by Onwujekwe and colleagues, using the contingent valuation method in an attempt to examine what people would be WTP for the service and to examine implementation issues arising from the findings. The results of the study showed that between 79% and 91% of households were willing-to-pay for annual re-treatment of nets, with the amount people were willing to pay ranging between $0.05 and $5.26, with a median amount of $0.21 (Onwujekwe et al. 2000).

These two studies illustrate that it is possible to use WTP in developing countries and in relation to malaria. Thus it may be possible to take this kind of analysis a stage further and use WTP to value the health benefits of a malaria control programme or activities as part of a CBA. However, the data requirements of such an analysis would however be large and possibly prohibitive. Moreover, given the poor predictive value of The Gambian WTP study the usefulness of the methodology requires further evaluation. Further studies are being carried out on appropriate techniques for measuring the WTP for ITMN in Africa (Dgedge 1999, Mujinja 1999, Onwujekwe 1999) and the results may improve the potential for using WTP to measure health benefits in CBA.

### 2.2.7 RELEVANCE OF COST-BENEFIT ANALYSIS TO MALARIA CONTROL INTERVENTIONS

CBA is the most comprehensive measure of the value of activities, however, it is perhaps the most difficult type of evaluation to undertake fully and it is beset with both practical and theoretical problems. The human capital method for the monetary valuation of health outcomes in CBA has been widely disregarded (Evans

and Hurley 1995, Gold et al. 1996, Gomes 1993, Mills 1991) and was therefore not considered to be a suitable technique to use in this study. WTP is a relatively new technique in the field of malaria, which has only been applied in situations regarding the choice of an appropriate price for specific malaria control interventions, rather than as a means of valuing health state preferences in a CBA. The WTP approach raises serious equity concerns and may result in the conclusions of a study being weighted in favour of the preferences of more wealthy groups, in addition to this the concepts of probabilities and risk involved in WTP studies may make it difficult to use in some countries. These issues and practical difficulties rule out WTP as an appropriate means of calculating the value of health benefits in a CBA. The revealed preference approach is impractical in developing countries due to labour market imperfections and the difficulties of collecting sufficient quality data.

CBA is suggested as a means of identifying whether the outcome of a specific programme or activity is desirable itself, whereas CEA and CUA implicitly assume that an outcome is worthwhile achieving and look at the most efficient way of achieving it. The body of evidence on the burden of malaria in sub-Saharan Africa strongly indicates that malaria control is a worthwhile objective and that the benefits of reducing malaria would be substantial.

CBA is used if the consequences of alternative programmes are not identical and if it is not possible to express the outcomes of each alternative in a common unit of output (Drummond et al. 1997). In this study the outcomes of each alternative control strategy can be measured in a common unit of output, that of cases prevented by each alternative considered. CBA was therefore seen as an unnecessary and inappropriate tool for use in this analysis.

## 2.3 CHAPTER SUMMARY

This chapter has described the various forms of economic evaluation, and reviewed the use of each tool in the economic evaluation of malaria control

interventions. Of the various evaluation tools, CEA was considered the most appropriate form of analysis to use in this study since the activities being considered have the same common unit of output (cases prevented) but different costs and effectiveness in achieving it. CMA is insufficient to capture all relevant information and CUA is inappropriate because it is not possible to convert the intermediate outcome measure from the MEWS model used in this study into an estimate of QALY's gained by the intervention. CBA is fraught with methodological difficulties and is at any rate considered unnecessary to answer the question posed in this study. The following chapter goes on to describe various aspects of CEA in greater detail and link this form of analysis with modelling, malaria control theory and the evaluation of other epidemic prone diseases.

Table 2-1 Cost-Benefit Ratio's of Malaria Control Interventions

| Reference | Country | Method | Cost-Benefit ratio |
|---|---|---|---|
| (Barlow 1968) | Sri Lanka | Insecticide | 146 |
| (Griffith et al. 1971) | Thailand | Chemoprophylaxis | 6.5 |
| (Khan 1966) | Pakistan | Eradication programme | 4.9 |
| (Livnadas and Athanassatos 1963) | Greece | Eradication programme | 17.3 |
| (Niazi 1969) | Iraq | Eradication programme | 6.0 |
| (Ortiz 1968) | Paraguay | Insecticides | 3.6 |
| (Ramaiah et al. 1998) | India | Control programme | 9.3 |
| (San Pedro 1967-8) | Philippines | Eradication programme | 2.4 |
| (Democratic Republic of Sudan 1975) | Sudan | Control programme | 4.6 |

Source: (Barlow and Grobar 1985), cited in (Mills 1991) (original reference unobtainable)

Table 2-2 Cost-Effectiveness of Spraying or Vector Control Measures (Adapted from (Mills 1991)

| Country | Intervention | Annual Cost/Person Protected | Cost/Case Prevented | Cost/Death Averted | Reference |
|---|---|---|---|---|---|
| | | All in 1984 US$ | | | |
| Nigeria | Spraying | 1.63 | - | - | (Bruce-Chwatt and Archibald 1959) |
| Liberia | Case detection and treatment, spraying and larviciding | 6.64 | 12.30 | - | (Hedman et al. 1979) |
| LDCs | Spraying | 2.97 | - | 892.2 | (Walsh and Warren 1979) |
| Nigeria | Case detection and treatment, vector control | - | 233.15 | - | (Molineaux and Grammicia 1980) |
| Sudan | Spraying | 0.75 | - | - | (El Gaddal et al. 1985) |

Note: LDCs = Less Developed Countries

# CHAPTER 3 – MODELLING: IN COST-EFFECTIVENESS ANALYSIS AND MALARIA CONTROL THEORY

## 3 OVERVIEW OF CHAPTER

This chapter provides a background to the use of models in the health economic evaluation 'toolbox'. The roles for modelling in economic evaluation are discussed along with a description of the various forms of sensitivity analysis applicable to models and a critique of modelling based upon the debate between internal and external validity. A more specific description of the various types of modelling techniques used in cost-effectiveness analysis of malaria control interventions and interventions in epidemics of other infectious diseases is then given. This review highlights the neglected use of population dynamic malaria models in cost-effectiveness analysis, giving an example of the approach applied to another infectious disease, schistosomiasis. The existing theory behind such an approach for malaria is then described.

## 3.1 THE ROLES OF MODELLING IN HEALTH ECONOMIC EVALUATION AND COST-EFFECTIVENESS ANALYSIS

Modelling is being increasingly utilised in a range of disciplines including economic evaluation. Modelling offers a means of representing the complexity of the real world in a simplified and comprehensible form using numbers and mathematical and/or statistical relationships (Brennan and Akehurst 2000). Measurement and modelling are complimentary activities in cost-effectiveness analysis, which utilises various modelling techniques developed in other disciplines (including epidemiology, statistics, operations research and decision science) to forecast or predict events where little or no data exists, (Drummond et al. 1997). Modelling is essential if important decisions must be made before relevant data is available or when existing data is not sufficient. Moreover, in some situations measured data may be totally unobtainable for ethical, political, time or cost reasons (Buxton et al. 1997) in which case modelling is the only option.

The roles of modelling are manifold and have been identified and discussed in a number of recent papers (Brennan and Akehurst 2000, Buxton et al. 1997, Sheldon 1996). Sheldon identifies four uses for modelling in economic evaluation:

1. Analysing data (for example in the analysis of randomised control trial (RCT) results or in combining the results of a number of RCT's in meta-analysis)
2. Extrapolating data
3. Decision analysis
4. Preliminary evaluation of health technologies.

Points 2, 3, and 4 are relevant to this thesis and within these categories decision analysis models and epidemiological models for the extrapolation of results are of particular interest. The following sections will describe the role of sensitivity analysis in economic evaluations and issues of internal and external validity with particular relevance to modelling studies. The various types of and uses for decision analysis and epidemiological modelling in cost-effectiveness analysis under these two categories will then be discussed. Clearly there will still be some degree of overlap between these categorise which is discussed in the text where relevant.

## 3.2 SENSITIVITY ANALYSIS IN MODELLING

If the results of models are to be trusted and used to inform resource allocation and policy decisions they must be rigorously tested using sensitivity analysis. Sensitivity analysis is a mechanism for testing the robustness of models against a range of values which reflect the uncertainties involved (Sheldon 1996) it is used to examine the robustness of an estimated result over a range of alternative values for uncertain parameters (Drummond et al. 1997). Lack of sensitivity analysis or weak and biased testing can be a major downfall of evaluations employing modelling techniques.

Poor sensitivity analysis may be a result of selection bias regarding what variables to test; some variables may be ignored or tested using an unrealistic range of variables. Justification should therefore be given for the variables tested and the test range chosen. Interpretation of sensitivity analysis is arbitrary because there are no guidelines as to what degree of variation in results is acceptable, in addition the variation of uncertain parameters in a one-way sensitivity analysis (altering one parameter at a time) may not adequately capture interactions between parameters.

The criticisms of traditional sensitivity analysis have lead to the development of probabilistic sensitivity analysis by Monte Carlo simulation (Drummond et al. 1997). If the uncertain parameter(s) is/are of a stochastic nature, uncertainty can be represented using a probability distribution and Monte Carlo simulation can be used to assess the importance of this uncertainty on the model results. In Monte Carlo simulation, a distributional form (for example, normal, Poisson, binomial) is assumed for an estimated (non-sampled) variable, this is known as parametric bootstrapping. Repeated samples are then drawn from the distributions in order to determine an empirical distribution function for the results and key combinations of results, such as the cost-effectiveness ratio (Drummond et al. 1997).

The nature of the analysis carried out will determine whether it is sensitivity analysis, statistical analysis or both, which is the appropriate tool for testing the robustness of the model. Drummond *et al.* suggest the following main categories as guidelines. Firstly, in the case of deterministic cost-effectiveness analysis, where cost and effect variables are analysed as point estimates, a detailed sensitivity analysis using plausible ranges for variables should be used to explore uncertainty. This kind of analysis is most common for the early assessment of new medical technology, where some form of analysis is required for policy making. Secondly, partially stochastic cost-effectiveness analysis, where effectiveness has been estimated from clinical trials but costs have been estimated using non-sampled data,

should be examined using a combination of both techniques. This kind of combination of stochastic and deterministic data is common in decision analytic models. Thirdly, wholly statistical cost-effectiveness analysis, where both costs and effects are sampled from a study population, should be tested using formal statistical tests. This is only appropriate if cost and effectiveness data has been derived from random samples.

## 3.3 INTERNAL & EXTERNAL VALIDITY AND CRITIQUE OF MODELLING IN ECONOMIC EVALUATION

Criticism of the use of models in economic evaluation often focuses around the relative internal and external validity of models compared with experimental or measured data (for example from clinical trails). Issues of internal and external validity are becoming important as economic evaluations are increasingly required to inform decisions (Walker and Fox-Rushby 2000). Internal validity relates to the methodological quality of a study, for example randomised control trials (RCT) have a high degree of internal validity because they are relatively free from bias which means that it can be assumed with confidence that the intervention in question caused the effects seen. External validity relates to the generalisability of results either from place to place or from a trial situation into practice.

In terms of external validity, economic evaluations using the results of RCT may compare badly to those which use models because they do not necessarily reflect actual conditions accurately and may not offer precise information on the possible end points of an intervention that would be necessary for evaluation. A model can be designed to reflect actual conditions and reused in different settings with the alteration of key variables. Problems of lack of internal validity can be addressed by ensuring that the methodology of an evaluation using modelled data is clearly explained and therefore open to criticism and also that the causal relationships assumed by any model are supported by the best available evidence. Guidelines and suggestions for good modelling practice are also being developed in

order to help clarify and tackle the problems of lack of internal validity in modelling studies (Anonymous 2000, Brennan and Akehurst 2000, Buxton et al. 1997, Nuijten et al. 1998, Schultz et al. 1996)]

## 3.4 COST-EFFECTIVENESS ANALYSIS USING DECISION ANALYSIS MODELS

*"A decision model is usually developed to assist decision-makers in making choices relating to the evaluated options. Typically, the objective of a decision model is to obtain a clearer understanding of the relationships between incremental costs and their consequences."* (Anonymous 2000).

Decision analysis models use a variety of techniques to synthesise the best available information about healthcare processes and their implications in order to inform decisions (Anonymous 2000). They are used to structure the decision problem logically and to order existing data in a helpful way, integrating data from different sources on the various components of a decision. Alternative strategies are then compared by comparing all possible outcomes, probabilities and utilities of each outcome (Sheldon 1996).

Decision analysis models are useful to inform decisions in the absence of hard data and are particularly useful if the magnitude of key variables is unknown and experimentation is not possible. In planning and as a preliminary evaluation technique they can be used to prioritise future data collection (Buxton et al. 1997) and to highlight the key uncertain variables influencing cost-effectiveness (Sheldon 1996).

An advantage of the decision analysis modelling approach is the explicit way in which the problems are structured which may begin with the construction of a decision tree. The decision tree is a graphic representation of the problem, starting with the decision and tracing out all probable pathways and consequences that can arise over time. The depiction of the problem in this way allows the identification of

necessary data components for example costs, probabilities and utilities (Drummond et al. 1997). The decision analysis approach has also been described as "*appealing*" and "*intellectually robust*" (Sheldon 1996), however it may be subject to bias because of the bringing together of information from different sources (lack of internal validity). The lack of internal validity of decision analytic models can be offset by their high degree external validity or generalisability, which means that they can be easily adapted for use in different situations. Other advantages of this approach are described by Drummond *et al.* who suggest that it provides a flexible and timely framework for analysis and highlights missing data, which can then be replaced with estimated data and tested using sensitivity analysis (Drummond et al. 1997).

The nature of the relationships and data used in individual decision analysis models may be either statistical (deterministic or stochastic) or rule-based, however in the use of decision analysis modelling in the cost-effectiveness evaluation of malaria control interventions models have been informed using mostly statistical relationships. For example Graves used a decision analysis model to evaluate the cost-effectiveness of insecticide treated bednets compared to a hypothetical vaccine, informing the model with point estimates of effectiveness from the literature (Graves 1998). Goodman *et al.* also used a decision tree structure to evaluate the effectiveness of alternative malaria case management strategies in terms of DALYs averted per patient in a model population (Goodman et al. 2000). Probabilities in the decision tree were calculated using data based on estimates from a wide range of African countries and expert opinion. The data was in the form of point estimates and probability functions which were then evaluated using Monte Carlo simulation methods. Sudre (Sudre et al. 1992) and Schultz (Schultz et al. 1996, Schultz et al. 1995, Sudre et al. 1992) also used decision analysis models informed using point estimates of effectiveness from published studies and expert opinion.

### 3.4.1 COST-EFFECTIVENESS ANALYSIS OF INTERVENTION IN EPIDEMICS USING DECISION ANALYSIS MODELS

Schoenbaum *et al.* used formal decision analysis to analyse the decision faced by the American public health authorities regarding whether or not to vaccinate the entire population against a possible epidemic of a new influenza virus (Schoenbaum et al. 1976). The net benefits of immunisation were calculated by subtracting the total costs of the vaccine programme from the total benefits. Total benefits were calculated by multiplying the costs incurred as a result of an epidemic by the probability of an epidemic occurring and then by vaccine efficacy. Vaccination programme costs were calculated for different target age groups using the cost of past public vaccine programmes, the estimated cost of the vaccine and the costs of vaccine adverse reaction (calculated using the human capital approach). Benefits were calculated from the estimated direct costs of treating the estimated number of cases and the indirect costs of influenza illness and death in terms of lost productivity (human capital approach). Estimates of vaccine efficacy, acceptance and adverse reaction rates, the probability of an epidemic occurring and its likely severity in terms of age-specific morbidity and mortality were obtained using the Delphi survey technique.

The study was able to identify acceptance rates where the costs of the programme equalled the benefits for each of the alternative target age ranges of the vaccine programme, subject to alterations in the discount rate used. As the probability of the epidemic increased these break-even acceptance rates were reduced. Expected benefits also increased or decreased in line with increases or decreases in vaccine efficacy. The authors concluded that if the programme was limited to adults of 25 years or older and acceptance rates were 59% or above the programme would be economically justifiable. They also identify the advantages of structuring the problem as a formal decision analysis. Firstly, that once the framework has been developed it can be used for analysing alternative strategies.

Secondly, formal decision analysis indicates whether a particular strategy will break even, yield net costs or benefits and thirdly, can be used to identify the conditions for obtaining maximum benefits.

Elbasha *et al.* used a decision analysis model to analyse the cost-benefit of a subtype-specific surveillance system for identifying *E. coli* outbreaks in the USA. The authors used a threshold approach to identify how many cases the system would have to avert to recover all its cost and found that a system does not need to prevent a large number of cases to yield return on the resources invested in it (Elbasha et al. 2000).

Naficy *et al.* used a decision analysis framework to carry out a cost-effectiveness analysis of treatment and vaccination strategies to control cholera epidemics in sub-Saharan African refugee settings (Naficy et al. 1998). The problem was structured using a decision tree, which was used to compare the costs and outcomes of six alternative strategies to each other and to the baseline standard of care considered routine in refugee settings. The alternatives were:

Pre-emptive treatment (PT) with the necessary staff, facilities and supplies to manage a cholera outbreak set up at the inception of the camp

Reactive treatment (RT) with the necessary staff, facilities and supplies set after the outbreak has been recognised

PT combined with pre-emptive vaccination (PV) carried out at the inception of the camp

PT combined with reactive vaccination (RV) once an outbreak has been recognised

RT combined with PV

RT combined with RV

The probability of an epidemic occurring and its likely epidemiological parameters were derived from detailed epidemiological data from 21 epidemics occurring in refugee camps. Cost data for each strategy were obtained from a large relief agency used to provide medical care in such settings. Results were given in terms of cost per cholera case prevented and cost per cholera death averted and the study identified that provision for managing cholera outbreaks at the inception of refugee camps (PT) was the most cost-effective option. In other words the optimal (most cost-effective) strategy was pre-emptive as opposed to reactive. They also identified the threshold price level which the vaccine must fall below to make its use in conjunction with PT a cost-effective alternative.

## 3.5 EXTRAPOLATING RESULTS AND EPIDEMIOLOGICAL MODELLING

If a trial is not long enough to capture all the information required for economic evaluation, models may be used to extrapolate benefits (or costs) beyond the duration of the trial, assuming constant benefits or another, more complex function (Sheldon 1996). This sort of extrapolation has been criticised as being unreliable and it has been argued that it cannot be used as a substitute for longer follow up periods following trials (Sheldon 1996). Buxton *et al.* argue that reliance on short term outcome data is justified where there is good reason to believe that the intervention will not have long run effects on the outcome (Buxton et al. 1997), therefore reliance on extrapolation methods may be avoidable in certain cases.

The general health economics literature tends to define a relatively narrow role for epidemiological modelling in cost-effectiveness analysis (see for example (Buxton et al. 1997, Drummond et al. 1997, Sheldon 1996)). This role is limited to providing a link between biological end points or intermediate outcomes and final health outcomes, particularly in situations where the final outcome of a disease takes years to develop and clinical trials do not extend for long enough periods of time (Sheldon 1996).

Epidemiological models for extrapolation either over time or to a final outcome measure may be statistical or rule-based in nature, however the majority of epidemiological models used in cost-effectiveness analysis of malaria control interventions have been statistical in nature (examples are given below); the rule-based models has been somewhat neglected.

### 3.5.1 EXAMPLES OF EPIDEMIOLOGICAL EXTRAPOLATION MODELS IN COST-EFFECTIVENESS ANALYSIS OF MALARIA CONTROL INTERVENTIONS

There have been a number of studies using population life tables as a baseline against which to evaluate the effectiveness of insecticide treated mosquito nets (Coleman et al. 1999, Evans et al. 1997, Guyatt et al. 1999). The Evans and Guyatt studies used point estimates for the reduction in morbidity and mortality achieved by the intervention and calculated the effectiveness of the intervention based on the difference between the standard life table and the modified life expectancies after the intervention. Coleman *et al.* used a similar approach however, ranges as opposed to point estimates were used and the results were estimated using Monte Carlo simulation.

Goodman *et al.* used statistical modelling techniques to extrapolate the results of a model of childhood malaria morbidity and mortality which predicted deaths and morbidity averted due to a number of interventions (insecticide treated nets, residual spraying of houses and chemopropylaxis) into years of life lost (YLLs) and years of life lived with disability (YLDs) (Goodman et al. 2000). Further modelling was then used to convert the YLLs and YLDs into DALYs (disability adjusted life years) averted per child. This study also used the results of a meta-analysis (Lengeler 1998) also a form of modelling, to estimate the effectiveness of insecticide treated nets. Goodman *et al.* also fitted empirical observations to an existing deterministic mortality model to estimate the effects of low birth weight on

child survival in order to estimate the cost-effectiveness of interventions affecting malaria in pregnancy.

### 3.5.2 RULE-BASED DYNAMIC EPIDEMIOLOGICAL MODELS

Cost-effectiveness analyses of interventions for infectious diseases have also exploited the use of rule based dynamic epidemiological models. Such models are useful because of the paucity of data on infectious diseases occurring in less developed countries modelling therefore provides a necessary addition to available information and is sometimes the only option for use in evaluations. However, in spite of the use of statistical epidemiological models to extrapolate results and inform decision analysis in a number of cost-effectiveness evaluations of malaria control interventions, the use of rule-based dynamic epidemiological models of malaria has been almost completely ignored.

The neglect of dynamic epidemiological models of malaria for use in cost-effectiveness analysis is deleterious since the nature of the disease means that interventions reducing immediate factors such as parasite prevalence or the number of infected individuals will have knock-on effects on the transmission dynamics of the disease. This positive externality of reducing transmission may be missed by evaluations using non-dynamic statistical models to predict or extrapolate outcomes.

The transmission and population dynamics of infectious diseases have important implications on the cost-effectiveness of interventions for their control. It is therefore vital that these dynamics be taken into consideration in any economic evaluation of disease control interventions, particularly in areas where a high degree of seasonality or inter-annual variation in transmission exists. Suitably designed and tested epidemiological models combined with relevant cost data provide a tool with which to evaluate the cost-effectiveness of alternative disease control interventions. An excellent example of this approach can be found in the cost-effectiveness analysis of schistosomiasis control described in further detail below.

In the economic analysis of schistosomiasis control, cost-effectiveness studies have been carried out which estimate the effectiveness of interventions in terms of immediate cure rates (i.e. reduction in prevalence) (Korte et al. 1986, Prescott 1987). Such static analyses have been criticised as neglecting the long-term effects of intervention and the impact on transmission of reductions in prevalence (Guyatt and Tanner 1996). As an extension to static analysis, which tends to use a reduction in disease prevalence as the measure of effectiveness, a prevalence based model of transmission has been used to simulate the effectiveness of alternative control strategies over a seven year period (Rosenfield et al. 1977).

Whilst such approaches capture the effects of interventions on transmission, thus offering more accurate descriptions of the effectiveness of interventions, they are limited in terms of their applicability to other setting, since this requires epidemiological data which may not be available (Guyatt and Tanner 1996). The approach is also limited because of the complexities that exist between the intensity of infection and individual and community morbidity, which are not captured through the use of prevalence measures (Guyatt and Tanner 1996). To overcome this limitation a biological model of intestinal nematodes including the distribution of infection as a dynamic entity, which can reflect reinfection and the use of anthelmintics, and can therefore measure the impact in terms of disease prevention of alternate strategies was developed (Medley et al. 1993).

This model was linked to cost data and used to carry out a cost-effectiveness analysis of alternative frequencies of mass anthelmintic treatment for the control of Ascaris infection (Guyatt et al. 1993). The model was used to compare mass chemotherapy programmes with varying frequency of treatment, however the authors note that it could also be used to examine the effects of variations in coverage, drug efficacy, epidemiological parameters and unit costs. They conclude,

*"the evaluation of effectiveness clearly requires the use of models that capture the dynamics of parasite transmission"* (Guyatt and Tanner 1996).

This statement is equally applicable in the economic evaluation malaria control strategies, which also have a strong dynamic component, particularly in epidemics.

## 3.6 POPULATION DYNAMIC MODELS OF MALARIA AND CONTROL THEORY

The use of dynamic epidemiological models to inform control policy has been recognised by Bailey in his 1982 book 'The Biomathematics of Malaria', in which he traces the history of modelling the population dynamics of malaria up to the point where:

*"forecasts of the likely consequences of different available intervention strategies will be able to assist decision-makers"* (Bailey 1982)

In the same way that Drummond *et al.* suggest that economics must borrow analytical techniques from other disciplines (Drummond et al. 1997), Bailey argues that the problems of malaria control should be thoroughly investigated through multidisciplinary approaches, where the overall objectives are to increase understanding of a wide range of interlocking phenomena and to make recommendations of wide practical value to planners and decision makers. Bailey goes on to describe control theory and its use in defining the components of an optimal control problem and finding its solution a description of which follows below.

### 3.6.1 CONTROL THEORY

The main aspects of control theory in defining the components of an optimal control problem and finding its solution, as laid down by Bailey, are as follows:

1. The dynamics of the system under investigation must be specified by a model which identifies the transmission mechanisms involved assuming that:

a) The operation of the system generates certain measurable costs or rewards

b) Initially the system is not deliberately controlled although it will be subject to the constraints inherent in the modelling structure

2. Various interventions or control actions are specified which may change the operation of the system as well as entailing additional costs

3. The control policy or rules prescribing what control action is to be chosen at any time must be laid down

4. A cost function must be specified to assign a total cost to the operation of the system

5. The optimal policy that prescribes the control actions for which the total cost is as small as possible is then determined

### 3.6.2 HISTORY AND BACKGROUND TO CONTROL THEORY

The roots of control theory lie in the early malaria models developed by Ross (Ross 1911) and later Macdonald (Macdonald 1952). The first mathematical formulations of the population dynamics of malaria were developed by Ross (Ross 1911) who identified the principal epidemiological factors involved in transmission which could be used to estimate the number of healthy people infected in a given period of time. These factors were the:

- Average population in the locality
- Average proportion of the population infected
- Proportion of infected individual who are infectious
- Average number of mosquitoes per person in the locality per month
- Proportion of uninfected mosquitoes which feed on man

- Proportion of mosquitoes which survive through the extrinsic incubation period
- Proportion of infectious mosquitoes which feed on man
- Recovery rate of infected individuals per month

George Macdonald reformulated Ross's early model into a more manageable structure (Macdonald 1957) and identified vector longevity as the single most important variable in the force of transmission (Spielman 1993). Macdonald's model combines the susceptibility of the mosquito, the infectivity of man, the duration of the extrinsic incubation period of the parasite, the frequency at which the vector bites man and the longevity of the mosquito, to give an estimate of the sporozoite rate (the proportion of mosquitoes with sporozoites in their salivary glands).

Macdonald derived the following expression for the sporozoite rate ($s$):

$$s = \frac{P^n ax}{ax - \ln P}$$

Where:

$a$ = the average number of blood meals on man taken by a mosquito in a day

$P$ = the probability that a mosquito will survive through one day

$n$ = the time in days taken for completion of the extrinsic cycle

$x$ = the proportion of bites on man which are infective to the mosquito

The sporozoite rate was then incorporated into an expression for the inoculation rate (the mean number of bites inflicted on one individual by mosquitoes infected with sporozoite rates which are actually infective). The expression is as follows:

$$h = mabs$$

Where:

$h$ = the proportion of the population receiving inocula in one day

$m$ = density of vector relative to man

$b$ = the proportion of those anophelines with sporozoites in their glands which are actually infective.

Macdonald also included a recovery rate function ($r$) to derive the proportion of people who are infectious at a given time. Using the sporozoite rate, the probability of mosquito survival and the extrinsic incubation period Macdonald estimated the reproductive rate, i.e. the number of new infections arising from each infection which he then be used to look at the situations of stability of transmission, epidemics and the theory of control. The reproductive rate was of particular interest to malariologists at this time where eradication was considered possible by using control interventions to reduce the reproductive rate below 1.

In 1964 Garrett-Jones proposed the use of vectorial capacity as a means of assessing the daily reproduction rate and a measure of the effectiveness of vector control. Vectorial capacity was defined as

"*the average number of inoculations with a specified parasite, originating from one case of malaria in unit time, that the population would distribute to man if all the vector females biting the case became infected*". (Garrett-Jones 1964)

It was expressed using the terms laid down by Macdonald (see above) as follows:

$$\frac{ma^2bp^n}{r(-\ln p)}$$

Garrett-Jones stated that the vectorial capacity of a particular vector population would be subject to natural variations because of variations in the relative density, longevity and man biting habits of the vector. He proposed that before the

start of a spray programme these variations could be assessed to reveal the month of steepest upward trend in transmission, which would happen earlier in the season than the month of maximum transmission. Then, given a fixed regime of control, assessments of vectorial capacity might indicate whether the trend of transmission is consistently downwards or upwards in certain localities and months (i.e. whether the intervention is successful or not). He also argued that vectorial capacity could be used to indicate the danger of malaria transmission becoming re-established in areas where malaria no longer existed.

The ideas and approaches developed by Ross, Macdonald and Garrett-Jones were subject to much constructive criticism and development. This led to their adaptation to obtain more realistic models that could handle aspects such as changing immunity in humans, annual variations in mosquito populations and in particular, time dependent vectorial capacity. Advances were also made in the application of a given model to specific field situations as opposed to drawing parameter estimates from available relevant data (Bailey 1982). The inclusion of aspects such as human immunity and seasonal variations in mosquito population density were unnecessary from the point of view of eradication theory, however they became crucial in control theory which aims to achieve a new balance between host and parasite populations within a given period of time. A key contribution to control theory was made by Dietz in 1971 and later superseded by Dietz, Molineux and Thomas in 1974 (Dietz 1971, Dietz et al. 1974).

The Dietz (1971) model was developed in collaboration with epidemiologists, entomologists and immunologists for direct application to data from a field project involving villages in Northern Nigeria. The model was initially unable to account for seasonal fluctuations, although it did give a good fit to the yearly average age distribution of malaria prevalence. It was therefore modified with the less certain

parameters estimated from field data and was consequently able to achieve a satisfactory goodness of fit to the data (Dietz et al. 1974).

This work has been recognised to represent a major breakthrough in the practical modelling of malaria dynamics (Bailey 1982, Nedelman 1985). The model was successfully applied to two specific field areas (Molineaux et al. 1978), lending it further credibility.

In his review on the historical perspectives of the bio-mathematics of malaria, Bailey suggests that a continuation of the work carried out to date may lead to the establishment of one or more models, which will explain known facts in an adequate manner, allowing predictions to be made with sufficient accuracy for decision-makers to select malaria control strategies with appreciably improved effectiveness (Bailey 1982). Since Baileys remarks a number of models have indeed been applied to the problem of examining the effectiveness of malaria control interventions, with the aim of improving malaria control strategies.

One such study of particular relevance to this work is that of Saul who used a simulation model of epidemic or seasonal malaria transmission [presented in an earlier paper (Saul et al. 1990)] to examine the effect of vaccines against different stages of the malaria parasite (Saul 1993). The model was developed from the models of Macdonald (Macdonald 1957) and Garrett-Jones (Garrett-Jones 1964) with the major difference being the adoption of cyclical rather than constant vector feeding behaviour. Macdonald implicitly assumed that the probability of a mosquito feeding on a human in any time period does not depend on the immediate history of the mosquito. Saul points out that this is not true since a mosquito, which has taken a full blood meal, will not feed again for some time. A further assumption of Macdonald's model, that of constant daily probability vector survival, is also relaxed by Saul in favour of a constant probability of surviving for one feed to the next (as used by Birley (Birley 1984))

The Saul model was used to simulate the number of cases present at the end of the transmission season with alternative vaccine types, efficacy and coverage under conditions of constant human and mosquito populations. Simulations were run with various levels of vectorial capacity (i.e. 0.01, 0.1, 1 and 10) which were held to be constant throughout the transmission season. From this analysis the critical factors affecting vaccine effectiveness were identified as effective coverage of the vaccine, the length of the transmission period, the vectorial capacity and the size of the initial inoculum.

One of the criticisms of population dynamic malaria models to date is the failure to explicitly allow for seasonal changes in the vector population (Nedelman 1985). Dietz *et al.* modelled this phenomenon implicitly by using a seasonal pattern for vectorial capacity, however inter-annual variations were neglected because the seasonal vectorial capacity used was the average of a number of years worth of data (Dietz et al. 1974). Saul also used changes in a base line value of vectorial capacity to allow for changes in underlying vector populations, however no monthly or seasonal variation in vectorial capacity was modelled. Nedelman also identified that no existing models deal with clinical symptoms, such as fever, explicitly (Nedelman 1985).

Although the impact of seasonal changes in the vector population have not been examined in population dynamic malaria models, a body of work aimed at understanding the likely effect of climate change on malaria transmission has examined the links between climate variables and malaria transmission. Craig *et al.* developed a statistical climate based distribution model which they suggest could be used to look at the impact of climate change on malaria transmission and combined with population, morbidity and mortality data to estimate the burden of disease and aid strategic control of malaria (Craig et al. 1999). Lindsay and Birley used a simple mathematical model to look at the effects of temperature on the ability of *An.*

*maculipennis* to transmit *P. vivax* malaria (Lindsay and Birley 1996). Martens used a statistical modelling approach to examine how climate change might affect global malaria transmission (Martens 1997, Martens 1995). Lindsay and Martens used this model to look at the implications of climate change scenarios on highland malaria in Africa and more specifically in Zimbabwe (Lindsay and Martens 1998).

The relationships identified and applied in the body of research on climate change and malaria transmission highlight the possibility of explicitly relating malaria transmission both spatially and temporally to climate variables such as temperature, rainfall and (less clearly) humidity. It is therefore possible to use these relationships to drive dynamic models of malaria transmission [such as those developed by Ross, (Garrett-Jones 1964, Macdonald 1952, Ross 1911, Saul et al. 1990)] and then use control theory to define a control problem and find its solution. The remainder of this thesis aims to do just that.

## 3.7 CHAPTER SUMMARY

This chapter has outlined the crucial roles of modelling in CEA. In particular its usefulness in decision analysis modelling and for extrapolating limited data. The use of modelling in the CEA of malaria control interventions and intervention in epidemics of other infectious diseases was reviewed, revealing that the use of population dynamic epidemiological models for evaluating malaria control interventions is a useful but neglected tool. The usefulness of population dynamic models for informing control policy was described using control theory illustrated with examples of models used to inform control policy in the past. The limitations of previous models were identified, in particular the failure to explicitly address seasonal variation in transmission. It was then suggested that the existing research on the relationship between climate variables and malaria transmission could be used to develop a population dynamic model of malaria transmission driven by climate variables which would address this limitation. The model can then be

combined with cost data and used as described in control theory to determine the optimal control policy.

# CHAPTER 4 - A MODEL OF MALARIA TRANSMISSION

## 4 OVERVIEW OF CHAPTER

This chapter describes the development of a climate driven dynamic model of malaria transmission. It provides information on the data set used to inform the development of the model, the structure of the model and the assumptions made. The model is then presented as a series of sub-models.

## 4.1 MODEL DEVELOPMENT

A generic dynamic model of malaria transmission, driven by temperature and rainfall was developed from existing rule-based biological models of the relationship between temperature and entomological variables (Detinova 1962, Lindsay and Birley 1996) and existing models of malaria transmission (Macdonald 1952, Saul et al. 1990). The model is designed for use in areas where the seasonal nature of malaria and epidemics does not allow for the development of immunity and where the frequency of epidemics is insufficient to allow any immunity to develop. The development of immunity is therefore excluded from the model structure. In addition, any occurrence of "rebound mortality" caused by interventions which prevent the development of immunity is not possible in such circumstances and is therefore not considered in the analysis of interventions.

Although the intention was to develop a generic climate driven malaria transmission model, preliminary testing of the model structure was carried out using epidemiological and meteorological data from the Western highlands of Kenya where malaria is unstable and prone to epidemics (Rees 1994). The Kenyan data set consisted of a time series of daily climate and malaria cases for the period January 1987 to August 1995 collected by Dr David Sang, Ministry of Health, Kenya. The malaria cases were in-patient malaria cases by day recorded at Kapsabet hospital in the Nandi district. The climate data was obtained for the nearest

meteorological station, (a distance of 40Km away) Eldoret Meteorological Station (station ID 63686, longitude 0.53, latitude 35.28, elevation 2133m) (NOAA 1996). It consists of daily minimum and maximum temperature (from which the arithmetic mean is calculated) and daily rainfall in mm.

Exploration of these data sets enabled key parameters in the model and their structural relationships to be identified and incorporated into the model. After this preliminary phase, which assisted the model development (see below) the generic model was then tested and fitted using a data set from Zimbabwe (chapter 5) and used in an analysis of the cost-effectiveness of malaria early warning systems for malaria control in Zimbabwe (chapter 7).

## 4.2 OVERVIEW OF GENERIC MODEL

The generic model uses mean monthly maximum temperature and the cumulative monthly sum of rainfall to calculate values for key parameters. These are then combined to give the number of new infections, super infections and people recovering which is then used to calculate the number of humans infected with malaria each month. The model is described as a series of six sub-models for simplicity and a brief outline of each sub-model follows below.

The first sub-model describes the number of mosquitoes as a function of rainfall. This sub-model only considers female mosquitoes since males do not take blood meals and therefore cannot transmit malaria.

The second sub-model describes the relationship between temperature and the length of the gonotrophic or feeding cycle. The gonotrophic cycle length is the period of time between successive egg laying. Although the length of the gonotrophic cycle is know to be related to humidity the relationship has not been clearly defined and was therefore not included in this sub-model.

The third sub-model describes the relationship between temperature and the sporogonic cycle length. The sporogonic cycle is the time taken for the parasite to undergo necessary development in the vector to enable the vector to transmit malaria. Sub-models two and three are based on the work carried out by Detinova (Detinova 1962).

The fourth sub-model describes vector survivorship in terms of survival probability per gonotrophic cycle and per day (Lindsay and Birley 1996). Combined with sub-model three (sporogonic cycle model) this allows calculation of the probability of the vector surviving long enough for sporogonic development to be completed. The vector survivorship sub-model also incorporates the effects of a residual spray programme, which is considered in terms of its impact upon the probability of vector survival per gonotrophic cycle.

The fifth sub-model describes the determination of the sporozoite rate. The sporozoite rate is the proportion of vectors with infectious pathogens in their salivary glands. The sporozoite rate sub-model used was developed in a paper by Saul *et al.* (Saul et al. 1990).

The sixth sub-model is the human infection model which calculates the number of new infections, superinfections and recoveries per month. These are combined to give an estimate of the total number of malaria infections at the start of the following month.

Sub-models one to five calculate variables which are not affected by values for the previous month therefore a sub-script indicating time is not included in these sub-models. The values in sub-model six are affected by values in the previous month hence a sub-script for time is included in this sub-model. The following assumptions are made throughout the generic model;

1. Vector and host populations are homogenous.

2. The probability of an individual vector surviving from one gonotrophic cycle to the next is constant and therefore independent of the age of that individual.

3. Vectors which become infectious remain infectious.

4. Feeding of an already infected vector on an infectious host has no effect on the course of the infection in the vector.

5. Vectors bite randomly.

6. Infected individuals who are bitten again by an infected vector will be superinfected. This is not counted as a new infection but will mean that the individual is not able to recover until the following month where recovery will then be governed by the probability of recovery.

The proportion of multiple or mixed blood meals due to interrupted feeding may not be significant for transmission. However, it is such a complex variable that it was outside the scope of this thesis and was therefore ignored in the model where all blood meals were assumed to be carried out in full on a single host.

## 4.3 MATHEMATICAL DESCRIPTION OF MODEL

### 4.3.1 SUB-MODEL 1 MOSQUITO POPULATION

A linear relationship is assumed between monthly rainfall ($R$) and the number of mosquito's emerging each month of the form:

$$q = \mu R \tag{1}$$

In order to derive the relationship between rainfall and vector numbers a literature review was carried out to establish the number of bites per person per night by month in locations across Africa (E. Savage and M. Thomson unpublished data). The locations were geo-referenced and then the climatic rainfall data for the relevant month and location was extracted from a climate surface data set (Hutchinson et al. 1995). The relationship between rainfall and the number of bites

per person per night for each location was plotted and examined. The best approximation was given by a linear relationship between the two.

### 4.3.2 SUB-MODEL 2 GONOTROPHIC CYCLE LENGTH

The gonotrophic cycle ($U$) is defined as the length of time between successive blood meals. It can be broken down into three phases, as described by Beklemishev (1940) cited in (Detinova 1962). Firstly, the search for the host and the bite, secondly, the digestion of the blood-meal and the maturation of the ovaries and thirdly, the search for a suitable water body and oviposition (egg-laying). Phase one and three are considered together as $\upsilon$, and phase 2 is $u$, hence gonotrophic interval length is given by:

$$U = \upsilon + u \tag{2}$$

Phase one and three ($\upsilon$) is assumed to be a constant and the duration of phase two of the cycle ($u$) is known to be directly related to temperature and humidity and can be calculated using the formula developed by Detinova for given humidity ranges (Detinova 1962). The formula is expressed as follows:

$$u = \frac{f_U}{T_U - g_U} \tag{3}$$

Where $T_U$ is temperature adjusted by + $l$ °C to account for the difference between the outside air temperatures (where the data were collected) and the temperature of the premises used as the main day resting places of the mosquitoes.

$$T_U = T + l \tag{4}$$

This correction factor ($l$) described by Detinova is specific to each location based on the local climate and style of premises. $f_U$ is the degree days needed to complete development and $g_U$ is a development threshold below which development ceases. Table 4-1 shows the results of Detinova's work on *An.*

*maculipennis* for given humidity ranges, (results were not available for *An gambiae*). The sub-model uses the formula given for relative humidity of 70-80% i.e. $f_U = 36.5$ and $g_U = 9.9$

Substituting (4) into (3) and then into (2) gives the total gonotrophic cycle length:

$$U = \upsilon + \left( \frac{f_u}{(T + l) - g_u} \right) \tag{5}$$

### 4.3.3 SUB-MODEL 3 SPOROGONIC CYCLE LENGTH

The length of the sporogonic cycle is the length of time from the female mosquito taking a blood meal to the appearance of sporozoites in its salivary glands. This process is highly dependent on temperature and has been expressed in the following form by Detinova (Detinova 1962):

$$N = \frac{f_N}{(T_N - g_N)} \tag{6}$$

Where $f_N$ represents degree days needed to complete development, taken here as 111°C for *P. falciparum* and $g_N$ represents the threshold below which development ceases, taken here as 18°C which is the unadjusted minimum temperature stated by Detinova.

Temperature ($T_N$) must also be adjusted here to account for differences between indoor and outdoor resting temperatures, however the method is slightly more complex since sporogonic development takes place while the vector is both indoors and outdoors. A weighting system, based on the period of time the vector spends indoors (phase 2 ($u$) of the gonotrophic cycle) as a proportion of time, is used to adjust temperature. The proportion of time spent indoors is given by ($u/U$). This is multiplied by the difference between indoor and outdoor resting temperatures ($\pm l°C$) to give a weighted correction factor of:

$$T_N = T + l\left(\frac{u}{U}\right) \tag{7}$$

Hence substituting (7) into (6) gives

$$N = \frac{f_N}{\left(T + \frac{lu}{U}\right) - g_N} \tag{8}$$

### 4.3.4 SUB-MODEL 4 VECTOR SURVIVORSHIP

The probability of vector survival is expressed firstly, in terms of survival per gonotrophic cycle and secondly, using the length of the gonotrophic cycle ($U$), as a daily probability of survival ($P$), as suggested by Lindsay and Birley (Lindsay and Birley 1996). The probability of a vector surviving each gonotrophic cycle is given by $\alpha$ which is constant and independent of the length of the gonotrophic cycle as suggested by Hii *et al.* (Hii et al. 1990). Hence the probability of daily survival is given by:

$$P = \alpha^{1/U} \tag{9}$$

This assumes that a mosquito's probability of daily survival decreases as the feeding cycle gets shorter (as temperature increases in this sub-model).

In order to model the affects of a residual spray programme the sub-model defines two populations of mosquitoes those covered and not covered by the spray programme. The proportion of the population affected by a spray programme is given by the percentage coverage achieved by the spray programme (C), and the proportion not affected by the spray programme is ($1$-$C$). The percentage of vectors surviving each gonotrophic cycle is expressed as $\alpha$ in the population not covered by the spray programme (as described above). This is initially reduced by a factor $\beta$ in the population covered by the spray programme and then increases linearly back

towards $\alpha$ throughout the effective residual life of the insecticide. Hence for the total population:

The mean probability of surviving gonotrophic cycle is:

$$\alpha(1-C)+\alpha\beta C \qquad (10)$$

Substituting (10) into (9) gives

The mean probability of daily survival ($P$) is:

$$\left(\alpha(1-C)+\alpha\beta C\right)^{1/U} \qquad (11)$$

The probability of the vector surviving sporogeny is crucial for the transmission of malaria to occur. This is expressed a function of the probability of daily survival ($P$) and the length of the sporogonic cycle ($N$) (as described above). Probability of surviving sporogeny is:

$$P^N \qquad (12)$$

## 4.3.5 SUB-MODEL 5 SPOROZOITE RATE

The sporozoite rate ($S$) is the proportion of vectors with infectious pathogens. Before describing the sporozoite rate sub-model, four terms must be defined:

($h$) is the proportion of human blood fed mosquitoes i.e. those feeding on humans rather than other species e.g. cattle.

($x$) is the proportion of humans that are infectious.

($k$) is the probability of the vector becoming infected per infectious meal

($v$) is the probability of the pathogen becoming infectious in the vector

Thus the probability of the vector *not* becoming infectious as a result of a single feed is:

$$1-xhkv \qquad (13)$$

The sporozoite rate was derived in the manner described by Saul et al. (Saul et al. 1990) and is shown below. For convenience the method shown uses the probability of surviving the gonotrophic cycle for an unsprayed population (α), in a sprayed situation this is substituted for $\alpha(1-C)+\alpha\beta C$.

Where there are $n$ vectors feeding for the first time on a host per day, then the total number of vectors feeding per host will be:

$$n+n\alpha+n\alpha^2+\ldots \tag{14}$$

The sum of the infinite series (14) can be simplified to:

$$\frac{n}{(1-\alpha)} \tag{15}$$

The total number of vectors biting a single host today that will survive a sporogonic cycle is:

$$\frac{nP^N}{(1-\alpha)} \tag{16}$$

As shown previously in (13) the probability of a vector not becoming infectious as a result of a single feed is:

$$1-xhkv \tag{13}$$

One sporogonic cycle ago, the number of vectors biting for the first time and not becoming infected is:

$$n(1-xhkv) \tag{17}$$

In addition to these vectors, a number of vectors will be biting for the 2nd time, having not being infected previously and not becoming infected this time, given by:

$$n(1-xhkv)\alpha(1-xhkv) \tag{18}$$

And a 3rd time having not being infected previously and not becoming infected this time, given by:

$$n(1-xhkv)\alpha(1-xhkv)\alpha(1-xhkv) \tag{19}$$

And so on

Thus the number of vectors remaining uninfected one sporogonic cycle ago is:

$$n(1-xhkv)+n\alpha(1-xhkv)+n\alpha^2(1-xhkv)=\frac{n(1-xhkv)}{1-\alpha+xhkv\alpha} \tag{20}$$

Of these vectors the number of vectors old enough to be infectious but remaining uninfectious today (as opposed to one sporogonic cycle ago) is (20) multiplied by the probability of surviving the sporogonic cycle (12):

$$\frac{n(1-xhkv)P^N}{(1-\alpha+xhkv\alpha)} \tag{21}$$

The number of infectious vectors feeding per day can be found by subtracting expression (21) from expression (16). By dividing this figure by the total number of vectors feeding (expression (15) and rearranging, the proportion of vectors which are infectious, or, the sporozoite rate (S) is:

$$S=\frac{xhkvP^N}{(1-\alpha+xhkv\alpha)} \tag{22}$$

## 4.3.6 SUB MODEL 6 HUMAN INFECTION

The number of infectious mosquitoes biting humans is given by:

$$Sqa \tag{23}$$

Where ($S$) is the sporozoite rate ($q$) is the number of mosquitoes (as described in mosquito population sub-model), and ($a$) is the person biting habit. The

person biting habit represents the *frequency* at which mosquitoes feed on humans as opposed to other vertebrates and is given by the expression:

$$a = \frac{h}{U} \tag{24}$$

Where ($h$) is the proportion of human blood fed mosquitoes (as described above) and ($U$) is the gonotrophic cycle length.

Where the total human population is equal to ($d$), the probability of a human receiving a bite from a specific mosquito is:

$$\frac{1}{d} \tag{25}$$

Therefore the probability of a human *not* getting bitten by a specific mosquito is:

$$1 - \frac{1}{d} \tag{26}$$

Thus the probability of a human not being bitten by any infectious mosquitoes is:

$$\left(1 - \frac{1}{d}\right)^{Sqa} \tag{27}$$

The probability of a human receiving an infectious bite ($R$) is therefore:

$$R = 1 - \left(1 - \frac{1}{d}\right)^{Sqa} \tag{28}$$

An infectious bite received by a human is classed as a 'new infection' if it is on an uninfected human ($d$-$I$), and a 'superinfection' if it is on an already infected human ($I$). The number of new infections arising is given by:

$$F = R(d - I) \tag{29}$$

The number of superinfections is given by:

$$Z = RI \tag{30}$$

Infected humans who are not superinfected are able to begin recovery with a fixed probability of recovery ($r$), hence the number of people recovering at time t ($c$) is:

$$c = (I - Z)r \tag{31}$$

The number of infected humans at time t ($I_t$) is simply the number of infected humans at time t-1 ($I_{t-1}$), minus the number of people recovering at time t ($c_t$), plus the number of people newly infected at time t ($F_t$). Thus

$$I_t = I_{t-1} - c_t + F_t \tag{32}$$

Similarly, the number of uninfected people in the population at time t is:

$$d - I_t = d - I_{t-1} + c_t - F_t \tag{33}$$

Table 4-2 provides a summary of the variables used in the model with the notation used to represent them.

Table 4-1 Phase II of Gonotrophic Interval at Different Humidities (Detinova, 1962)

| Phase II of Gonotrophic Interval | |
|---|---|
| Relative Humidity Range | Formula |
| 30-40% | $\frac{65.4}{T_u - 4.5}$ |
| 70-80% | $\frac{36.5}{T_u - 9.9}$ |
| 90-100% | $\frac{37.1}{T_u - 7.7}$ |

Table 4-2 Summary of Variables Used in Model

| Notation | Description |
|---|---|
| *(T)* | *Temperature in °C* |
| *(R)* | *Rainfall in mm* |
| *(d)* | *Human Population* |
| *($\mu$)* | *Rainfall to Mosquito Constant* |
| *(h)* | *Proportion of Human Blood Fed Mosquitoes* |
| *(l)* | *Difference Between Indoor and Outdoor Resting Temperature (°C)* |
| *(C)* | *Percentage Coverage Achieved by Spray Programme* |
| *($\alpha$)* | *Proportion of Vectors Surviving Feeding Cycle in Unsprayed Population* |
| *($\alpha\beta$)* | *Proportion of Vectors Surviving Feeding Cycle in Sprayed Population* |
| *(k)* | *Probability of Vector Becoming Infected per Infectious Meal* |
| *(v)* | *Probability of Pathogen Becoming Infected in Vector* |
| *(r)* | *Probability of Recovery* |
| *(q)* | *Number of Mosquitoes* |
| *($\upsilon$)* | *Length of Phase 1 & 3 of Gonotrophic Cycle* |
| *(u)* | *Length of Phase 2 of Gonotrophic Cycle* |
| *(U)* | *Total Gonotrophic Cycle Length* |
| *(N)* | *Sporogonic Cycle Length* |
| *(a)* | *Human Biting Habit* |
| *(P)* | *Mean Probability of Mosquito Survival* |
| *($P^N$)* | *Probability of Vector Surviving Sporogeny* |
| *($I_t$)* | *Number of Infectious People at Time t* |
| *(x)* | *Proportion of People who are Infectious* |
| *(xk)* | *Probability of Vector Becoming Infected per Bite* |
| *(S)* | *Sporozoite rate* |
| *(R)* | *Probability of a Human Receiving an Infectious Bite* |
| *(d-I)* | *Number of Uninfected People* |
| *(F)* | *Newly Infected Humans* |
| *(Z)* | *Number of People Receiving Superinfection* |
| *(C)* | *Number of People Recovering* |

# CHAPTER 5 - APPLYING AND FITTING THE GENERIC MODEL USING DATA FROM ZIMBABWE

## 5 OVERVIEW OF CHAPTER

The first part of this chapter describes the way in which the generic model was used to predict recorded malaria case data from Hwange district in Zimbabwe using meteorological data from the area and information on the malaria control activities carried out. It also describes the techniques used for estimating the value of unknown variables. The second section then examines the sensitivity of the generic model to changes in the values of input variables. From now on any mention of the model will refer to the generic model.

## 5.1 DESCRIPTION OF STUDY AREA

The Matabeleland North Province of Zimbabwe lies in the north west of the country, bordering with Zambia to the north and Botswana to the west. It has an area of 75025km$^2$, and an estimated population of 735000 people of which an estimated 124803 are under five years of age (Health Information Unit 1995). Malaria in Matabeleland North is seasonal, normally beginning in December and continuing until May with the peak transmission occurring during March/April, after the rains.

Hwange district has one of the highest incidences of malaria in Matabeleland North, although all districts in the province are affected by malaria. Average monthly minimum and maximum temperatures in Hwange district were 13.6°C and 29.4°C during the period of analysis and mean annual rainfall was 482mm. Malaria transmission in this district is therefore highly seasonal and inter-annual variability in reported case numbers is high and is associated with rainfall as in the 1996 epidemic year (see Figure 5-1 below). Hwange district was chosen for the analysis because variation in cases numbers are clearly related to weather anomalies and

meteorological, epidemiological and costing data (see Chapter 6) was available over a number of years.

The malaria case data used to validate the model is clinically diagnosed out-patient case numbers reported by the district health service to the central level Health Information and Surveillance Unit at the Ministry of Health and Child Welfare in Harare. It has long been known that in the absence of confirmation by examination of the blood for malaria parasites, the use of clinical symptoms alone may result in extensive misdiagnosis since many non-malaria febrile illnesses will be diagnosed as being malaria (WHO 2001). However, slide positivity rates in March 1996 at Hwange district hospital (Victoria Falls) reached over 65%. Compared to 1997 and 1998, 1996 was also found to have unusually high hospital malaria in-patients and deaths (source: Victoria Falls Hospital records).

In Zimbabwe as in many other malarious countries, presumptive malaria cases are used along with other information reported from districts by the Ministry to inform resource allocation decision making. Therefore, despite known limitations clinical data on malaria is the only available source of information on which to base this analysis.

## 5.2 METHODOLOGY

### 5.2.1 RUNNING AND TESTING THE MODEL

Monthly temperature and rainfall data from Hwange Meteorological Station for the period January 1993 to December 1997 were placed into the model along with annual population data from the district (see Table A-1 in Appendix for climate data). Initial values of model variables were estimated based on data or *a priori* assumptions and placed into the model which was then run. The models ability to predict the relative changes in malaria cases reported in the Hwange district during the period January 1994 to June 1998 (source: National Health Information and Surveillance Unit, Ministry of Health and Child Welfare) was measured by cross

correlating the model results for the sum of new infections ($F$) and super infections ($Z$) with the actual number of cases recorded at government health facilities. This was used because it is assumed that the case data will reflect not only new infections but also individuals who are still carrying parasites but are no longer clinically sick who receive an new infection and are therefore sick again.

### 5.2.2 FITTING AND SCALING THE MODEL

The variables were then altered one at a time with the model being rerun each time a variable was changed and the results of the cross correlation recorded. The value of each variable that predicted cases with the highest correlation coefficient was used in the proceeding analysis. This process was repeated for all variables until the value of each variable that yielded the highest correlation coefficient was identified. The 'solver' function in Excel (Microsoft 1993) was then used to further improve the correlation between the model results and the case data. The solver function determines the maximum or minimum value of one cell by changing other cells and in this case was used to maximise the correlation between modelled and actual cases by varying unknown model inputs.

Once the set of variable yielding the highest correlation coefficient had been identified the model was scaled to the case data based on the following assumptions and methodology. The model predicts all cases occurring within Hwange district for the given period of time, however not all malaria infections will result in a case appearing at the health centre and being recorded in the number of malaria cases used to fit the model. Since the analysis is limited to the provider perspective (see Chapter 6) only cases reporting and incurring costs at government health facilities are relevant. A further parameter was therefore introduced into the model representing the proportion of cases in the community reporting at the government run health facilities ($\lambda$). Cases predicted by the model were multiplied by this proportion to achieve the best match of the modelled case numbers with the

actual case numbers, the resulting data was defined as 'cases reporting by month' and is used for the cost-effectiveness analysis in Chapter 7.

The best match was obtained using the following method. The sum of cases predicted by the model was subtracted from the sum of actual cases and the result squared to obtain a positive value:

$$(\text{Sum of cases predicted by model} - \text{Sum of actual cases})^2 \qquad (34)$$

The 'solver' function in Excel (Microsoft 1993) was then used to obtain the value of $\lambda$ which minimised the value of equation 34.

Although this method ensures that the number of cases predicted by the model is in line with the actual number of cases recorded in the Hwange district malaria statistics it is unlikely to reflect the actual number of malaria cases in the district or the number of true malaria cases reporting at health centres and facilities in Hwange for the following reasons. A large proportion of malaria cases will not be recorded in government figures as the patients will never access formal government health facilities; it has been estimated that in parts of Africa over 80% of all malaria cases and deaths will occur in the community and will not be recorded at health facilities (WHO 2001). Patients may have a preference for self treatment, traditional medicines/healers or may simply be too far away from government facilities to access them. The level of access in Hwange district is unlikely to be as low as 20% since Zimbabwe has a relatively good health infrastructure compared to many parts of Africa, however the proportion of patients reporting at government health facilities will certainly be less than 100%. The malaria statistics used in the analysis are clinical malaria cases and the majority of them will not have been confirmed by laboratory diagnosis. There is therefore likely to be some degree of over and misdiagnosis of malaria, particularly in the dry season.

### 5.2.3 CHOICE OF INITIAL VALUE AND/OR RANGE OF VALUES TESTED IN SENSITIVITY ANALYSIS

Once the set of variables yielding the highest correlation coefficient had been identified and the model had been scaled to obtain cases reporting each month (as described above), individual variables were varied one at a time in order to examine the sensitivity of the model to changes in variable values. During this process variables were identified for two-way or multi-way sensitivity analysis which was then carried out. The following sections describe the choice of initial parameter value and provide justification for the range of values tested in the sensitivity analysis.

#### 5.2.3.1 HUMAN POPULATION SIZE

The population estimates for Hwange district were obtained from the National Heath Information and Surveillance Unit, Department of Epidemiology and Disease Control, Ministry of Health and Child Welfare for the period 1994-1997. The estimate for 1999 was obtained from Hwange District Health Service. No data was available for 1993, or 1998, therefore the linear trend of the series (missing value function in SPSS Software (SPSS Inc. 1999) was used to estimate values of the population for the missing years. The estimates of the population of Hwange district used in the analysis are shown in Table 5-1 below.

#### 5.2.3.2 INITIAL NUMBER OF INFECTED PEOPLE

The model begins in January 1993, one year before data on the number of malaria cases is available. This was done for two reasons, firstly to obtain a longer data set as it was known (from the initial construction of the model) that lags may be involved therefore some overlap of years was useful and secondly to allow the model to "settle in" for a year. The value of the initial number of infected people had therefore to be estimated, arbitrary values of $I_{t=0}$ between 100 and 5000 (0.07% - 3.4% of the total population in the first year) were therefore tested.

### 5.2.3.3 RAINFALL TO MOSQUITO CONSTANT

Very little is known about the relationship between rainfall and vector numbers so it was difficult to know what range of numbers to test for the value of the constant ($\mu$) in the rainfall to mosquito sub model. Therefore the lowest value of ($\mu$) that still resulted in transmission was identified, this was then increased and compared to the actual number of cases until the value with the highest correlation and closest approximation to actual case numbers was identified. Values of between 250000 and 1500000 were tested with 250000 being the lower limit for the model to predict a realistic number of cases.

### 5.2.3.4 PROPORTION OF HUMAN BLOOD FED MOSQUITOES

The proportion of human blood fed mosquitoes ($h$) depends on the preference of the vector species and the availability of human or other blood meals. Values of $h$ between 0 and 1 were tested in the model.

### 5.2.3.5 DIFFERENCE BETWEEN INDOOR AND OUTDOOR RESTING TEMPERATURE

The difference between outdoor and indoor resting temperatures ($L$) will depend upon the style of dwelling and on what activities are carried out and the number of people inside the dwelling. No information was available on likely values for $L$ therefore it was varied between an arbitrary range of 0 and 10°C.

### 5.2.3.6 SPRAY PROGRAMME COVERAGE

Residual spraying was carried out annually in the district during the period of analysis, however data on the coverage achieved by the spray programme was not available for all years. Limited information was available regarding coverage in more recent years and this was used to provide an estimate of the possible coverage achieved by the programme in previous years. The lack of data was further complicated by the ambiguous use of the term 'coverage' in source information, which does not refer to coverage of the total district but actually refers

to coverage of the target area delineated for the spay programme. Reported coverage percentages therefore had to be converted to actual district coverage for use in the model, this was problematic since information on the size of the target area was not available. Actual coverage therefore had to be estimated from the available information and used to inform the choice of estimates of coverage used in the analysis.

Spray programme coverage figures as a percentage of the target population from Hwange district were available for 1995/96, 1996/97, 1997/98 and 1998/99. In 1998/99 the total population was estimated to be 167343, and the actual population covered was estimated to be 39416, which is 23.6% (24%). Coverage in this year was reported to be 90%, therefore the target population must have been 43796 people, which is equivalent to 26% coverage of the total population. Data on the number of people covered was not available for years prior to 1998/99 therefore coverage had to be estimated and varied in the sensitivity analysis. Percentage coverage of the target population cannot be used to estimate coverage without information on the target population size, coverage was assumed to be the same for all years since no information was available on changes in the target population size. Actual coverage in recent years was estimated to range between 24-32%, 24% was used as the baseline value of coverage in all years, however values of 0%, 50%, 75% and 100% were also tested (see Chapter 7).

For the 1995/96 spray season the only information available regarding coverage was a reported coverage of 55%, this could not be used to calculate actual coverage since no information on the size of the target area was available. The start date of the spraying activities was 9$^{th}$ December 1995 and the spray programme activities ceased on 21$^{st}$ January 1996. In 1996/97 the reported coverage was 85.2% (source: Personal Communication with District Environmental Health Officer) and the actual population covered was estimated to be 47821

(source: Matabeleland North Malaria Review Meeting, Zambezi River Lodge, 22-24 June 1998). Using this information the target population was estimated to be 56128 (36% of the total population), which represents actual coverage of 31%. The start date of the spray programme was 1st November 1996 and the end date was 21st January 1997. The same data was available for 1997/98 which yielded an actual coverage of 32%, spray programme start and end dates were 1st November 1997 and 21st January 1998 respectively. In 1998/99 the estimated population covered was 39416 (source: Provincial Medical Office Matabeleland North) which is 24% of the total district population in that year.

### 5.2.3.7 PROBABILITY OF VECTORS SURVIVING FEEDING CYCLE

The value of $\alpha$ is the probability of vectors surviving each feeding cycle and is considered to be fixed throughout the model, however it is reduced by a factor of $\beta$ when spraying is carried out. The reduction in survivorship caused by spraying is assumed to occur as soon as the spray programme is completed to its defined level of coverage, for example if the spray programme is completed during January its effectiveness will start and be at a maximum in January. The residual action of the insecticide used is assumed to last for six months with a linear decline in effectiveness such that after 6 months the insecticide is ineffective.

Survivorship is critical to malaria transmission and altering $\alpha$ or $\beta$ dramatically alters the number of cases predicted by the model. The value of $\alpha$ is usually in the range of 0.4-0.6 (Hii et al. 1990). In view of the importance of these variables, in particular the value of each relative to the other, which dictates the effectiveness of the intervention, data was obtained from the literature to inform the choice of values for $\alpha$ and $\beta$. Magesa *et al.* found that the mean ovarian age grade of *An. gambiae* in traditional Tanzanian villages before and after DDT house spraying was 1.229 and 0.400 respectively (Magesa et al. 1991). The ovarian age grade is determined by dissection of the ovaries to count the number of dilatations

left in the ovariole stalks subsequent to each ovulation and oviposition which corresponds to the number of gonotrophic cycles undergone (Gilles and Warrell 1993). These values were used to calculate the value of α and αβ as follows:

If the probability of vectors surviving sporogeny before spraying is $\alpha$, the mean ovarian age grade of the population at any given time $\bar{t}$ is given by:

$$\bar{t} = \frac{\int_0^\infty t(\alpha)^t \, dt}{\int_0^\infty \alpha^t \, dt} = -\frac{1}{\ln \alpha} \qquad (34)$$

With spraying the probability of surviving the feeding cycle is given by $\alpha\beta$, similarly the mean ovarian age grade of the population at any given time after spraying is:

$$\bar{t} = \frac{-1}{\ln \alpha\beta} \qquad (35)$$

Hence before intervention substituting data from Magesa *et al.* (1991) into (34) gives:

$$\frac{-1}{\ln \alpha} = 1.229$$

Rearranging gives:

$$\alpha = e^{-1/1.229}$$

After intervention substituting values from Magasa *et al.* into (35) and rearranging gives:

$$\frac{-1}{\ln \alpha\beta} = 0.4$$

$$\alpha\beta = e^{-1/0.4}$$

In addition to the value of $\alpha$ shown above, other values ranging between 0 and 1 were tested. For $\alpha\beta$ values between 0 and $\alpha$ were tested.

### 5.2.3.8 PROBABILITY OF VECTOR BECOMING INFECTED PER INFECTIOUS MEAL AND PROBABILITY OF THE PATHOGEN BECOMING INFECTIOUS IN THE VECTOR

The probability of a vector becoming infected per infectious meal ($k$) and the probability of the pathogen becoming infectious in the vector ($v$) were varied between 0 and 1. The recovery rate ($r$) represents the probability of cases recovering within one month; this was varied between 1/2 and 1/200 with 0 also being tested.

## 5.3 RESULTS OF MODEL FITTING

This section describes the values of variables used in the model and the relationship between changes in these variables and the correlation between the actual case data and that predicted by the model.

### 5.3.1 VALUES OF VARIABLES ACHIEVING BEST FIT WITH DATA

Table 5.3.1 shows the value of each variable which achieved the highest correlation coefficient between the model output 'new infections and superinfections' (modelled cases) and the data set (actual cases), after using the solver function in Excel. Combining these variable with the population data (Table 5-1) and climate data (Table A-1, Appendix) predicted the actual case data with a lag of 4 months and a correlation coefficient of 0.825 ($r^2$=0.6814). Figure 5-2 shows a scatter plot of actual cases against modelled cases and a fitted trend line, illustrating that the model tends to over predict case numbers. Figure 5-3 illustrates the modelled and actual reported malaria cases. The model clearly picks out the seasonality of transmission and also the magnitude of each malaria season. The double spike in modelled cases in 1997 is a result of the rainfall that year which followed the same pattern (see Figure 5-1). Actual cases would be unlikely to follow this exact pattern therefore aggregating modelled cases by season may be useful to avoid unrealistic monthly variation caused by short term rainfall patterns.

Further analysis regarding the models ability to predict the magnitude or severity of malaria seasons was carried out by comparing the deviation from the mean value for each month for modelled and actual cases. The average value for modelled and actual cases was calculated by month to create an annual pattern. The value of modelled and actual cases for each month in the data set was then subtracted from the mean for modelled and actual cases respectively to calculate the deviation from the mean for each month in the data set. Matched pairs of the deviation from the mean for each month of modelled and actual cases were then plotted on a scatter plot and a trend line was fitted (Figure 5-4). This analysis reveals that deviations from the mean in the actual cases are positively related to deviations from the mean in the modelled cases with an r-squared value of 0.8806. In other words, the model predicts well the magnitude of malaria each month.

The coverage achieved by the spray programme could not be varied using the solver function for reasons related to the model structure. In the manual varying of parameters to obtain the best fit with the data coverage of 50% improved the correlation coefficient very slightly to 0.828 ($r^2$ =0.6854) and the value of $\lambda$ necessary to set predicted cases equal to recorded cases was increased to 0.78. However, based on the available information on coverage which placed it at around 24% and in view of the small increase in correlation achieved by using coverage of 50%, a value of 24% was chosen in the baseline model (this was varied later in the sensitivity analysis and the cost-effectiveness analysis).

The values of $\alpha$ and $\alpha\beta$ were not varied using the solver function because of the critical relationship between the two values which it was considered should be based on actual data rather than varied to improve the fit of the model. However, during the sensitivity analysis other values of $\alpha$ were tested while all other parameters were held constant. This analysis revealed that, *ceteris paribus* the highest correlation coefficient of all values tested (see section on sensitivity analysis

of $\alpha$ for details of other values tested) was obtained with $\alpha$=0.44. Other values of $\alpha\beta$ were also tested in the sensitivity analysis revealing that a higher correlation coefficient (0.830, $r^2$ =0.6893) could obtained with $\alpha\beta$ equal to 0, in which case $\lambda$ (the proportion of case that report) would increase to 0.59. However in order to maintain the relationship between the value of $\alpha$ and $\alpha\beta$ obtained from the Magasa data (Magesa et al. 1991) and in view of the relatively small increase correlation achieved by altering the value of $\alpha\beta$ the original value was maintained.

## 5.4 RESULTS OF SENSITIVITY ANALYSIS

The following section describes the results of the sensitivity analysis in which the values of input parameters were varied one at a time in order to examine the impact on the model of altering each parameter and establish the relative sensitivity of the model to changes in each variable.

### 5.4.1 SENSITIVITY OF THE MODEL TO CHANGES IN THE INITIAL NUMBER OF INFECTED PEOPLE ($I_{t=0}$)

Values of $I_{t=0}$ tested ranged between 100 and 3000 as shown in Figure 5-5 below. As $I_{t=0}$ increases so the number of cases predicted by the model increases. The increase is greater during periods of lower transmission than in times of high transmission where increasing $I_{t=0}$ has limited effect on the already high levels of malaria. The sensitivity of the model to $I_{t=0}$ is reduced as the model continues because as we move further and further away from t=0 the importance of the initial number of infected people will be less and less. Therefore the longer the period of time the model is run so its sensitivity to $I_{t=0}$ will decrease. With long data sets the value of $I_{t=0}$ will become less and less important which is a positive aspect of the model since it would be difficult to obtain data on the value of $I_{t=0}$. Figure 5-5 shows the number of cases predicted by the model for different values of $I_{t=0}$. It illustrates that the model is robust to changes in the value of $I_{t=0}$ which works as a scaling factor particularly on the early model results.

### 5.4.2 SENSITIVITY OF THE MODEL TO CHANGES IN THE RAINFALL TO MOSQUITO CONSTANT ($\mu$)

The value of μ was varied between 250000 and 1500000 as shown in Figure 5-6 below. The model is sensitive to changes in the value of μ, particularly in relatively dry years when the value of μ plays a more important role than temperature in determining the level of transmission.

Unfortunately no *a priori* information is available on the exact relationship between rainfall and vector numbers since this is extremely difficult to quantify. However, the value of $\mu$ could be verified using data on the 'human biting rate' which can be obtained from the field. The human biting rate is the number of bites per person per night by the vector population and is normally quantified in the field using human bait catches. Macdonald defined the human biting rate as a product of the relative density of adult female anophelines to humans ($q\mu / d$ in this model) and the human biting habit ($a=h/U$ in this model) (Macdonald 1952), thus:

Human Biting Rate = $\frac{R\mu}{d}.\frac{h}{U}$

Rearranging gives:

$\mu = \frac{dU}{Rh}$. Human Biting Rate

Therefore the value of $\mu$ could be estimated from known variables using observed data on the value of the human biting rate. Data on the human biting rate for Hwange District by month was not available therefore the value of $\mu$ was determined by fitting the model to the data until the best correlation was achieved as described above.

### 5.4.3 SENSITIVITY OF THE MODEL TO CHANGES IN THE PROPORTION OF HUMAN BLOOD FED MOSQUITOES ($h$)

Values of $h$ between 0.1 and 1 were tested as shown in Figure 5-7. The model is extremely sensitive to changes in the value of the proportion of human blood fed mosquitoes ($h$) because it directly affects the person biting habit and the sporozoite rate. Higher values of $h$ increase the person biting habit leading to an increase in the probability of receiving an infected bite and therefore an increase in transmission. An increase in $h$ also increases the sporozoite rate, further increasing the probability of a human receiving an infected bite. Higher values of $h$ tend to overestimate the number of cases in less severe years and underestimate the number of cases in severe years. They also cause the model to reach a saturation point (see curves $h$=0.9, and $h$=1 in Figure 5-7) where all the population is either infected, or superinfected and as soon as people recover and enter the uninfected population they are immediately reinfected. Low values of $h$ underestimate all years; the timing of peaks and troughs is not affected by altering h although the model is sensitive to changes in the value of $h$ which reflects the importance of the proportion of human blood fed mosquitoes in reality.

### 5.4.4 SENSITIVITY OF THE MODEL TO CHANGES IN TEMPERATURE ADJUSTMENT FACTOR $l$

Values of $l$ between 1 and 10 were tested in the sensitivity analysis as shown in Figure 5-8. Decreasing $l$ increases the length of both the gonotrophic and sporogonic cycle (biological processes take longer at cooler temperatures). An increase in the length of the gonotrophic cycle will increase the probability of daily survival of the vector because survivorship is constant for each gonotrophic cycle. An increase in the length of the sporogonic cycle means that vectors must survive for longer in order for the parasite to fully develop. However, the increased probability of daily survival outweighs this affect, such that, the lower the value of $l$ the higher the number of cases predicted by the model. Increasing the temperature of indoor resting places ($l$) reduces transmission because of its affect on mosquito

survivorship. The warmer the indoor resting place the more quickly the mosquito digests it blood meal and lays its eggs and then goes out to feed again.

The mosquitoes probability of survival is expressed as survival per gonotrophic cycle, therefore the more frequently the mosquito seeks a bloodmeal the higher its chances of mortality. Again this affect outweighs the effect on the time needed for sporogonic development and higher values of $l$ reduce transmission according to the model. The effect of $l$ will depend on the actual temperature; at threshold temperatures the value of $l$ is critical in determining whether or not transmission occurs. For example, if unadjusted temperature is too low for the vector to survive sporogeny the value of $l$ may critically alter transmission. However, if temperature is within the limits suitable for transmission the value of $l$ will be less important unless it is sufficiently high to take temperature beyond the limit for transmission.

The model is relatively insensitive to changes in $l$, particularly in periods of low transmission and for relatively low values of $l$.

### 5.4.5 SENSITIVITY OF THE MODEL TO CHANGES IN COVERAGE ($C$)

Values of coverage ($C$) between 0% and 100% were tested as shown in Figure 5-9 below. Changing the percentage coverage achieved by a spray programme leaves the model results largely unchanged at times with high transmission, however at the margins increasing coverage can prevent secondary epidemic peaks occurring. For example in June-September 1995 a second epidemic peak is prevented with coverage of 100% and is dramatically reduced with coverage of 50% compared to the scenario with 0% or 24% coverage. Similar situations occur in 1996 and 1997. Thus the model accurately reflects one of the situations identified by Najera where residual spraying is indicated:

*"the prevention of malaria transmission in areas where the epidemic is expected to recur or to spread in the forthcoming transmission season. It* [residual

spraying] *is also one of the main methods of preventing epidemics in areas where a forecasting system has detected an increased epidemic risk*" (Nájera 1998)

### 5.4.6 SENSITIVITY OF THE MODEL TO CHANGES IN PROPORTION OF VECTORS SURVIVING FEEDING CYCLE IN UNSPRAYED POPULATION ($\alpha$)

The variable $\alpha$ was varied between 0.1 and 1 in the sensitivity analysis as shown in Figure 5-10 (only values between 0.3 and 0.8 shown on the chart for clarity). Vector survivorship is critical to malaria transmission therefore varying $\alpha$ has dramatic effects on the model results with low values of $\alpha$ virtually eliminating transmission and high values exaggerating cases in less severe years in relation to the number of cases in severe years. Values of $\alpha$ around 0.6 and above cause the model to reach saturation point at every peak season, where almost everyone is in a state of infection, superinfection or has just recovered from infection. The chosen value of $\alpha$ (=0.44) causes the model to approach this saturation point only in the 1995 malaria season as a result of the heavy rains preceding that season. This is also reflected in the actual case data (as shown in Figure 5-1 above). The model is highly sensitive to changes in $\alpha$.

### 5.4.7 SENSITIVITY OF THE MODEL TO CHANGES IN PROPORTION OF VECTORS SURVIVING FEEDING CYCLE AFTER SPRAYING ($\alpha\beta$)

Values of $\alpha\beta$ between 0 and $\alpha$ were tested in the sensitivity analysis shown in Figure 5-11. The model is relatively insensitive to changes in the proportion of vectors surviving the feeding cycle after spraying as mentioned previously.

This sensitivity analysis only tested changes in the value of $\alpha\beta$ however, since the value of this variable will begin to increase as the insecticide loses efficacy the effects of changes in the value of $\alpha\beta$ at different times in relation to the transmission cycle are also important. At higher levels of coverage altering the value of $\alpha\beta$ will have a greater impact on the model because a higher proportion of the vector population will be affected by the changes.

### 5.4.8 SENSITIVITY OF THE MODEL TO CHANGES IN THE PROBABILITY OF THE VECTOR BECOMING INFECTIOUS PER INFECTIOUS MEAL ($k$)

Values of $k$ between 0.2 and 1 were tested in the sensitivity analysis as shown in Figure 5-12 below. Reducing the probability of the vector becoming infectious per infectious meal reduces transmission and low values of $k$ virtually eliminate transmission.

### 5.4.9 SENSITIVITY OF THE MODEL TO CHANGES IN PROBABILITY OF PATHOGEN BECOMING INFECTIOUS IN THE VECTOR ($v$)

Values of $v$ between 0.2 and 1 were tested in the sensitivity analysis as shown in Figure 5-13. Reducing the probability of the pathogen becoming infectious in the vector ($v$) reduces transmission throughout the model particularly in periods of already lower transmission. The model is relatively sensitive to changes in $v$.

### 5.4.10 SENSITIVITY OF THE MODEL TO CHANGES IN THE LENGTH OF PHASE 1 & 3 OF GONOTROPHIC CYCLE ($\upsilon$)

Values of the length of phase 1 and 3 of the gonotrophic cycle ($\upsilon$) between 0.5 and 4 were tested in the sensitivity analysis as shown in Figure 5-14. Transmission increases rapidly with increases in $\upsilon$ from 0.5 up to 2, further increases in $\upsilon$ to values above 2 have less effect on transmission.

### 5.4.11 SENSITIVITY OF THE MODEL TO CHANGES IN THE PROBABILITY OF RECOVERY ($r$)

Values of $r$ between 0 and 0.9 were tested in the sensitivity analysis shown in Figure 5-15. Values of $r$ greater than 0.4 reduce transmission dramatically with higher values preventing transmission altogether because infection is cleared before it has chance to be passed on. In periods of high transmission when a high proportion of people are affected, the model is less sensitive to changes in the probability of recovery. Overall the model is relatively insensitive to changes in $r$.

### 5.4.12 TWO-WAY SENSITIVITY ANALYSIS

The one-way sensitivity analysis identified that the model sensitivity to changes in $\alpha\beta$ depended upon the coverage achieved by the spray programme.

Two-way sensitivity analysis was therefore carried out on these variables to identify the model sensitivity to $\alpha\beta$ at different levels of spray programme coverage.

The results of this analysis are shown in Figure 5-16. They illustrate that the model is relatively insensitive to changes in $\alpha\beta$ at all levels of coverage. However, the impact of altering coverage is one of the variables under the control of the malaria control programme and is of critical importance to this thesis. Chapter 7 therefore goes on to investigate the impact of altering coverage of spraying on the cost and effectiveness of malaria control programmes in the Hwange district.

### 5.4.13 SUMMARY OF SENSITIVITY ANALYSIS

One way sensitivity analysis was carried out on all variables in the model to identify the relative sensitivity of the model to changes in each parameter within reasonable ranges. The ranges were selected based on *a priori* information where possible or on arbitrary ranges where no information was available to inform the range. Where necessary two-way sensitivity analysis was carried out to identify the affects of varying two connected variables and further analysis of critical variables will be carried out as part of the cost effectiveness analysis. Table 5-3 provides a summary of the findings of the sensitive analysis.

The summary identifies whether an increase in the variable will lead to an increase or decrease in the level of transmission predicted by the model. Variables which cause an increase in transmission when increased, are positively related to transmission and variables which cause a decrease in transmission, are negatively related to transmission. The summary also indicates the relative sensitivity of the model to changes in the variable and identifies possible means of verification of the variable value.

Table 5-1 Population of Hwange District 1993-1999

| Year | Population Data | Linear Trend of Population Data |
|---|---|---|
| 1993 | N/A | 135573 |
| 1994 | 141178 | 141178 |
| 1995 | 146102 | 146102 |
| 1996 | 150822 | 150822 |
| 1997 | 155747 | 155747 |
| 1998 | N/A | 161613 |
| 1999 | 167343 | 167343 |

Table 5-2 Value of Variables Achieving the Highest Correlation with the Case Data

| Variable Description | Variable Name | Value Yielding Highest Correlation Coefficient |
|---|---|---|
| Number of people initially infected | $(I)$ | 500 |
| Constant in the rainfall to mosquito sub model | $(\mu)$ | 992123 |
| Proportion of human blood fed mosquitoes | $(h)$ | 0.38 |
| Difference between indoor and outdoor temperature | $(l)$ | 1 |
| Percentage coverage achieved by spray programme | $(c)$ | 0.24† |
| Percentage of vectors surviving each feeding cycle in unsprayed population | $(\alpha)$ | $e^{-1/1.229\,t}$ |
| Percentage of vectors surviving each feeding cycle in sprayed population | $(\alpha\beta)$ | $e^{-1/0.4\,t}$ |
| Probability of vector becoming infected per infectious meal | $(k)$ | 1 |
| Probability of pathogen becoming infectious in the vector | $(v)$ | 0.4 |
| Length of phase 1 and 3 of gonotrophic cycle | $(\upsilon)$ | 1.26 |
| Probability of recovery | $(r)$ | 0.182 |
| Lag | | 4 Months |
| Proportion of Cases Reporting at Health Facility | $(\lambda)$ | 0.54 |

Note † Indicates that the variable was not altered using the solver function and variable value chosen was based on *a priori* information rather than by fitting.

Table 5-3 Summary of Findings of Sensitivity Analysis (for definition of terms see Table 4-2)

| Variable | Summary of Findings |
|---|---|
| $(I_{t=0})$ | Positively related to transmission<br>Sensitive at the beginning of the model, becoming less so as the model continues to run<br>Difficult to identify true value |
| $(\mu)$ | Positively related to transmission<br>Sensitive, particularly in dry years when transmission may not occur with lower values of $\mu$.<br>Could be scaled using information on the human biting rate where available |
| $(h)$ | Positively related to transmission<br>Extremely sensitive, critical variable in the model<br>Could be identified from entomological field data |
| $(l)$ | Negatively related to transmission<br>Relatively insensitive within range tested<br>Could be identified from field studies although low priority |
| $(C)$ | Negatively related to transmission<br>Relatively insensitive depending on value of $\alpha\beta$ (efficacy of chemical, with high efficacy coverage will become more important)<br>Routinely collected information (NB total coverage not just coverage of target area) |
| $(\alpha)$ | Positively related to transmission<br>Extremely sensitive, critical variable in model<br>Can be obtained from entomological studies |
| $(\alpha\beta)$ | Positively related to transmission<br>Relatively insensitive, even at higher level of spray programme coverage<br>Can be obtained from entomological investigation of spray programme effects |
| $(v)$ &$(k)$ | Positively related to transmission<br>Relatively insensitive to changes between 0.4-1, reducing either below 0.4 reduces transmission<br>Can be obtained from experimental/study data |
| $(\upsilon)$ | Positively related to transmission<br>Relatively insensitive within reasonable range, more sensitive in low transmission periods<br>Can be obtained from entomological studies |
| $(r)$ | Negatively related to transmission<br>Relatively insensitive, particularly for values less than 0.2<br>Can be obtained (in different form) |

Figure 5-1 Reported Malaria, Mean Maximum Temperature and Rainfall in Hwange District

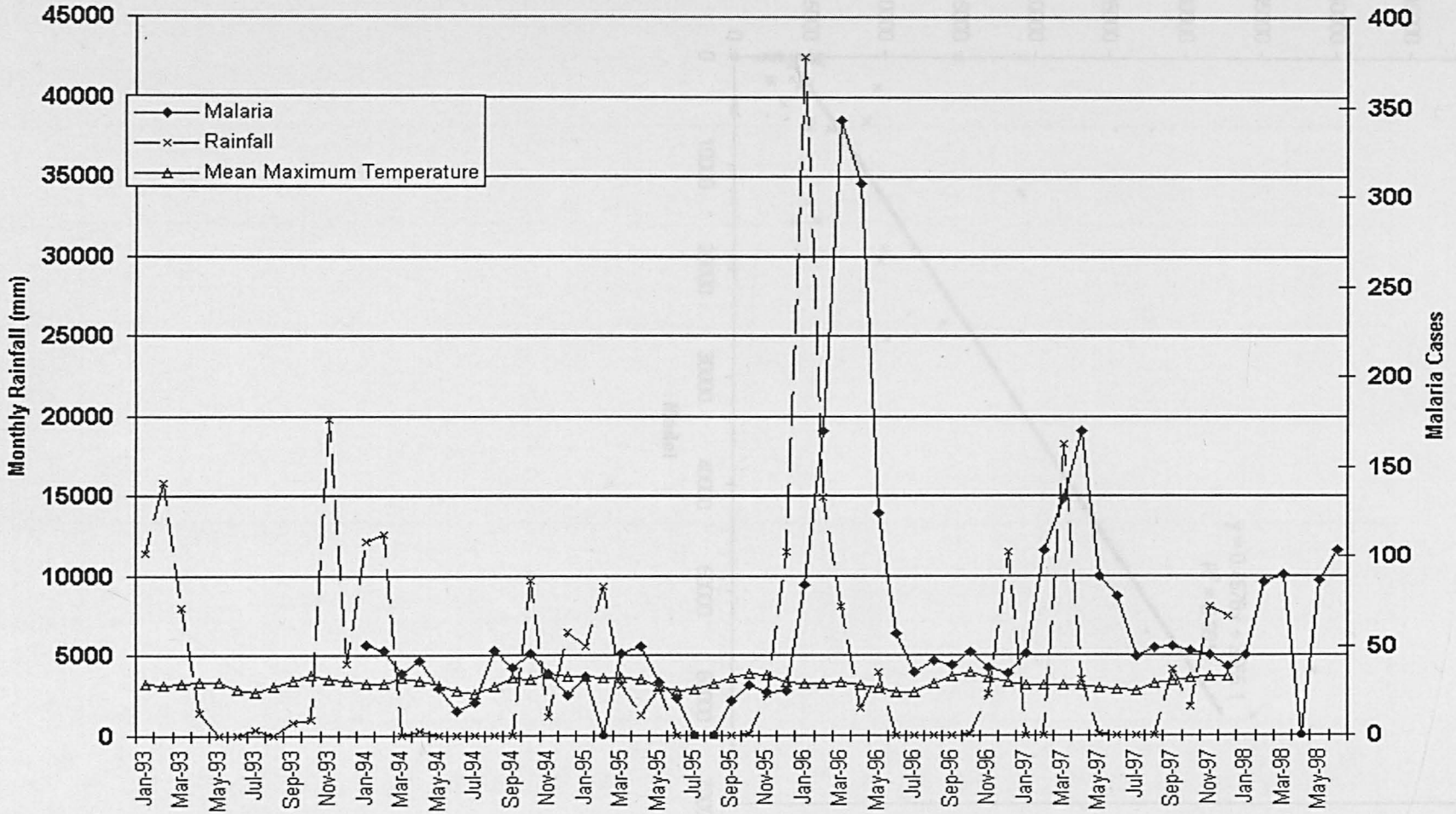


Figure 5-2 Scatter Plot of Model Results for 'Cases Reporting by Month' against Reported Malaria

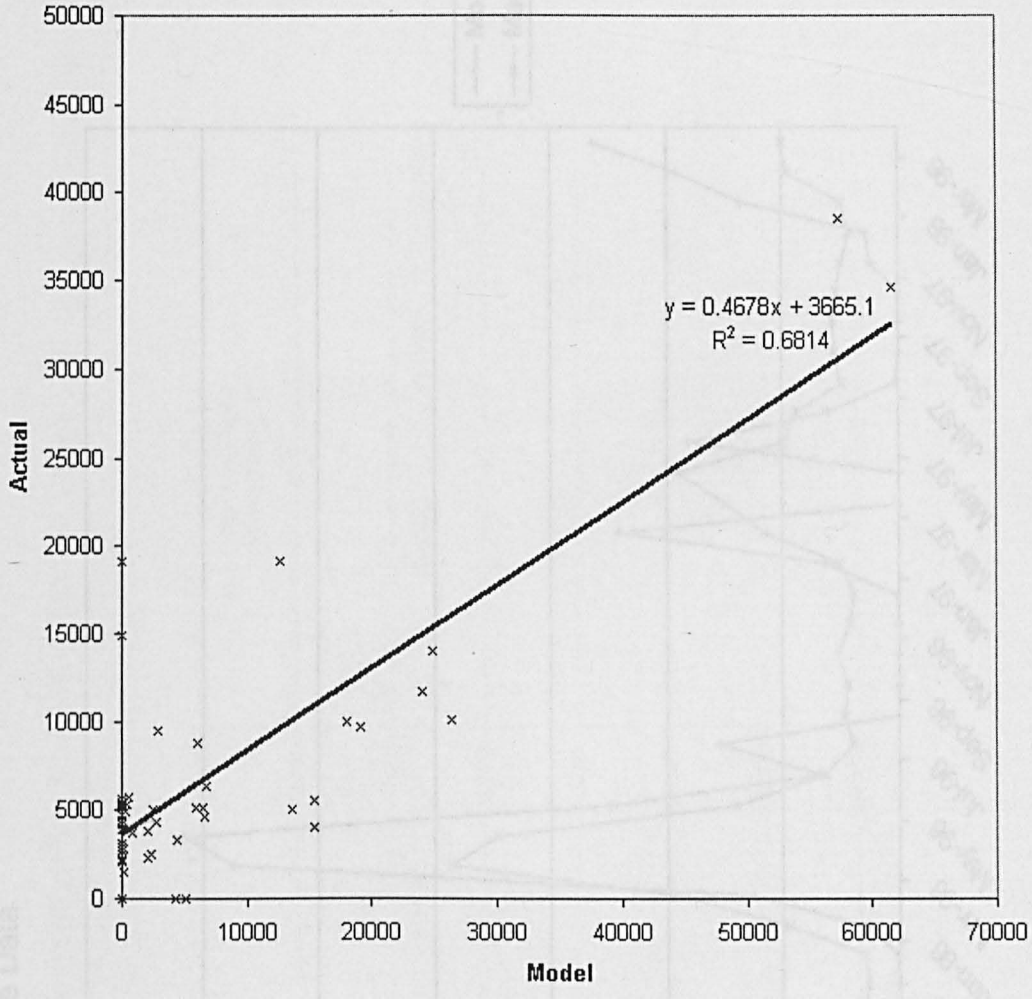


Figure 5-3 Modelled and Actual Reported Malaria Case Data

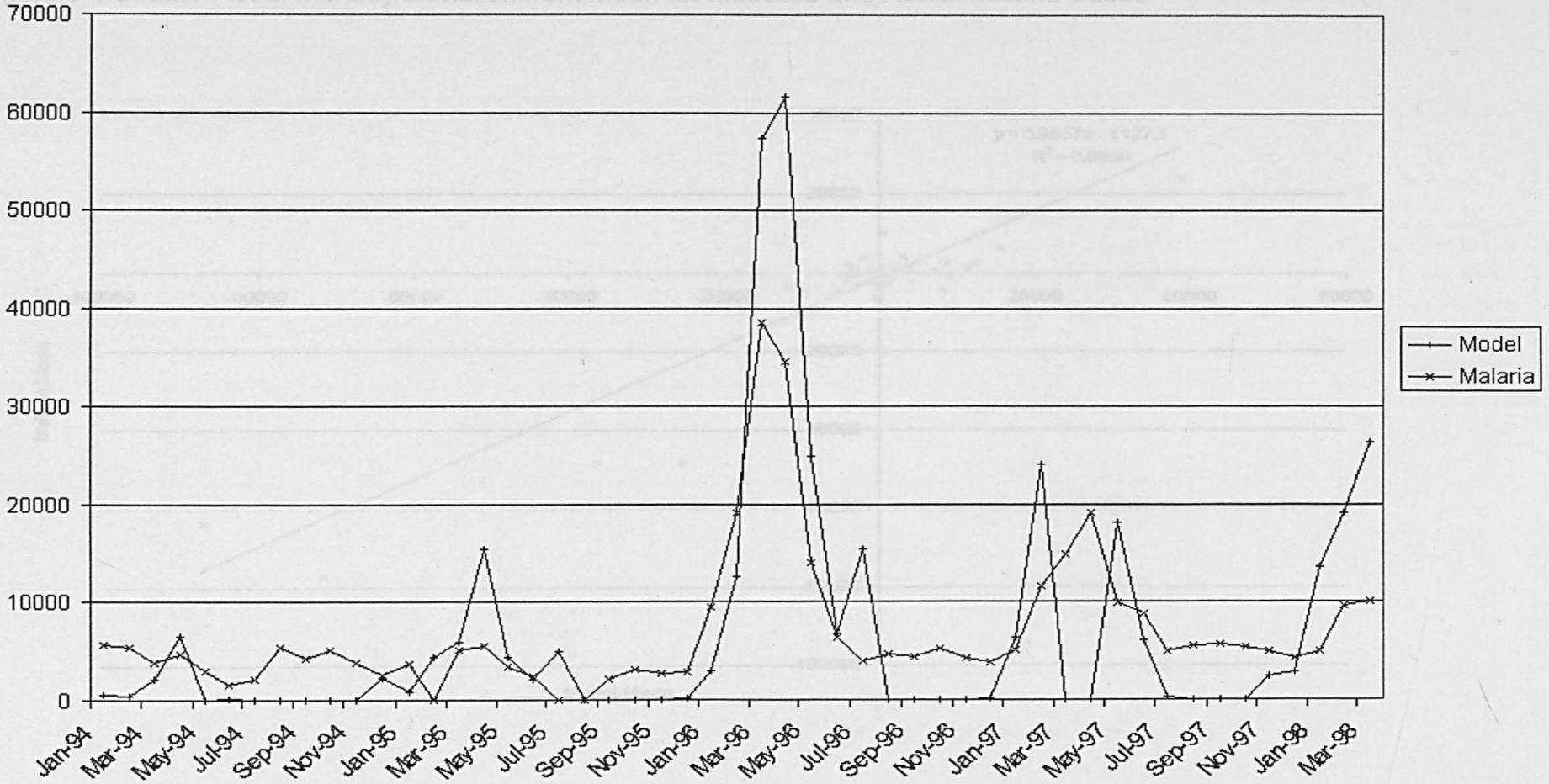


Figure 5-4 Scatter Plot of Monthly Deviation from Mean for Modelled and Actual Malaria Cases

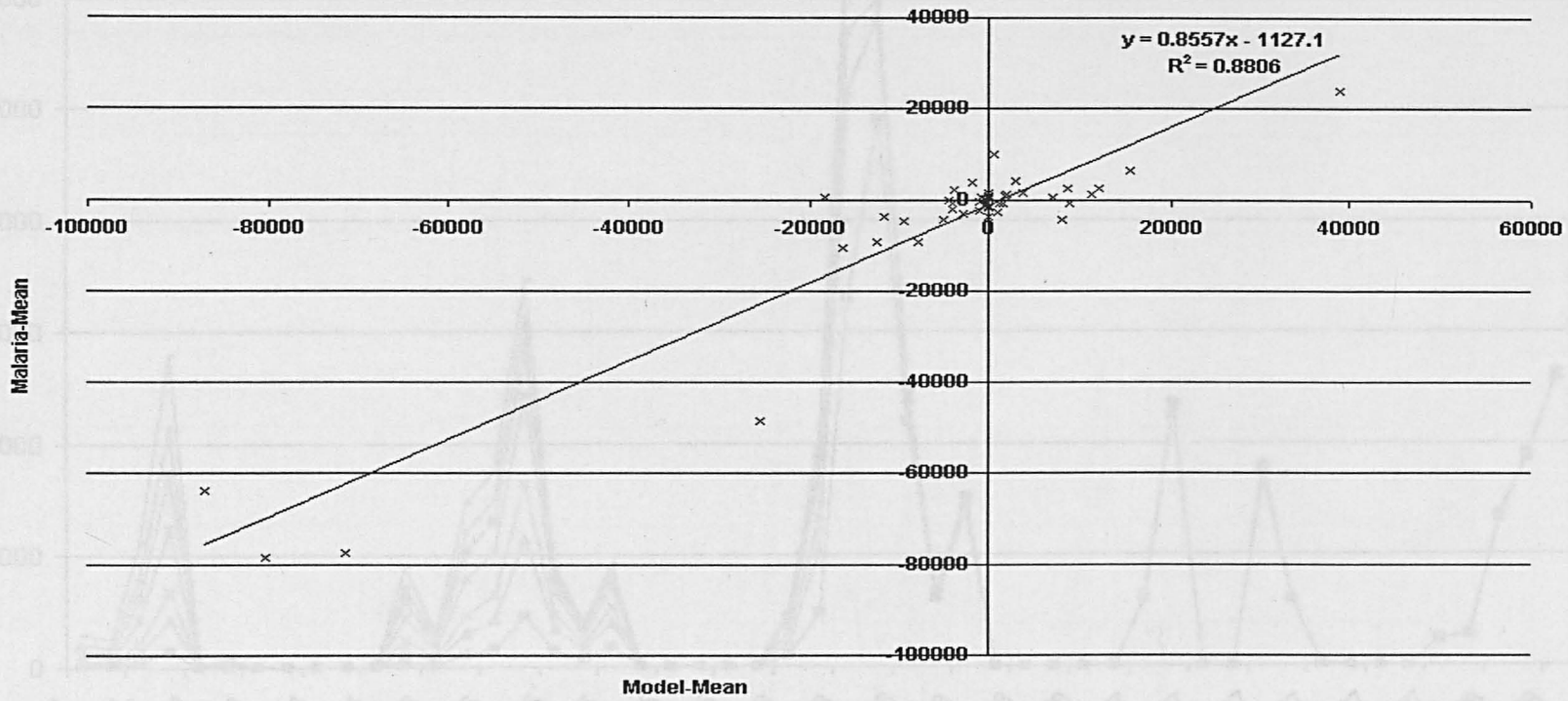


Figure 5-5 Sensitivity of the Model to Changes in the Initial Number of Infected People ($I_t=0$)

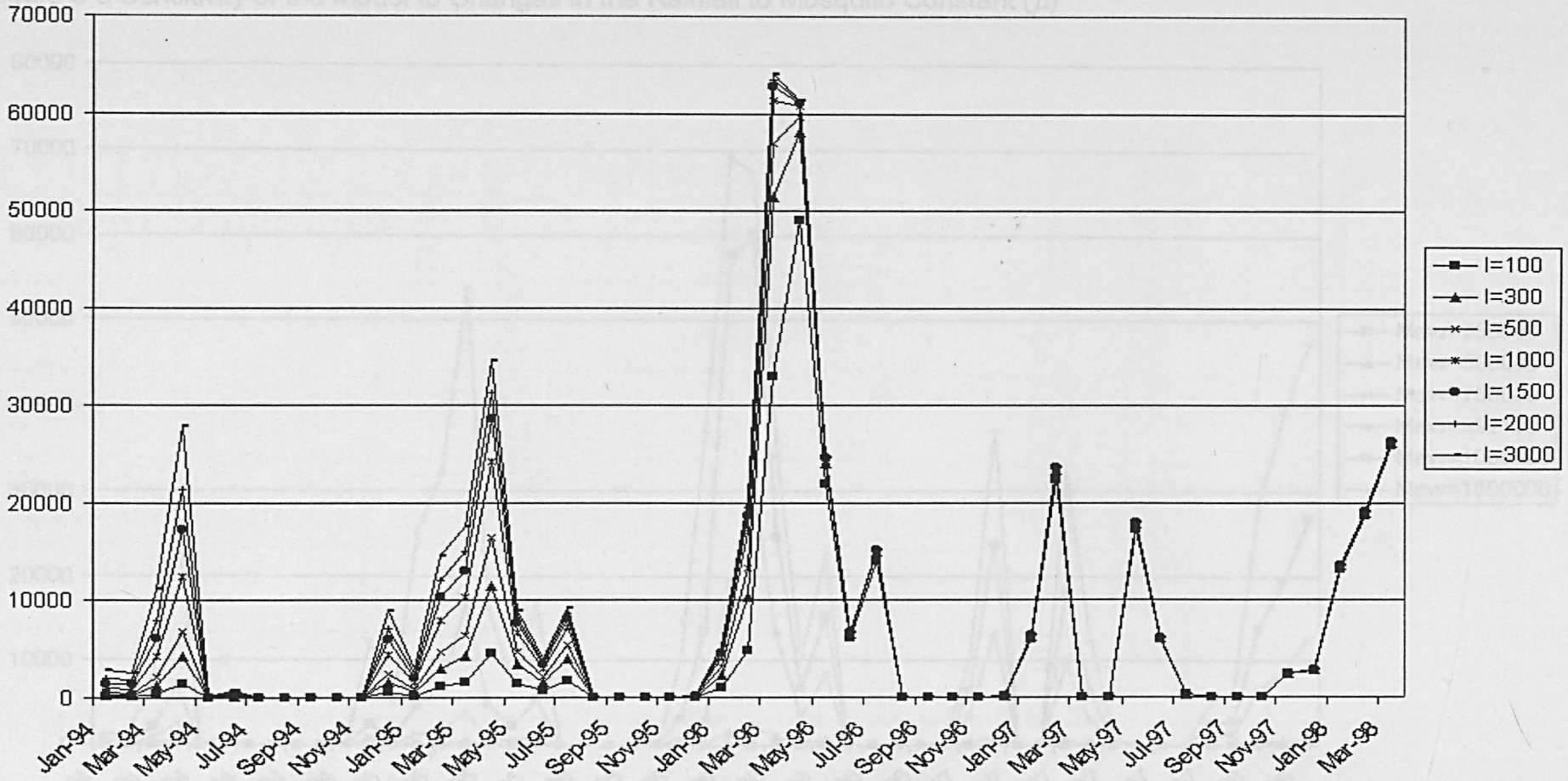


Figure 5-6 Sensitivity of the Model to Changes in the Rainfall to Mosquito Constant ($\mu$)

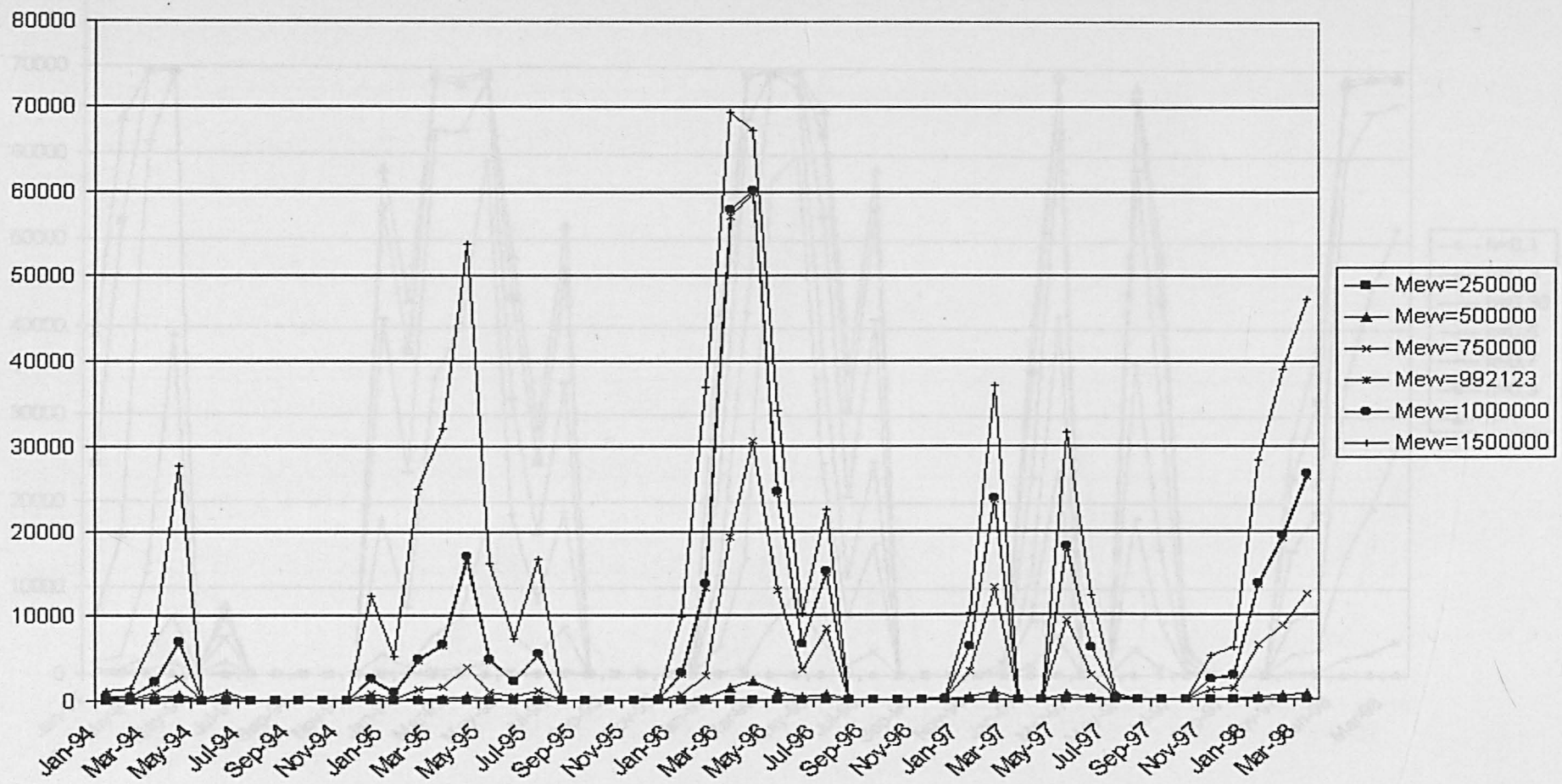


Figure 5-7 Sensitivity of the Model to Changes in the Proportion of Human Blood Fed Mosquitoes ($h$)

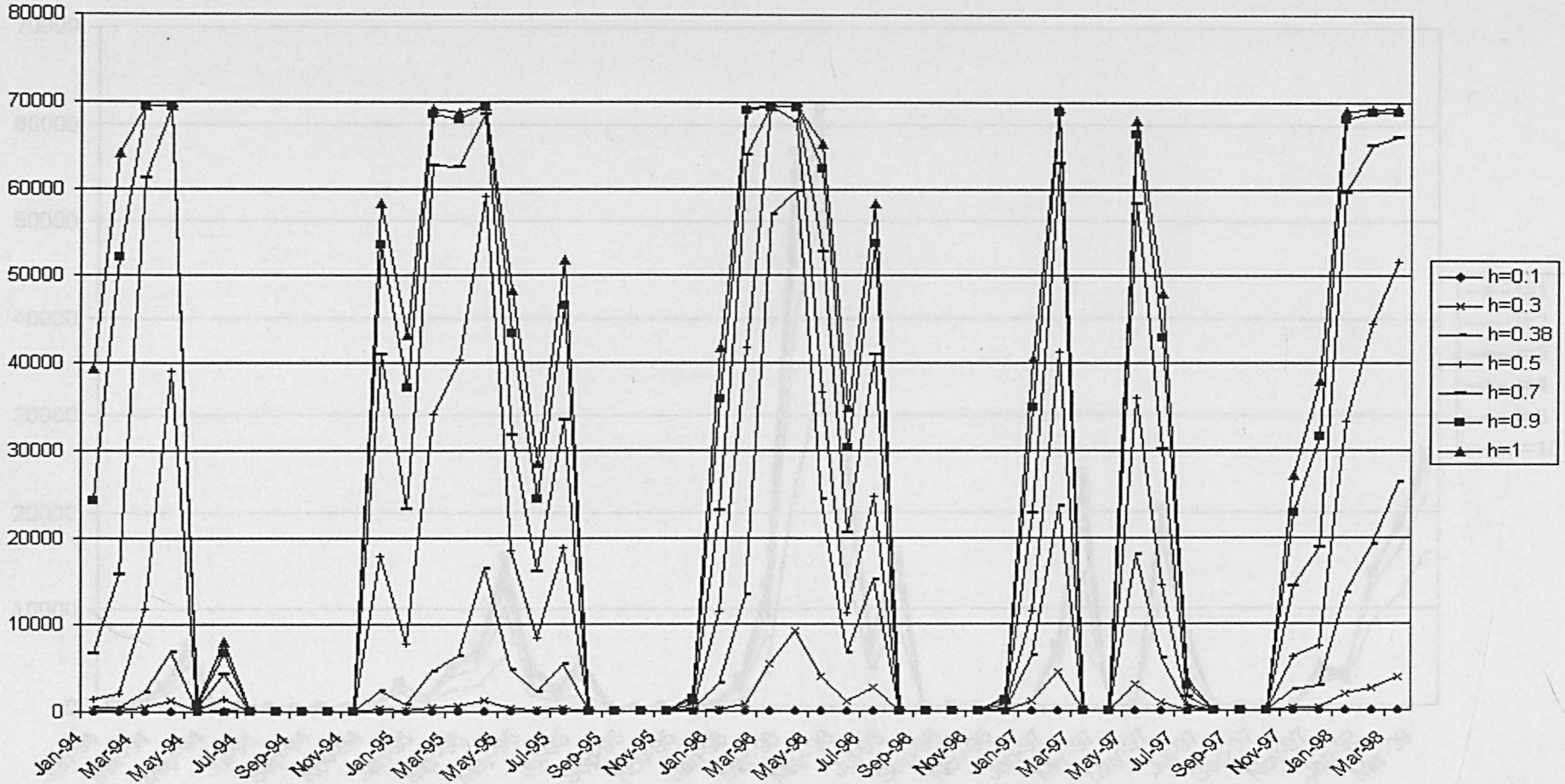


Figure 5-8 Sensitivity of the Model to Changes in the Temperature Adjustment Factor ($l$)

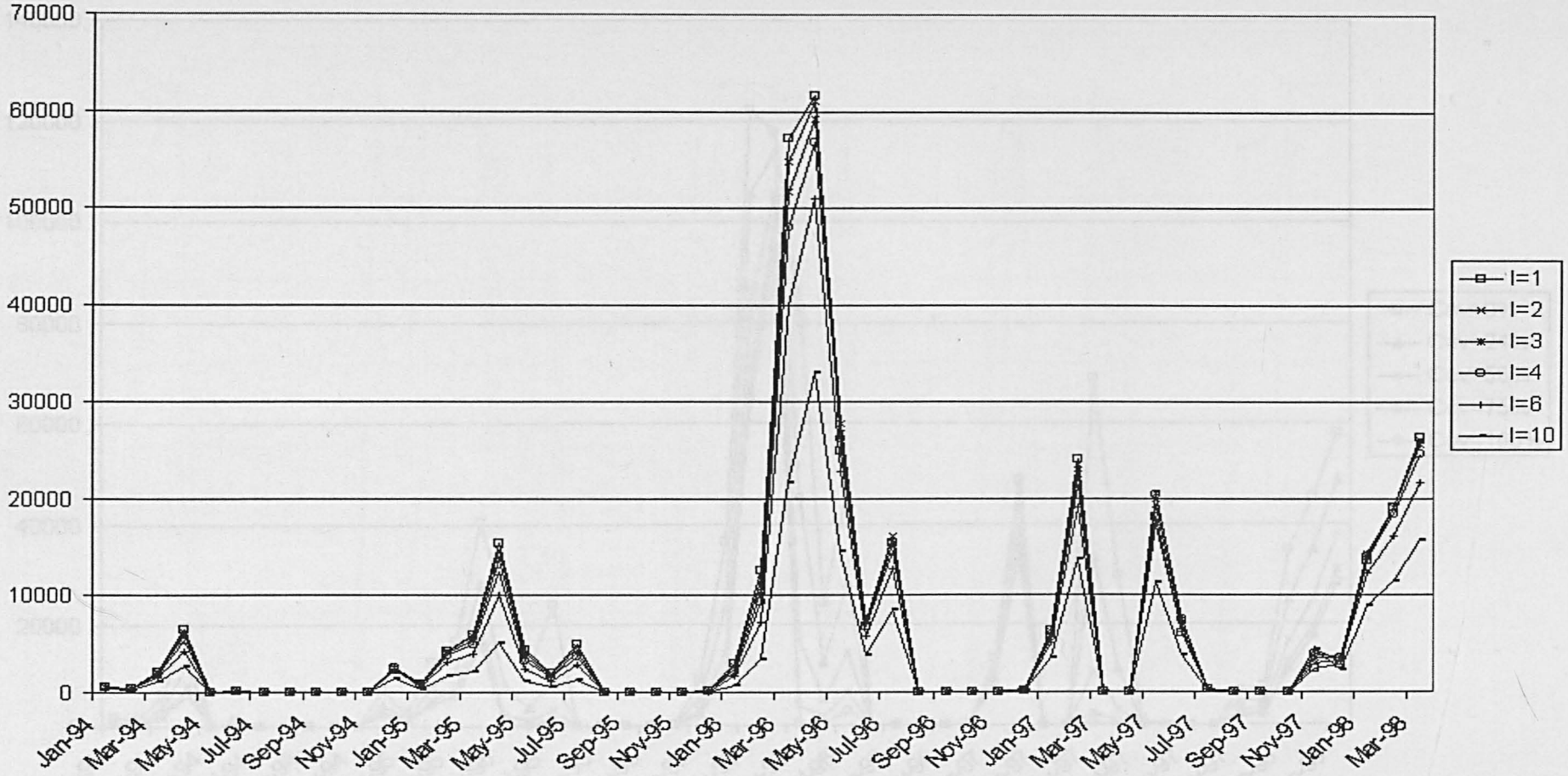


Figure 5-9 Sensitivity of Model to Changes in Coverage ($C$)

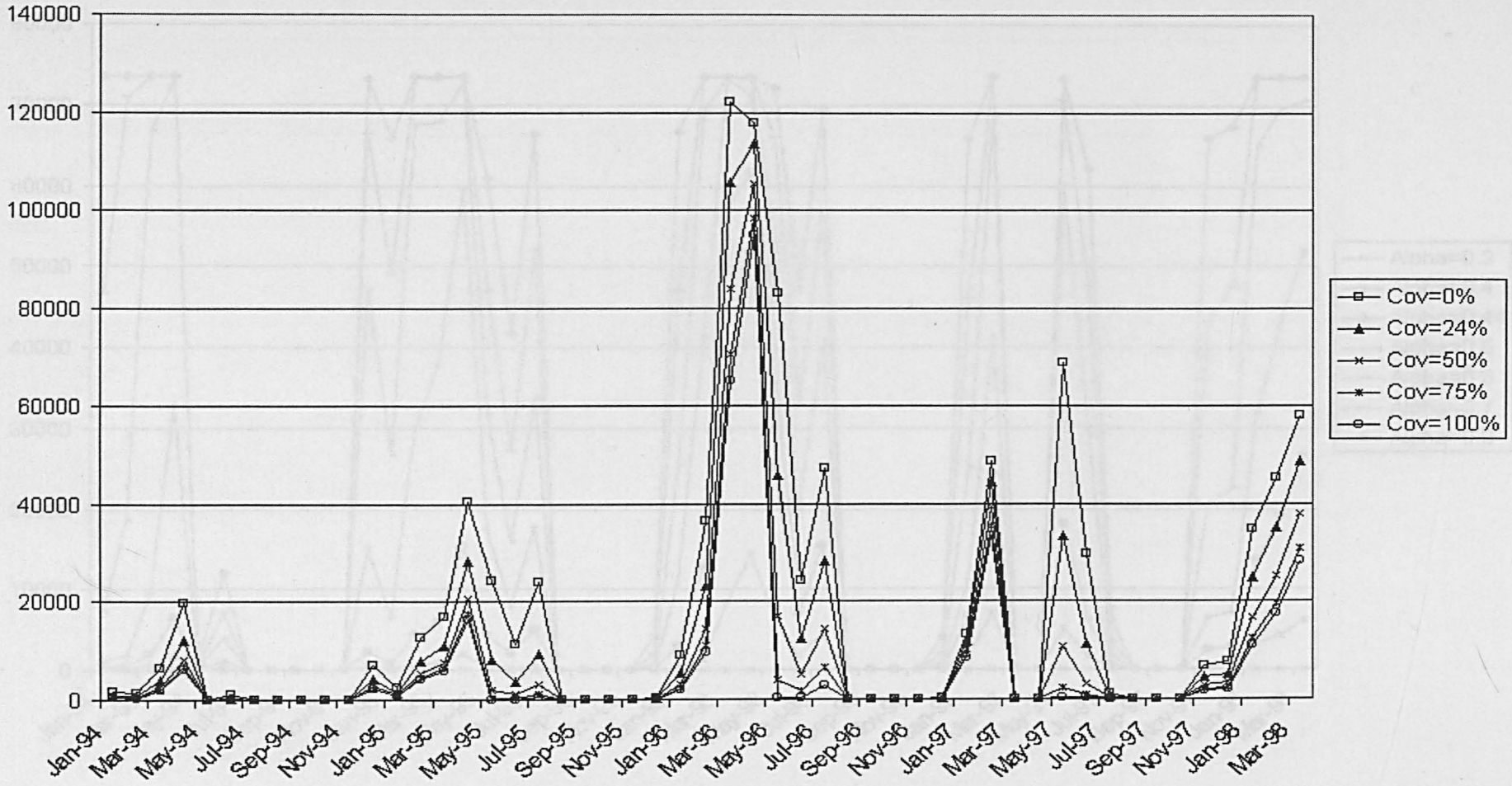


Figure 5-10 Sensitivity of the Model to Changes in the Proportion of Vectors Surviving the Feeding Cycle in Unsprayed Population ($\alpha$)

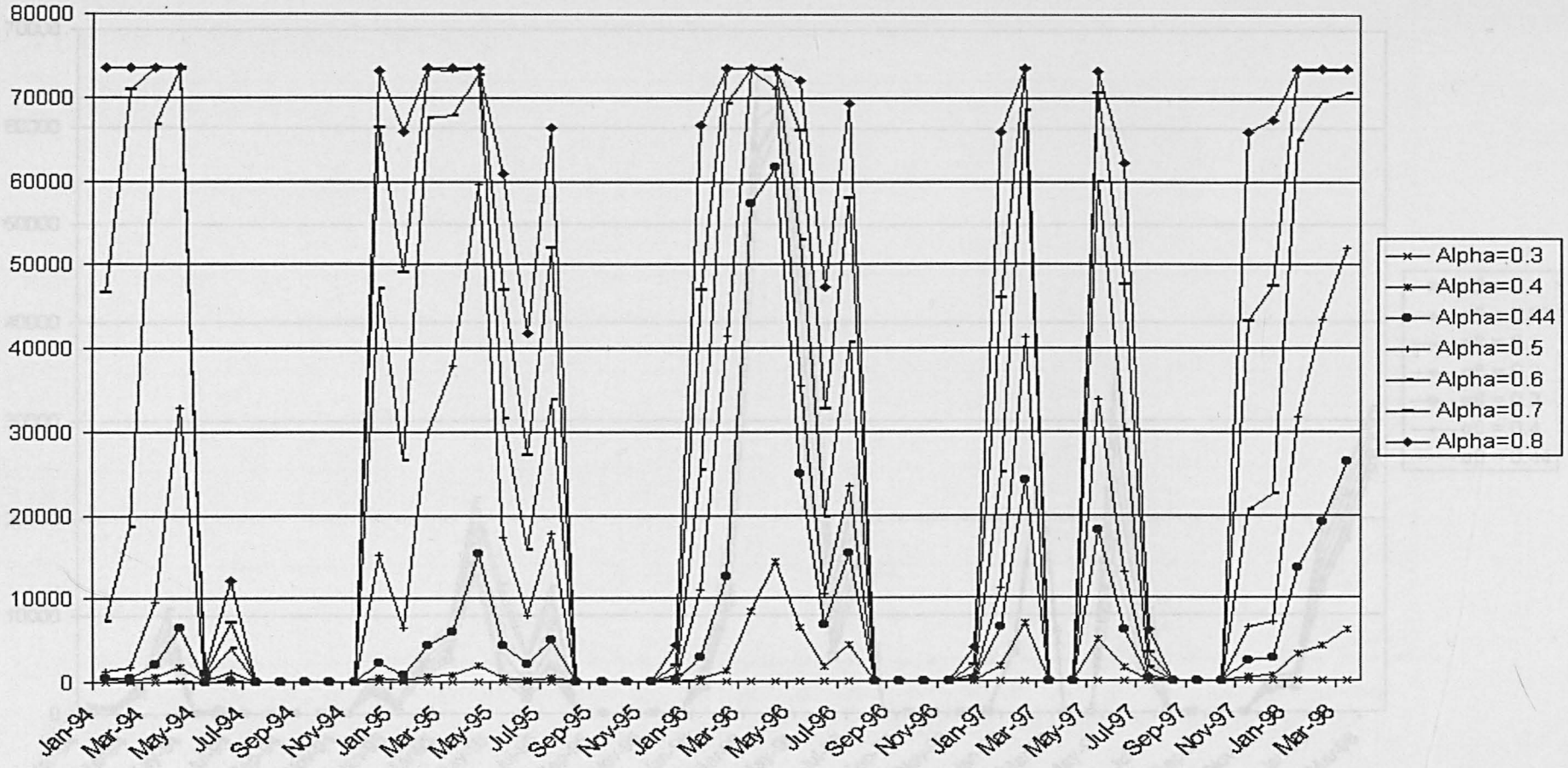


Figure 5-11 Sensitivity of the Model to Changes in the Proportion of Vectors Surviving Feeding Cycle in Sprayed Population ($\alpha\beta$)

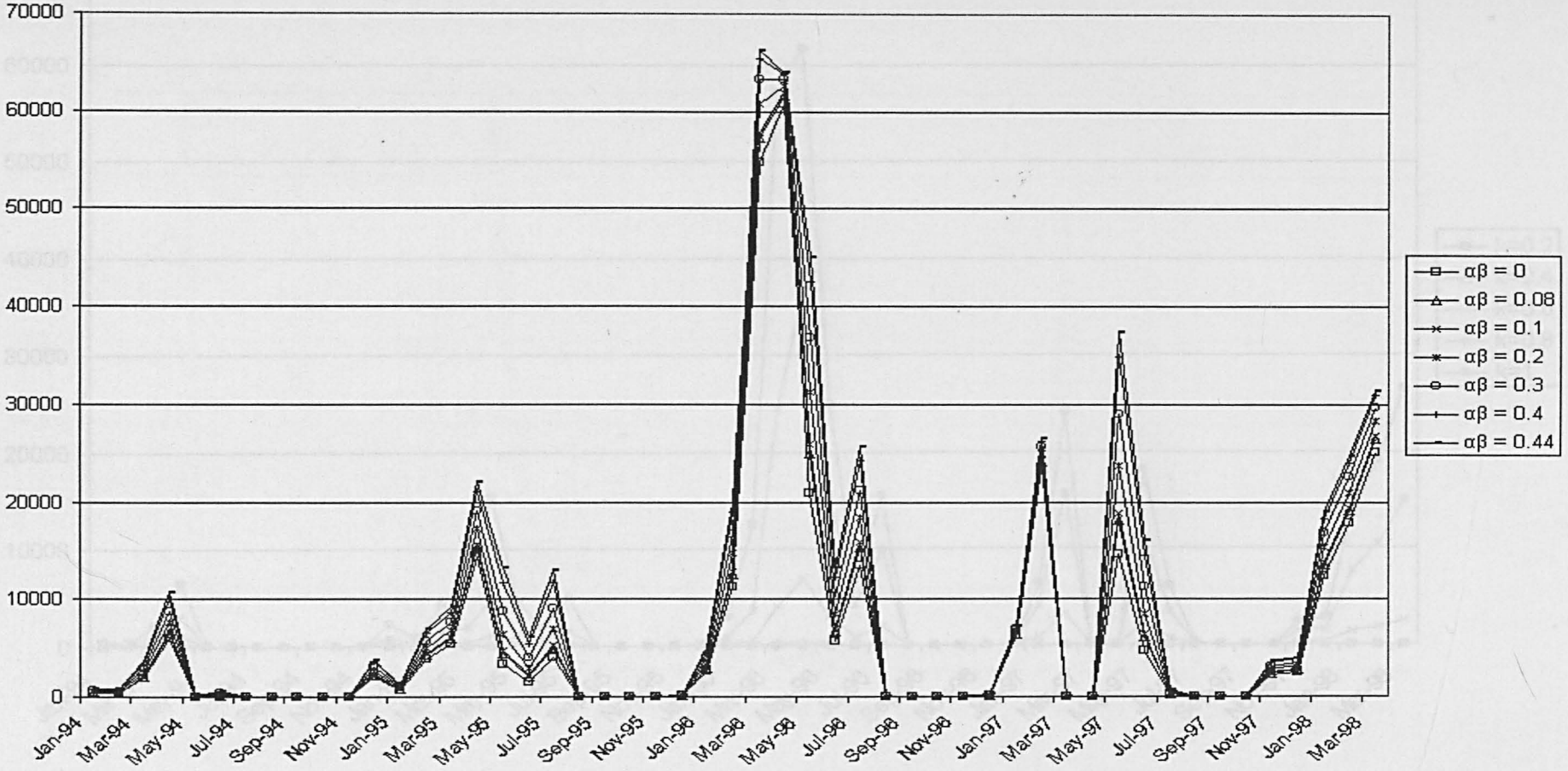


Figure 5-12 Sensitivity of Model to Changes in Probability of Vector becoming Infected per Infectious Meal ($k$)

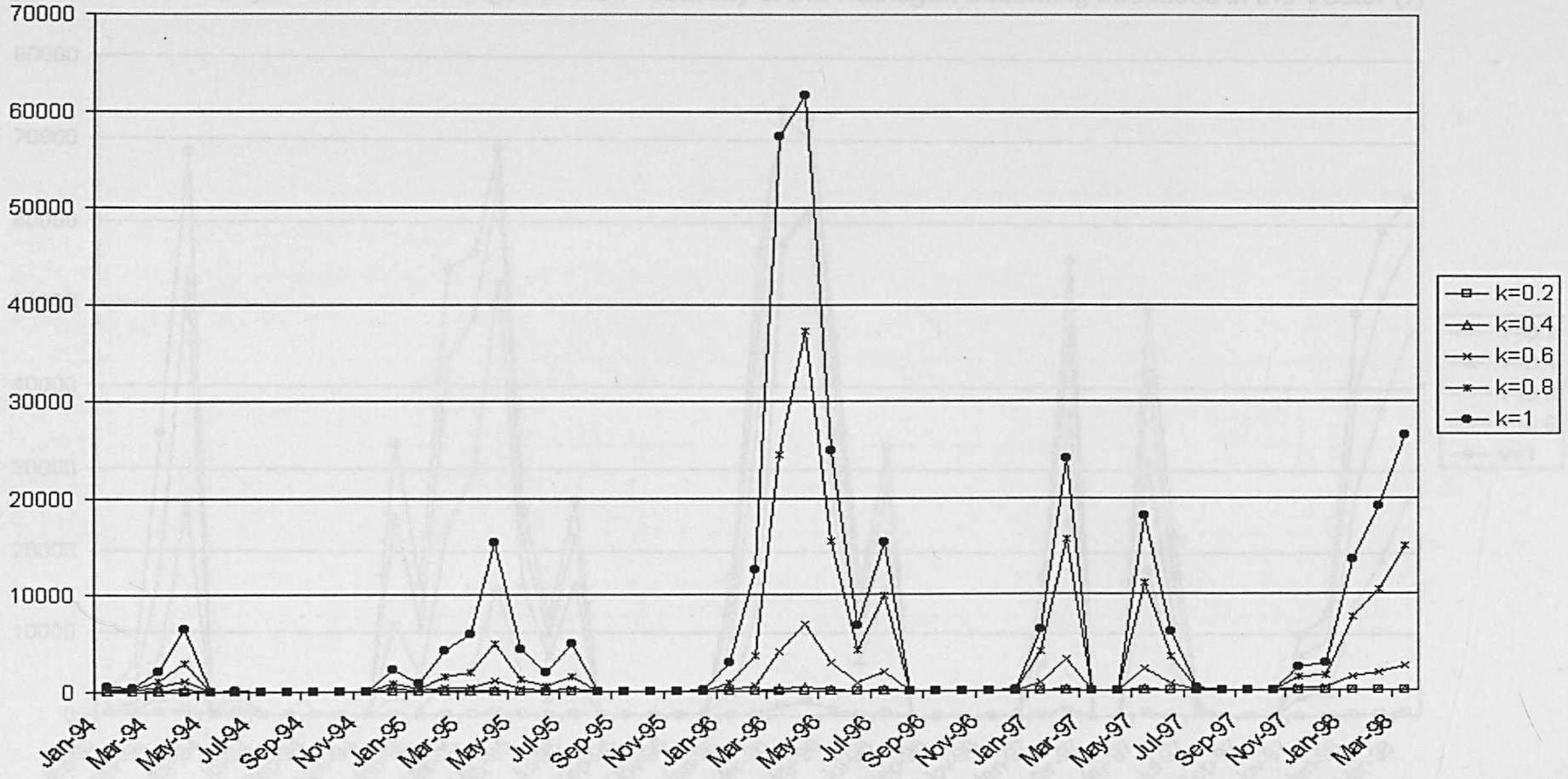


Figure 5-13 Sensitivity of Model to Changes in the Probability of the Pathogen becoming Infectious in the Vector ($v$)

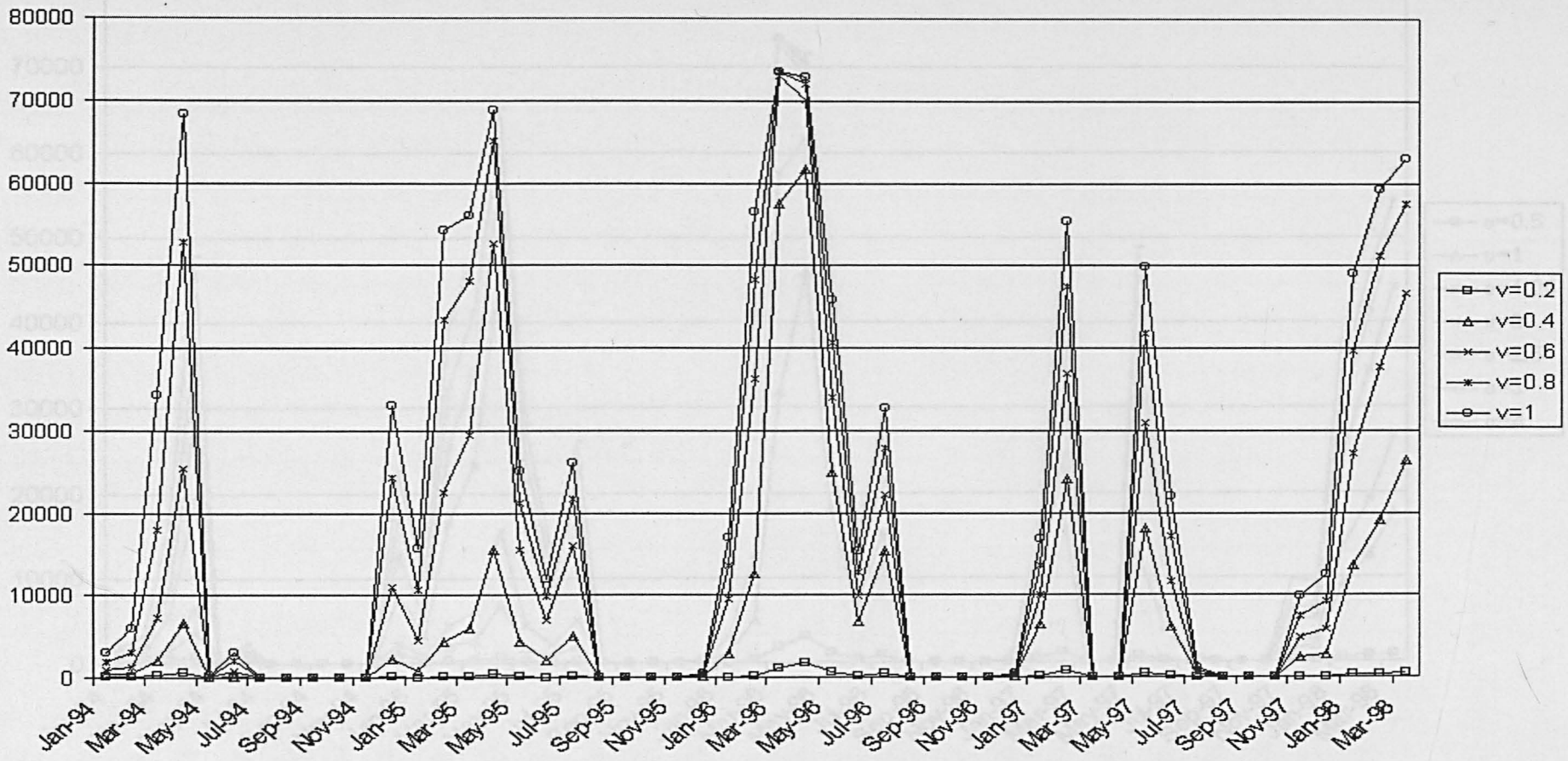


Figure 5-14 Sensitivity of Model to Changes in Length of Phase 1 & 3 of Gonotrophic Cycle ($\upsilon$)

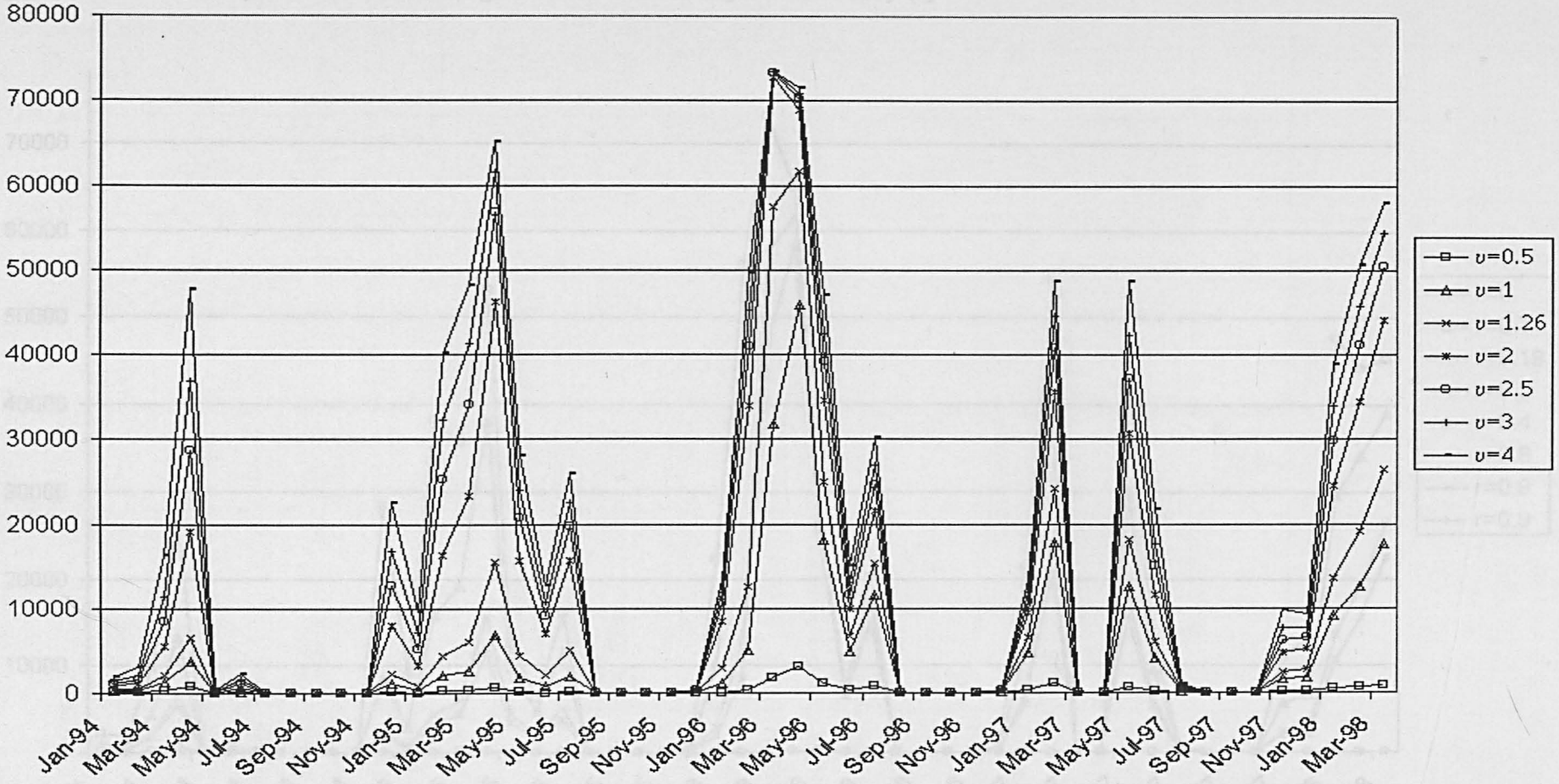


Figure 5-15 Sensitivity of Model to Changes in the Probability of Recovery ($r$)

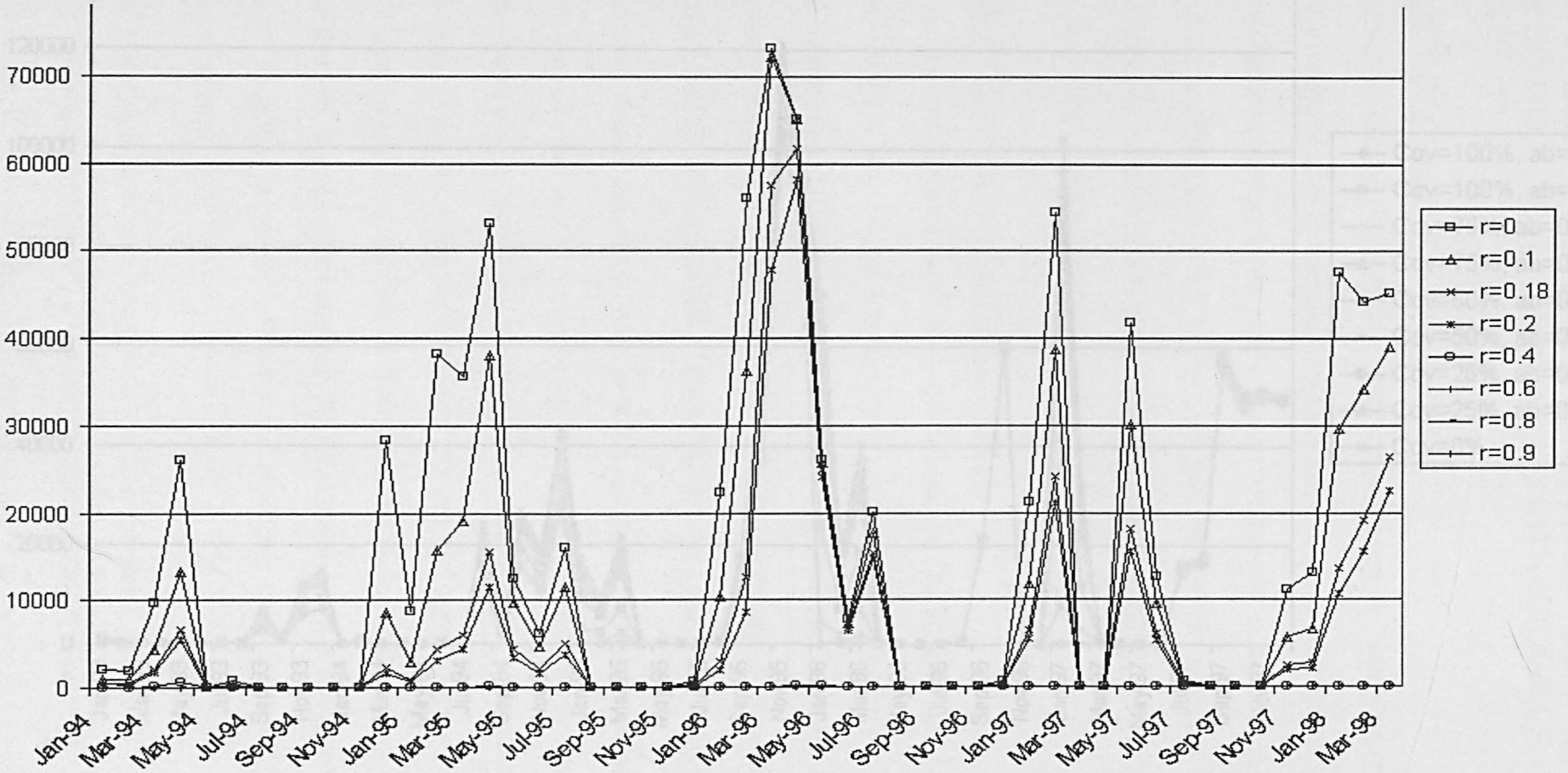
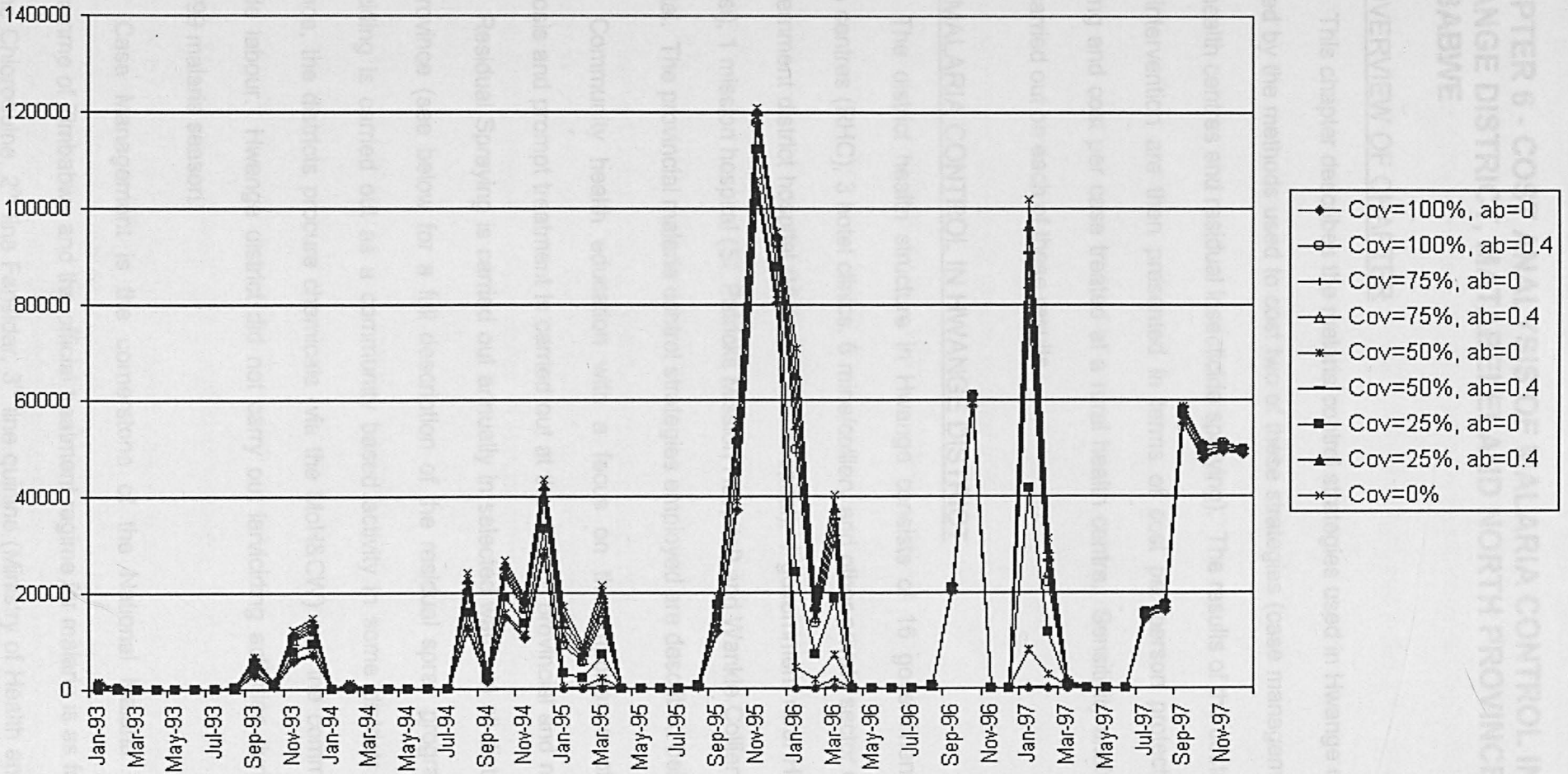


Figure 5-16 Sensitivity to Changes in Coverage ($C$) and Probability of Vectors Surviving Feeding Cycle in Sprayed Population ($\alpha\beta$)



# CHAPTER 6 - COST ANALYSIS OF MALARIA CONTROL IN HWANGE DISTRICT, MATABELELAND NORTH PROVINCE, ZIMBABWE

## 6 OVERVIEW OF CHAPTER

This chapter describes the malaria control strategies used in Hwange district followed by the methods used to cost two of these strategies (case management at rural health centres and residual insecticide spraying). The results of the costing for each intervention are then presented in terms of cost per person protected by spraying and cost per case treated at a rural health centre. Sensitivity analysis is then carried out on each of these results.

## 6.1 MALARIA CONTROL IN HWANGE DISTRICT

The district health structure in Hwange consists of 16 government rural health centres (RHC), 3 hotel clinics, 6 mine/colliery and other private sector clinics, 1 government district hospital (Victoria Falls Hospital), 1 government rural Hospital (Lukosi), 1 mission hospital (St. Patricks Mission Hospital) and Wankie Colliery mine hospital. The provincial malaria control strategies employed are described below.

Community health education with a focus on the importance of early diagnosis and prompt treatment is carried out at the district, provincial and national level. Residual Spraying is carried out annually in selected wards in all districts of the province (see below for a full description of the residual spray programme). Larviciding is carried out as a community based activity in some districts of the province, the districts procure chemicals (via the MoH&CW) and the communities provide labour. Hwange district did not carry out larviciding activities during the 1998/99 malaria season.

Case Management is the cornerstone of the National Malaria Control Programme of Zimbabwe and the official treatment regime for malaria is as follows:- 1st line Chloroquine, 2$^{nd}$ line Fansidar, 3$^{rd}$ line quinine (Ministry of Health and Child

Welfare 1995). "Chloroquine holders" at the village level [school health masters (SHM), village chief's, etc.] have been trained to diagnose and provide 1st line treatment to suspected malaria patients. The rural health centres (RHC) staffed by a trained nurse/s, provide 1st line and 2nd line treatment and referral for treatment failures and severe and complicated malaria cases. In 1998/9 quinine was introduced into some RHC for the first dose before referral. The degree of parasite resistance to these drugs was not clear at the time of the study although the Ministry of Heath and Child Welfare (MoH&CW) was carrying out research in order to establish this. District level hospitals provide out patient services for simple malaria cases and in-patient care for severe and complicated cases. Very occasionally patients may be referred to the central hospital in Bulawayo for treatment.

Drug stock management, which involves assessing the availability of necessary drugs at the RHC, district and provincial levels (which are recommended to maintain a 'buffer stock') is recommended in the National Malaria Control Programme 5 Year Plan (Ministry of Health and Child Welfare 1995), however in practice this does not seem to be widely or routinely carried out. Similarly, the National Malaria Control Plan of Zimbabwe recommends that chemoprophylaxis be provided to children under five, pregnant women, foreigners and visitors to malarious areas, however little evidence of routine provision of chemoprophylaxis was found.

Zimbabwe has a national malaria surveillance system which includes a weekly 'rapid notification system', sentinel site surveillance of slide positivity rates and chloroquine resistance monitoring. The weekly rapid notification system involves the use of in-patient and outpatient monitoring forms. "T5" forms are completed by RHC and outpatients departments in hospitals providing information on the number of presumptive malaria cases by age. "T9" forms provide information on the number and age of inpatient malaria admissions. These forms are filled in at

district and provincial level and returned to the central level, where they are analysed and discussed at weekly meetings by the senior staff in the department of Epidemiology and Disease Control (EDC) at the Ministry of Heath and Child Welfare (MoH&CW). The data is compared to past years data in order to identify and monitor outbreaks of malaria and decide what action (if any) should be taken. The speed of the 'rapid notification system' depends upon the speed at which the central level receives data. At the time the data in this study was collected it took between 8-10 days minimum and 3 weeks maximum for data to reach the MoH&CW although the increasing use of e-mail may have reduced this time.

Sentinel surveillance sites have been established to carry out and report on slide positivity rates and chloroquine resistance. According to the Standard Treatment Guidelines on Malaria a blood slide should be taken in all cases of severe and complicated malaria and when treatment failure occurs (Malaria control technical sub-committee on case management and drug sensitivity 1998). Monitoring the slide positivity rate may provide a better indicator of the changing malaria situation than simply monitoring malaria 'cases' which will include misdiagnosis, however in practice slides were often not taken or not examined due to a shortage of trained staff or equipment. Chloroquine resistance monitoring was being carried out in sentinel sites by staff from the Blair Research Laboratory (part of the MoH&CW) along with other operational research programmes.

### 6.1.1 DESCRIPTION OF THE RESIDUAL SPRAY PROGRAMME IN ZIMBABWE

The cycle of the annual spray programme begins with the chemicals being procured using a tender system administered at the central level in Harare. Chemicals are normally tendered in US$ or Z$ to include delivery and/or freight costs to Harare. Payment is made by the Department of Epidemiology and Disease Control after the chemical is delivered. In recent years, the depreciation of the Zimbabwe dollar (Z$) (see Table A-2, Appendix) has meant that by the time

payment is made the cost of the chemical in Z$ has increased substantially from the time the tender bid was accepted. Once the chemicals have been delivered to Harare they are stored at the Blair Research Centre until the Provinces collect them in large trucks. They are then stored at the Provincial level to await collection or distribution to the Districts.

The recruitment and training of the spray teams is organised at district level. Training is normally carried out by 'team leaders' who are experienced spaymen or, if this is not possible by the District Environmental Health Officer (DEHO). Spaymen are employed on a casual basis for three months and training takes place at the beginning of this time for a period of one-to-two weeks. Spray teams and all the necessary equipment are transported to the initial spray sites by a truck driven by the team leader.

In Hwange district two teams of 17 men consisting of 16 spray men and one "warner", carry out the spray programme. A "warner" goes ahead of the team to warn villagers that the team is coming, ensure that they have emptied their homes of furniture and fetched sufficient water to dilute the chemical. Spray men follow and carry out the spraying. The teams travel on foot or if long distances are involved they will be picked up by a truck and driver and transported to the next village. The teams carry sufficient chemical for the days spraying with them in its undiluted form. Workers camp overnight in between each days work and a guard is hired to watch over the campsite and chemicals while the spray teams are at work.

Supervision is extremely limited and often *ad hoc.* for example the District Environmental Health Officer (DEHO) may be passing a spray team and therefore be able to check on them. Supervision has been recognised as vital to the programme success and to this end in 1998/99 supervisors were employed and given access to a vehicle for the first time to help improve the situation.

Prior to the start of the spray programme community education is carried out by the environmental health technician (EHT) of the local rural health centres (RHC). The EHT will call or attend a meeting of village chiefs, elders and other important members of the local community to educate them on malaria and the object of the spray programme. He will also inform them of what is required of the households (i.e. emptying homes of furniture and gathering sufficient water for the spray men to dilute the chemical) and when the spray team is expected to be in the area. The community leaders will then pass this information on to households.

## 6.2 COSTING METHODOLOGY AND DATA COLLECTION

The purpose of the study was to calculate the annual cost of the Hwange district spray programme from the provider perspective for the 1998/99 malaria season. The time period for data collection limited the study to the provider perspective however the nature and extent of the involvement of householders in the spay programme was identified although it was not costed. Data was collected from a variety of sources (commitment registers, invoices, requests for funds to central office, log books and other records) at the District, Provincial and National levels. This information was combined with qualitative information gained through formal and informal meetings with staff involved in the programme and used to construct a detailed estimate of the total cost of the programme at district level.

Data on the cost of chemicals was collected from the Department of Epidemiology and Disease Control (EDC), MoH&CW and from the District level for the 1998/99 season. Costs collected from both levels were used to cross check and confirm the data.

Data on the staff and equipment requirements for the 1998/99 malaria season for Matabeleland North province was obtained from the provincial level. This information provided details of staff employed and salaries/wages paid, as well as cost data for equipment purchased for the 1998/99 season. The data on staff

and salaries was used to calculate total labour costs for the 1998/99 season spray programme in Hwange district using information gained from the district level on the number of staff hired.

Information on the organisational structure and operation of the spray programme, the quantity of each piece of equipment used and its useful life was gathered by discussions with the DEHO and the Provincial Environmental Health Officer (PEHO). This information was used to construct a list of the equipment needed to carry out the spray programme for Hwange District. The number of each item used was multiplied by its cost with capital items being annualised using a discount rate of 5% over their useful life.

The vehicles used in the spray programme are held at a provincial vehicle pool and have to be booked out for use during spray programme activities. The distance travelled is recorded and the district pays the vehicle pool a fixed amount per km depending on the type of vehicle. This fee comes out of the district field vote therefore information on the distance travelled and amount spent on transport (excluding the cost of drivers which is included under labour) was available from the District Environmental Health Officer. The use of this figure in the costing assumes that it accurately reflects the cost of maintaining and running the vehicles as well as the capital cost of the items.

The costs of community education were gathered during visits to three rural health centres (RHC) in the Hwange district. The environmental health technician (EHT) in each RHC was interviewed to assess the length of time spent on community education prior to the spray programme and any other costs associated with the activity. The cost of EHT time was calculated using data on the wage for EHT, which was gathered from the provincial level.

Administration and organisation of the spray programme will incur costs at the district, provincial and national (MoH&CW) levels. For example these will

include the cost of staff time at the MoH&CW incurred during the tender process for the chemicals, the organisation of their distribution and any meetings and administration carried out by staff at district, provincial or national level. Storage costs will also be incurred while the chemicals are at the central level waiting to be collected by the provinces and at the provincial level whilst awaiting collection by the districts. A proportion of the running and capital costs of the building in which these activities take place could therefore also have been included in the analysis however, these costs were considered to be minimal, particularly in relation to the substantial amount of effort that would be needed to cost them and they were therefore excluded from the analysis. Furthermore, it was not necessary to include overhead and capital costs of buildings in the analysis since all other activities would be carried out from camps (e.g. spraying activities) which have been costed or in the community (e.g. community education) which is excluded from the provider perspective.

All cost data was collected in the actual currency used for each transactions (all in Z$ apart from chemical purchase) and converted into US$ for the presentation of results using the exchange rates shown in Table A-2, Appendix. All results are given in 1999 US$.

## 6.3 RESIDUAL SPRAY PROGRAMME COSTING RESULTS

### 6.3.1 CHEMICAL COST

In 1998/99 two different chemicals were used in the Hwange District spray programme. Firstly, a deltamethrin based insecticide procured from a Zimbabwean company, Ecomark Limited, under the tradename 'K-Othrin'® and secondly, a lambda-cyhalothrin based insecticide produced by Zenaca Public Health under the tradename 'Icon'®. K-Othrin was purchased by the litre (l) and priced in Z$ and Icon was purchased by the kilogram (kg) and priced in US$. In order to compare these chemicals in a meaningful way the cost was examined in terms of cost per 'charge'.

A charge of each chemical is the amount that must added to a fixed amount of water (10 litre's) to produce a solution of the recommended concentration. A charge of K-Othrin is 60ml and a charge of Icon is 62.5 grams. The cost and quantity of each chemical procured was used to calculate the cost per charge for each chemical in US$ and the results are shown in Table 6-1.

The cost of Icon was US$5.31 per charge and the cost of K-Othrin was US$5.17 per charge. A total of 6187 charges of Icon were used by Hwange district which had been allocated to the district by the central level MoH&CW. An additional 1000 charges of K-Othrin were purchased by the district from their own budget. The total expenditure on chemicals for the 1998/99 malaria season in Hwange district was US$38022.97.

### 6.3.2 LABOUR COSTS

In 1998/99 a total of thirty spraymen were hired for three months at a cost of US$15.77 per person per month. Two 'warners' were hired for three months at a cost of US$15.77 plus an additional monthly subsistence allowance (paid to warners because they travel ahead of the camp and may therefore have to find alternative accommodation on some occasions) of US$0.89 per person per month, giving a total wage of US$16.66. Two camp guards were employed on a daily basis for a period of 22 days per month (at weekends spraymen were expected to be around camp so no guard was necessary) at US$0.94 per person per day. A single driver was required to transport the staff and equipment of both teams, for three months at a monthly wage of US$58.14. Two supervisors were hired for four days each month (total of 12 days each) at a daily wage of US$1.83 per person to check on the progress of the spray teams. Two team leaders were also employed for three months at the provincial level to co-ordinate the spray team activities for a monthly wage of US$78.31 per person. In order to allocate a portion of this provincial cost to Hwange district the total cost of team leaders wages was multiplied by the number

of spray teams in Hwange (2) divided by the total number of spray teams in Matabeleland North (11 - two spray teams in each of 6 districts and one in one district (source: Provincial Environmental Health Officer Matabeleland North).

The total labour cost (excluding community education activities) for the Hwange District spray programme was US$1947. The breakdown of labour costs in 1998/99 by each employee type is as follows: spraymen account for the largest amount of labour costs US$1418.95 (74%) followed by drivers US$ 174.41 (9%), guards US$124.04 (6%) and warners US$99.97 (5%). Supervision only accounts for 2% (US$43.85) of total labour costs, which is low considering the vital importance of supervision to the success of a spray programme. The results of the labour costing are shown in Table 6-2.

### 6.3.3 EQUIPMENT REQUIREMENTS AND COSTS

The equipment used in the spray programme was itemised under the following categories. 'Spraying' - includes all equipment used in the actual process of spraying the dwellings and maintaining the spray pumps. 'Mixing equipment' - includes the items needed for the mixing of the chemical. 'Protective gear' - includes all the items needed to protect the spraymen from the chemical and clean themselves afterwards. 'Camping equipment' - includes all the items necessary for the men to set up camps. The 'Miscellaneous' category includes any other items.

The unit cost (1998 purchase price converted into US$) of each item was obtained from a purchase order at the provincial medical office with the exception of the pump spares/maintenance kits for which no information could be found. This had to be estimated as follows: the cost per spray pump was Z$4300, which is equivalent to US$113 (1999 US$), this corresponds with the maximum price of spray pumps estimated by Goodman *et al.* (Goodman, 1999) of US$120 (US$1995) from the Hudson Price Catalogue (1996). Hence the estimate of the maximum cost

per spares/maintenance kit cited by Goodman *et al.* of US$10 was used (Hudson Price Catalogue, cited in Goodman *et al.* 1999).

The useful life in years of each item, was estimated in discussion with the Provincial Environmental Health Officer (PEHO) (shown next to each item in table 3). Those items with a useful life of 1 year are consumed by the end of the annual spray round. Items with useful life of greater than 1 year have been annualised according to their useful life and a discount rate of 5% (annuity factor obtained from table provided in Drummond *et al.,* 1997). The quantity and value of each item (annualised for capital items) was multiplied to provide the total cost of each item/(s), which are summed to show the total equipment cost per team.

The total cost of equipment per spray team with capital items annualised at a discount rate of 5% was US$2559. In 1998/99 two spray teams were used to cover the Hwange district, therefore the total cost of equipment with capital items annualised at 5% was US$5118.

The breakdown of equipment costs by category is as follows: Protective gear and camping equipment account for the largest proportion of total equipment costs at 43% and 39% respectively. Spraying equipment, including pumps and spare parts account for 17% of the total equipment costs, mixing and miscellaneous equipment account for the remaining amount. The results of the equipment costing are shown in Table 6-3.

### 6.3.4 TRANSPORT COSTS

The vehicle used for supervisory purposes covered a distance of approximately 2500km at a cost of US$0.148/km and the vehicle used to transport the spray teams travelled a distance of approximately 7500km at a cost of US$0.145. The total cost of these two activities' transport was US$1459. The transport costs for the Hwange district spray programme are shown in Table 6-4.

### 6.3.5 COMMUNITY EDUCATION

After speaking with the environmental health technician (EHT) at three rural health centres it was estimated that the EHT spent approximately two days organising, preparing for and attending the meeting of community leaders prior to the spray programme. The meeting would normally take place outside in a communal meeting area around or near to the health centre. No transport or subsistence costs would therefore be imposed on the provider and the only cost was the EHTs time. (In previous years the EHT was able to supply food and drink at the meeting, however in 1998/99 this was stopped due to financial cut backs).

It was assumed that for each of the 16 government run RHC in Hwange district an EHT would spend the equivalent of two days on community education. The daily rate of pay for an EHT in 1998/99 was calculated from the monthly wage (taken from the mid-point of the salary range for EHTs) by assuming that the EHT worked for 20 days per month (i.e. not weekends). This was multiplied by the number of days spent on community education (2) and the number of heath centres in Hwange district (16) to obtain the total cost of community education prior to the spray programme. The estimated total cost of community education in Hwange district was US$518.

### 6.3.6 TOTAL COST OF HWANGE DISTRICT SPRAY PROGRAMME

The total cost of the Hwange district spray programme for the 1998/99 malaria season are summarised in Table 6-5. The total cost was US$47065.35 with chemical costs forming the vast majority, 81% (US$38022.97) of total programme costs. Equipment costs were US$5118 (11%) and labour costs (excluding labour used in community education) were US$1947 (4%). Transport and community education costs accounted for only 3% and 1% respectively of total programme costs.

### 6.3.7 COST PER PERSON PROTECTION COVERED

The number of structures sprayed in Hwange district was 24236 which, was estimated to cover a population of 39416 people (Source: Hwange District Environmental Health Office and Matabeleland North Provincial Environmental Health Office). The average cost per person covered by the spay programme is therefore US$1.07.

## 6.4 SENSITIVITY ANALYSIS OF SPRAY PROGRAMME COSTS

Since the results of the costing were obtained from actual data there is little uncertainty about the values of most of the parameters. However, sensitivity analysis was carried out on the variables which were either crucially important to the results (chemical choice), subject to possible future variation within the programme (amount of supervision) or for which the estimate obtained was not entirely satisfactory (cost of transport). The cost to the population of the spray programme were also excluded from the analysis because of the choice of perspective however, these costs are likely to be minimal, including only the cost of time spent removing and replacing furniture from houses sprayed and obtaining water for the dilution of the chemical. At most this is likely to be equivalent to the opportunity cost of a days labour forgone in other household activities.

Chemical costs form the largest proportion of total spray programme costs in Hwange district. However, since the cost of the chemicals was very similar it was not considered necessary to carry out sensitivity analysis on this aspect of the costing.

Sensitivity analysis was carried out to investigate the cost of increased supervision because supervision is critical to the success of the spray programmes. Supervision costs involve the cost of paying supervisors and the cost of transporting them between sites. The cost of supervision was estimated for employing two supervisors for 8 days and 16 days per month instead of for 4 days which was the

actual amount. For 8 days of supervision the cost of supervisory labour and transport was doubled. With two supervisors working 8 days per month, the total cost of labour was increased by 2% and the total cost of transport increased by 25%. Overall, the total cost of the spray programme would be US$42632, which is less than 1% more than with 4 days of supervision. With two supervisors working 16 days per month the cost of labour was increased by 7% and the cost of transport was increased by 76%. Overall the total cost of the spray programme would be US$43459, which is approximately 3% greater than the total cost with 4 days of supervision

The cost of transport in the spray programme was subjected to sensitivity analysis since the cost used is the cost paid by the district to the central vehicle pool and this may not accurately reflect the cost of vehicles. The cost per km was therefore arbitrarily increased by 25% and 50% to examine the sensitivity of the results to this input. A 25% or 50% increase in the cost per km increases total programme costs by 0.86% or 1.7% respectively.

The spray programme costs are not sensitive to changes in the choice of chemical because chemical prices are very similar, however the efficacy of each chemical would need to be considered. Altering the amount of supervision has little impact on the overall cost of the programme, however it may affect the effectiveness of the programme significantly by improving the coverage and quality of spraying. When the cost of transport was altered arbitrarily (by 25% and 50%) it had little impact on the overall cost of the programme. This is reassuring since it means that the value used for the cost of transport has limited impact on the results of the costing.

## 6.5 CASE MANAGEMENT COSTS AT THREE RURAL HEALTH CENTRES IN HWANGE DISTRICT

In rural communities in Hwange district the most accessible government provided health care is village level chloroquine holders or the rural health centres (RHC). Cases of suspected malaria treated by VCH are recorded in the statistics of the nearest RHC, which will also supply the chloroquine to VCH. The costs of treatment by village chloroquine holders (VCH) to the government will be the costs of chloroquine and any cost incurred during the training of the chloroquine holders. The cost of drugs will be the same for cases treated by VCH or at the RHC, however it is likely that the cost to the government of treating cases in RHC is greater than treatment by VCHs because of staff and overhead costs. However, the number VCHs in the community was small at the time the costing was carried out and therefore all malaria cases recorded by the RHC were assumed to be treated in the RHC.

Data was collected from three RHC in the Hwange district (Jambezi, Mwemba and Lupote) for the period July 1998 to June 1999. This period was chosen so that a complete uninterrupted transmission season (December to May) was captured. For each health centre, data was collected on staff establishment involved in case management (i.e. environmental health technicians were excluded), total patients seen and malaria cases treated by age. Wage information was collected from the provincial level using the mid-point on the salary scale for each type of worker. Malaria cases as a proportion of total patients seen per month was used as a proxy to allocate a proportion of monthly staff costs to malaria. A monthly proxy was used rather than an annual average in order to accurately capture the cost implications of the seasonal variation in malaria transmission.

The replacement cost of a health centre was obtained from the central level. This was annualised over its useful life, which was assumed to be twenty years, at a discount rate of 5%. The annualised cost was divided by twelve to give the

annualised cost per month and a proportion of this cost was allocated to malaria based on the same proxy used for allocating staff costs.

Drug costs were obtained from the Government Medical Stores (GMS) in Harare and used to calculate a cost per standard dose of the 1st line treatment for the following age groups: under five year olds, five to fourteen year olds and fifteen year olds and above. The number of cases in each age group treated was multiplied by the cost per standard dose to obtain an estimate of the total drug costs (2nd and 3rd line treatment costs are considered in the sensitivity analysis below).

The total costs of treating malaria cases at the RHC level was calculated for each health centre and divided by the number of cases treated to obtain an average cost per malaria case treated.

## 6.6 RESULTS OF CASE MANAGEMENT COSTING

The full compliment of staff at a RHC in Zimbabwe is two nurses (one each of State Registered Nurse (SRN) and State Certified Nurse (SCN)), one nurse aid and a general hand. The monthly wage for each of these employees is as follows: SRN US$429.08/month, SCN US$327.44/month, nurse aid US$120.42/month and general hand US$90.92/month.

The replacement cost of a health centre was obtained from a quantity surveyor at the MoH&CW in Harare. The figure stood at US$215986, which is equivalent to an annual cost of US$17331 or a monthly equivalent (to be allocated to malaria using the proxy) of US$1444.

The standard dosage assumptions and cost per dose is shown in Table 6-6. The estimated drug cost of treating an infant (under five year old) is US$0.057, the cost for a 5 to 14 year old is US$0.051 and the cost of treating an adult is US$0.141.

Table 6-7 shows the number of malaria cases treated by age and month at each RHC, and malaria cases as a proportion of the total number of patients treated

by month. The proxy used to allocate shared costs to malaria, malaria cases as a proportion of all cases seen by month is also shown in the table.

The proxies were used to estimate the total annual salary cost of treating malaria patients at each clinic according to the staff at each clinic. Lupote and Jambezi clinic had a full compliment of staff, however Mwemba clinic was missing a state certified nurse (SCN) from its staff. The estimated staff costs at each clinic were US$4097 at Lupote, US$3651 at Jambezi and US$3690 at Mwemba. The average staff cost was US$3813 or 39% of total costs. Capital costs were allocated to malaria according to the proxies resulting in total annual capital cost due to malaria of US$5449, US$5507 and US$6114 for Jambezi, Mwemba and Lupote respectively. The average capital cost was US$5690 or 58%. The total drug costs calculated according to the age of malaria patients and the standard dosages and costs were as follows: Lupote US$621, Jambezi US$297 and Mwemba US$179. The average drug cost was US$366 or 4%

The average cost per malaria case treated was the lowest at Lupote RHC at a cost of US$1.71 per case treated, followed by Jambezi RHC where the average cost was US$3.11. The highest average cost per case treated was at Mwemba RHC where the figure was US$4.93, more than double the cost at Lupote. The average cost per case treated in all the health centre's was US$2.63.

The breakdown of total costs into the proportion spent on each category yields the following results for each health centre. The highest proportion of total cost is allocated to the capital cost of the building for each clinic at values of 56%, 58% and 59% for Lupote, Jambezi and Mwemba respectively. This is followed by staff costs, which account for 38%, 39% and 39% at Lupote, Jambezi and Mwemba respectively. Finally drug costs account for only 6%, 3% and 2% at each clinic (same order respectively). These results are summarised in Table 6-8.

## 6.7 SENSITIVITY ANALYSIS OF CASE MANAGEMENT COSTS

The costing of the case management represents the minimum cost of case management of uncomplicated malaria at government run health centres in Hwange district. The actual cost of case management from the provider perspective is likely to be substantially higher for a number of reasons. Firstly, the amount of drugs used per case may be higher due to drug wastage or expiry of buffer stocks of drugs before they are used. Secondly, 2nd line drugs may be provided by the RHC for cases with suspected treatment failure and 3rd line drugs may be available at RHC level for referral cases, this was not included in the costing. Thirdly, the referral of severe and complicated malaria cases will incur costs to the provider. These will be comprised of transport costs to and treatment costs at district level health services (for example the district hospital at Victoria Falls). Finally, the costs of equipment and overheads in the RHC was not included in the costing because the amount of time that would be required to obtain the data was not considered to be justified as the facilities were extremely basic and overhead costs likely to be very low.

The first variable to be altered in the sensitivity analysis is the amount of drugs used per case. An estimate of the amount of drugs wasted could not be obtained from Zimbabwe therefore a review of the literature was carried out to obtain estimates of drug wastage. Goodman *et al.* used an estimate of 25%, therefore drug costs were increased by 25% in each RHC (Goodman et al. 2000). This increased drug costs in Jambezi RHC from US$297 to US$371 (from 3.2% to 3.9% of total costs), in Mwemba RHC from US$179 to US$223 (from 1.9% to 2.4% of total costs) and in Lupote RHC from US$220 to US$776 (from 5.7% to 7.1% of total costs). The average drug cost increased from US$220 to US$275 (from 3.7% to 4.6% of total costs). Overall increasing drug costs by 25% increased the average cost per case treated from US$3.25 to US$3.27 which is equivalent to a percentage increase of 0.7%.

In Malawi Daly *et al.* found that in the treatment of sexually transmitted disease, drug wastage accounted for 54% of total observed drug costs (Daly et al. 1998). Applying 54% wastage to the figures for drugs in the three RHC increases drug costs to US$457 (4.8%), US$275 (2.9%) and US$957 (8.6%) (% of total costs accounted for by drugs in brackets) for Jambezi, Mwemba and Lupote respectively. The average cost of treating a case increased by 1.6% to US$3.30.

The Zimbabwean Standard Treatment Guidelines on Malaria specify that the 2nd line treatment (sulphadoxine and pyrimethamine (SP)) should be given to cases with suspected treatment failure and that 3rd line treatment (quinine by IV infusion) should be given to severe and complicated cases (Malaria control technical sub-committee on case management and drug sensitivity 1998). Treatment failure is considered if patients return to the health facility feeling unwell and if there are no signs of other conditions or of severe and complicated malaria. It was not possible to establish how many of the cases in each health centre were actually treated with the 2nd line drug, however two studies were identified from the literature and used to provide estimates of this. No data or studies could be found which provided information on the number of severe complicated cases receiving the 3rd line treatment from RHC. Some of the cases recorded in the RHC statistics will be treatment failures reporting for a second time, and these patients should have received the 2nd line drug. The sensitivity of the cost estimate to the number of patients requiring each line of treatment was therefore examined using a combination of sensitivity analysis and scenario analysis informed by data from published studies.

A study in the Kariba district, Mashonaland West province of Zimbabwe found that early treatment failure (by day 3) occurred in 21% of cases (Mharakurwa et al. 1998). A further study in the Hurungwe district, Mashonaland West Province of Zimbabwe found that the 1st line drug, chloroquine was a successful in 85.7% of

cases and failed in 14.3% of cases (Barduangi et al. 1998). Assuming that all cases which receive the 2nd line will have also received the 1st line on a previous visit recorded in the RHC statistics and applying the treatment failure rates reported by Mharakurwa *et al.* gives 84% of total recorded cases treated with the 1st line drug and 16% of total recorded cases treated with the 2nd line drug (if 81 patients receive 1st line and 19 receive 1st and 2nd line, a total of 119 visits have been made, hence 100/119 visits receive 1st line (84%) and 19/119 visits receive 2nd line). Applying the treatment failure rates reported by Barduagni *et al.* gives 86% of total recorded cases receiving the 1st line drug and 14% of cases receiving the 2nd line drug.

The costs for treatment with the 2nd line drug are lower than those for the 1st line drug. An infant dose of SP (under 4 years) costs US$0.007, a child dose (between 4 and 10 years or less than 60kg in weight) costs between US$0.015 and US$0.029 (depending on the age and weight of the child) and an adult dose of SP costs US$0.044. The 3rd line drug regimen consists of quinine IV infusion which costs US$1.17 for the first loading adult dose (the only dose given at the RHC). Some of the cases recorded at the RHC will have received the 2nd line drug treatment, and since the cost of the 2nd line drug is lower per dose than the cost of the 1st line drug applying the cost of the 1st line to all cases will overestimate the drug costs. However if the cost of 3rd line treatment, which is substantially higher than both the 1st and 2nd line drugs is included the figure is less likely to be an overestimate.

The scenarios described in Box 6-1 below illustrate how inclusion of 2nd and 3rd line drug costs affects the result of the costing.

Box 6-1 Scenarios for the Inclusion of 2nd and 3rd Line Drug Costs

Drug Costs
1st line = US$0.14 per adult dose
2nd line = US$0.04 per adult dose
3rd line = US$1.17 per adult dose

Scenario 1
100 visits treated with the 1st line drug costs US$14.00

Scenario 2 (Mharakurwa, 1998)
84 visits treated with the 1st line drug and 16 visits treated with the 1st and 2nd line drug costs US$12.40.
A decrease of US$1.60 compared to scenario 1.
Equivalent to 1.4 doses of the 3rd line drug

Scenario 3 (Barduangi, 1998)
88 visits treated with the 1st line drug and 12 visits treated with the 1st and 2nd line drug costs US$12.80
A decrease of US$1.20 compared to scenario 1
Equivalent to 1 dose of the 2nd line drug

Scenario 1 is the situation assumed in the costing study, where all visits are treated with the 1st line drug. Scenario 2 is the situation informed by data from the Mharakurwa study where 84% of visits (equivalent to 81% of patients) are treated successfully with the 1st line treatment and 16% of visits (equivalent to 19% of patients) are treated with the 2nd line drug. In this case the cost reduction resulting from the inclusion of some visits receiving 2nd line treatment would be offset by the cost of 1.4 doses of the 3rd line treatment. Scenario 3 is the situation informed by data from the Baraduangni *et al.* study where 88% of visits (equivalent to 86% of patients) are treated successfully with the 1st line treatment and 12% of visits (equivalent to 14% of patients) are treated with the 2nd line drug. In this case a single dose of the 3rd line drug would be sufficient to offset the reduction in the cost of drugs. The reduction in estimated cost resulting from the inclusion of an estimate of the level of 2nd line treatment taken from the literature is likely to be offset by the inclusion of a single dose of the 3rd line treatment, this is equivalent to 1 in 100 visits being treated with the 3rd line.

High levels of drug wastage or the introduction of 2nd and 3rd line drugs into the analysis only has a limited effect on the average cost per case treated in the RHC since the capital cost of the RHC and staff costs represent the largest proportions of total costs. It can therefore be assumed that the costs reported here are fairly robust.

Table 6-1 Chemical Costs

| Type of Chemical | Chemical Quantity | | Cost Per Litre/Kg | Chemical Unit Cost/Charge | Total Chemical Cost |
|---|---|---|---|---|---|
| | In Litres/Kg | In Charges | | | |
| Icon | 386.69 | 6187 | 85.00 | 5.31 | 32852.97 |
| K-Othrin | 60.00 | 1000 | N/A | 5.17 | 5170.00 |
| Total | N/A | 7187 | N/A | N/A | 38022.97 |

Table 6-2 Labour Costs for 1998/99 Hwange District Spray Programme

| Occupation | Quantity | Monthly or Daily Wage (US$) | Number of Month or Days Hired | Total Cost (US$) | % of Total Labour Costs |
|---|---|---|---|---|---|
| Spraymen | 30 | 15.77 | 3 | 1418.95 | 74 |
| Warners | 2 | 16.66 | 3 | 99.97 | 5 |
| Drivers | 1 | 58.14 | 3 | 174.41 | 9 |
| Guards | 2 | 0.94 | 66 | 124.04 | 6 |
| Supervisors | 2 | 1.83 | 12 | 43.85 | 2 |
| Team Leaders | (2*2/11)=0.36 | 78.31 | 3 | 85.43 | 4 |
| TOTAL | N/A | N/A | N/A | 1946.65 | 100 |

Table 6-3 Quantity, Useful life and Total Cost of Equipment used by a Spray Team

| Item Use Category | Item | Number per Team | Estimated Useful Life (Years) | Total Cost/Year (US$; @5%) |
|---|---|---|---|---|
| Spraying | Spray Pumps | 15 | 5 | 388.87 |
| | Pump Spares/Maintenance kit | 2 | 2 | 10.67 |
| | Pump Hose (M) | 16 | 1 | 16.71 |
| | Haver Sack/Knapsacks | 15 | 2 | 16.85 |
| | Shifting Spanner | 1 | 2 | 0.70 |
| Mixing Equipment | Galvanised Buckets | 15 | 5 | 17.54 |
| | Strainers | 15 | 5 | 1.09 |
| Protective Gear | Overalls | 35 | 1 | 240.64 |
| | Rubber Gloves | 15 | 2 | 5.26 |
| | Farm Shoes/ Rubber Boots (Pairs) | 15 | 2 | 758.07 |
| | Floppy Hats | 15 | 2 | 10.68 |
| | Rain Coats | 15 | 5 | 15.55 |
| | Face Shields | 15 | 5 | 4.52 |
| | Respirator Cartridges | 15 | 1 | 38.76 |
| | Soap Bars | 120 | 1 | 18.79 |
| Camping Equipment | 4 Men Tents | 5 | 5 | 696.36 |
| | Roof Tents | 1 | 5 | 108.52 |
| | Ground Sheeting (Sq M) | 20 | 2 | 21.06 |
| | Hurricane Lamps | 5 | 2 | 4.77 |
| | Torches | 5 | 2 | 3.51 |
| | Water Cooling Bags | 1 | 1 | 0.78 |
| | Hoe | 1 | 5 | 0.12 |
| | Axe | 1 | 5 | 1.11 |
| | Pick | 1 | 5 | 1.02 |
| | Pick Handle | 2 | 1 | 1.67 |
| | Shovels | 2 | 5 | 1.81 |
| | Stretcher Bed Frames | 18 | 5 | 20.62 |
| | Stretcher Bed Canvas | 18 | 2 | 96.02 |
| | Folding Chairs | 18 | 5 | 13.13 |
| | Chair Canvasses | 18 | 2 | 30.32 |
| | Folding Tables | 5 | 5 | 4.22 |
| Miscellaneous | Hessian Sacking (Sq M) | 10 | 1 | 5.22 |
| | Exercise Books | 20 | 1 | 1.57 |
| | Ball Pens | 20 | 1 | 2.61 |
| TOTAL COST PER TEAM | | N/A | N/A | 2559.17 |
| TOTAL COST HWANGE DISTRICT | | | | 5118.34 |

Table 6-4 Transport Costs for Hwange District Spray Programme

| Purpose | Distance Travelled (km) | Cost per KM (US$) | Transport cost (US$) |
|---|---|---|---|
| Transport of Spraymen | 7519 | 0.145 | 1089.68 |
| Supervision | 2503 | 0.148 | 369.34 |
| TOTAL | 10022 | N/A | 1459.02 |

Table 6-5 Total Cost of Hwange District Spray Programme by Cost Item

| Cost Item | US$ | % of Total Cost |
|---|---|---|
| Chemicals | 38022.97 | 81 |
| Labour (Excluding Community Education) | 1946.65 | 4 |
| Transport | 1459.02 | 3 |
| Equipment | 5118.34 | 11 |
| Community Education | 518.37 | 1 |
| TOTAL | 47065.35 | 100 |

Table 6-6 Standard Dosage Assumptions and Drug Costs for 1st Line Treatment

| Drug | Dosage | | |
|---|---|---|---|
| | Under 5 years | 5-14 years | 15+ years |
| Chloroquine Syrup(ml) | 25 | 0 | 0 |
| Chloroquine (per tablet) | 0 | 4 | 10 |
| Paracetamol (per tablet) | 5 | 10 | 30 |
| Total Drug Cost (US$) | 0.057 | 0.051 | 0.141 |

Table 6-7 Malaria Cases by Age and total Cases at RHCs

| JAMBEZI RHC | | | | | | |
|---|---|---|---|---|---|---|
| Date | Malaria Cases by age | | | | Total OPD | Proxy – Malaria as proportion of total cases |
| | 0-4 Years | 5-14 years | 15 years + | Total Malaria | | |
| Jul-98 | 31 | 27 | 52 | 110 | 442 | 0.249 |
| Aug-98 | 20 | 8 | 63 | 91 | 459 | 0.198 |
| Sep-98 | 32 | 19 | 65 | 116 | 441 | 0.263 |
| Oct-98 | 59 | 31 | 94 | 184 | 564 | 0.326 |
| Nov-98 | 33 | 25 | 83 | 141 | 628 | 0.225 |
| Dec-98 | 39 | 17 | 90 | 146 | 554 | 0.264 |
| Jan-99 | 108 | 85 | 227 | 420 | 832 | 0.505 |
| Feb-99 | 156 | 167 | 324 | 647 | 1218 | 0.531 |
| Mar-99 | 140 | 172 | 300 | 612 | 1368 | 0.447 |
| Apr-99 | 93 | 82 | 95 | 270 | 930 | 0.290 |
| May-99 | 30 | 43 | 89 | 162 | 577 | 0.281 |
| Jun-99 | 45 | 24 | 55 | 124 | 640 | 0.194 |
| TOTAL | 786 | 700 | 1537 | 3023 | 8653 | N/A |
| **MWEMBA RHC** | | | | | | |
| Jul-98 | 6 | 22 | 20 | 48 | 292 | 0.164 |
| Aug-98 | 6 | 15 | 26 | 47 | 268 | 0.175 |
| Sep-98 | 6 | 6 | 6 | 18 | 231 | 0.078 |
| Oct-98 | 2 | 10 | 20 | 32 | 291 | 0.110 |
| Nov-98 | 5 | 6 | 22 | 33 | 295 | 0.112 |
| Dec-98 | 12 | 4 | 8 | 24 | 243 | 0.099 |
| Jan-99 | 71 | 53 | 138 | 262 | 498 | 0.526 |
| Feb-99 | 138 | 90 | 178 | 406 | 530 | 0.766 |
| Mar-99 | 180 | 212 | 220 | 612 | 839 | 0.729 |
| Apr-99 | 60 | 57 | 145 | 262 | 469 | 0.559 |
| May-99 | 34 | 17 | 68 | 119 | 325 | 0.366 |
| Jun-99 | 8 | 9 | 22 | 39 | 304 | 0.128 |
| TOTAL | 528 | 501 | 873 | 1902 | 4585 | N/A |
| **LUPOTE RHC** | | | | | | |
| Jul-98 | N/A | N/A | N/A | N/A | N/A | N/A |
| Aug-98 | 40 | 33 | 88 | 161 | 720 | 0.224 |
| Sep-98 | 22 | 15 | 45 | 82 | 481 | 0.170 |
| Oct-98 | 30 | 22 | 59 | 111 | 600 | 0.185 |
| Nov-98 | 28 | 10 | 44 | 82 | 789 | 0.104 |
| Dec-98 | 35 | 16 | 62 | 113 | 525 | 0.215 |
| Jan-99 | 76 | 90 | 170 | 336 | 975 | 0.345 |
| Feb-99 | 139 | 163 | 337 | 629 | 1532 | 0.411 |
| Mar-99 | 257 | 684 | 917 | 1858 | 2932 | 0.634 |
| Apr-99 | 308 | 604 | 888 | 1800 | 1915 | 0.940 |
| May-99 | 144 | 210 | 408 | 762 | 1130 | 0.674 |
| Jun-99 | 86 | 121 | 212 | 419 | 1262 | 0.332 |
| TOTAL | 1165 | 1968 | 3230 | 6353 | 12861 | N/A |

Table 6-8 Summary of RHC Costs

| Cost (US$) & Patients Treated | Jambezi | % of Total Costs | Mwemba | % of Total Costs | Lupote | % of Total Costs | Mean | % of Total Costs |
|---|---|---|---|---|---|---|---|---|
| Staff Cost | 3651 | 39 | 3690 | 39 | 4097 | 38 | 3813 | 39 |
| Capital Costs | 5449 | 58 | 5507 | 59 | 6114 | 56 | 5690 | 58 |
| Drug Costs | 297 | 3 | 179 | 2 | 621 | 6 | 366 | 4 |
| Total Cost | 9397 | 100 | 9376 | 100 | 10833 | 100 | 9868 | 100 |
| Malaria Patients Treated | 3023 | N/A | 1902 | N/A | 6353 | N/A | 3759 | N/A |
| Average Cost per Patient | 3.11 | N/A | 4.93 | N/A | 1.71 | N/A | 2.63 | N/A |

# CHAPTER 7 – COST-EFFECTIVENESS ANALYSIS TO ESTIMATE THE POTENTIAL BENEFITS OF A MEWS

## 7 OVERVIEW OF CHAPTER

The model described in chapter 4 was combined with the results of the costing analysis of residual spraying and case management (chapter 6) to investigate the cost-effectiveness and net cost-effectiveness of various scenarios for each year in the data set. The methodology and results of the cost-effectiveness analysis are presented and discussed in this chapter. Limitations and possible further applications of the model structure are discussed.

## 7.1 METHODOLOGY

The cost of spraying per person covered was found to be US$1.07 (in 1999 constant US$) in the costing analysis, this was assumed to be fixed and used to calculate the cost of spray programmes with alternative levels of population coverage. In the costing analysis the average cost per case of case management was found to be US$4.93 from Mwemba RHC which was the highest cost per case found out of the three health centres in which the costing was carried out (see section 5.6 above). This was used because the estimates were known to be conservative since they excluded certain provider costs such as the cost of 2$^{nd}$ and 3$^{rd}$ line drugs and the costs of case management of referred severe and complicated cases, and any other cases treated at hospitals. The cost per case of case management was assumed to be fixed and was used to calculate the total cost of case management under the alternative scenarios.

A number of scenarios were evaluated against a 'do nothing' alternative in which the only malaria control strategy employed is case management. The 'do nothing' alternative was derived from the 'baseline' scenario which aimed to mimic as closely as possible what occurred in Hwange district during the period under analysis. The 'baseline' scenario was determined from the model which achieved

the highest correlation with the Hwange case data using available *a priori* information from Hwange district such as population size, spray programme coverage and completion dates (as described in section 5.2.2 above). It assumes a spray programme coverage of 24% and spray programme effectiveness from the beginning of January declining linearly over a six month period so that after six months no residual effect of spraying remains. The 'do nothing' alternative used the same values as the 'baseline' scenario except that the effects of the spray programme were removed. This was done by reducing the level of coverage in the model from 24% to 0%. The 'baseline' scenario represents the malaria control situation without a MEWS, control activities are routinely carried out each year and no information on the likely risk or severity of an epidemic is used in the decision making process.

A number of scenarios (including the 'baseline' scenario) were evaluated against the 'do nothing' alternative. These scenarios can be considered as two sets:

Firstly, a set of scenarios considering varying levels of spray programme coverage. The varying levels of coverage considered were 0% ('do nothing' alternative), 24% ('baseline' scenario), 50%, 75% and 100% coverage, all effective from January as in the 'baseline' scenario.

Secondly, a set of scenarios considering a spray programme effective from different points in time. From this point forward any mention of spray timing will refer to the effectiveness on-set date which is assumed to occur from the beginning of each month. This set of scenarios considered spray programmes with 24% coverage effective from January and also from the five months before and for the two months after the baseline scenario on-set time.

The model was run separately for each of the scenarios described above and the results of 'cases reporting by month' (section 5.2.1) were recorded by month for each scenario and aggregated by year to give the total number of cases each

year under each scenario. This data was used to calculate the number of cases prevented by each scenario compared to the 'do nothing' alternative. The percentage change in the number of cases prevented with varying levels of coverage and with varying effectiveness on-set times compared to the 'do nothing' alternative was also calculated.

The cost of adding each spray programme coverage scenario to the 'do nothing' alternative was calculated separately for each year by multiplying the cost per person covered, by the number of people covered. The number of people covered was calculated by multiplying the total population by the percentage coverage achieved by the spray programme. It was not necessary to calculate the cost of spray scenarios with varying times, since it is only the timing of spraying, not the coverage that is being altered in this part of the analysis, therefore the spray programme cost for 24% coverage is used for the timing scenarios. (For spray programmes with higher levels of coverage the relevant cost could easily be substituted from the coverage costs above.)

The costs of adding the spray programme to the 'do nothing' alternative for each scenario and the number of cases prevented by each scenario were used to calculate the incremental cost per case prevented by spraying compared to the 'do nothing' alternative. The percentage change in incremental cost per case prevented for each coverage and timing scenario compared to the 'baseline' scenario was also calculated.

The total annual cost of malaria control for each scenario by year was calculated by adding the cost of case management, calculated by multiplying the number of cases reporting each year by the cost per case of case management, to the cost of the spray programme. This was then used to calculate the net change in total malaria control costs under each scenario compared to the 'do nothing' alternative.

Finally, the net incremental cost per case prevented by spraying compared to the 'do nothing' alternative was calculated by dividing the net change in total malaria control costs by the number of cases prevented in each scenario.

The above analysis was carried out using a model that runs continually for the whole period; in other words the malaria in one year will affect the malaria in the following year. It was used to simulate the effects of spraying with a uniform level of coverage each year throughout the whole period (e.g. coverage is 24% every year from 1993-1998) and a uniform spray coverage on-set time (e.g. October every year throughout the period) depending on the scenario being modelled. These scenarios are referred to as 'uniform scenarios'.

A further analysis was carried out to examine the effects of varying the coverage and timing of spraying each year. This analysis involved selecting the coverage levels and timing for each year from the 'uniform scenarios' which yielded the lowest total malaria control costs for that year. These were placed into the model so that the levels of timing and coverage varied each year; this is referred to as the 'optimal policy' scenario. The results of the 'optimal policy' scenario were compared to results of selected 'uniform scenarios' in order to examine how the 'follow on' effects of control interventions in previous years affect the malaria in the following year.

Note that for the following analysis only the timing scenarios for 1993 with the 'baseline' on-set effectiveness date (January) and the two months following this could be included because the models begins in January 1993 therefore it is not possible to see the effects of interventions beginning before this point. The model results for all coverage scenarios and the three timing scenarios in 1993 are included even though it was not possible to validate these results since no malaria data for 1993 was available. Given that the model was able to predict other year's data successfully there is reason to believe that the results for 1993 will be relatively

accurate furthermore, the model predicted very low malaria case numbers in 1993 which is consistent with clinical malaria cases reported Nationally in that year (source: National Health Information and Surveillance Unit, MoH&CW). Therefore, in the interest of working with a longer data set they are included. Also note that the data for 1998 is only January –March, although only part of the year this is included in the following analysis since it covers most of the malaria season.

## 7.2 RESULTS OF UNIFORM SCENARIOS

### 7.2.1 TOTAL NUMBER OF CASES

The number of cases under each coverage scenario and timing scenario by year are shown in Figure 7-1 and Figures 7-2 and 7-3 respectively. Table 7-1 shows the results of the total number of cases in all scenarios including the 'do nothing' alternative and the number of cases prevented by each scenario compared with 'do nothing' is shown in Table 7-2.

Figure 7-1 illustrates that increasing the level of spray coverage always reduces the number of cases, however altering the timing of spraying has a more complicated impact on the number of cases (see figures 7-2 and 7-3). In order to examine how the number of cases alters with changing levels of coverage or on-set timing in each year the percentage change in the number of cases compared to the 'do nothing' scenario for changing coverage and timing was calculated. The results are shown in Figures 7-4 and 7-5 respectively.

The percentage change in cases resulting from varying levels of coverage (January effectiveness on-set date) follows a similar pattern in all years, declining rapidly at first and then levelling out as coverage is increased further. The greatest percentage reduction by spraying with any level of coverage was achieved in 1993, which was a low year for malaria, and the least percentage reduction was achieved in 1996, an epidemic year. However, in terms of reduction in actual case numbers the number are far higher for 1996 than for 1993. Spraying with the baseline level of

coverage (24%) achieves a reduction in cases of over 92000 for 1996 and only 322 in 1993 when compared with the 'do nothing' alternative.

The pattern of the percentage change in cases caused by varying the onset time of the spray programme with (coverage fixed at 24%) varies between years. In 1993 the highest reduction in cases compared to the 'do nothing' alternative is achieved by a spray programme which is effective from January, this reduces cases by 58% compared to the 'do nothing' alternative. In 1994 spraying effective from September leads to the greatest reduction in the number of cases, by 80% compared to the amount that would occur with the 'do nothing' alternative. The reduction in cases achieved by spraying declines steadily with spraying effective from after September so that spraying effective from January only reduces cases by 41% compared to the 'do nothing' alternative, this figure is reduced further to 16% and 8% with spraying effective from February and March respectively.

In 1995, spraying effective from September achieves the highest percentage reduction in cases of 90% compared to the 'do nothing' alternative. Spraying any earlier is less effective at reducing case numbers as a consequence of the assumed reduction in efficacy of the insecticide. Spraying in November yields a reduction in case numbers of 85% compared to the 'do nothing' alternative, and spraying in January or March only reduces cases by 53% and 26% respectively compared to the 'do nothing' alternative. In other words the number of cases prevented by spraying declines with a spray programme completed after September compared with a spray programme completed by September. The pattern for 1996 is similar with the greatest percentage change in cases being achieved with spraying in October (75%), declining to 50% for spraying in December and 23% in February. Spraying effective prior to October, would reduce the percentage change in cases by 74% and 63% for September and August respectively, compared to the 'do nothing' alternative.

The results for 1997 indicate that spraying effective from October would achieve the highest percentage reduction in cases of 68%. Spraying later so that the insecticide were fully effective between the beginning of November to January would lead to a percentage reduction in cases of between 53%-51%, spraying as late as March would reduce cases by only 27% compared to the 'do nothing' alternative. In 1998 spraying so that maximum effectiveness occurs at the start of September would achieve the highest percentage reduction in case numbers of 79% compared to a 'do nothing' alternative. Spraying effective from January would only reduce the number of cases by 43%, and spraying effective from March by 32%.

Scenarios with varying effectiveness on-set times were assumed to have coverage of 24%, however given that increasing coverage leads to higher numbers of cases being prevented, spraying at the optimal times identified with higher coverage would prevent greater numbers of cases.

### 7.2.2 INCREMENTAL COST OF SPRAYING

The cost of adding spraying with varying levels of coverage to the 'do nothing' alternative is shown in Figure 7-6. The incremental cost of adding a spray programme with each level of coverage increases year on year due to increases in the human population.

In this analysis the cost of a spray programme with varying levels of coverage increases linearly with the percentage coverage since it is assumed that the cost of spraying is constant per person covered. However, this assumption may not always hold true. Assuming zero spare capacity in the spray programme (all inputs are being used to their maximum) additional labour and equipment will be needed to increase coverage. If the input costs and relative proportions (see Table 6-5) of labour and capital equipment are maintained after increasing coverage, then the average cost per person protected will remain unchanged. However, in certain

circumstance the average costs may increase. For example where additional equipment is required and obtained but will not be employed at full capacity.

It is also likely that the marginal cost of finding and spraying the last few more remote dwellings will increase with high levels of coverage. This may also be important when comparing the cost per person protected by spraying in rural and urban areas.

Increasing coverage may lead to reductions in the cost per person protected through economies of scale such as bulk buying of chemicals which account for approximately 80% of the cost (see Table 6-5).

In summary, the average cost assumed in the analysis is most likely to be correct for values of coverage close to 24%, as identified in the costing. In order to achieve coverage of 50% in the same time period as 24% coverage, all inputs would have to be doubled therefore the average cost is likely to be approximately the same, similarly for 75%. However, the cost per person protected at 100% coverage may be higher for the reasons mentioned above.

### 7.2.3 INCREMENTAL COST PER CASE PREVENTED WITH SPRAYING COMPARED TO 'DO NOTHING' ALTERNATIVE

The incremental cost per case prevented by adding a spray programme of varying levels of coverage is shown in Figure 7-7 for 1993 and Figure 7-8 for 1994 to 1998. The results illustrate that the cost per case prevented by spraying varies dramatically from US$267.45 per case prevented with 100% coverage in 1993 (where malaria was predicted to be low) to US$0.42 per case prevented with 24% coverage in 1996 (an epidemic year). Given that the cost per case of case management is assumed to be fixed at US$4.93 (see Section 6.6) preventing a case by spraying could be considered to be a cost-effective intervention as long as the cost of preventing an individual case is below this cost. Coverage of 24% in 1994

and any level of coverage in 1995, 1996, 1997 and 1998 yield a cost per case prevented of below US$4.93.

Since the number of cases prevented by the 'do nothing' alternative is zero, the percentage change in cost per case prevented was calculated from the 'base line' scenario, this is shown in Figure 7-11. Figure 7-11 illustrates that 1996, an epidemic year has the lowest percentage change in cost per case prevented with all levels of coverage. Moreover, diminishing marginal returns to coverage, where the increase in coverage is less than the increase in cost per case prevented, sets in at a higher level of coverage than in years with less transmission.

Assuming a level of coverage of 24%, varying the timing of the spray programme so that it is effective earlier or later than January can affect the cost per case prevented as shown in Figure 7-9 (for 1993) and 7-10 (for 1994-1998). Since the relationship between varying the timing of spraying and the increase in cost per cases prevented is different for each year, the percentage change in cost per cases prevented was calculated to examine the relationship more carefully. The percentage change in cost per case prevented caused by altering the timing of spraying compared to the 'baseline' scenario is shown in Figure 7-12 for 1993 and 1994 and in Figure 7-13 for 1995 to 1998. In 1993 the most cost-effective spaying scenario is to spray with 24% coverage in January, spraying later than January, in February or March would increase the cost per case prevented dramatically, by 262% and 1601% respectively.

In 1994, the incremental cost per case prevented with a spray programme coverage of 24% effective from January can be reduced by 48% compared to the 'do nothing' alternative with spraying effective from September. Spraying in February or March would increase the cost per case prevented by 167% and 397% respectively.

In 1995 spraying effective from January costs US$0.87 per case prevented, this can be reduced to US$0.51 (a reduction of 41%) by spraying so that maximum effectiveness occurs at the start of September. Spraying as late as February or March can increase the cost per case prevented by 71% and 103% compared with the 'baseline' scenario to US$1.49 and US$1.77 respectively. Similarly in 1996 the cost per case prevented of a spray programme effective from January (US$0.42) can be reduced by 56% by an effectiveness on-set time of October. Leaving spraying until as late as February or March can increase the cost per case prevented by 48% and 69% to US$0.63 and US$0.71 respectively.

The analysis also reveals that in 1997 the cost per case prevented can be reduced by 25% by spraying which is effective from October and in 1998 the cost per case prevented could be reduced by 45% by spraying in September.

### 7.2.4 TOTAL COST OF MALARIA CONTROL

The total cost of malaria control represents the cost of case management and spraying (except for the 'do nothing' alternative where no spraying is carried out) and is illustrated in Figure 7-14 for varying levels of spray programme coverage. Figure 7-15 and Figure 7-16 show the total cost of malaria control with varying on-set times of spraying effectiveness for the periods 1993-1995 and 1996-1998 respectively. Figures 7-17 and 7-18 illustrate the percentage change in total cost achieved with varying scenarios of coverage and timing respectively for the period 1994 to 1998 (1993 not shown on figure due to high numbers involved).

In 1993 (results shown on Figures 7-15 and 7-16 but not on figures 7-17 or 7-18 due to large numbers) the total cost of malaria control was relatively low due to the very low numbers of cases. Therefore, adding a spray programme with any level of coverage causes a massive percentage increase in total costs, so that compared to the 'do nothing' alternative, adding a spray programme with 24% coverage would increase total costs by 1206%, 50% coverage would increase total

costs by 2549% and 100% coverage would increase total costs by 5169%. However, even with 100% coverage total malaria control costs are still relatively low compared to costs in other years.

In 1994 the spray coverage which leads to the lowest total cost is 24%, which reduces total cost by 6% compared to a 'do nothing' alternative. Spraying with coverage of 50%, 75% or 100% would increase total costs compared to a 'do nothing' alternative by 13%, 43% and 78% respectively. Spraying in September would minimise total costs of malaria control to 44% less than the 'do nothing' alternative.

In 1995 a spray programme with 50% coverage achieves the highest reduction in total costs (53%) out of the levels of coverage tested compared to the 'do nothing' alternative. Coverage of 24% would however yield a reduction in total costs of 80% if effective from September compared to a 'do nothing' alternative.

1996 has the highest malaria control costs compared to all other years, particularly with the 'do nothing' alternative. Implementing a spray programme with 24% coverage effective from January could reduce total costs by 31%, bringing the spray programme forward so that it is effective from October could reduce total control costs by a 42% compared to the 'do nothing' alternative. Total costs are reduced as the level of spray programme coverage increases even up to 100% coverage which yields an additional 1% reduction in coverage compared to 75% coverage. In 1997 coverage up 75% continues to achieve a reduction in total costs compared to the 'do nothing' alternative with October being the month which yields the highest reduction in total costs (62%).

The results for total cost in 1998 must be treated with caution since only three months data was available, however it appears that 100% coverage would achieve the greatest reduction in total costs with a spraying effectiveness on-set time of September reducing costs further compared to the 'do nothing' alternative.

In years of low transmission a spray programme is unlikely to yield a reduction in total malaria control costs. However, in epidemic or high transmission years a cost reduction may be achieved through the introduction of a spray programme resulting in a reduction in case numbers and consequently in case management costs. In high transmission years a spray programme with relatively low coverage may achieve large percentage reductions in total cost, in particular if timed early enough to have a large impact on the early stages of an epidemic curve. These reductions may continue up to coverage levels of 100% however, the percentage reduction in costs achieved by incremental increases in coverage will decline after a certain point in each year under each given scenario.

### 7.2.5 NET INCREMENTAL COST PER CASE PREVENTED OF SPRAYING COMPARED TO 'DO NOTHING' ALTERNATIVE

Net incremental cost per case prevented includes the additional cost of spraying and any cost savings made possible by a reduction in the case management costs which would have arisen had spraying not been carried out. Figure 7-19 and figure 7-20, illustrate the net incremental cost per case prevented by implementing a spray programme with varying levels of coverage for 1993 and 1994-1998 respectively. Figure 7-21 and 7-22 illustrate the net incremental cost per case prevented by implementing a spray programme with 24% coverage at various times for 1993 and 1994-1998 respectively.

The net incremental cost per case prevented by spraying in 1993 is relatively high for all spray programme coverage, ranging between US$103.11 per case prevented with 24% coverage and US$262.52 per case prevented with 100% coverage. In 1994 coverage of 24% actually yields a net reduction in costs with the net incremental cost per case prevented equal to -US$0.70 (i.e. a saving) compared to the 'do nothing' alternative. Coverage of greater than 24% has a positive net incremental cost per case prevented ranging between US$1.08 for coverage of 50% and US$5.48 for coverage of 100%. In 1995 to 1998 inclusive, initiating a spray

programme of any level of coverage tested results in a net incremental cost effectiveness of less than zero, this means that the intervention is both more effective and less costly than the 'do nothing' alternative.

In all years (except for 1993 for which results are not available) bringing the timing of the spray programme forward from January can further increase the cost-effectiveness of intervention. For example in 1994 spraying in September as opposed to January can improve the net incremental cost-effectiveness of spraying from -US$0.70 to -US$2.74. On the other hand spraying any later than January in this season would no longer yield net cost savings and would begin to incur costs of US$6.38 and US$16.12 per case prevented for February and March respectively. In all years except for 1994 a spray programme with 24% coverage will yield net cost savings at any given implementation time tested in the model, however these tend to decline the later the spraying is initiated. This is logical since an earlier spray programme can have a bigger impact as an epidemic is starting out and the effects on transmission are likely to be greater than when an epidemic has already taken hold.

### 7.2.6 SUMMARY OF RESULTS OF UNIFORM SCENARIOS

According to the net cost-effectiveness analysis, with 24% coverage the optimal spray effectiveness on-set times will be January in 1993 (data not available for earlier spray times), September in 1994 and 1995, September or October in 1996, October in 1997 and September in 1998. Furthermore, the results of the total cost analysis (see section 7.2.4) indicate that the following levels of coverage would yield the lowest total cost for each year, 0% coverage in 1993, 24% coverage in 1994, 50% coverage in 1995, 100% coverage in 1996, 75% coverage in 1997 and 100% coverage in 1998.

The more severe the transmission season the more cases are likely to be prevented by a spray programme; moreover the more severe the season the higher

the marginal increase in cases prevented gained by increasing spray coverage. Total costs of malaria control (case management and spraying costs) in all scenarios and the 'do nothing' alternative tend to be much higher in the high transmission years. However, total costs in the 'do nothing' alternative are higher than at least one scenario with a spray programme in all years except for 1993. The point at which increasing coverage leads to a rise in total costs is higher in high transmission years and does not happen at all below 100% coverage in 1996 and 1998.

The incremental cost per case prevented between varying coverage scenarios increases with coverage in all years. The cost per case prevented tends to be lower in high transmission years than low transmission years. The net incremental cost-effectiveness analysis showed that in most years spraying leads to a reduction in total costs, with the percentage change in reduction decreasing as coverage increases.

Increasing the coverage of a spray programme decreases the total number of cases although after a certain point (between 50% and 75% in this analysis) the percentage reduction in cases achieved is less than the percentage increase in coverage.

### 7.2.7 CHOICE OF OUTCOME MEASURE

In this analysis the outcomes of each scenario have been expressed in a number of different ways:

1. The total number of cases occurring by year with each intervention scenario
2. The incremental cost of spraying compared to the 'do nothing' alternative
3. The incremental cost per case prevented of spraying compared to the 'do nothing' alternative

4. The total cost of malaria control
5. The net incremental cost per case prevented of spraying compared to the 'do nothing' alternative.

To interpret the information from this study in a useful way it is helpful to refer back to the section on control theory (section 3.6.1 point 3) which specifies that

*'The control policy or rules prescribing what control action is to be chosen at any time must be laid down'*

This means that in order to define an optimal strategy we must first identify what the rules prescribing the control actions are, in other words which of the reported outcome measures (outcomes 1-5 above) the decision-makers are interested in optimising.

Decision-makers interested in optimising outcome 1 will be aiming to minimise the number of cases (equivalent to maximising the number of cases prevented). It is unlikely that decision-makers would be interested in or able to minimise the number of cases since this calls for a strategy of 100% coverage each year which is extremely unlikely to be affordable, particularly given the higher marginal cost of achieving the final few percentage points of coverage (i.e. moving from 75% to 100%). This strategy would also be a sub-optimal strategy for decision-makers concerned with achieving a cost-effective use of resources as the incremental cost of preventing the final few cases would be very high.

In order to identify the optimising strategy for outcome 2 a further assumption that decision-makers are subject to a budget constraint for spraying expenditure must be imposed. If this is the case decision-makers will be keen to spend money on spraying up to but not beyond their budget constraints. This situation is likely to be a more accurate representation of reality than the one described above, however

it gives decision makers no preference for the cost-effective use of resources, only the desire to spend within budget.

Optimising outcome 3 is appropriate in situations where it has already been decided to pursue cost-effective interventions. This may be determined by the use of a threshold value that the decision-maker was willing to pay to prevent a malaria case possibly based on the cost of treating a case as mentioned in this analysis or alternatively compared to all other possible uses of resources. It has been pointed out that information on the cost-effectiveness of all alternative interventions and uses of resources will not be available (Evans and Hurley 1995), however threshold values for desirable interventions do exist (Jamison et al. 1993) and may be used in this situation.

If decision makers wish to optimise using outcome 4, they are likely to be seeking to reduce the total cost of malaria control and should therefore choose strategies accordingly taking into consideration that expenditure on spraying will be off-set to a greater or lesser extent by savings on case management. They are assuming that resources not spent on case management will actually be freed up and may be spent elsewhere. The extent to which this is true will depend on the proportions of case management expenditure made up of items that can be reduced if there is less malaria. The main example of this would be drug costs. Capital costs (found to be relatively high in this analysis) and staff costs are unlikely to be able to be reduced in low malaria seasons however, a reduction in malaria cases at hospitals and clinics will leave staff and facilities available for use by patients with other conditions.

Finally, if decision makers choose to optimise based on net incremental cost-effectiveness (outcome measure 5) they would also be assuming resources were going to be freed up for use elsewhere, moreover using this outcome measure

would ensure that spray coverage was only increased up to the point where diminishing marginal returns sets in.

Table 7-3 describes the optimal results by year that would be chosen by decision-makers interested in optimising each of the five outcome measures. The table illustrates that the optimal time to intervene is the same with any choice of outcome measure, however the level of coverage chosen varies considerably depending on the outcome measure chosen for optimisation. For example in 1995 the optimal level of coverage based on outcome measure 1 is 100%, for outcome measure 2 it will be subject to a budget constraint, for 3 it will be subject to a cost-effectiveness threshold, for 4 it will be 50% and for outcome measure 5 it will be 24%.

Given that outcome measure one is unrealistic, no generic information is available on the budget constraints for spraying activities, and that the cost-effectiveness thresholds for desirable interventions that do exist are expressed in terms of DALYs, the remainder of this discussion will focus on optimal coverage strategies based on outcome measures 4 and 5. The results for optimal spray timing are the same for any outcome measure chosen.

### 7.2.8 OPTIMAL TIMING

The model suggests that spraying should be at its full effectiveness i.e. be completed, from the beginning of September or October in order to achieve the optimal results whatever outcome measure is being used. This timing coincides with spraying being completed before the start of the rainy season (which begins in September/October) which is the recommended completion time put forward at a malaria control meeting in Southern Africa (WHO Workshop on Prevention and Control of Malaria Epidemics in Southern Africa, Windhoek, Namibia, 19-23 August 1996, S. J. Connor, personal communication).

Spray programme start and finish dates from Hwange indicate that spraying activities take between 2-3 months to complete with 24% coverage. This means that in order to achieve coverage of the target area by September/October spraying would have to commence between June and July – almost six months sooner than when it actually occurs!

Since the effectiveness of spray programmes may be determined more by the behaviour of households, for example whether they re-plaster or wash down walls after spraying has been carried out, than the efficacy of the insecticide the potential benefits of early spraying must be off-set against the increased risk that the chemical will be removed or covered up before it has chance to affect the vector population. An understanding of the publics' knowledge, attitudes and practice with regard to household spraying is therefore essential in the planning of a spray programme. Public education on the purpose of spraying may be necessary to ensure the maximum possible effectiveness of spraying is achieved, however the additional effectiveness due to increased public awareness must of course be offset against the additional cost of public education.

### 7.2.9 OPTIMAL COVERAGE

If outcome measure 5 is being used the optimal level of coverage is always 24% (except for 1998 where results are incomplete). Given that many countries are unlikely to be in a position to increase the amount of chemicals purchased, it is encouraging to note that spraying before the onset of the rains will improve efficiency in terms of net incremental cost-effectiveness by more than increasing coverage.

Based on outcome measure 4, the model suggests that certain levels of coverage will be appropriate each year depending on the level of transmission, so that in a high transmission year high coverage will be the strategy which minimises total cost and in lower transmission years low or zero coverage will be the optimal

strategy. Taking this option leaves decision-makers with choices to make on where or who to target for the spray programmes and perhaps more importantly in terms of the politics of malaria control where not to spray. Using outcome measure 5 suggests the optimal strategy would be coverage of 24% each year (except for 1998 where results are incomplete) which also requires choices on where not to spray to be made.

Maps of malaria transmission and the natural geography of an area combined with information on the population demographics, access to health facilities, history of malaria risk and various other sources of information may be used to help make these choices (Snow et al. 1996) but ultimately difficult choices would have to be made and justified. The planning required in order to define different levels of coverage in some areas each year may be problematic and add extra costs to a spray programme compared to a situation where the same places are sprayed each year.

On the other hand selective spraying in space and time or changing the insecticide from pyrethroid to organophosphate, may help to reduce the speed of development of insecticide resistance by the vector. This may reduce costs in the long run if it prolongs the useful life of insecticides, thus delaying the switch to a more expensive product.

Assuming that decision-makers are aiming to optimise outcome measure 4 so that spraying takes place before the rains and coverage varies with transmission intensity, the decision whether to spray and at what level of coverage must be made well before the rains begin. If spraying takes between two and three months and must be completed by the beginning of October the decision must be made in July. The implications of this in terms of what information is available to inform decisions this early will be discussed in chapter 8.

## 7.3 RESULTS OF 'OPTIMAL POLICY' SCENARIO

The 'optimal policy' scenario as determined by the total cost outcome measure from the 'uniform' scenarios (see section 7.2.7) is shown in Table 7-4 below. The optimal level of coverage ranges between 0 and 100% and spray timing is either September or October (the results for spraying before January 1993 are not available). The total costs of this 'optimal policy' scenario are also shown in Table 7-4.

The 'optimal policy' for each year was determined in the above analysis assuming that the same (uniform) control policy was used every year over the time period, for example spraying with 24% coverage every September. Determining an optimal policy for each year rather than using a uniform strategy could mean that changes in the policy one year will have knock on effects in the following year. In order to determine how important these effects may be the total costs of the 'optimal policy' scenario for each year were compared to the total cost of the following 'uniform' scenarios for each year: the 'do nothing' alternative (no spraying), the 'baseline' scenario, 24% coverage from September, and 24% coverage from October (shown in Table 7-5 and illustrated in Figure 7-23).

The analysis reveals that the 'optimal strategy' derived from the 'uniform' scenarios does not reduce total malaria control costs every year compared to the 'uniform' scenario with 24% coverage in September. In 1994, 1995 and 1998 the total costs of the uniform scenario with 24% coverage in September are lower than the total cost of the optimal scenario. However, the total cost of the 'optimal scenario' are always lower than the uniform scenario with 24% coverage in October; the 'baseline' scenario and the 'do nothing' alternative. Moreover, the average total annual cost of malaria control over the period is lower with the 'optimal strategy' than with any of the uniform strategies tested. Therefore, over a number of years

the 'optimal' strategy is indeed the lowest total cost option, saving far more in the years of high transmission than it costs in the years of medium or low transmission.

These results indicate that varying the coverage and timing of spraying each year does have follow-on effects. For example zero spraying in one year will affect the malaria transmission in the following year if a higher gametocyte carrier rate (number of infectious individuals) is carried over into the next year than would have been the case with a higher level of coverage. Spraying earlier in a previous year also means that the residual effect of the insecticide will not last for as long into the following year, which may also increase the gametocyte carrier rate. Using a chemical with a longer residual action would reduce the 'follow on' effects caused by early spraying.

This analysis demonstrates the way in which the generic model structure can be used to investigate the effects of altering control strategies in a more detailed manner than field studies would normally permit. Other examples of the questions the generic model structure could be used to investigate are given in section 7.6.

## 7.4 COMPARISON WITH OTHER STUDIES

Few other studies calculate a cost per person protected (figure used in this analysis US$1.07 in 1999 constant US$), or cost per case prevented of residual spraying programmes (ranging between US$0.42 and US$108.04 for baseline scenarios in 1993 to 1998, in 1999 US$), however for comparison purposes the results of existing studies are briefly reported here (further details can be found in section 2.4.4.4). None of the studies provide estimates of the cost per case prevented in epidemic areas.

A study by Hedman *et al.* examined the effectiveness of a malaria control programme including indoor spraying, chemoprophylaxis and anti-larval measures in Northern Liberia (Hedman et al. 1979). The cost per person protected was estimated to be US$4-5 including all control costs. Mills re-estimated the cost per

person protected by the control programme at US$6.64 and a cost per case prevented at US$12.30 (in 1984 US$) (Mills 1991).

Walsh and Warren used a WHO estimate of the average cost for house-to-house spraying with DDT of US$2 per capita annually (Anonymous 1974), to estimate the cost per adult and infant death averted (US$250) and the cost per infant death averted (US$600). Mills re-calculated these estimates to estimate the annual cost per person protected with vector control (US$2.97) and the cost per death averted (US$892.20) (both in 1984 US$) (Mills 1991).

The Garki project in a highly endemic area of Nigeria attempted to estimated the effects of house spraying alone or in combination with mass drug administration. Although cost-effectiveness ratios were not calculated, information was provided on the cost of the Garki project (Molineaux and Grammicia 1980). Mills estimated that the cost per case prevented by case detection and treatment and vector control was US$233.15 (in 1985 US$) (Mills 1991).

El Gaddel *et al.* described the malaria control problems in an irrigated area of the Sudan. Spraying with malathion was estimated to cost US$0.50 per capita and spraying with fenitrothion increased the cost to US$0.60 per capita (El Gaddal et al. 1985). Mills recalculated the figures presented in the study to produce an estimate of US$0.75 per person protected in 1985 US$ (Mills 1991).

Goodman *et al.* collected cost data from a number of published studies and estimated that the cost per house sprayed ranged between US$3.71-$8.93 and the cost per capita protected was between US$0.24 and US$6.70 (Goodman et al. 2000). Using the ingredients approach the mean cost per child was found to be US$7.33 per child protected in very low income countries with one spray round per year and US$14.65 with two rounds per year.

In his modelling analysis of the public health effects of a malaria vaccine in areas of seasonal or epidemic malaria transmission, Saul found that even with a relatively low effective coverage of 30% a substantial reduction in the number of malaria cases occurred (Saul 1993). He also found that the reduction in the number of cases achieved by the vaccine was dependent upon the vectorial capacity and the length of the transmission season. These results are fully consistent with the results in this study, which shows that even with relatively low spray programme coverage of 24%, cases can be reduced by between 34% and 58% depending on the severity of the transmission season (vectorial capacity provides an indication of the severity of the transmission).

The results of this study lend support to the arguments put forward by Hammer who points out that since the degree of prevalence of malaria in the same area can vary over time, calculations of the cost-effectiveness of control efforts will also vary inversely with the prevalence rate (Hammer 1993). He goes on to argue that this limits the usefulness of cost calculations based on a single year and that policy options must be evaluated based on their expected value averaged over the distribution of prevalence occurring at different times for the area. Hammer suggests that this is particularly important if costs include a fixed component that must stay in place regardless of the prevalence at any time. In the case of spraying the latter part of Hammer's argument is not particularly relevant since the fixed costs component is relatively small, however with other interventions (in particular case management) it will certainly be applicable.

In animal health decision making it is recognised that the timing of an intervention is crucial in determining the overall cost-effectiveness of alternate strategies as has been illustrated by this analysis. For example, (Corwin 1997) describes how strategically timed de-worming of cattle herds with anthelmintic drugs can be used to maintain parasitism at a sub-clinical or economical level. Corwin

also suggests that computer programmes for analysis of the seasonality of the epidemiology of gastrointestinal parasites and of herd performance could predict appropriate timing and cost benefit for control measures.

## 7.5 LIMITATIONS

The results of this analysis are expressed as intermediate units of output i.e. total number of cases or cost per case prevented. This may limit the comparability of the study results with those reporting a final health outcome such as DALYs or deaths averted. However, it was not possible to use a final unit of output because there was insufficient basis from which to further extrapolate the model results. The information on age specific mortality rates in the study area was extremely limited, moreover the human population modelled was not broken down by age. Estimates of the number of deaths averted could have been calculated using estimates of population age structure and age specific mortality from other settings, however the results would not be particularly robust. Attempting to extrapolate such estimates of morbidity and mortality into an outcome measure such as the DALY would further compromise their reliability.

The results of the analysis are subject to the assumptions and estimates used. One of the main assumptions was that the cost of protecting a single person with spraying is constant and independent of either coverage or timing. This assumption of constant costs with increasing coverage was discussed previously in terms of the increasing marginal cost of protecting the last person, however the assumption of constant cost with varying timing of spraying has not been discussed. The costs of carrying out spraying later may be higher than those of spraying earlier for a number of reasons. Spraying later in the season, in particular during or after a period of heavy rain may make access to remote areas more difficult. If roads have been damaged motor vehicles may be required for longer periods of time or may have to be abandoned in favour of air transport (e.g. helicopters) thus increasing

transport costs. The decision to spray as an emergency measure following heavy rains or a peak in cases may also mean increased costs if chemicals or other supplies have to be purchased quickly or imported from suppliers who may not necessarily be the cheapest. If the cost per person protected with spraying does increase the later spraying is carried out this will lend further weight to the results regarding the timing of spraying in this analysis.

The cost of case management used is known to be a conservative estimate excluding the cost of severe cases (see section 6.5) which may require expensive treatment procedures such as blood transfusion, IV treatment etc. In an epidemic situation the costs of case management may be increased further with emergency treatment strategies such as the setting up of field hospitals and active case detection. For example in 1996 six field hospitals were set up in Hwange district at a cost of US$38000, in 1997 four were set up for six months at a cost of US$20000 (source: unpublished data collected by E. Worrall and C. Hongoro 1999). The avoidance of such costs through effective prevention strategies would free up resources and in 1996 would have actually paid for the spray programme (see table 6.3.6).

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, the proportion of newborns weighing less than 2500g (Brabin 1983, McGregor 1984, Shulman et al. 1996). Low birthweight is of particular concern since it is associated with increased neonatal mortality, particularly in women during their first pregnancy (primigravidae) (Greenwood et al. 1994, McCormick 1985). An epidemic may therefore cause a drop in birthweight of babies born in the months following it, and a rise in infant mortality. The costs of such affects and benefits of preventing them have not been

included in this analysis, however their inclusion would be likely to strengthen the case for early intervention by improving the cost benefit of epidemic prevention.

The assumption that insecticide effectiveness degrades linearly over a period of six months used in this study was used for mathematical convenience and may not accurately reflect the true nature of degradation. Information on the true nature of chemical efficacy over time is limited and at times contradictory, a brief review of available evidence and discussion regarding the implications for this study follows.

The first part of a two part study by (Le Sueur et al. 1993) used daub wall samples (mud and cow dung) collected from three high-risk malaria areas in the Natal province of South Africa to test the residual efficacy of lambda-cyhalothrin (ICON®) against *Anopheles arabiensis*. The study results were different between and within areas however, the percentage mortality in the vector population exposed to the chemical declined to just above the level achieved with the control after about 13 weeks in one area. In another area the percentage mortality achieved by the chemical declined after only 4 weeks in one sample but lasted 13-14 weeks in the other sample. In a third area the chemical seemed to last approximately 13 weeks in one sample and beyond 14 weeks in another sample. The organic content of the daub was identified as a possible cause of the varying efficacy although no firm conclusions could be made. The study also pointed out that unlike DDT, ICON® can be sprayed onto the contents of huts (e.g. furniture) and that the residual efficacy of the chemical on wood surfaces is known to be good (100% effective after 24 weeks). The Le Suere results indicate that the six month efficacy used in this study may over estimate the cost-effectiveness of residual spraying, however, it is unclear to what extent since the material used to build houses may be different in Zimbabwe to the materials used in the Le Sueur study.

The second part of the above mentioned study (Sharp et al. 1993) was designed to evaluate the persistence and efficacy of lambda-cyhalothrin used as an interdomiciliary insecticide in daub huts (as opposed to daub samples tested in a laboratory) against *An. arabiensis* and its efficacy compared to DDT. Based on bioassay data, lambda-cyhalothrin spraying in January was found to be effective 5 months later in May with 100% effectiveness in one location and 91.7% in another. DDT was 100% effective in both locations at this time. The Sharp results indicate that the six month efficacy used in this study may underestimate the cost-effectiveness of residual spraying. However, exit trap data from the Sharp study showed that the percentage survival of blood fed mosquitoes ranged from a low of 55% caught leaving the lambda-cyhalothrin sprayed huts to 82% of those caught leaving DDT sprayed huts. It is unclear from the Sharp study how or if the percentage survival changed over the period of the study therefore no conclusions on the decline in insecticide efficacy can be drawn. However, these results do have implications for this thesis because the results regarding the effectiveness of the insecticide (section 5.2.3.7) were taken from a single study based on spraying with DDT even though it is known that lambda-cyhalothrin was the actual chemical used in Zimbabwe. DDT is shown by the Sharp study to be less effective than lambda-cyhalothrin at killing blood fed anophelines based on the exit trap data, although it is slightly more effective based on bio-assay data. The effectiveness of DDT compared to lambda-cyhalothrin in terms of its affect on vector survival per gonotrophic cycle (the unit of analysis in the generic model) could not be established from available evidence and was therefore assumed to be the same. If further information became available on any of these issues an alternative effectiveness degradation function, chemical type and/or cost function could easily be incorporated into the model structure and economic evaluation.

The perspective of the analysis (provider perspective) may ignore important equity considerations such as how alternative strategies affect the costs and consequences of malaria imposed on households. This is crucial if interventions are aimed at reducing the effects of malaria on individual vulnerable groups such as the poor. Since a spray programme will cost households little or nothing other than the time costs of emptying homes of furniture and gathering sufficient water for the spray men to dilute the chemical (see section 6.1.1 and 6.4), preventing cases by spraying would be a relatively equitable intervention as it could be seen as preventing the costs to households of people, falling sick, paying for treatment and even dying from malaria. A further consideration regarding equity and the provider perspective would be the decision on whether to concentrate spray activities in the more easily accessibly, relatively wealthy urban areas which are likely to be well served with case management facilities, or whether to aim to improve equity by spraying in more remote, poorer and less well served rural areas. Spraying in rural areas may be more costly due to accessibility problems and less densely distributed populations, however decision makers may decide that the additional cost of spraying rural areas is off-set by the value of improving equity and reducing mortality at the community level. (See section 8.3 for further discussion of the household perspective)

As previously mentioned the reliance on clinical data for this analysis is not ideal, however since no other data was available this was the only option. Immunity was excluded from the model since its development is limited in areas of seasonal or epidemic malaria, however the model could be applied to infants who lack immunity in endemic areas or the model structure could be developed in order to include the effects of acquired immunity.

## 7.6 FURTHER APPLICATIONS OF THE MODEL STRUCTURE

The model structure developed in this thesis is extremely flexible. It has already been noted that it could be used to examine varying chemical types and to investigate the follow on effects of spraying in previous years. It could also be used to examine the cost-effectiveness of spraying under varying epidemiological, entomological and meteorological circumstances simply by feeding in alternative data or parameter values.

In addition the model has been designed to allow other interventions to be evaluated. For example a parameter ($j$) representing the proportion of mosquitoes which successfully feed before the intervention was included in the model structure, even though this was not used for evaluating the effects of spraying. This parameter could be used to estimate the effects of distributing bed nets to a proportion or the entire population, changes in the human biting habit caused by the use bed nets could also be included if required. Insecticide treated bed nets could be modelled using a reduction in this parameter and a reduction in vector survivorship as used to model spraying could be included if a mass killing effect was anticipated. The difference in cost-effectiveness with and without a mass killing effect could therefore be evaluated.

Mass administration of parasite clearing drugs could be modelled by altering the number of infective individuals according to estimates of drug efficacy. The importance of the affects of treating malaria cases with the drug sulphadoxine and pyrimethamine (SP) which may increase the amounts of gametocytes available to the mosquito, thus possibly enhancing transmission could also be examined. The model could also be used to examine any combination of the above mentioned control interventions, however its use in cost-effectiveness analysis is limited by the availability of good quality location specific cost data for interventions.

The advantage of using this dynamic model to examine the cost-effectiveness of alternative intervention strategies is that it allows the effects on transmission to be examined. This aspect of the impact of control interventions may be less important in endemic situations where the affects on transmission are more likely to be constant. However, in epidemic situations as has been clearly demonstrated the effects on transmission can be significantly altered by the time that an intervention is used in relation to the transmission season.

The model also provides climate-based estimates of various entomological parameters such as the gonotrophic cycle length, sporogonic cycle length and the human biting rate. There is potential for such variables to be combined with climate and other data sets (such as population data) and used to produce maps indicating the spatial and temporal variation in these variables (Thomson et al. 2001). A further output of the model not used in this analysis is a climate driven estimate of vectorial capacity. This is currently being combined with spatial and temporal climate data within a geographical information system in order to produce vectorial capacity maps for all Africa (S. J. Connor, Ph.D. research).

Sub-models 1-4 (section 4.3.1-4.3.4) describe the mosquito life cycle in relation to climate, this part of the model could therefore potentially be used as the basis for the development of transmission models linked to cost-effectiveness analysis for other mosquito born diseases such as filariasis or yellow fever.

## 7.7 CHAPTER SUMMARY

This chapter has described the results of the analysis carried out to establish the total number of cases, incremental cost of spraying, incremental cost per case prevented, total cost of malaria control and net incremental cost per case prevented for the 'uniform' scenarios. The question of which of these outcome measures to use in the remaining analysis was discussed and total cost and net incremental cost per case prevented were chosen. The implications for the optimal timing and

coverage of the spray programme were evaluated using the chosen outcome measures in the uniform scenarios. Whichever of these two outcome measures are used, the optimal timing for the spray programme is the same (around September or October each year). Using the net incremental cost per case prevented outcome measure the optimal coverage is 24% every year, however using the total cost outcome measure the optimal level of coverage varies each year.

The 'optimal strategy' based on the total cost outcome measure was re-examined using the model to investigate 'follow on' effects where changes in the control strategy one year would lead to changes in the 'optimal strategy' in the proceeding year. This analysis revealed that some 'follow on' effects did exist but that overall based on the whole six year period the 'optimal strategy' resulted in lower total costs than any of the 'uniform strategies'.

The major limitations of the analysis were revealed as being the assumptions and estimates used in the analysis. In particular the lack of data on the cost of spraying at varying levels of coverage, the paucity of data on the cost and amount of severe case management, and the limited availability of information regarding the efficacy of the insecticide particularly in a format that could be used in the model structure. Further applications and extensions of this approach were identified including the application of the model to other interventions, countries and even diseases.

Table 7-1 Total Number of Cases Occurring under Varying Scenarios

| Scenario's | 'Do Nothing' | Spraying Coverage (effective from January) | | | | Spraying Effective from (coverage 24%): | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Year | Alternative | 24% | 50% | 75% | 100% | August | September | October | November | December | January | February | March |
| 1993 | 559 | 237 | 88 | 33 | 16 | 483 | N/A | N/A | N/A | N/A | 237 | 470 | 540 |
| 1994 | 20671 | 12106 | 8114 | 6624 | 6155 | 5125 | 4120 | 5604 | 5990 | 8289 | 12106 | 17467 | 18949 |
| 1995 | 81202 | 38153 | 22505 | 17010 | 15261 | 10103 | 8247 | 9231 | 11995 | 19674 | 38153 | 55989 | 59961 |
| 1996 | 273457 | 181743 | 132277 | 105821 | 95254 | 101987 | 72184 | 67302 | 85159 | 136578 | 181743 | 211573 | 219234 |
| 1997 | 123551 | 60168 | 37872 | 28317 | 25018 | 54179 | 40350 | 39010 | 57809 | 61390 | 60168 | 81104 | 89581 |
| 1998 | 104481 | 59079 | 43191 | 34257 | 30842 | 29499 | 21893 | 28733 | 45809 | 60329 | 59079 | 69210 | 71342 |

Table 7-2 Total Number of Cases Prevented under Varying Scenarios Compared to 'do nothing' alternative

| | Spraying Coverage (effective from January) | | | | Spraying Effective from (coverage 24%): | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Scenario | 24% | 50% | 75% | 100% | August | September | October | November | December | January | February | March |
| 1993 | 322 | 471 | 526 | 542 | N/A | N/A | N/A | N/A | N/A | 322 | 89 | 19 |
| 1994 | 8565 | 12557 | 14048 | 14516 | 15546 | 16551 | 15068 | 14681 | 12382 | 8565 | 3205 | 1722 |
| 1995 | 43049 | 58697 | 64191 | 65941 | 71098 | 72955 | 71970 | 69206 | 61528 | 43049 | 25212 | 21241 |
| 1996 | 91714 | 141181 | 167636 | 178204 | 171471 | 201273 | 206156 | 188298 | 136879 | 91714 | 61884 | 54224 |
| 1997 | 63383 | 85679 | 95234 | 98533 | 69372 | 83201 | 84541 | 65742 | 62161 | 63383 | 42448 | 33971 |
| 1998 | 45402 | 61290 | 70224 | 73638 | 74982 | 82588 | 75748 | 58672 | 44152 | 45402 | 35271 | 33139 |

Table 7-3 Optimal Strategy (Coverage and Timing) for Each Outcome Measure

| Outcome Measure | 1 Total Cases | | 2 Incremental Cost of Spraying | | 3 Incremental Cost per Case Prevented | | 4 Total Cost of Malaria Control | | 5 Net Incremental Cost per case Prevented | |
|---|---|---|---|---|---|---|---|---|---|---|
| Year | Cov. | Tim. | Cov. | Tim. | Cov. | Tim. | Cov. | Tim. | Cov. | Tim. |
| 1993 | 100 | Jan‡ | Increases with coverage therefore subject to budget constraint | Timing doesn't impact on incremental cost | Increases with coverage therefore subject to cost effectiveness threshold | Jan‡ | 0 | Jan‡ | 24 | Jan‡ |
| 1994 | 100 | Sep | | | | Sep | 24 | Sep | 24 | Sep |
| 1995 | 100 | Sep | | | | Sep | 50 | Sep | 24 | Sep |
| 1996 | 100 | Oct | | | | Sep/ Oct | 100 | Oct | 24 | Sep/ Oct |
| 1997 | 100 | Oct | | | | Oct | 75 | Oct | 24 | Oct |
| 1998 | 100 | Sep | | | | Sep | 100† | Sep | 100† | Sep |

‡ No data available for intervention before January 1993
† No data available for cases after March 1998

Table 7-4 Coverage, Timing, Cases and Costs in 'Optimal Policy' Scenario

| Year | Optimal Coverage | Optimal Timing | Cases with Optimal Policy | Case Management Costs with Optimal Policy | Spray Costs with Optimal Policy | Total Cost with Optimal Policy Scenario |
|---|---|---|---|---|---|---|
| 1993 | 0 | January | 559 | 2755 | 0 | 2755 |
| 1994 | 24 | September | 4910 | 24204 | 36255 | 60459 |
| 1995 | 50 | September | 775 | 3822 | 78165 | 81987 |
| 1996 | 100 | October | 427 | 2106 | 161380 | 163485 |
| 1997 | 75 | October | 140 | 690 | 124987 | 125677 |
| 1998 | 100 | September | 64 | 314 | 166649 | 166963 |

Table 7-5 Total Cost of 'Optimal Policy' Scenario and Selected 'Uniform' Scenarios

| Year | 'Do Nothing' Alternative (No Spraying) | 'Baseline Scenario' (24% coverage from January) | Optimal Policy | 24% Coverage from September | 24% Coverage from October |
|---|---|---|---|---|---|
| 1993 | 2755* | 35981 | 2755* | N/A | N/A |
| 1994 | 101909 | 95938 | 60459 | 56565* | 63880 |
| 1995 | 400324 | 225614 | 81987 | 78177* | 83029 |
| 1996 | 1348145 | 934725 | 163485* | 394599 | 370528 |
| 1997 | 609107 | 336626 | 125677* | 238923 | 232314 |
| 1998 | 515090 | 331256 | 166963 | 147926* | 181648 |
| Mean | 496222 | 326690 | 100221* | 183238 | 186280 |

* Indicates lowest cost in each year

Figure 7-1 Total Number of Cases Occurring by Year under Varying Coverage Scenarios

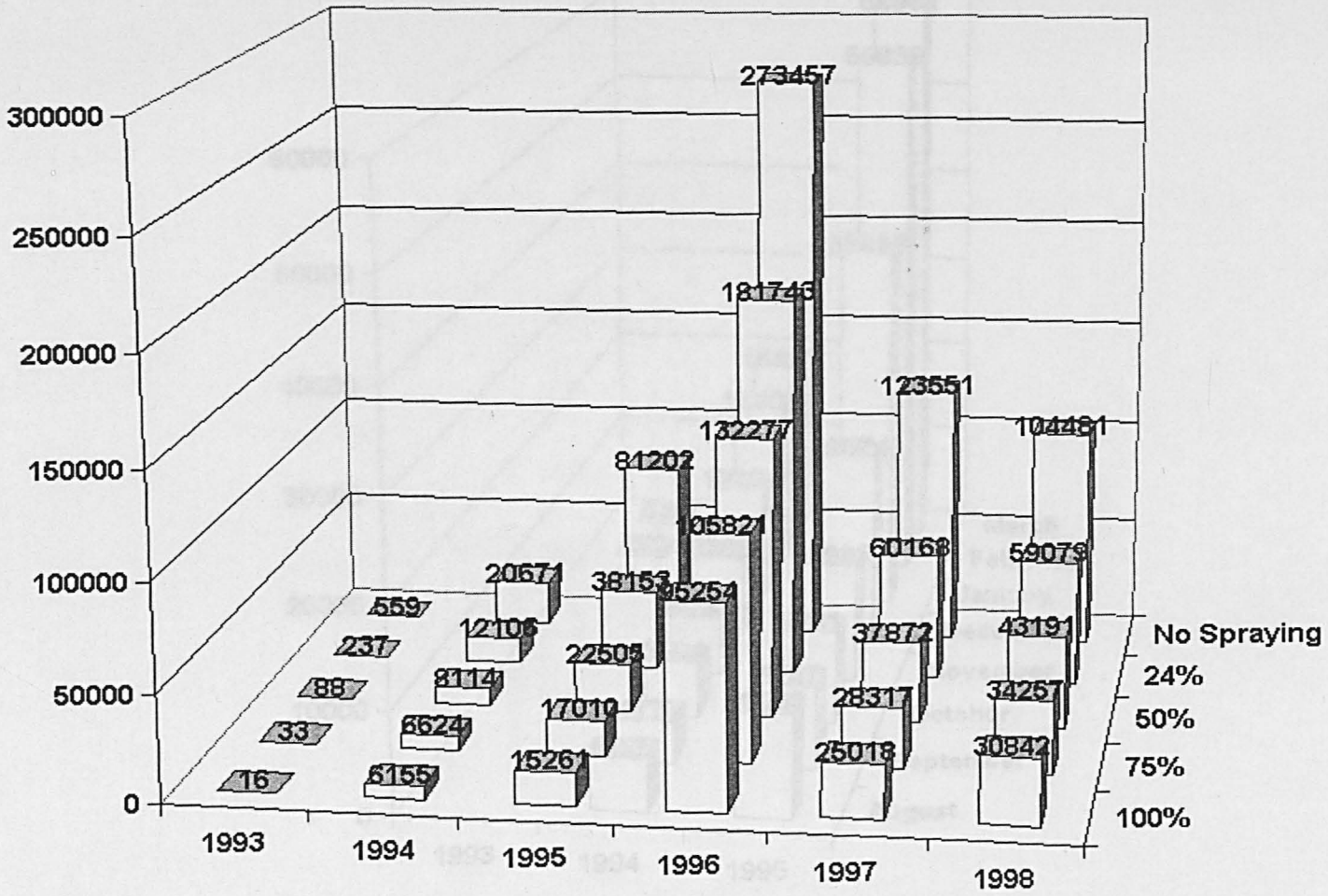


Figure 7-2 Total Number of Cases Occurring by Year under Varying Timing Scenarios (Baseline Coverage) (1993-1995)

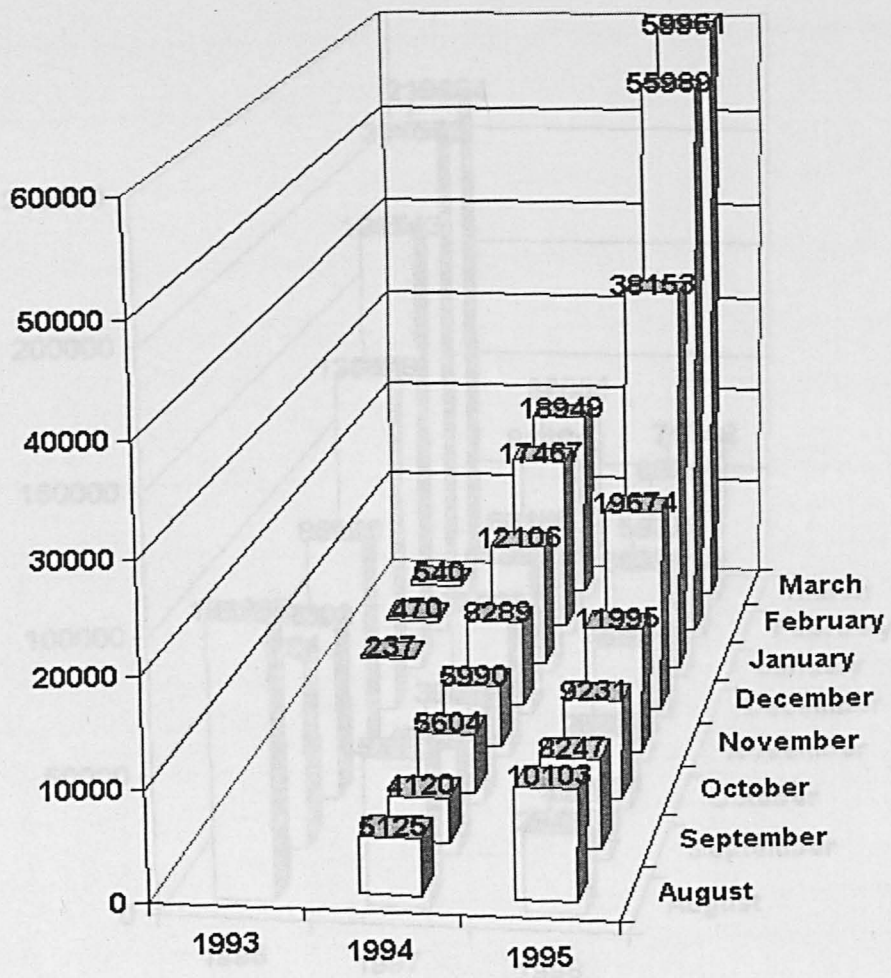


Figure 7-3 Total Number of Cases Occurring by Year under Varying Timing Scenarios (Baseline Coverage) (1996-1998)

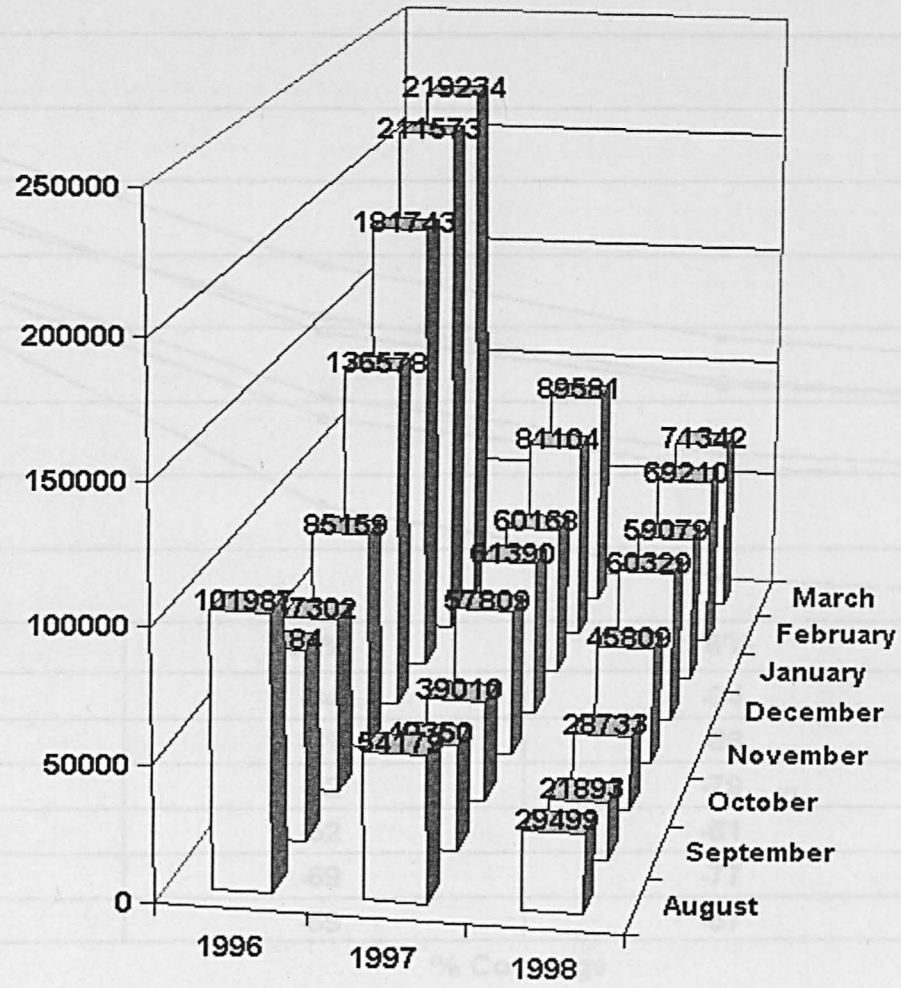
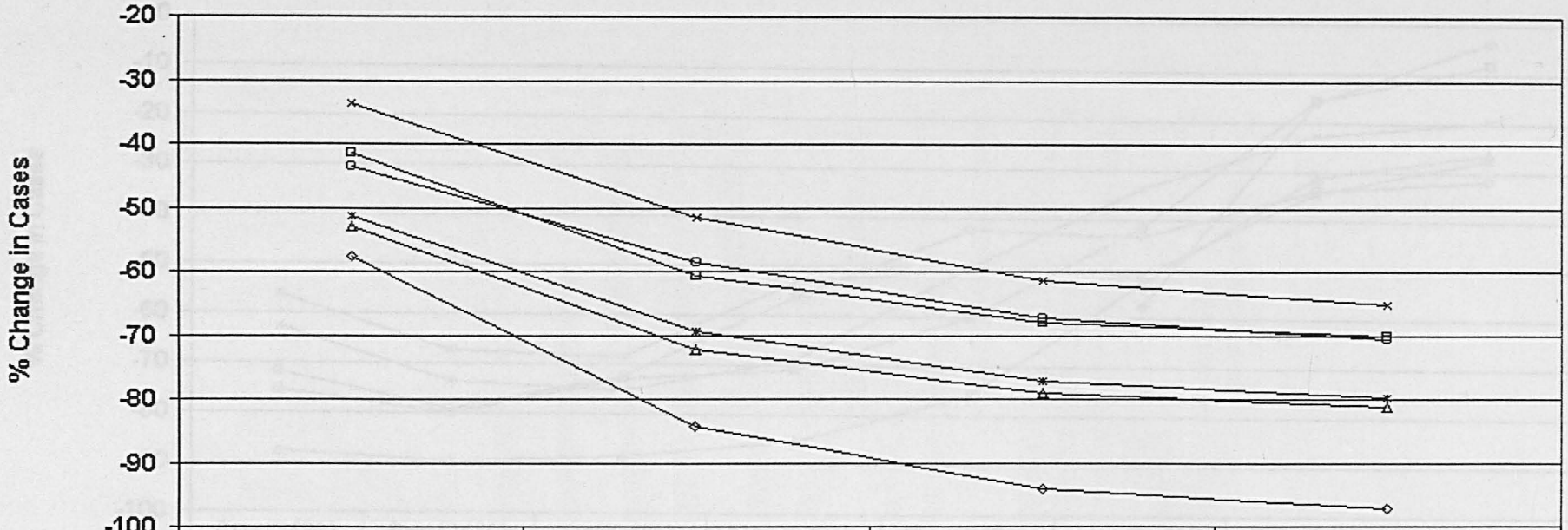


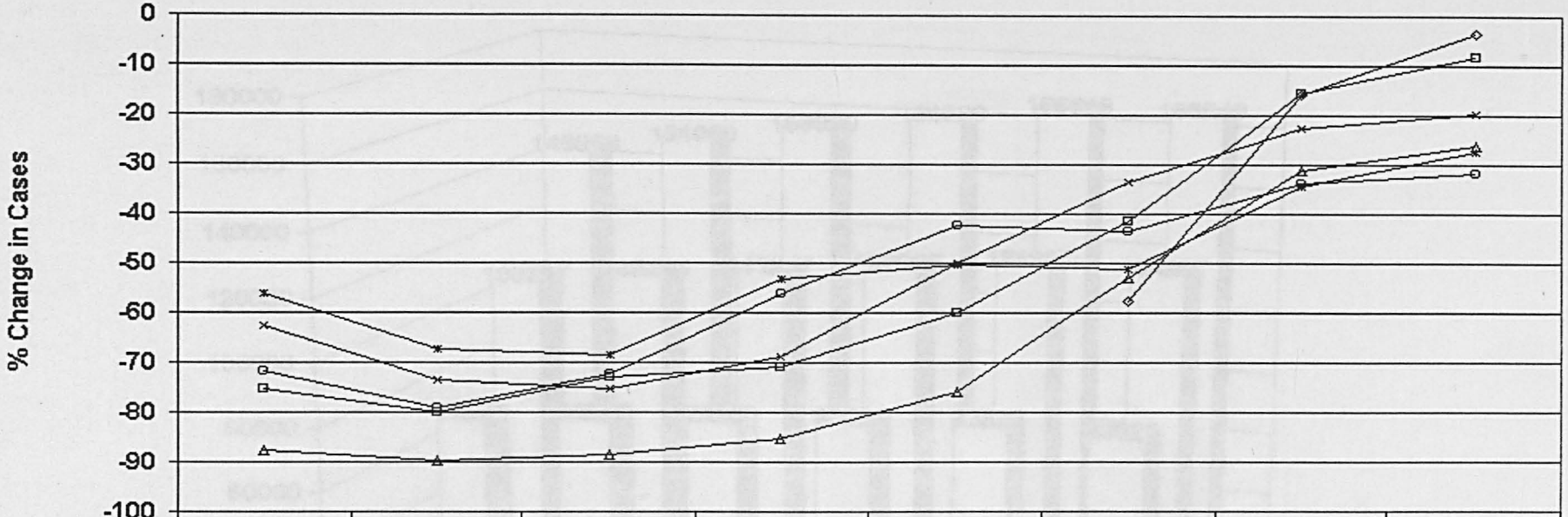
Figure 7-4 Percentage Change in Cases with Varying Levels of Coverage Compared to 'Do Nothing' Alternative




| | 24% | 50% | 75% | 100% |
|---|---|---|---|---|
| 1993 | -58 | -84 | -94 | -97 |
| 1994 | -41 | -61 | -68 | -70 |
| 1995 | -53 | -72 | -79 | -81 |
| 1996 | -34 | -52 | -61 | -65 |
| 1997 | -51 | -69 | -77 | -80 |
| 1998 | -43 | -59 | -67 | -70 |

% Coverage

Figure 7-5 Percentage Change in Cases with Varying Timing Scenarios Compared to 'Do Nothing' Alternative




| | Aug(24%) | Sep(24%) | Oct(24%) | Nov(24%) | Dec(24%) | Jan(24%) | Feb(24%) | Mar(24%) |
|---|---|---|---|---|---|---|---|---|
| 1993 | | | | | | -58 | -16 | -3 |
| 1994 | -75 | -80 | -73 | -71 | -60 | -41 | -16 | -8 |
| 1995 | -88 | -90 | -89 | -85 | -76 | -53 | -31 | -26 |
| 1996 | -63 | -74 | -75 | -69 | -50 | -34 | -23 | -20 |
| 1997 | -56 | -67 | -68 | -53 | -50 | -51 | -34 | -27 |
| 1998 | -72 | -79 | -72 | -56 | -42 | -43 | -34 | -32 |

Spray Effectiveness On-Set Time (Cov=24%)

Figure 7-6 Incremental Cost of Adding a Spray Programme with Varying Levels of Coverage Compared with 'Do Nothing' Alternative

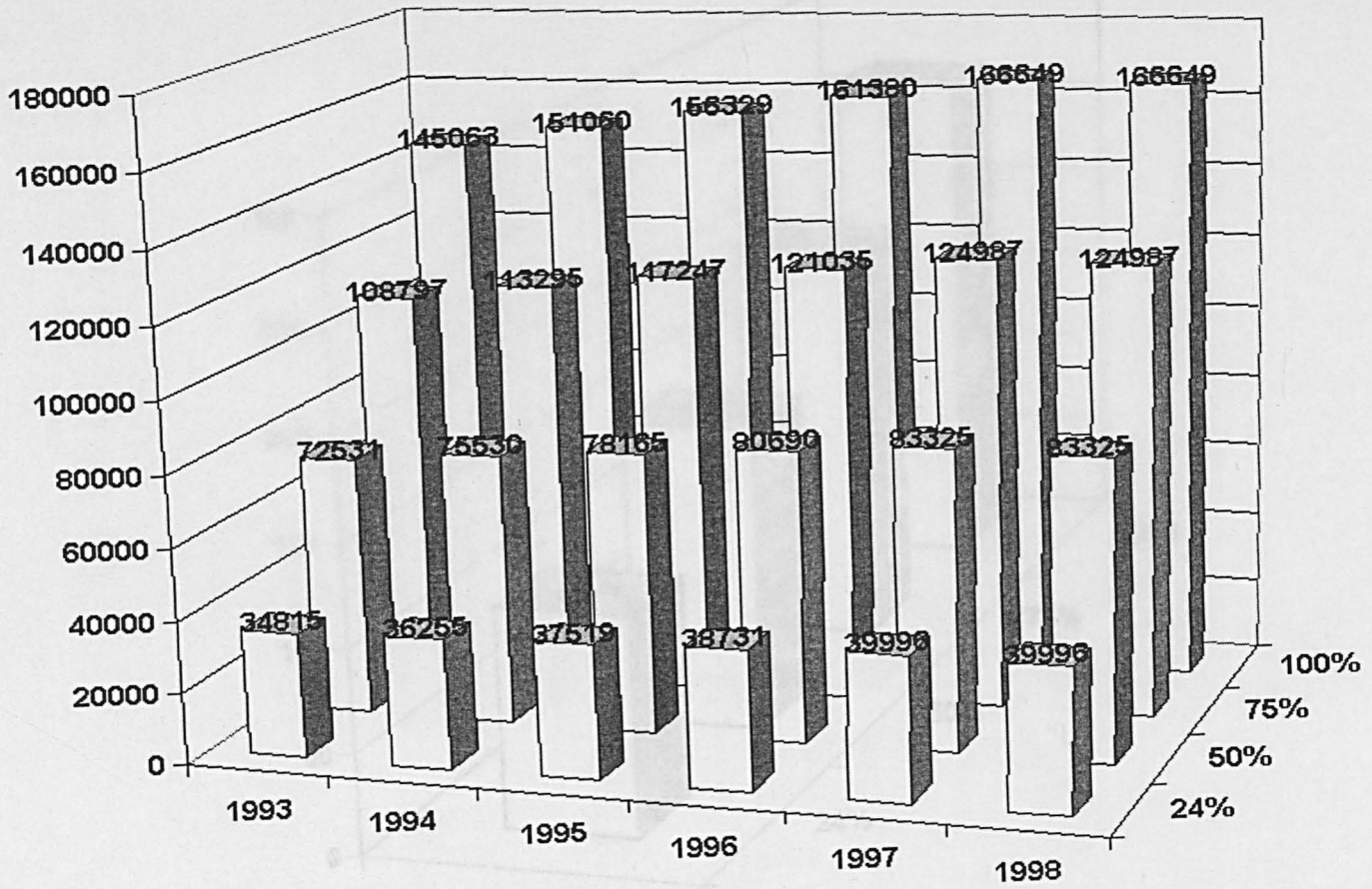


Figure 7-7 Incremental Cost Per Case Prevented of Adding a Spray Programme with Varying Coverage to 'Do Nothing' Alternative (1993)

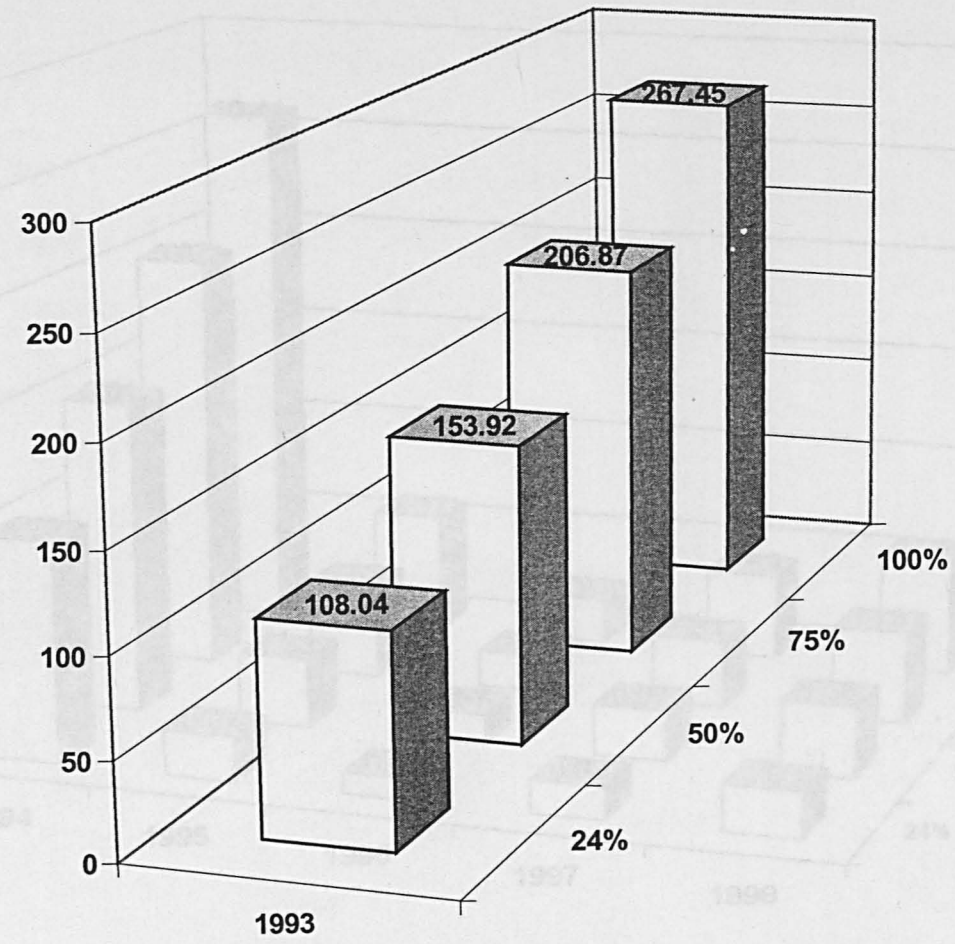


Figure 7-8 Incremental Cost Per Case Prevented of Adding Spray Programme with Varying Coverage to 'Do Nothing' Alternative (1994-1998)

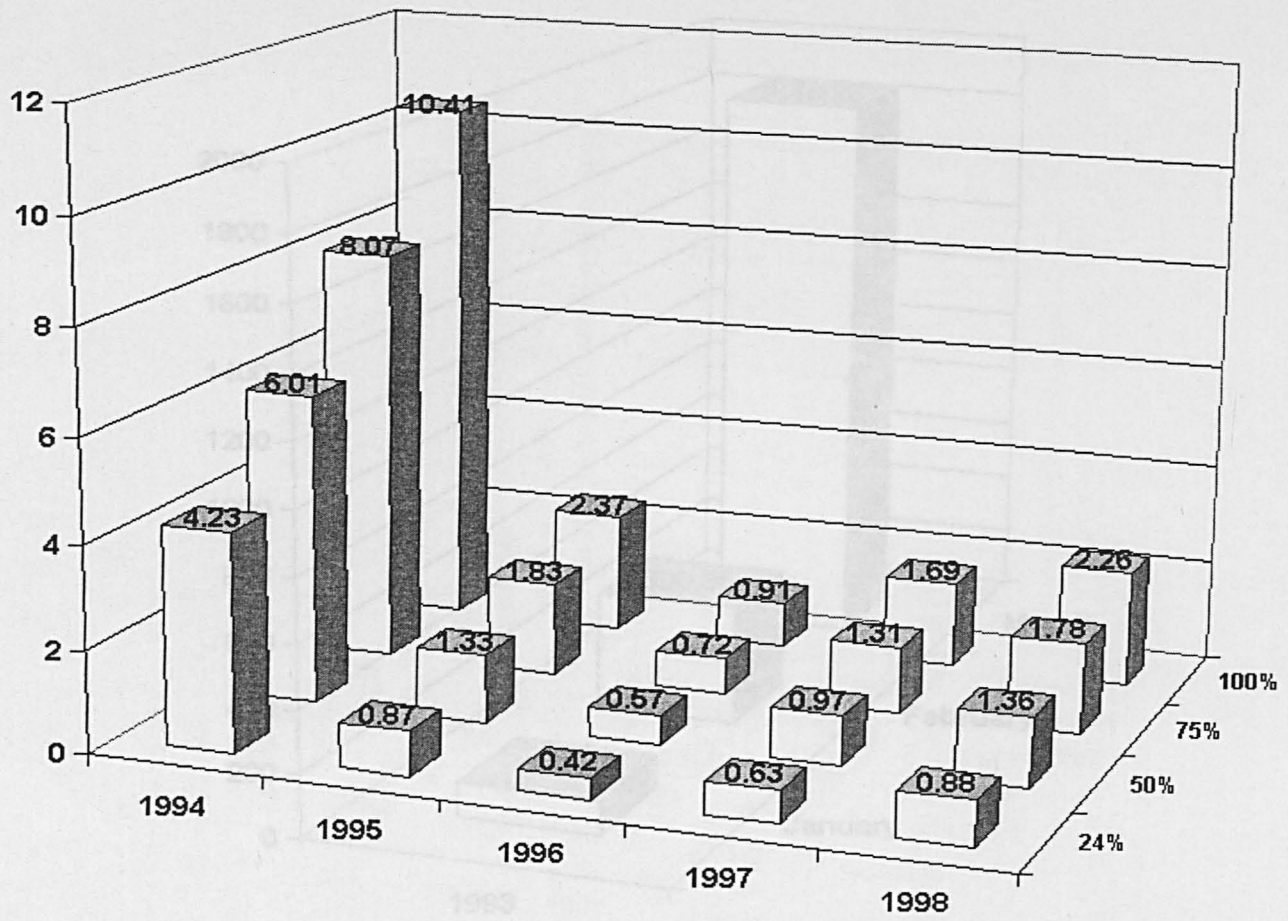


Figure 7-9 Incremental Cost per Case Prevented of Adding a Spray Programme with Varying Effectiveness on-set Times to 'Do Nothing' Alternative (1993)

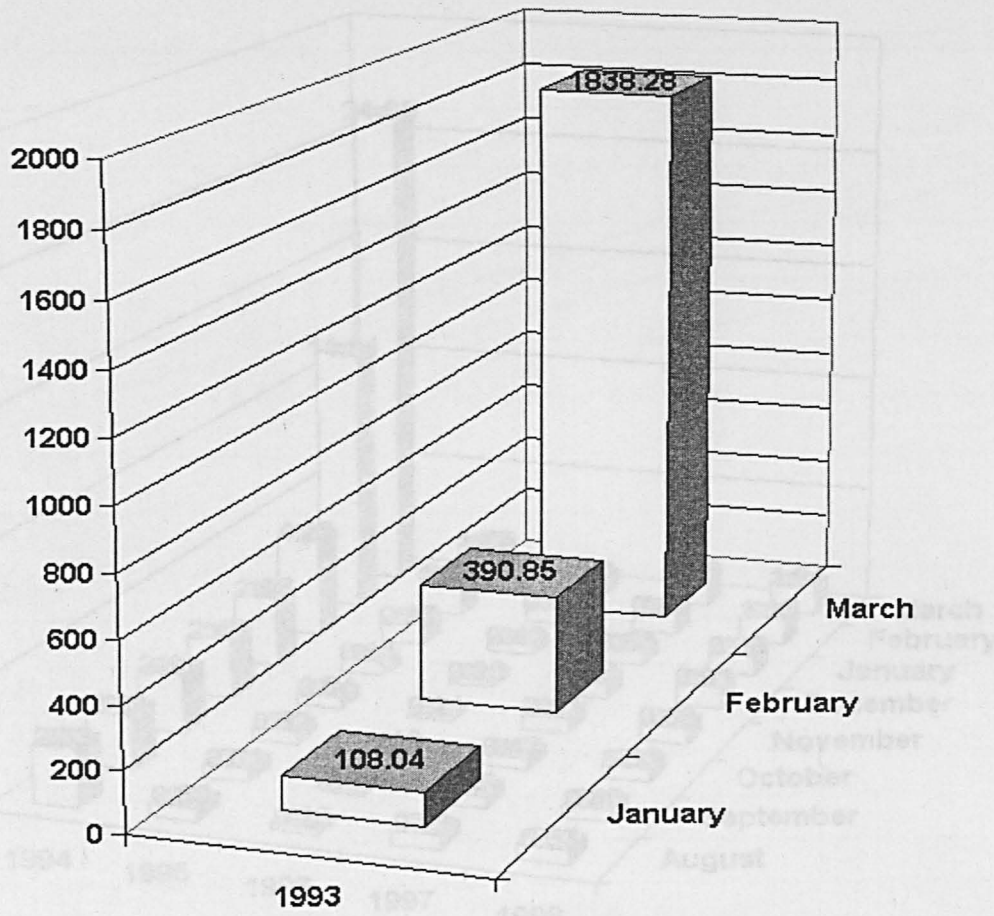


Figure 7-10 Incremental Cost per Case Prevented of Adding a Spray Programme with Varying Effectiveness on-set Times to 'Do Nothing' Alternative

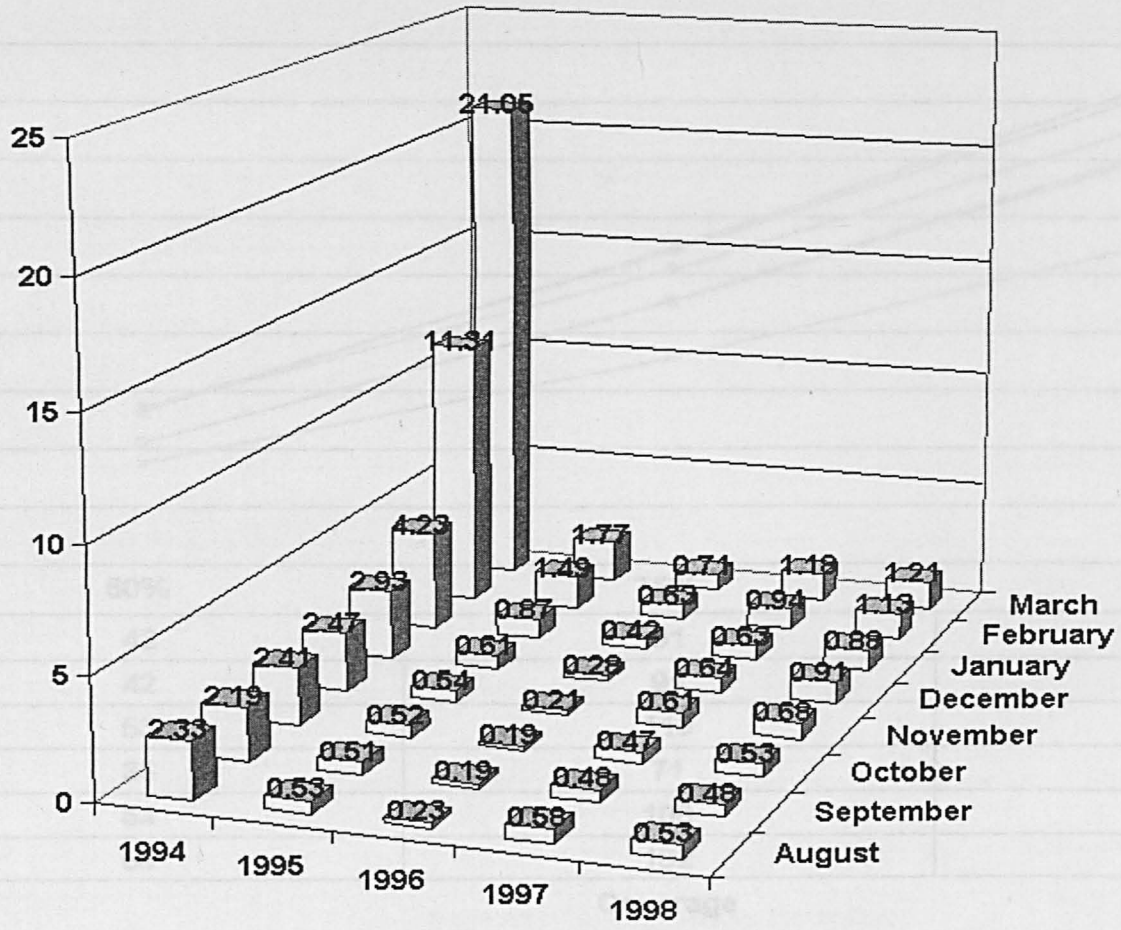
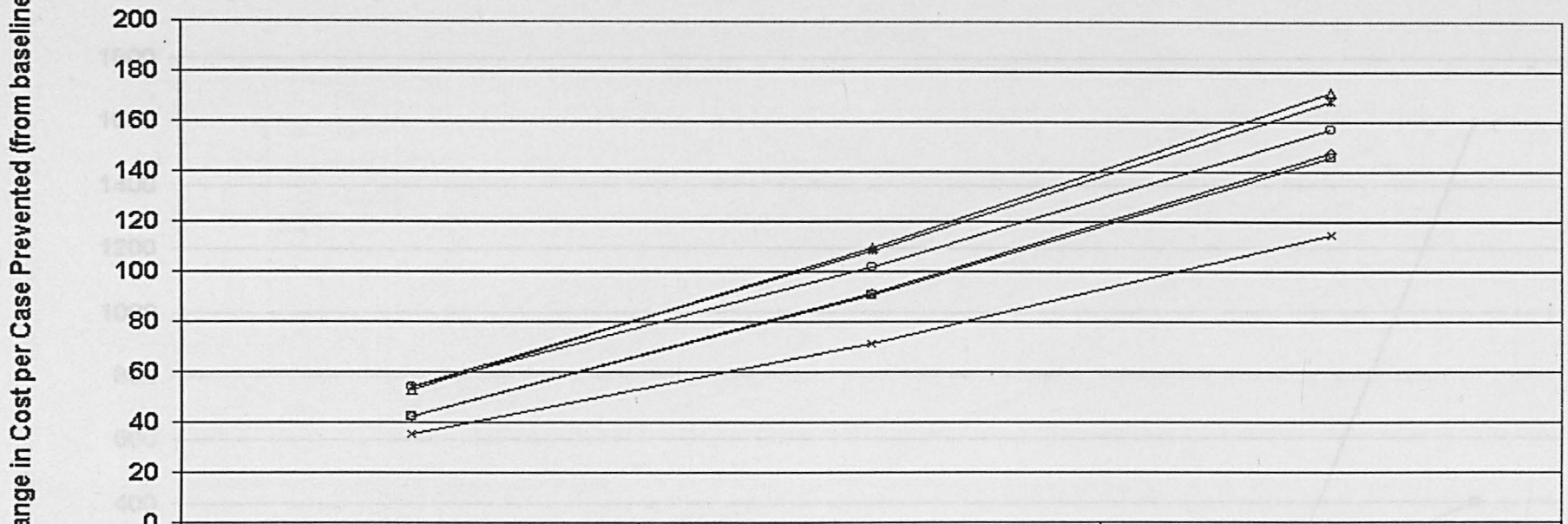
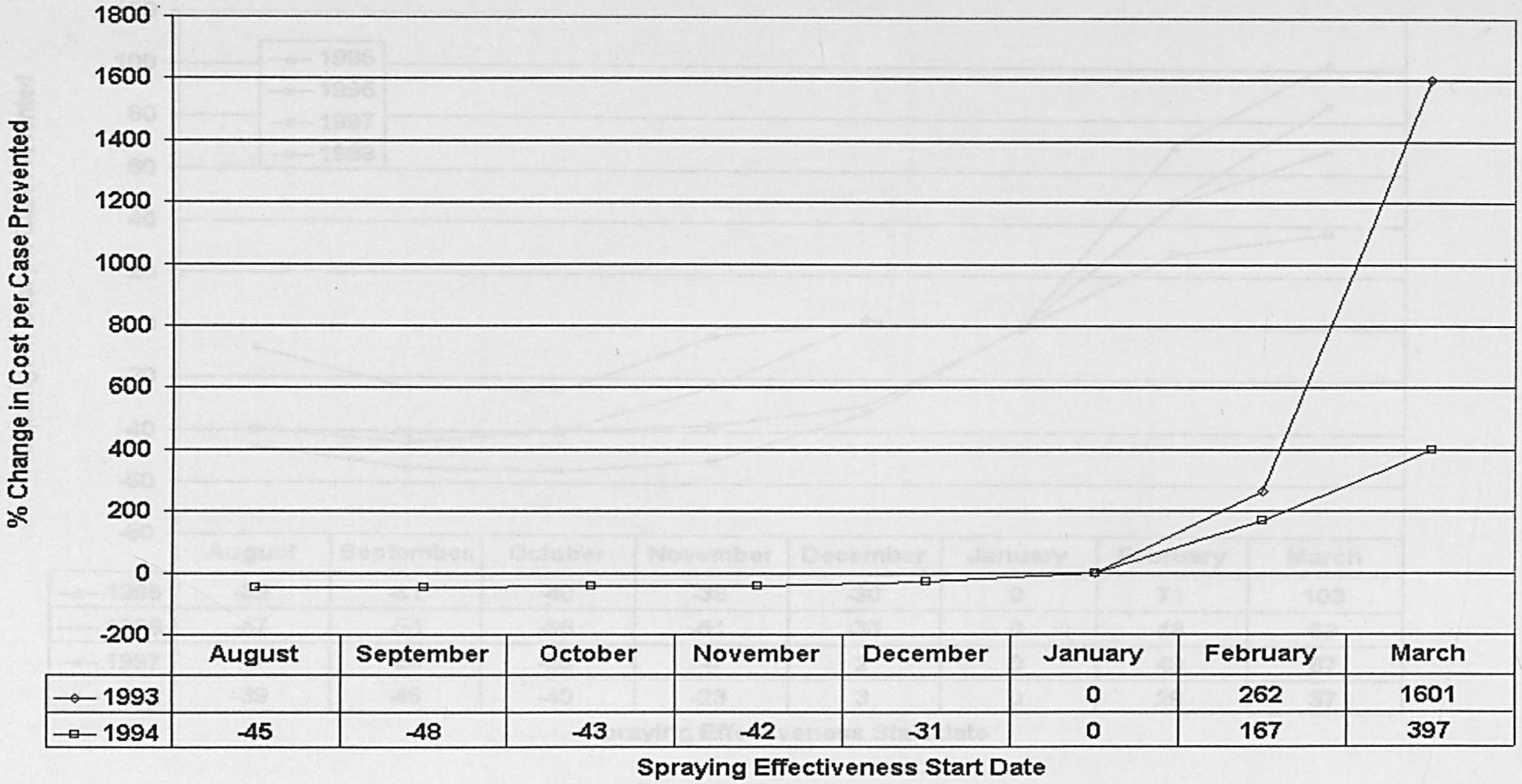


Figure 7-11 Percentage Change in Cost per Case Prevented by Varying Coverage Compared with 'Baseline' Scenario



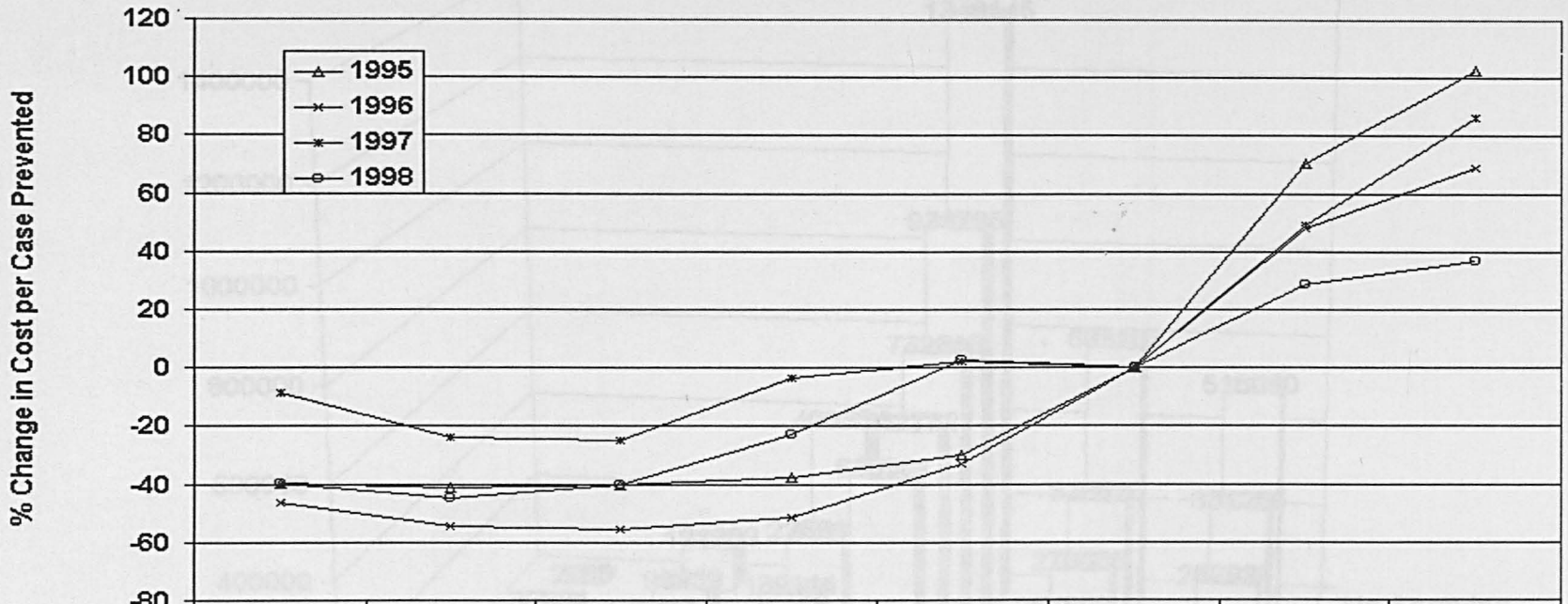

| | 50% | 75% | 100% |
|---|---|---|---|
| 1993 | 42 | 91 | 148 |
| 1994 | 42 | 91 | 146 |
| 1995 | 53 | 110 | 172 |
| 1996 | 35 | 71 | 114 |
| 1997 | 54 | 108 | 168 |
| 1998 | 54 | 102 | 157 |

Figure 7-12 Percentage Change in Cost per Case Prevented by Varying Spraying Effectiveness Start Date Compared with 'Baseline' Scenario (1993-1994)




| | August | September | October | November | December | January | February | March |
|---|---|---|---|---|---|---|---|---|
| 1993 | | | | | | 0 | 262 | 1601 |
| 1994 | -45 | -48 | -43 | -42 | -31 | 0 | 167 | 397 |

Figure 7-13 Percentage Change in Cost per Case Prevented by Varying Spraying Effectiveness Start Date Compared to 'Baseline' Scenario (1995-1998)




| | August | September | October | November | December | January | February | March |
|---|---|---|---|---|---|---|---|---|
| 1995 | -39 | -41 | -40 | -38 | -30 | 0 | 71 | 103 |
| 1996 | -47 | -54 | -56 | -51 | -33 | 0 | 48 | 69 |
| 1997 | -9 | -24 | -25 | -4 | 2 | 0 | 49 | 87 |
| 1998 | -39 | -45 | -40 | -23 | 3 | 0 | 29 | 37 |

Spraying Effectiveness Start date

Figure 7-14 Total Cost of Malaria Control with Varying Levels of Coverage

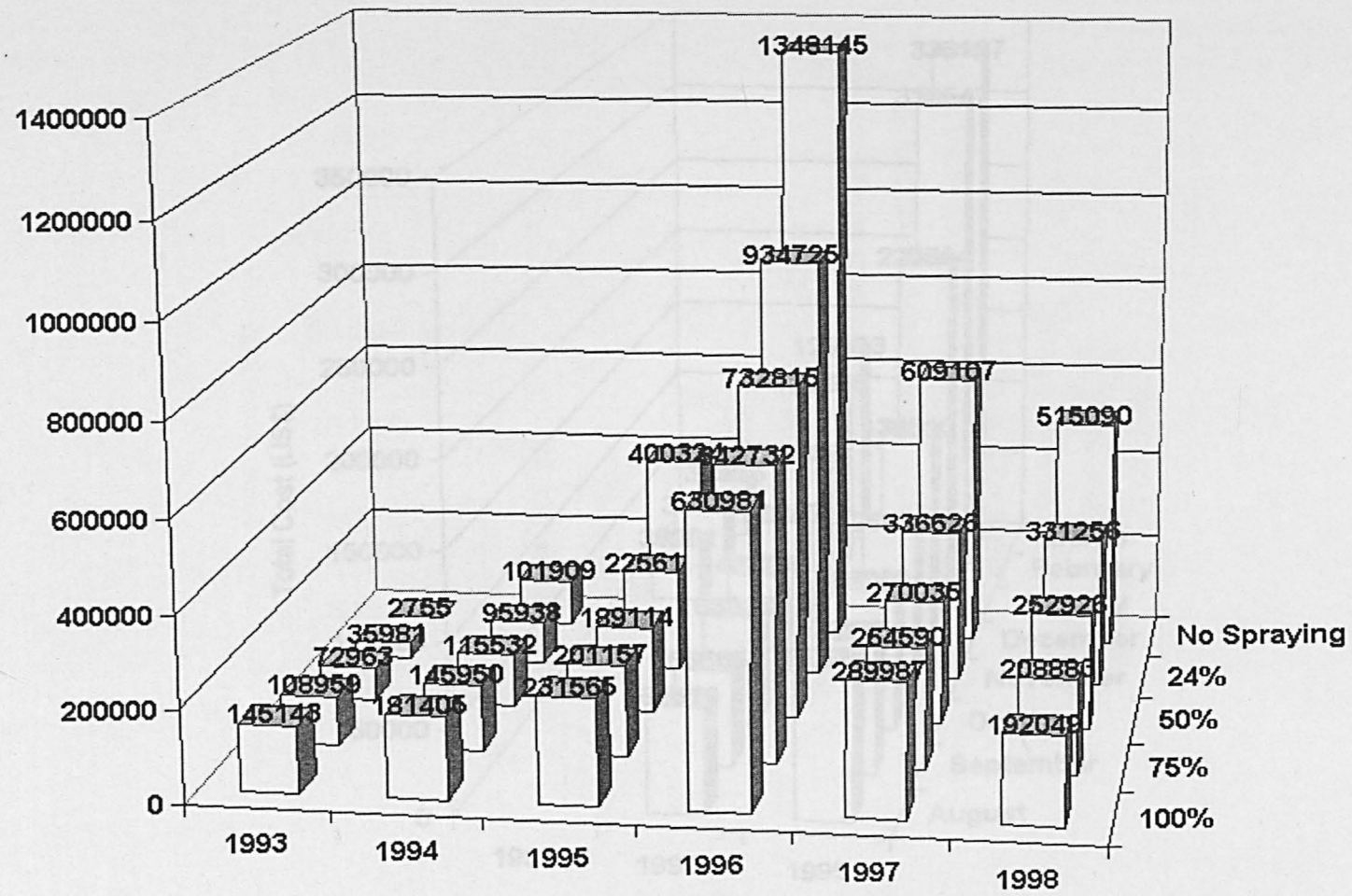


Figure 7-15 Total Cost of Malaria Control with 24% Coverage and Varying Effectiveness On-Set Times (1993-1995)

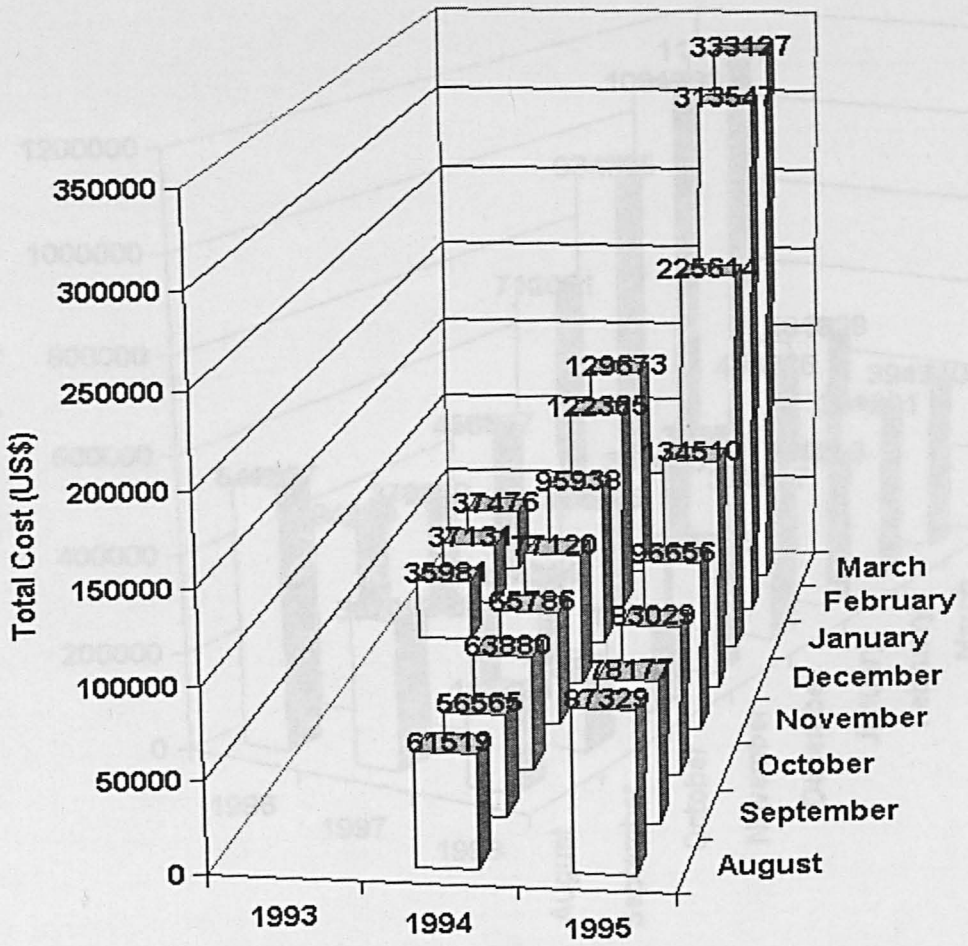


Figure 7-16 Total Cost of Malaria Control with 24% Coverage and Varying Effectiveness On-Set Times (1996-1998)

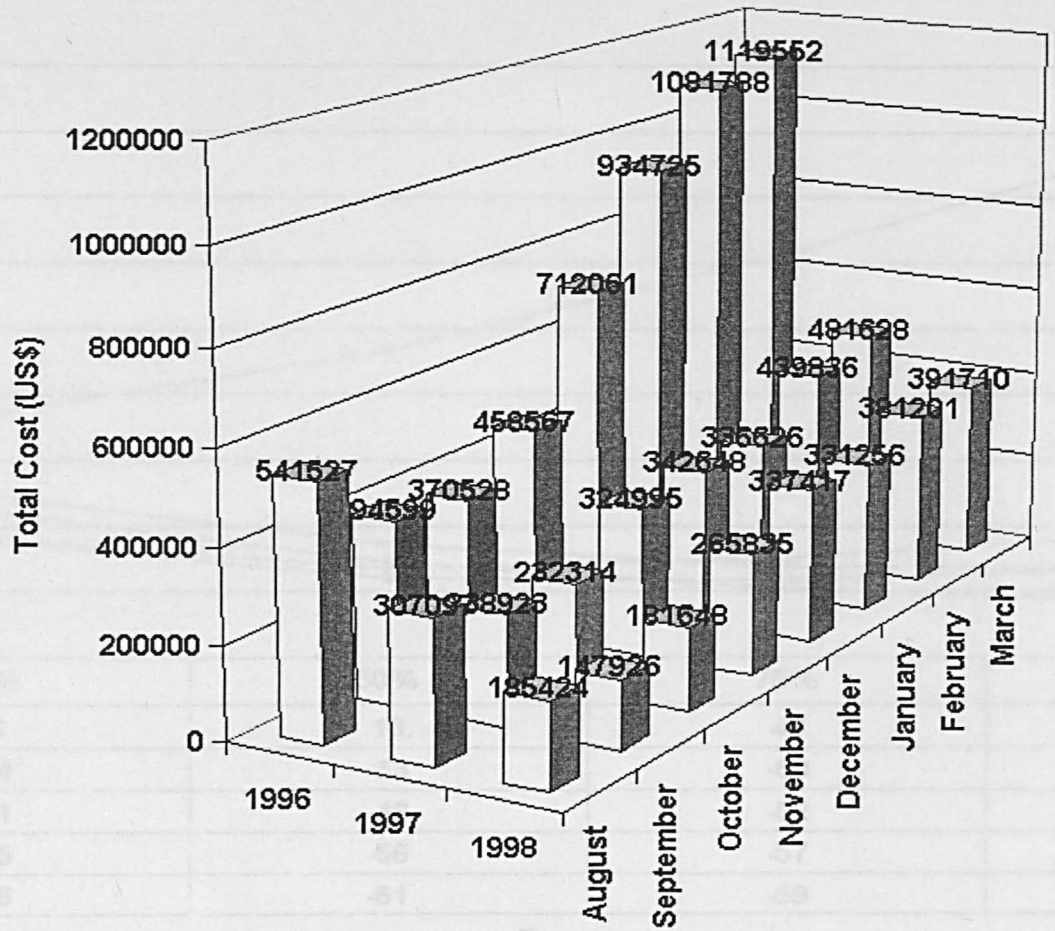
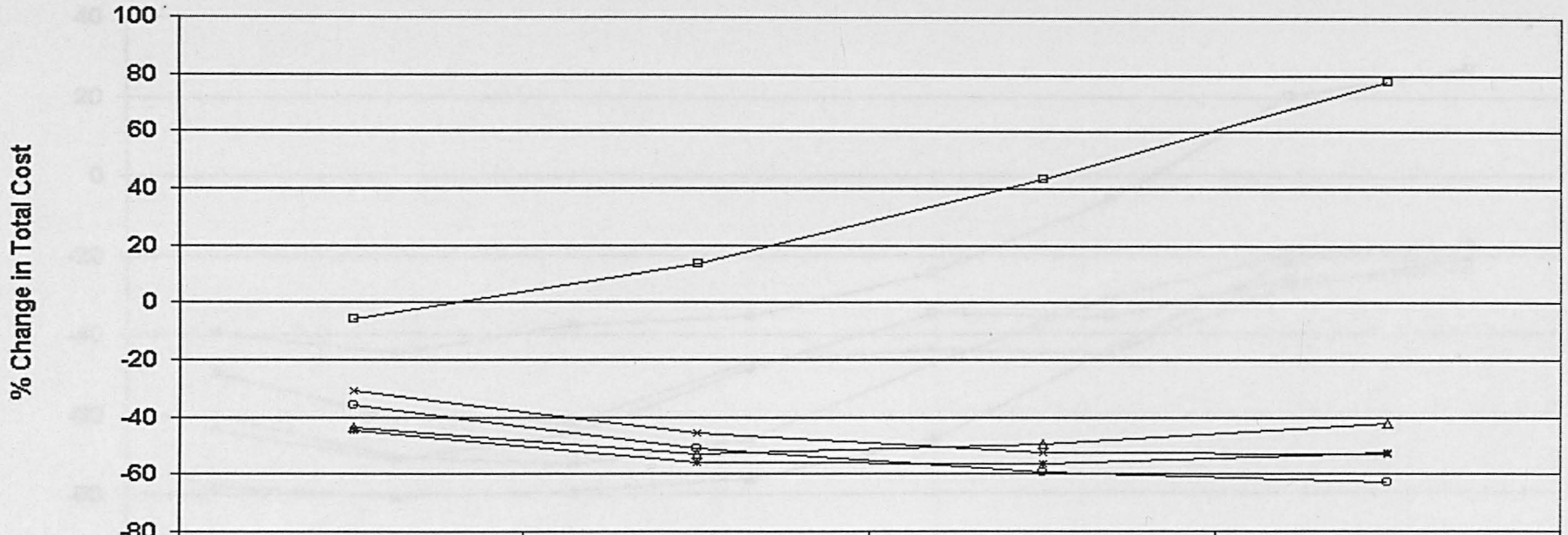


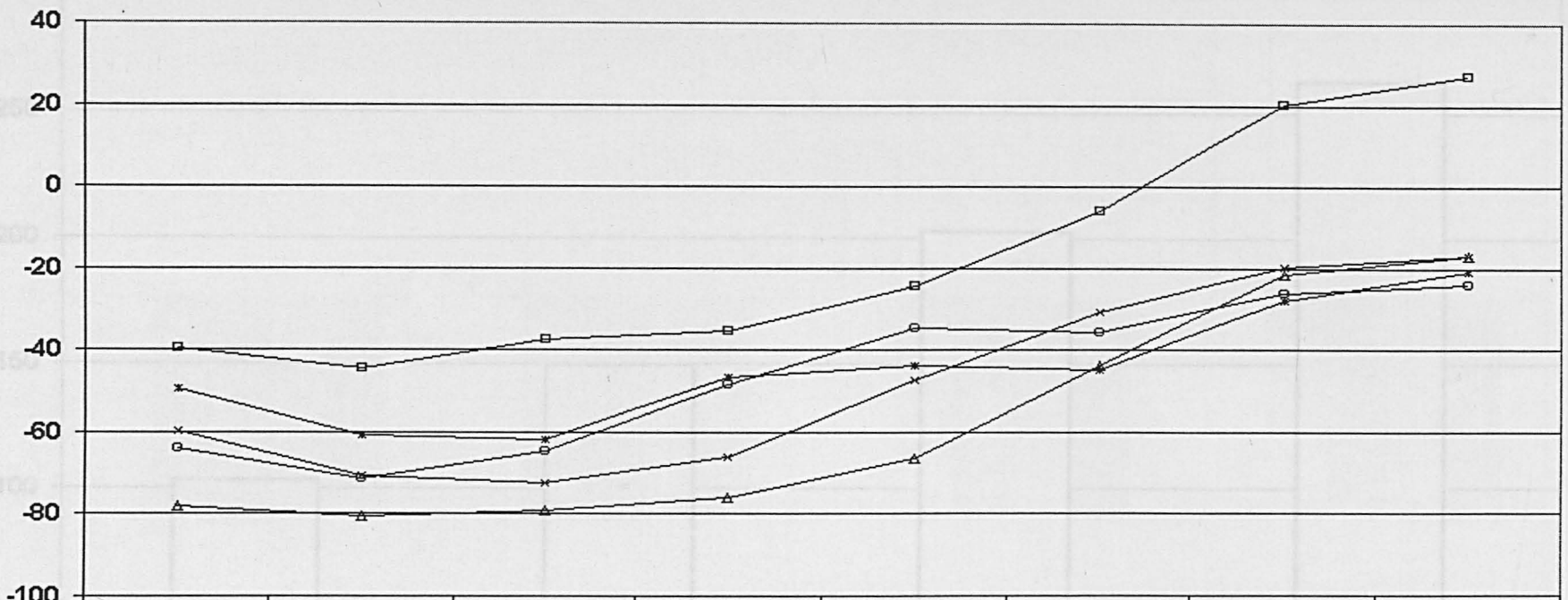
Figure 7-17 Percentage Change in Total Malaria Control Cost with Varying Spray Coverage Compared with 'Do Nothing' Alternative (1994-1998)




| | 24% | 50% | 75% | 100% |
|---|---|---|---|---|
| 1994 | -6 | 13 | 43 | 78 |
| 1995 | -44 | -53 | -50 | -42 |
| 1996 | -31 | -46 | -52 | -53 |
| 1997 | -45 | -56 | -57 | -52 |
| 1998 | -36 | -51 | -59 | -63 |

Coverage

Figure 7-18 Percentage Change in Total Malaria Control Costs by Varying Spray Effectiveness On-Set Time Compared with 'Do Nothing' Alternative (1994-1998)




| | August | September | October | November | December | January | February | March |
|---|---|---|---|---|---|---|---|---|
| 1994 | -40 | -44 | -37 | -35 | -24 | -6 | 20 | 27 |
| 1995 | -78 | -80 | -79 | -76 | -66 | -44 | -22 | -17 |
| 1996 | -60 | -71 | -73 | -66 | -47 | -31 | -20 | -17 |
| 1997 | -50 | -61 | -62 | -47 | -44 | -45 | -28 | -21 |
| 1998 | -64 | -71 | -65 | -48 | -34 | -36 | -26 | -24 |

Figure 7-19 Net Incremental Cost per Case Prevented by Spraying with Varying Levels of Coverage (1993)

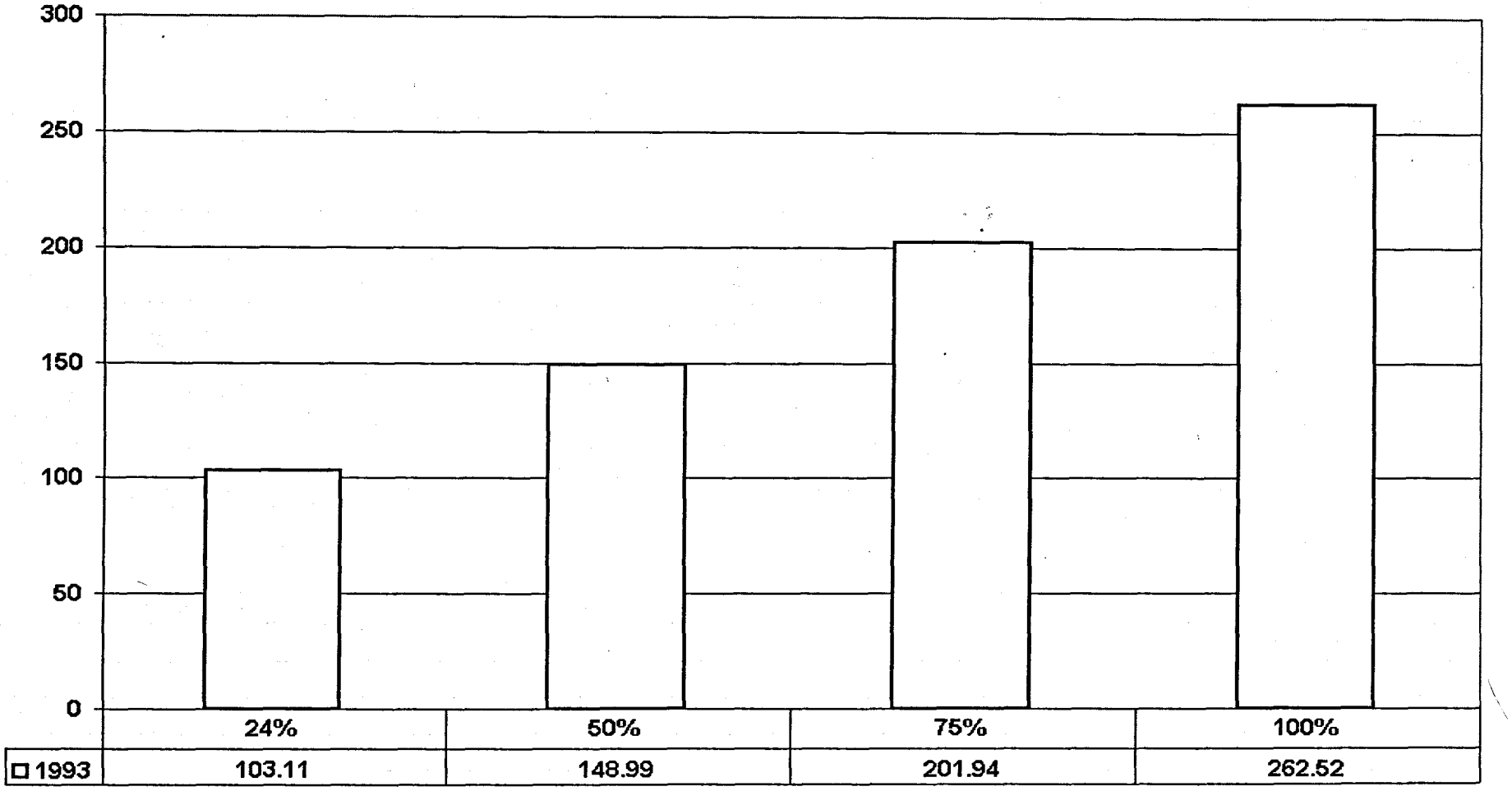
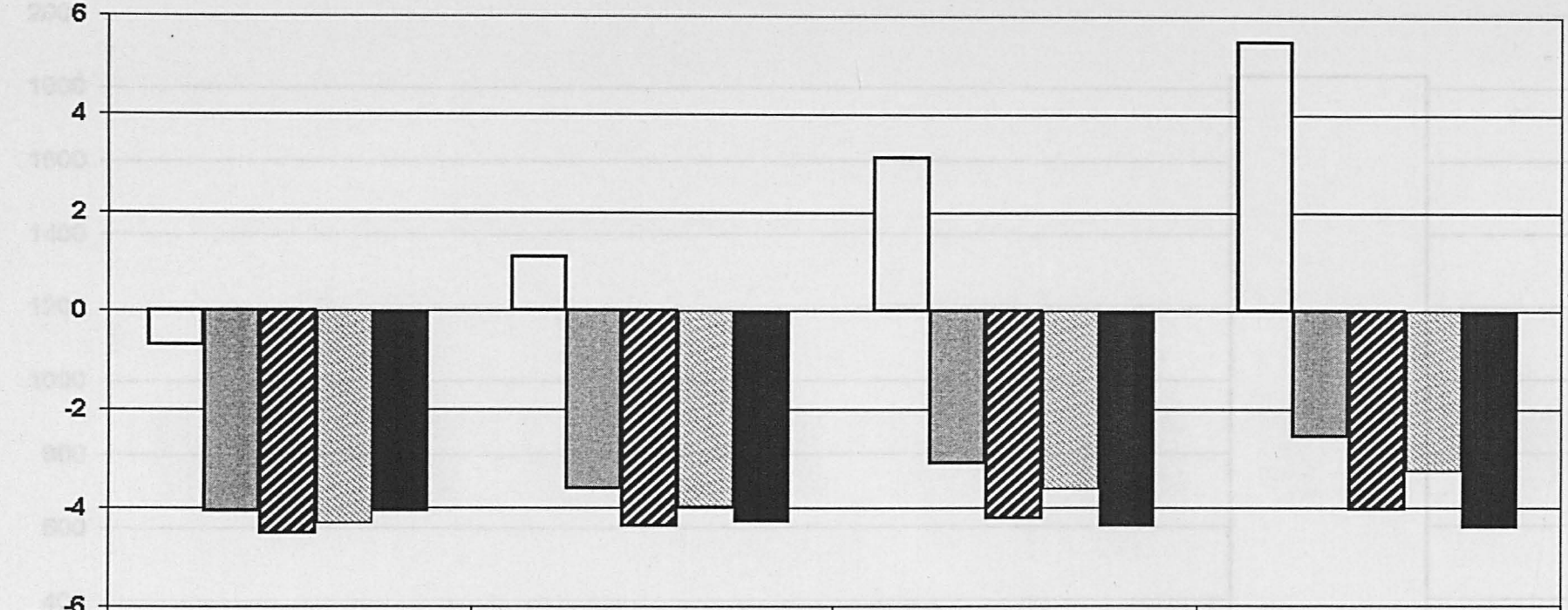


Figure 7-20 Net Incremental Cost per Case Prevented by Spraying with Varying Levels of Coverage (1994-1998)




| | 24% | 50% | 75% | 100% |
|---|---|---|---|---|
| 1994 | -0.70 | 1.08 | 3.14 | 5.48 |
| 1995 | -4.06 | -3.60 | -3.10 | -2.56 |
| 1996 | -4.51 | -4.36 | -4.21 | -4.02 |
| 1997 | -4.30 | -3.96 | -3.62 | -3.24 |
| 1998 | -4.05 | -4.28 | -4.36 | -4.39 |

Figure 7-21 Net Incremental Cost per Case Prevented by Spraying with Varying Effectiveness On-Set Times (1994-1998)

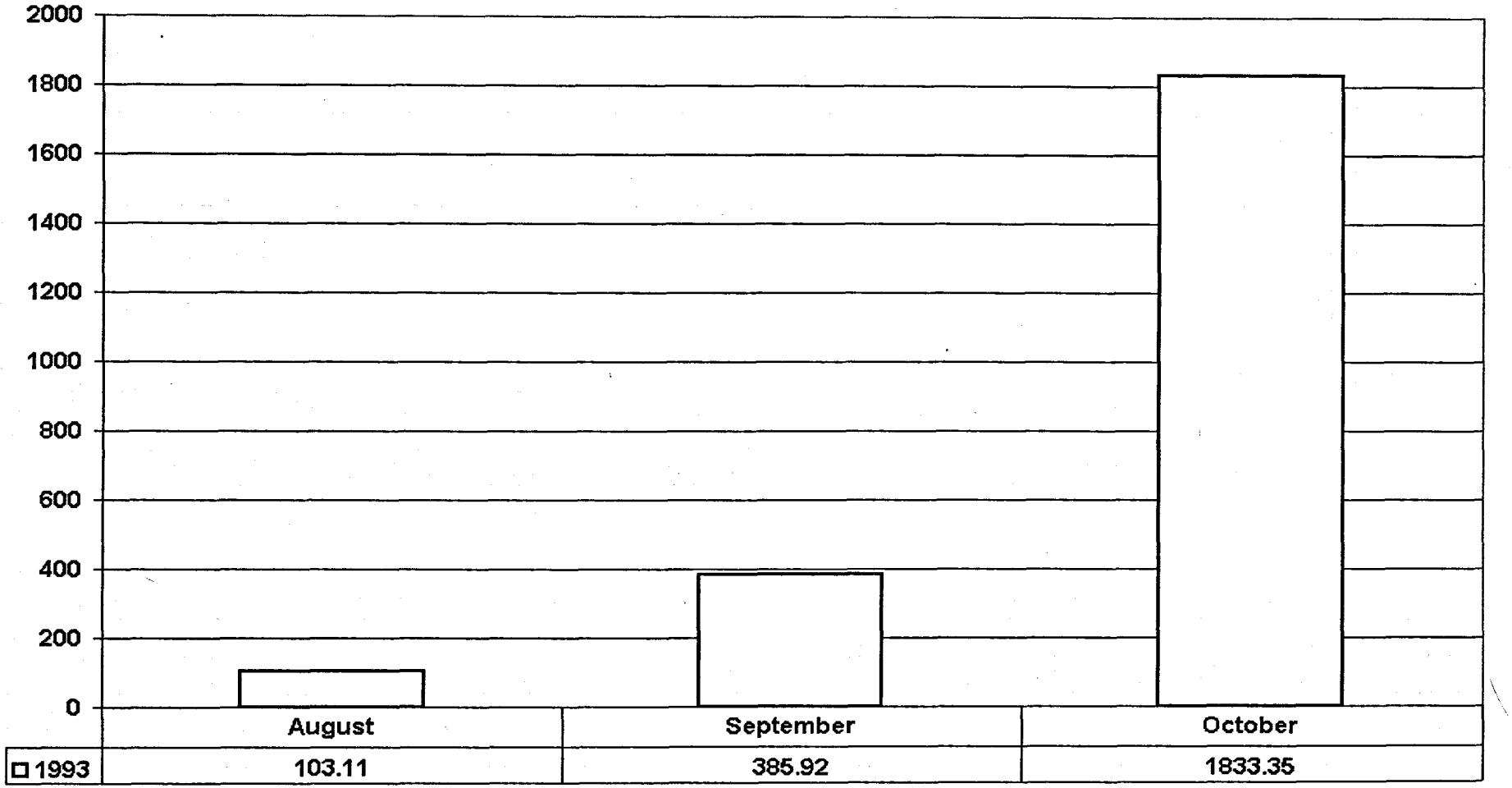
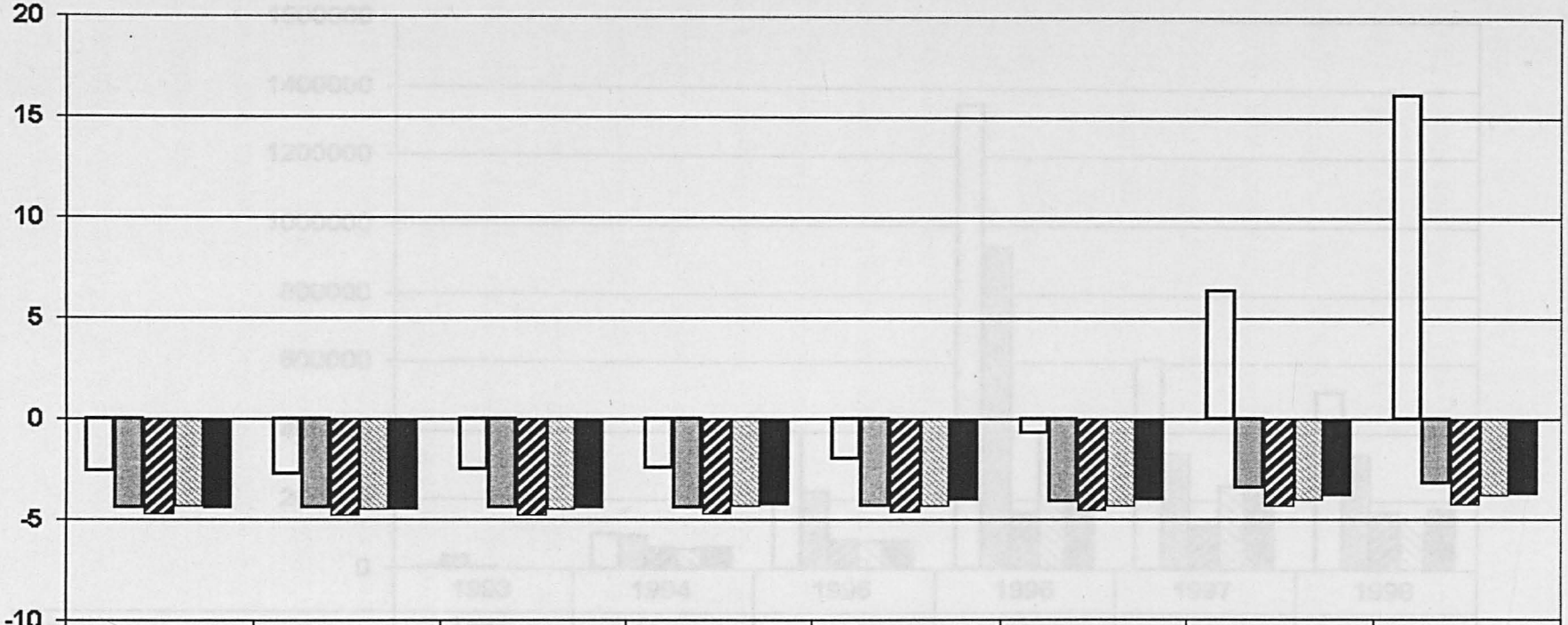
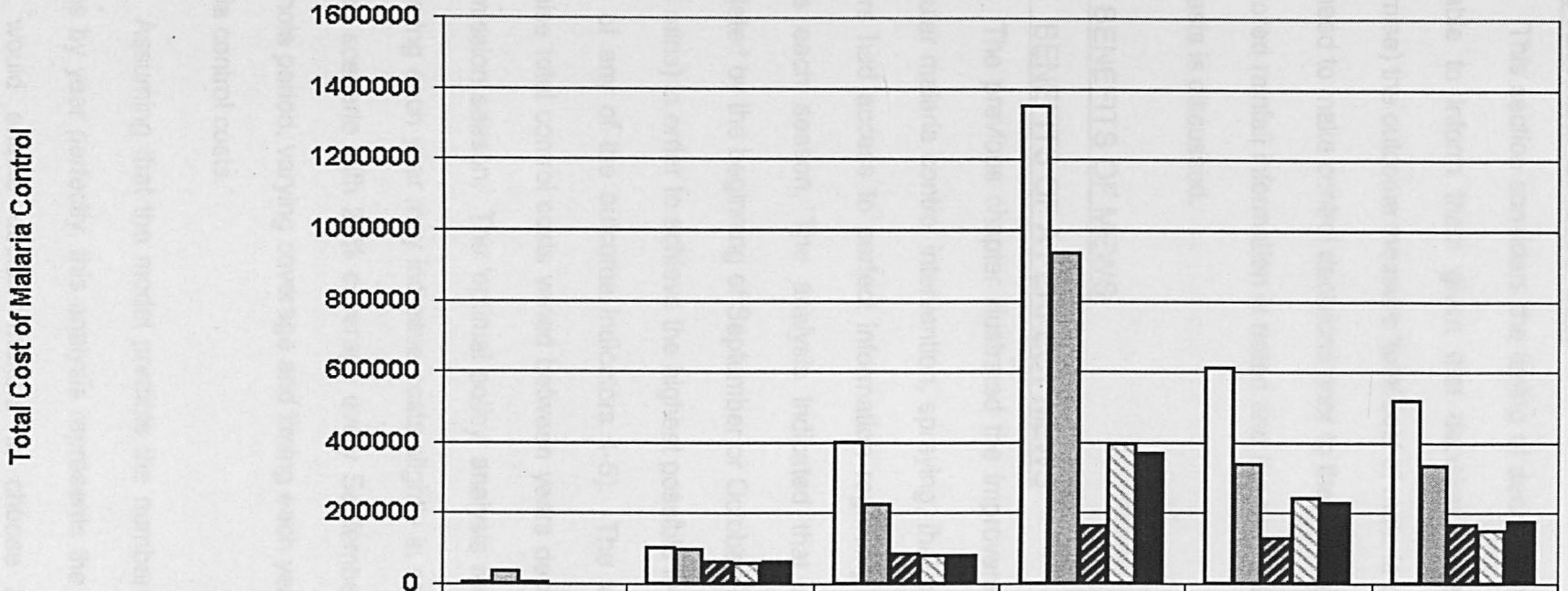


Figure 7-22 Net Incremental Cost per Case Prevented by Spraying with Varying Effectiveness On-Set Times (1994-98)




| | August | September | October | November | December | January | February | March |
|---|---|---|---|---|---|---|---|---|
| 1994 | -2.60 | -2.74 | -2.52 | -2.46 | -2.00 | -0.70 | 6.38 | 16.12 |
| 1995 | -4.40 | -4.42 | -4.41 | -4.39 | -4.32 | -4.06 | -3.44 | -3.16 |
| 1996 | -4.70 | -4.74 | -4.74 | -4.72 | -4.65 | -4.51 | -4.30 | -4.22 |
| 1997 | -4.35 | -4.45 | -4.46 | -4.32 | -4.29 | -4.30 | -3.99 | -3.75 |
| 1998 | -4.40 | -4.45 | -4.40 | -4.25 | -4.02 | -4.05 | -3.80 | -3.72 |

Figure 7-23 Total Cost of Malaria Control Under 'Optimal Policy' Scenario and Selected 'Uniform' Scenarios




| | 1993 | 1994 | 1995 | 1996 | 1997 | 1998 |
|---|---|---|---|---|---|---|
| Do Nothing' Alternative | 2755 | 101909 | 400324 | 1348145 | 609107 | 515090 |
| Baseline' Scenario | 35981 | 95938 | 225614 | 934725 | 336626 | 331256 |
| Optimal Policy' Scenario | 2755 | 60459 | 81987 | 163485 | 125677 | 166963 |
| 24% Coverage September | 0 | 56565 | 78177 | 394599 | 238923 | 147926 |
| 24% Coverage October | 0 | 63880 | 83029 | 370528 | 232314 | 181648 |

# CHAPTER 8 – THE BENEFITS AND COSTS OF MALARIA EARLY WARNING SYSTEMS FOR MALARIA CONTROL

## 8 OVERVIEW OF CHAPTER

This section considers the timing of decisions and availability of information available to inform them given that decision makers are seeking to optimise (minimise) the outcome measure 'total cost of malaria control' (outcome measure 4). The need to make control decisions prior to the rains and the resultant lack of timely monitored rainfall information is noted and the necessity to rely on seasonal rainfall forecasts is discussed.

## 8.1 BENEFITS OF MEWS

### 8.1.1 BENEFITS OF A PERFECT MEWS

The previous chapter illustrated the improvements in the efficiency of one particular malaria control intervention, spraying, that could be achieved if decision-makers had access to perfect information regarding the severity of transmission before each season. The analysis indicated that spraying would have to be completed by the beginning of September or October (depending on the on-set time of the rains) in order to achieve the highest possible level of efficiency (measured in terms of any of the outcome indicators 1-5). The level of coverage required to minimise total control costs varied between years depending on the severity of the transmission season. The 'optimal policy' analysis revealed that varying coverage and timing each year may increase costs slightly in some years compared with the uniform scenario with 24% coverage every September. However, on average for the whole period, varying coverage and timing each year would yield the lowest total malaria control costs.

Assuming that the model predicts the number of cases reporting at health centres by year perfectly, this analysis represents the benefits of a perfect MEWS, which would enable decision-makers to choose and implement the control

intervention with the optimal level of coverage at the optimal time. The benefits of a perfect system are quantifiable in terms of cost savings made to the Ministry of Health (MoH) by following the optimal policy compared to following the 'baseline' policy of fixed coverage (24%) in January each year. Table 8-1 shows the total cost of the 'baseline' policy and the optimal policy for each year. The cost saving from carrying out the optimal policy compared to the baseline is also shown (in 1999 constant US$).

This analysis is limited because in reality the model does not perfectly predict the variation in or actual number of cases reporting at health centres by year perfectly. However, the correlation coefficient between the model and the actual case numbers was high, 0.825, i.e. the variability in case numbers is predicted well, therefore the approximate magnitude of the figures in Table 8-1 above can be interpreted with a relatively high degree of confidence. Since the model was scaled to predict the actual number of cases reporting over the whole period rather than for individual years, the exact value of the figures in Table 8-1 are liable to some uncertainty within years. However, over the whole period the magnitude of the results will be correct.

### 8.1.2 BENEFITS OF A MEWS BASED ON MONITORED TRANSMISSION RISK INDICATORS (TEMPERATURE AND RAINFALL)

The model can be used to examine the benefits of a MEWS based on monitored information. In particular it can be used to examine the question of *'the timing at which decisions and actions must be made to control or mitigate malaria epidemics'* (WHO 2001) and how this will affect the benefits of this type of MEWS. A form of 'backwards reasoning' or 'backwards induction' will be used to examine this question starting from the time that spraying needs to be implemented to achieve the maximum efficiency and tracing the problem back to the information provided by the MEWS at this time.

In order to achieve the maximum level of efficiency (using any of the outcome measures 1-5) spraying would have to be completed to the required level of coverage (determined by outcome measure 4) by the start of September or October. If spraying takes two months and must be completed by these times, spraying must begin by the start of June or July. Therefore the decision on whether or not to spray, and at what level of coverage must be made in May or June respectively. However, in May/June, the only monitored weather information that will be available is up to and including April or May. According to the model the lag between these transmission risk indicators and malaria is four months, i.e. April and May temperature and rainfall predicts August and September malaria. August and September are (normally) prior to the on-set of the malaria season and therefore may not be useful to indicate the severity of the malaria season. Figure 8-1 represents the time that decisions on the level of spray coverage to be achieved must be taken in relation to rainfall and the 'baseline' timing and coverage of spraying.

A MEWS based on monitored transmission risk indices does not offer sufficient lead time to allow the optimum level of spray coverage to be determined early enough to allow it to be implemented at the optimum time. Since the optimal strategy cannot be achieved, decision-makers would have to trade-off the benefits and costs of spraying with the optimal level of coverage at the baseline time (Sub-optimal strategy a) against spraying at the optimal time with the baseline level of coverage (sub-optimal strategy b).

Table 8-2 illustrates the total cost of malaria control under sub-optimal strategies a and b. Sub-optimal strategy b yields the lowest total cost of malaria control in all years (apart from 1993 where results are incomplete) compared to sub-optimal strategy a. This means that it is better to spray at the optimal time (early) every year with the baseline level of coverage than to wait for information about the

coming transmission season on which to base coverage. Therefore out of the sub-optimal strategies available to decision makers using a MEWS based on monitored transmission risk indices, the strategy of early spraying with a fixed 'baseline' level of coverage is the most economically efficient overall.

### 8.1.2.1 OTHER INTERVENTIONS

This analysis has concentrated on two interventions, spraying and case management, which is used to represent the costs of malaria cases to the MoH, a proportion of which may be averted by a successful spray programme. Spraying was chosen for the analysis because of the lack of good quality economic data on the intervention existing in the literature (identified through the literature review – see section 2.2.2.4.2) and the availability of cost data in the study area (chapter 6). However, it was also of particular interest because of the following comments made by Nájera:

'*once the increase in morbidity has been recognized, there may be too little time to mobilize the required resources for effective vector control, before the transmission season has reached its peak*" (Nájera 1998)

*'Transmission control should be carried out as long as the epidemic has not exhausted itself before health services have recognised it, or had time to act'* (Nájera 1998)

and the point made by Connor, that epidemics may become political issues, leading to the initiation of a vector control programme well beyond the time period in which it could effectively reduce transmission (Connor et al. 1999). Moreover, the organisation and implementation of a spray programmes is likely to take longer or at least as long as other interventions which may be used as part of a response to control or mitigate the effects of a malaria epidemic [see section 1.7.1. for a full list of these as laid down in the WHO framework document (WHO 2001)]. Spraying could therefore be considered as a representation of the 'worst case scenario' in

terms of the usefulness of the lead time offered by MEWS based on monitored weather transmission risk indicators in relation to its necessary 'implementation time'.

As illustrated in the above analysis of spraying, the benefit of MEWS based on transmission risk indicators is less than would be offered by a perfect system but greater than the existing 'base line' scenario. However, such a MEWS would provide timely information on which to base decisions regarding the implementation of other interventions with shorter implementation times. For example weather data from October, November and December, which predicts the January, February and March (peak) transmission season could be used to inform choices regarding the appropriate levels of expenditure on public awareness campaigns, mobile clinics, field hospitals, community drug holders, staffing and anti-malaria drugs supply levels. Decisions regarding the provision of chemoprophylaxis to vulnerable groups such as pregnant women and children under five and measures to encourage or increase the personal use of mosquito nets and insecticide impregnated mosquito nets or other materials could also be informed. Appropriate levels of these interventions, implemented in a timely, manner based on the information provided by a MEWS, could be expected to reap benefits in terms of improved efficiency in resource use (measured in whatever manner appropriate) as was seen in the analysis of spraying. Moreover, the provision of adequate 1$^{st}$, 2$^{nd}$ and 3$^{rd}$ line drugs, IV facilities, HIV screening of blood for transfusion services prior to the on set of a severe epidemic could substantially reduce the mortality rate.

The structure set out and applied to spraying in this thesis could be used to quantify the benefits of any of the interventions mentioned above, subject to the availability of appropriate data on the costs and effects of each intervention. Indeed in order to estimate the total benefits of MEWS it would be necessary to quantify and sum the efficiency gains or reductions for all interventions where a MEWS

influences decisions regarding how, when and for whom to intervene. Unfortunately however, it is unlikely that such an evaluation will take place and there is a danger that MEWS will be judged on the basis of their first failures, which are likely to have political costs, rather than through rational economic analysis.

### 8.1.3 BENEFITS OF A MEWS BASED ON FORECASTED TRANSMISSION RISK INDICATORS (SEASONAL CLIMATE FORECASTS)

It has been proposed that seasonal climate forecasts could be incorporated into health surveillance, particularly as an aid to forecasting epidemic risk thus offering a greater lead time to promote more effective intervention (Connor et al. 1999). However, the possible use of MEWS based on forecasted transmission risk indicators, in particular excess rainfall, is subject to a similar trade-off to the one found between timing and information regarding the severity of transmission as described in section 8.2. In some situations a higher than average seasonal rainfall may be predicted from seasonal climate forecasts 1-6 months in advance – giving a maximum warning of an epidemic situation developing with 10 months early warning however the reliability of such forecasts is limited. Using seasonal climate forecasts of transmission risk indicators in a MEWS will increase uncertainty in the systems ability to predict malaria epidemics but at the same time it will improve the lead time offered by the MEWS.

The limited validation of seasonal climate forecasts which has been undertaken to date suggests that their reliability is limited to certain geographic areas and is greater in years associated with anomalous weather 'events' such as the El Niño Southern Oscillation (ENSO) (WHO 2001). For example the recent development of seasonal climate forecasting using atmospheric-ocean coupled models has lead to the successful prediction of the on-set and demise of the 1997/1998 ENSO event and its effect on weather in Africa (Stockdale et al. 1998). This event was associated with devastating malaria epidemics in East Africa (Brown

et al. 1998, Thomson et al. 2000). In spite of these recent advances, the accuracy of these forecasts is limited and in a best case scenario it is thought that seasonal climate forecasting can predict climate 'events' correctly in 6-7 out of 10 years (WHO 2001).

The use of seasonal climate forecasts for decisions on resource distribution for malaria control in Africa is limited, however a few examples have been identified.

Seasonal climate predictions from the SARCOF (Southern Africa Climate Outlook Forum: post season assessment meeting, Pilansburg, South Africa, 1998), were used by the Southern Africa Malaria Control unit of WHO (WHO-SAMC) to warn malaria control programmes within Southern Africa of a wetter than normal rainy season in 1998/1999 and therefore an increase in epidemic potential (WHO 1998). A number of countries in the region increased their level of preparedness as a direct result of these forecasts (WHO 2001).

Seasonal climate forecasts received by the malaria control unit in Swaziland in July 1997 indicated a high probability that the country would receive above average rainfall during the first season (September to December) and below average rainfall during the second season (December to April). The first part of the forecast proved to be correct and the earlier than usual preparations of the malaria control services paid off with spray activities initiated a month earlier than usual and all health facilities being well stocked with anti-malarials by November (Kunene 1998).

Warnings of the impending El Niño event and likely excess rainfall associated with it in east Africa, were made available to the malaria control services in Kenya prior to the short rains of 1997. This resulted in some increased preparedness activities in the epidemic prone areas of the highlands however, the resultant malaria epidemic in the semi-arid area of north-eastern Kenya had not

been anticipated and took the over-burdened health service by surprise with devastating consequences (Allan et al. 1998).

This limited anecdotal evidence hints at the potential benefit of using seasonal climate forecasts routinely in malaria control planning and decision making. The remainder this section provides a preliminary quantification of the possible benefits using the framework already developed in chapter 7 and sections 8.1. and 8.2 of this chapter. The benefits of a perfect seasonal forecast are examined followed by an examination of the benefits of a seasonal forecast with 60-70% accuracy as reported above.

### 8.1.3.1 BENEFITS OF A MEWS BASED ON PERFECT SEASONAL FORECAST INFORMATION

In October 1998 WHO-SAMC disseminated a "malaria forecast" based on a meteorological forecast, to malaria control teams, ministries of health and other relevant organisations and individuals throughout Southern Africa. The document warned that above normal rainfall and warmer temperatures were expected across Southern Africa between October 1998 and March 1999, resulting in increased malaria transmission potential (WHO 1998). Using the same 'backwards induction' as above (section 8.2) and assuming the same four month lag between rainfall and malaria (based on the model) this forecast predicts malaria at the time of the peak malaria season i.e. February, March and April. WHO-SAMC's decision to disseminate the forecast had to take place before the publication and dissemination of the document in October, it is therefore clear from this operational evidence that seasonal forecasts can be used as the basis for decision making from September onwards.

According to the analysis in section 8.1 the optimal time for the spray programmes to be completed is by September or October. Therefore the use of a perfect seasonal climate forecast within in a perfect MEWS would still offer

insufficient lead time to achieve the optimal spray timing scenario with the optimal level of coverage chosen specifically for the level of transmission each year. Again there would be alternative sub-optimal scenarios, two will be evaluated quantitatively here:

(i) To spray with the baseline level of coverage at the optimal time, without waiting for the forecast (i.e. the same as strategy (b) in section 8.2 above)

(ii) To base the decision on the level of coverage on the seasonal forecast and delay the timing. This would allow for spray completion with the optimal level of coverage by the start of December (allowing two months for completion from the forecast issue in September)

These two scenarios were evaluated using the model and the results of the total cost of malaria control under sub-optimal scenario are shown in table 8-3 below.

For all years apart from 1993 and 1997 sub-optimal strategy (i) is the lowest cost strategy compared with sub-optimal strategy (ii), it is also the lowest cost sub-optimal strategy on average over the time period. This indicates that the lead time offered by MEWS based on seasonal climate forecasts is not sufficient to make waiting for such information and basing a decision regarding the coverage level worthwhile, when compared with choosing a baseline level of coverage at an earlier point in time. However sub-optimal strategy (i) is still a lower cost alternative than the 'baseline' scenario and the 'do nothing' alternative. Moreover, as described in section 8.2.1 above spraying could be considered a 'worst case' intervention in terms of the lead time necessary to make decisions and implement the programme, other interventions may benefit from the added lead time offered by seasonal climate forecasts.

The above analysis assumed that the MEWS based on a seasonal climate forecast of transmission risk indicators would be correct 100% of the time, however this is not the case. Seasonal forecasts currently offer 60-70% accuracy at best meaning that any policy based on them will be subject to error, either predicting an epidemic which does not actually occur (false positive) or failing to predicting an epidemic (false negative). The potential costs of both these types of error are discussed in the following section on the costs of MEWS, under the heading of indirect costs (section 8.2.2).

## 8.2 COSTS OF MEWS

The above analysis has shown that the benefits of MEWS can be expressed and quantified in terms of improvements in efficiency of control interventions, resulting from more timely and appropriate intervention. However such benefits will not come without costs and the degree to which investing in MEWS represents an efficient use of resources will depend on the costs involved in establishing and maintaining a MEWS in relation to the amount of benefits.

The cost of a malaria early warning system can be separated into direct and indirect costs. Direct costs encompass research and development costs (sunk costs), implementation and running costs and indirect costs are the opportunity costs incurred if the system makes incorrect predictions, either false positives or false negatives.

### 8.2.1 DIRECT COSTS OF MEWS

The sunk costs of MEWS include the cost of development of climate forecasting models (Palmer and Anderson 1994, Palmer et al. 1998), linking the output of such models to meaningful predictions of malaria epidemic risk (Thomson et al. 2000) and defining the link between climate and malaria [see for example (Lindsay and Birley 1996, Martens 1997, Snow et al. 1999, Thomson et al. 2000)]. The international research community is undertaking this work and costs of these

activities are therefore being met by universities or the donor agencies that fund such activities.

Implementation costs are likely to be absorbed by national government Ministries of Health (MoH) at the national, regional and district levels with some help from donor organisations. An indication of the optimum level of investment and expenditure on the implementation of MEWS can be determined in part by the potential value of such systems when in place as outlined in this thesis.

Once systems are in place running costs may be incurred at all organisational levels within the MoH for example in terms of staff time needed to process and respond to information. The cost of gathering relevant climate and meteorological data may be shared with other government ministry's for example the food and agriculture or meteorology departments which routinely monitor appropriate variables. Table 8-4 displays the early warning indicators that may form part of a MEWS along with the sector that is likely to bear the cost of gathering or providing such information. The qualitative predictive accuracy of each indicator is also noted and can be compared to the qualitative length of time offered for action by each indicator.

Meteorological stations across Africa may provide the information necessary for weather/climate monitoring, however access to meteorological station data by health services may be limited for a number of reasons (such as lack of staff, poor equipment etc). If this is the case an alternative source of weather data can be obtained from meteorological satellites, possibly via the Internet. This data can be readily extracted and distributed to researchers at the district level or training can be given in the use and interpretation of historic and near real time satellite data (WHO 2001).

Seasonal forecasts offer the possibility that unusual increases in malaria transmission can be predicted from statistical or dynamic models, which provide

climate forecasts months in advance. However, over dependence on seasonal climate forecasts should be avoided because statistical models are limited by the lack of accurate time series of meteorological data for training the models and the current best case scenario for seasonal climate forecasting using multi-model systems is that the model will only be correct in 6-7 out of 10 years (WHO 2001).

### 8.2.2 INDIRECT COSTS OF MEWS

A MEWS may lead to indirect or opportunity costs being incurred. If the system makes incorrect predictions (either false positives or false negatives) opportunity costs will be incurred. In the case of a false positive the opportunity cost will be the value of the resources used unnecessarily that could have been used elsewhere. These costs can be minimised by using a *'graded control response* [which] *allows control organisations some capacity to further monitor and assess the situation before committing extensive resources'*, however, in some situations this may not be possible due to logistical constraints which mean there is only a single opportunity to deliver extra resources (WHO 2001). In the case of a false negative, the opportunity cost of the system will be the opportunity for early malaria control lost because of the error. If a malaria control system which employs a MEWS is being compared to the alternative of a malaria control without a MEWS then this would be the kind of opportunity cost that it is hoped the system will reduce in the long term.

## 8.3 COSTS AND BENEFITS OF MEWS AND EPIDEMICS

As stated above (section 7.5) one of the major limitations of this analysis is the perspective taken, that of the provider (MoH) which therefore excludes costs and benefits to the household and other sectors. In order to address this limitation further and examine its implications a theoretical framework has been developed to identify costs and benefits to other sectors.

Table 8-6 displays a framework for identifying the costs and benefits of malaria epidemics to the Ministry of Health and the household, with and without the use of a MEWS. The framework was based on the following assumptions drawn from the above analysis:

- Early intervention is more effective therefore the opportunity cost of later intervention is the benefits from early intervention that are foregone
- The Ministry of Health always incurs the fixed costs of routine control activities. However, this may be reduced in 'no epidemic' years by the introduction of a MEWS (e.g. some spraying may be stopped and drug stocks may be lower, however certain fixed costs e.g. of health centres and staff will remain).
- Households always make expenditure on prevention activities. This is considered to be an exogenous variable i.e. not related to the probability of an epidemic or the MEWS and will therefore be considered fixed. [In reality it is likely to be related to other factors such as women's income and social status of the household which do not change each year in a predictable way (Rashed et al. 2000).]
- A malaria control programme, which operates without the use of a MEWS, is represented by the 'baseline' control system, which is compared to a system that operates with a MEWS. There are two possible states of the world for each control system - 'epidemic' and 'no epidemic' - these are interpreted in terms of the MEWS forecast where a MEWS in place (i.e. MEWS correct and MEWS incorrect). The costs and benefits of each situation are described from the perspective of the Ministry of Health (MoH) and the household.

From the perspective of the MoH the direct costs of an 'epidemic' situation are the fixed costs of routine control activities and the costs of epidemic prevention and mitigation activities, the indirect cost is the cost of missed opportunity for early intervention. The benefits in this situation are the reduction in case management costs (and net total malaria control costs) resulting from successful preventive activities either before (routine activities) or after the onset of the epidemic. From the perspective of the household the costs of an epidemic situation will be the fixed expenditure on prevention activities, expenditure on treatment (direct costs) and the indirect cost of lost production or earnings for those made ill or killed by the epidemic and their carers. The benefits will be the reduction in treatment and indirect costs resulting from successful preventive activities and the reduction in indirect costs resulting from expenditure on treatment.

In the baseline situation with 'no epidemic' the MoH will incur the fixed costs of routine control activities and no benefits. The household will incur the fixed costs of expenditure on prevention activities and no benefits.

When a MEWS is in use it may either predict 'epidemic' or 'no epidemic' and in either situation the prediction may be correct or incorrect. When a MEWS is in use the MoH always incurs the fixed costs of the system and the fixed costs of routine control activities although these may be lower than in the baseline scenario. In addition, if the system predicts 'epidemic' and is correct the MoH will incur the cost of epidemic prevention and mitigation activities. The benefits will be the reduction in case management costs resulting from successful and early preventive activities (i.e. the benefit of early intervention). From the household perspective the costs will be the same as outlined in the baseline situation, however the expenditure on treatment and indirect costs should be lower. This is captured in the benefits cell as 'the reduction in direct and indirect costs resulting from successful and early preventive activities by households and the MoH'.

If the system predicts 'epidemic' and is incorrect (false positive) the costs to the MoH will be the same as for 'epidemic' correct however there will be no benefits to offset these costs. From the household perspective the costs of an incorrect 'epidemic' prediction will be the fixed expenditure on prevention activities and no benefits.

If a MEWS is in use and correctly predicts 'no epidemic' then the MoH will incur only the fixed cost of the MEWS and of routine control activities. The potential benefit is that the resources saved from the reduced cost of routine control activities may be allocated for use elsewhere. Households will incur the usual expenditure on preventive activities and no benefits.

If the MEWS predicts 'no epidemic' and is incorrect (false negative) the situation will be similar to the baseline 'epidemic' situation, except that the MoH will also incur the fixed cost of the MEWS. The household costs and benefits will be the same as in the baseline 'epidemic' situation.

### 8.3.1 A THEORETICAL FRAMEWORK OF THE COSTS AND CONSEQUENCES OF MALARIA EPIDEMICS

Table 8-6 illustrates how, as an epidemic situation increases in severity and size, the cost of the epidemic is felt by more and more sectors of the national and international health community and economy (note private sector costs of lost production are not included although these are likely to be felt at all scales of malaria problem). This indicates the magnitude and potential value that effective MEWS could have on the wider community if they could reduce the burden of epidemics. The diagram describes the scale of the malaria problem (along the left-hand side) and the levels where the cots will be incurred (along the top). A + in a cell illustrates that the malaria situation described will impact upon the group or sector described along the top, + (?) illustrates that the situation may impact on the group or sector described.

A single malaria case will only cost the sick individual and their household. If a small epidemic occurs in a village, households and the village health worker (VHW) or primary health care (PHC) network will meet the costs, possibly with some costs being met by village or local health centres or clinics if they are close by. If there are a number of village level epidemics the district level health services may shoulder some of the additional costs. District wide epidemics may require additional resources from provincial or regional health services especially if a number of districts are affected. When epidemics occur throughout large areas or provinces the Ministry of Health or national level health services are likely to be heavily involved and incur significant costs of the epidemic. National epidemics with countrywide epidemic levels of malaria may see the involvement of local or international NGO's providing additional treatment and control interventions. Further involvement from international bodies (such as WHO and UNICEF, other NGO's etc) is likely when an epidemic becomes a disaster situation for example if case fatality rates are high and existing health services are unable to cope.

## 8.4 DISCUSSION AND CONCLUSIONS

One of the main functions of a MEWS would be to ensure that control or intervention activities aimed at reducing epidemic potential, were carried out early enough to prevent or significantly reduce the effects of an epidemic. However, there are many uncertainties surrounding the economic implications of MEWS which need to be examined before implementation begins and which will need reassessment as more data becomes available on the use of MEWS in Africa.

The previous section has described the complexity of the possible economic effects of MEWS on the MoH and the household sectors of the economy. Uncertainty surrounds the costs associated with a system which incorrectly predicts or misses epidemics (indirect costs) as well as the direct costs and benefits of a system. At present it is therefore unclear what overall effect of the introduction of

MEWS would have on the economic burden of epidemic malaria to these sectors individually. Moreover, the economics of the introduction of MEWS may be complicated further by redistribution effects. For example if a MEWS results in increased costs to the MoH these may be offset by cost savings to households because of a reduction in the direct and indirect cost of epidemics as a result of effective epidemic control. Given that an estimated 80% of malaria cases never reach health facilities (WHO 2001) these effects may be substantial. If the benefits of reductions in the cost of malaria are felt at the household level, particularly in very poor households then a MEWS may have a redistribution effect. It is therefore important to establish how the costs of a system are distributed, so that a redistribution of benefits or costs to other sectors does not appear as a net change. This is particularly important if the system is to be examined from the societal perspective.

If the net costs of malaria control (including the household and MoH) using a MEWS are greater than without a MEWS it will be important to examine the benefits gained from this additional resource use and decide whether they represent the best use of additional resources. If the net costs of malaria control are lower with than without a MEWS, resources will be saved. In this case it will be important to examine the possibilities and benefits of a redistribution of these resources.

A MEWS may lead to false positives resulting in unnecessary expenditure on malaria control or false negatives leading to preventable cases and deaths occurring. Depending on the biases and causes of these errors in the system one type of error may be more likely to occur than the other, moreover, one type of error may be considered less acceptable than the other. An economic evaluation cannot answer value judgements regarding the value of cost saving compared to saving lives, decision makers must chose whether they prefer to risk the consequences of type one or type two errors and interpret the results of a MEWS accordingly.

The value and usefulness of a MEWS will depend on the frequency of epidemics in a given area. For example if an epidemic occurs every three years, a policy of annual control may be less costly and more beneficial than using a MEWS. On the other hand in an area where epidemics occur every seven or ten years a MEWS may be worthwhile. There will be some upper limit, depending on the costs of running MEWS and the likely costs of an epidemic where the frequency of epidemics is so low that a MEWS is not economically justifiable. Another important factor will be the accuracy of the system and the frequency and cost of type one and type two errors as described above.

It is the timing of interventions which will be crucially affected by a MEWS and consequent changes in the efficiency of malaria control interventions as a result of more timely implementation are critical in the evaluation of MEWS as a tool for improved malaria control in Africa. Using the framework developed in this thesis in conjunction with information on how much decision makers are willing to pay for given health effects, it would be possible to identify critical points in an epidemic cycle where certain activities are ruled out due to the costs and time it would take to implement them and their limited impact upon the epidemic at such late stages.

Jack points out that where project evaluations include choices among mutually exclusive projects such as alternatively timed activities, (for example a project started today compared to one deferred until tomorrow when its effects will be better known), it is vital to establish the counterfactual (i.e. what would have happened in the absence of each alternative) and compare alternatives to that scenario (Jack 1999). This has implications for the choice of alternatives against which to compare a MEWS and the malaria control strategy adopted as a result of the MEWS. It is likely that a MEWS will lead to control activities being carried out earlier than in a system without MEWS. These activities are likely to be the same in

many cases (because of health systems or cultures that may traditionally favour or support certain strategies) with only the timing aspect being different.

In order to compare the cost-effectiveness of intervention based on a MEWS against the counterfactual it was therefore necessary to compare the same control strategy implemented at a different time. The analysis could be developed further to include the possibility that a MEWS enables strategies that were currently ruled out as taking too long to implement to be appropriate for epidemics (e.g. residual household spraying for vector control) to be planned and implemented before the epidemic. Conversely it is possible that a MEWS will lead to strategies which are traditionally implemented late with limited effectiveness being ruled out as a cost-effective option. This will depend upon the amount that decision makers are willing and able to spend per given health effect achieved.

Jack also examines the role of risk and irreversibility in economic evaluations (Jack 1999). He argues that all alternatives will have some degree of risk attached to them, for example caused by cost overruns or lower than expected take up rates. Economic analyses need not take into account the cost of this risk if the project is small because, he argues, governments (or large decision making institutions) are in a position to diversify this risk. However, if projects incur a large degree of sunk investments (those which cannot easily, if at all, be converted for other uses once invested), then Jack suggests that this risk should be incorporated into the analysis. This may mean that the value of waiting to make a decision becomes important, because new information may become available which will alter the optimal decision. If a decision is easily reversible and the investment is largely recoverable then the value of waiting is not important, whether or not this is the case in specific situations will be up to decision makers to evaluate. The value of waiting is known as the option value and the higher the option value the greater the net benefits

needed to justify the activity because it may be beneficial to put it off until tomorrow when more information may be available.

This thesis has identified that for one intervention, spraying, which has low sunk costs, waiting to make a decision regarding epidemic malaria control intervention can in fact incur costs in terms of reduced cost-effectiveness of the intervention. Although decisions to spray are not revisable and the investment is not recoverable the option value of spraying may be negative, following Jacks argument logically this implies that the net benefits needed to justify the activity will be low, because it is not beneficial to put it off until tomorrow.

An estimate of the potential value of MEWS could be used to help inform decisions regarding what level of resources should be dedicated to their implementation. This decision will rest upon the level of reliability that can be expected from MEWS, which may in turn inform the question on how reliable a system should be before its application can be expected to reap net benefits. The answer to this question is likely to depend upon the time scale over which MEWS are to be evaluated. The framework developed in this thesis allows these and other questions to be structured and answered using the currently available data and also identifies crucial areas for future research and data gathering.

## 8.5 POLICY AND RESEARCH RECOMMENDATIONS

Country specific conclusions from the results of the evaluation carried out in this thesis would suggest that the Zimbabwean Ministry of Health should reconsider a number of aspects of the National Malaria Control Programme. Firstly, it may be beneficial to bring forward the planning cycle for malaria control and in particular residual spraying activities which, if they are to be carried out, should be completed around September/October.

Secondly, the decision on when and where to spray should be re-examined annually rather than being institutionalised (so that it is something which just

happens the way that it happens because it has always been done like that). Serious and timely consideration should be given each year to the implications for control strategy of the severity of malaria the previous year, the state of the populations' health and nutrition, and any meteorological indications which may indicate the severity of the coming malaria season. This information should be incorporated into control planning early and routinely. The necessary change to the decision making culture within the MoH may be difficult and long term, however an interim strategy that would still reap net benefits would be to simply bring forward the annual spray programme as described above.

Thirdly, the results of the costing analysis also showed that compared to the cost of the chemical, the increase in expenditure needed to improve supervision of the spray programme would be extremely small, yet the improvements in effectiveness could be great.

The malaria model developed in this thesis was highly successful in predicting the dynamics of malaria in the Hwange District of Zimbabwe where malaria is generally rainfall dependent. However, the initial model construction was carried out using data from the Nandi District of Kenya where the model results were also promising. Malaria in this region is temperature dependent, suggesting that this malaria model may be appropriate for predicting the on set and severity of malaria epidemics in a variety of epidemiological and meteorological settings, namely where malaria is rainfall or temperature dependant. In order for the model to be useful to malaria control personnel in such situations it will require "front-ending" and the production of a suitable manual, to make it highly user friendly. Once such a product is available it should be distributed amongst interested and appropriate parties (possibly district or regional level malaria control personnel) who will then be able to use the product, test the model and offer constructive suggestions for development and modification of the model structure. If during these pilot studies

the model is found to have value as a predictive tool for malaria in a broader range of locations than those examined in this thesis it should be further developed and incorporated into routine malaria control planning activities. If the model is not useful for predicting epidemics in other locations it will certainly still serve as a useful training tool to allow control staff to examine and understand the interactions between climate, control activities, the vector and human health. In any case the model should be used in the Hwange district where its results may be of great help to malaria control efforts.

In terms of examining the cost-effectiveness of malaria control interventions the model structure used in this thesis has shown that in epidemic situations the timing of the intervention is a critical variable in determining the cost-effectiveness of the intervention. This result has serious implications for the applicability of the results of CEA carried out in non-epidemic and endemic regions, and in epidemic situations with no consideration of the timing of the intervention, which are unlikely to accurately reflect the true cost-effectiveness of epidemic interventions. The model should be used to examine when and where such interventions can efficiently be used during the epidemic cycle in particular epidemiological conditions. It must also be stressed that the result of a cost-effectiveness evaluation from one setting cannot necessarily be transferred to another, especially if location specific parameters were used in the evaluation. The framework in this thesis was designed in such a way that it can be specifically tailored to local conditions and it should continue to be used in this way to prevent over generalisation and loss of meaning of results.

Finally in terms of further research, it is hoped that this thesis will be the first of many more economic evaluations that pay particular attention to the timing of interventions in epidemic situations, not just for malaria but for other diseases with a strong dynamic component. It is also suggested that evaluations of malaria control

interventions be focussed at a much lower level such as country, region or even district rather than continent wide. The use of epidemiological population dynamic modelling combined with location specific model validation and cost data can provide an excellent tool for evaluating possible or actual interventions which may be particularly useful for decision makers faced with limited information.

Table 8-1 Comparison of Total Cost to MoH of 'Baseline' and 'Optimal' Policy

| Year | 'Baseline' Scenario | 'Optimal Policy' Scenario | Cost Saving |
|---|---|---|---|
| 1993 | 35981 | 2755 | 33226 |
| 1994 | 95938 | 60459 | 35479 |
| 1995 | 225614 | 81987 | 143627 |
| 1996 | 934725 | 163485 | 771240 |
| 1997 | 336626 | 125677 | 210949 |
| 1998 | 331256 | 166963 | 164293 |

Table 8-2 Total Cost under Optimal and Sub-optimal Strategies with a MEWS Based on Monitored Indicators

| Year | Total Cost with Optimal Policy | (Sub-Optimal Strategy a) Total Cost with Optimal Coverage Baseline Timing | (Sub-Optimal Strategy b) Total Cost with Optimal Timing Baseline Coverage | (a-b) Difference |
|---|---|---|---|---|
| 1993† | 2755 | 2755 | 37570 | -34815 |
| 1994 | 60459 | 135172 | 60459 | 74713 |
| 1995 | 81987 | 300191 | 85331 | 214860 |
| 1996 | 163485 | 846818 | 430958 | 415860 |
| 1997 | 125677 | 271050 | 252850 | 18200 |
| 1998 | 166963 | 340867 | 148968 | 191899 |
| Mean | 100221 | 316142 | 169356 | 146786 |

† Note that optimal timing of spraying could not be identified because no data was available for spraying prior to January 1993.

Table 8-3 Total Cost under Optimal and Sub-optimal Strategies with a MEWS Based on Forecasted Transmission Indicators

| Year | Total Cost with Optimal Policy | (i) Total Cost with Optimal Timing and Baseline Coverage | (ii) Total Cost with Optimal Coverage December Timing | (i-ii) Difference |
|---|---|---|---|---|
| 1993 | 1166† | 35981† | 2755 | 33226 |
| 1994 | 50323 | 50323 | 99589 | -49266 |
| 1995 | 106947 | 66301 | 135687 | -69386 |
| 1996 | 409416 | 286768 | 338585 | -51817 |
| 1997 | 289066 | 204075 | 198419 | 5656 |
| 1998 | 715937 | 130946 | 273099 | -142153 |
| Mean | 262143 | 129065 | 174689 | -45623 |

† Note that optimal timing of spraying could not be identified because no data was available for spraying prior to January 1993.

Table 8-4 Summary of Early Warning Indicators

| Early Warning Indicator | Costs borne by | Predictive Accuracy | Length of Time Offered for Action |
|---|---|---|---|
| Seasonal Forecasting | Meteorological Agency | Low | Very Long |
| Weather Monitoring | Meteorological Agency | Medium | Long |
| Entomological Monitoring (EIR) | Health Service | Medium | Medium |
| Surveillance | Health Service | High | Short |
| Interpretation of all Indicators | Health Service | N/A | N/A |

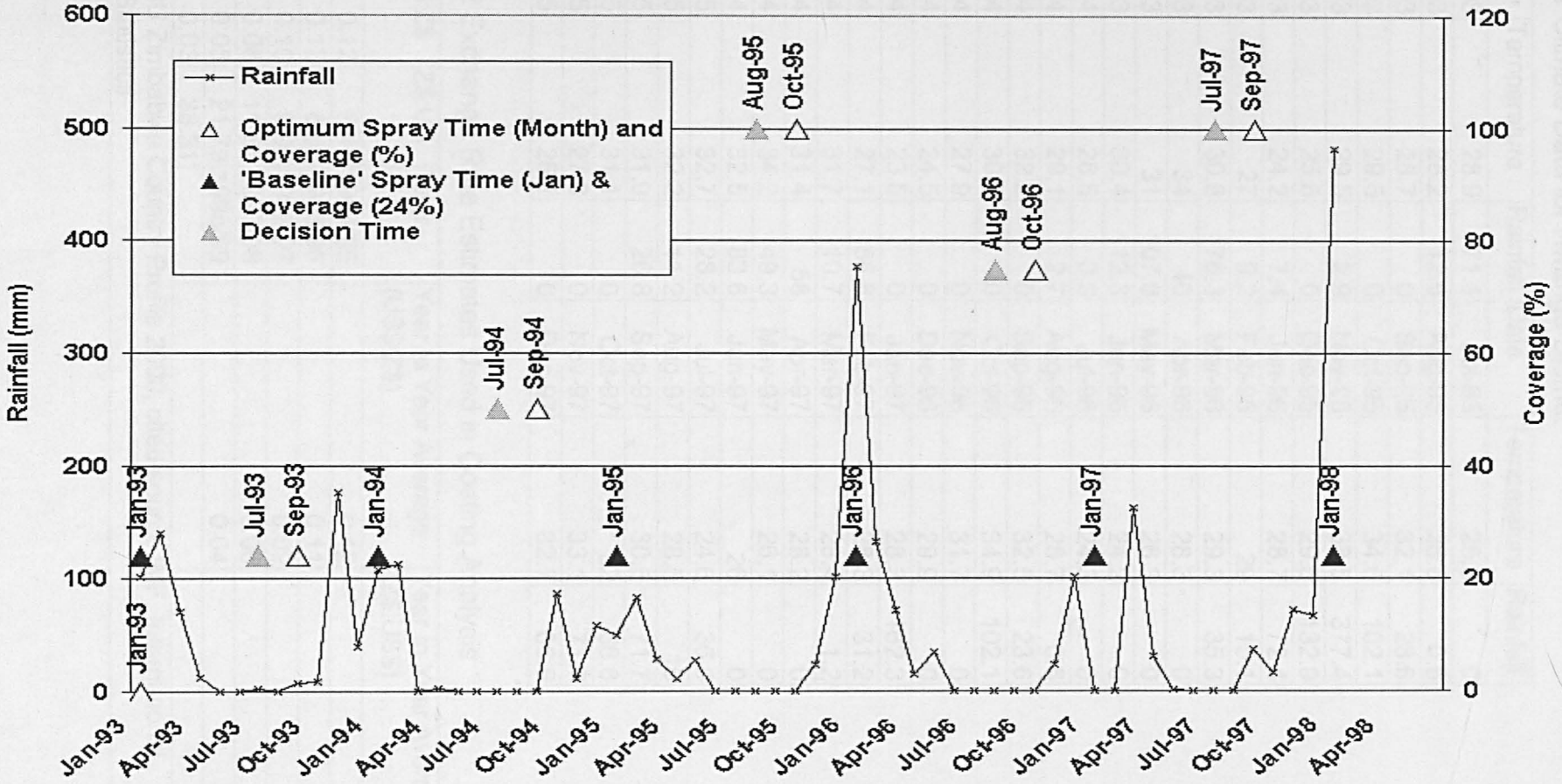
Table 8-5 Breakdown of Costs and Benefits to MoH and Households of Malaria control with and without MEWS

| Control System | | | No MEWS (Baseline Situation) | | MEWS In Use & Predicts 'Epidemic' | | MEWS in Use & Predicts 'No Epidemic' | |
|---|---|---|---|---|---|---|---|---|
| State of World | | | Epidemic | No Epidemic | MEWS Correct | MEWS Incorrect (False Positive) | MEWS Correct | MEWS Incorrect (False Negative) |
| Sector | Ministry of Health | Costs | Fixed cost of routine control activities + Cost of epidemic prevention and mitigation activities + Cost of missed opportunity for early intervention (= potential benefit of early intervention) | Fixed cost of routine activities | Fixed cost of routine control activities + Fixed costs of MEWS + Cost of epidemic prevention and mitigation activities | Fixed cost of routine control activities + Fixed cost of MEWS + Cost of epidemic prevention and mitigation activities | Fixed cost of routine control activities + Fixed cost of MEWS | Fixed cost of routine control activities + Fixed cost of MEWS + Cost of epidemic prevention and mitigation activities + Cost of missed opportunity for early intervention (= potential benefit of early intervention) |
| | | Benefits | Reduction in case management costs resulting from successful preventive activities | None | Reduction in case management costs resulting from successful and early preventive activities (benefit of early intervention) | None | Potential that resources saved from reduced fixed cost of routine control activities can be used elsewhere | Reduction in case management costs resulting from successful preventive activities |
| | Households | Costs | Expenditure on prevention activities + Expenditure on treatment + Indirect costs (lost production/earnings etc) | Expenditure on prevention activities | Expenditure on prevention activities + Expenditure on treatment + Indirect costs (lost production/earnings etc) | Expenditure on prevention activities | Expenditure on prevention activities | Expenditure on prevention activities + Expenditure on treatment + Indirect costs (lost production/earnings etc) |
| | | Benefits | Reduction in treatment & indirect costs resulting from successful preventive activities + Reduction in indirect costs resulting from expenditure on treatment | None | Reduction in direct and indirect costs resulting from successful and early preventive activities carried out by Households and MoH (benefit of early intervention) | None | None | Reduction in treatment costs resulting from successful preventive activities + Reduction in indirect costs resulting from expenditure on treatment |

Table 8-6 Theoretical Framework of the Costs of Malaria Epidemics to Other Sectors

| | Costs of Malaria incurred by: | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Scale of Malaria Outbreak/Epidemic | Individual or household | VHW/PHC network | Village/local health centre/clinic | District level health services | Provincial level health services | Ministry of Health (national level) | NGO's | International bodies (e.g. WHO) |
| Single Case | + | | | | | | | |
| Village Epidemic (small localised epidemic in a village) | + | + | + | | | | | |
| A number of small localised epidemics in villages | + | + | + | + | | | | |
| District Epidemic (whole district affected) | + | + | + | + | + (?) | | | |
| A number of districts affected | + | + | + | + | + (?) | | | |
| Provincial Epidemic (whole province/region affected) | + | + | + | + | + | + | | |
| A number of provinces/regions affected | + | + | + | + | + | + | + (?) | |
| National epidemic (country wide epidemic levels) | + | + | + | + | + | + | + | + (?) |
| National disaster (country wide epidemic with high case fatality rates, health services unable to cope) | + | + | + | + | + | + | + | + |

Figure 8-1 Rainfall, Decision Time, Completion Dates and Coverage Level for Optimum Spray Scenario and Baseline Coverage and Timing Scenario



# APPENDICES

Table A-1 Climate Data for Hwange District

| Date | Temperature | Rainfall | Date | Temperature | Rainfall |
|---|---|---|---|---|---|
| Jan-93 | 28.9 | 71.1 | Jul-95 | 25.5 | 0 |
| Feb-93 | 28.2 | 12.6 | Aug-95 | 28.8 | 0.6 |
| Mar-93 | 28.7 | 0 | Sep-95 | 32.1 | 23.6 |
| Apr-93 | 29.5 | 0 | Oct-95 | 34.6 | 102.1 |
| May-93 | 29.5 | 2.9 | Nov-95 | 33.5 | 377.4 |
| Jun-93 | 25.6 | 0 | Dec-95 | 29.5 | 132.9 |
| Jul-93 | 24.2 | 7.4 | Jan-96 | 28.7 | 72.4 |
| Aug-93 | 27 | 9.2 | Feb-96 | 29 | 15.1 |
| Sep-93 | 30.8 | 176.3 | Mar-96 | 29.3 | 35.3 |
| Oct-93 | 34 | 40 | Apr-96 | 28.3 | 0 |
| Nov-93 | 31 | 107.8 | May-96 | 26.3 | 0 |
| Dec-93 | 30.4 | 112.3 | Jun-96 | 24.2 | 0 |
| Jan-94 | 28.8 | 0.3 | Jul-96 | 24.3 | 0 |
| Feb-94 | 29.1 | 2.7 | Aug-96 | 28.7 | 0.6 |
| Mar-94 | 32.2 | 0 | Sep-96 | 32.5 | 23.6 |
| Apr-94 | 30.8 | 0 | Oct-96 | 34.9 | 102.1 |
| May-94 | 27.9 | 0 | Nov-96 | 31.7 | 0 |
| Jun-94 | 24.5 | 0 | Dec-96 | 29.9 | 0 |
| Jul-94 | 23.5 | 0 | Jan-97 | 28.3 | 162.3 |
| Aug-94 | 27.1 | 86.6 | Feb-97 | 28.3 | 31.2 |
| Sep-94 | 31.7 | 10.7 | Mar-97 | 28.4 | 1.2 |
| Oct-94 | 31.4 | 58 | Apr-97 | 28.2 | 0 |
| Nov-94 | 34.2 | 49.3 | May-97 | 26.1 | 0 |
| Dec-94 | 32.5 | 83.6 | Jun-97 | 26 | 0 |
| Jan-95 | 32.7 | 28.2 | Jul-97 | 24.6 | 36.9 |
| Feb-95 | 32.2 | 11.2 | Aug-97 | 28.5 | 16 |
| Mar-95 | 31.9 | 26.8 | Sep-97 | 30.6 | 71.7 |
| Apr-95 | 31.1 | 0 | Oct-97 | 32 | 66.6 |
| May-95 | 27.3 | 0 | Nov-97 | 33.1 | 71.7 |
| Jun-95 | 25.1 | 0 | Dec-97 | 32.7 | 66.6 |

Table A-2 Exchange Rate Estimates Used in Costing Analysis

| Year | US$:Z$ | Z$:US | Year | Year to Year Average (US$:Z$) | Year to Year Average (Z$:US$) |
|---|---|---|---|---|---|
| 1994 | 0.12 | 8.15 | 1994/95 | 0.12 | 8.41 |
| 1995 | 0.12 | 8.66 | 1995/96 | 0.11 | 9.29 |
| 1996 | 0.10 | 9.92 | 1996/97 | 0.09 | 10.91 |
| 1997 | 0.08 | 11.89 | 1997/98 | 0.06 | 16.84 |
| 1998 | 0.05 | 21.79 | 1998/99 | 0.04 | 30.05 |
| 1999 | 0.03 | 38.31 | | | |

Source: EIU Zimbabwe Country Profile 2000, cited source IMF, International Financial Statistics

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